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Challenging Removal of Embedded Fishbone in Tongue: Multimodal Technique, Surgical Approach and Consideration of Migration

Page 59-62

Original Investigations

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Turkish Archives of Otorhinolaryngology
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Türk Otorinolarengoloji Arşivi

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Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

Aims and Scope

The Turkish Archives of Otorhinolaryngology (Turk Arch Otorhinolaryngol) is the scientific, peer reviewed, open access journal of the Turkish Otorhinolaryngology Head and Neck Surgery Society. The journal is released at three-month intervals, in March, June, September and December, and one volume of the journal comprises four issues. The journal's publication language is English.

The aim of the journal is to publish qualified original clinical, experimental and basic researches on ear, nose, throat, head and neck diseases and surgery, reviews that contain sufficient amount of source data conveying the experiences of experts in a particular field, case reports and original images of rare clinical pictures which would shed light on the clinical practice and which were not previously published, letters from the readers and experts concerning the published studies, articles about general practice and subject of the journal with historical content, memories of scientific significance, educative and catechetical manuscripts about medical deontology and publication ethics.

Target audience of the journal includes academic members, specialists, residents and other relevant health care professionals in the field of ear, nose, throat, and head and neck disorders and surgery.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Turkish Archives of Otorhinolaryngology is indexed in PubMed Central, PubMed, Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, DOAJ, EBSCO, CINAHL and ProQuest.

Processing and publication are free of charge with the journal. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available at www.turkarchotolaryngol.net. The journal guidelines, technical information, and the required forms are available on the journal's web page.

All expenses of the journal are covered by the Turkish Otorhinolaryngology Head and Neck Surgery Society. Potential advertisers should contact the Editorial Office. Advertisement images are published only upon the Editor-in-Chief's approval.

All published content is available online, free of charge at www.turkarchotolaryngol.net. Printed copies of the journal are distributed to the members of the Turkish Otorhinolaryngology Head and Neck Surgery Society, free of charge.

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Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

Instructions to Authors

CONTEXT

The Turkish Archives of Otorhinolaryngology (Turk Arch Otorhinolaryngol) is an international, scientific, open access periodical published by independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of the Turkish Otorhinolaryngology Head and Neck Surgery Society, and published quarterly in March, June, September and December. The publication language of the journal is English.

The aim of the journal is to publish qualified original clinical, experimental and basic researches on ear, nose, throat, head and neck diseases and surgery, reviews that contain sufficient amount of source data conveying the experiences of experts in a particular field, case reports and original images of rare clinical pictures which would shed light on the clinical practice and which were not previously published, letters from the readers and experts concerning the published studies, articles about general practice and subject of the journal with historical content, memories of scientific significance, educative and catechetical manuscripts about medical deontology and publication ethics.

EDITORIAL AND PUBLICATION PROCESS

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

PEER REVIEW PROCESS

Manuscripts submitted to The Turkish Archives of Otorhinolaryngology will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

ETHICAL CONSIDERATIONS

Ethical Guidelines

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 201, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. Submission which do not have ethical approval will be reviewed according to COPE's Research, Audit and Service Evaluations guideline. Such manuscripts can be rejected after editorial review due to the lack of ethics committee approval.

For manuscripts concerning experimental research on humans, a statement should be included that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo.

It is the authors' responsibility to protect the patients' anonymity carefully. For photographs that may reveal the identity of the patients, signed releases of the patient or their legal representative should be enclosed, and the publication approval must be provided in the Methods section.

For studies carried out on animals, an approval research protocols by the Ethics Committee in accordance with international agreements (Guide for the care and use of laboratory animals, 8th edition, 2011" and/or "International Guiding Principles for Biomedical Research Involving Animals, 2012") is required. Also, the measures taken to prevent pain and suffering of the animals should be stated clearly in such studies.

Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Methods section of the manuscript.

Plagiarism and Ethical Misconduct

The Turkish Archives of Otorhinolaryngology is extremely sensitive about plagiarism. All submissions are screened by a similarity detection software (iThenticate by CrossCheck) at any point during the peer-review and/or production process.

When you are discussing others' (or your own) previous work, please make sure that you cite the material correctly in every instance.

Authors are strongly recommended to avoid any form plagiarism and ethical misconduct that are exemplified below.

Self- plagiarism (text-recycling): Overlapping sections or sentences with the author's previous publications without citing them. Even if

you are the author of the phrases or sentences, the text should not have unacceptable similarity with the previously published data.

Salami slicing: Using the same data of a research into several different articles. Reporting the same hypotheses, population, and methods of a study is into different papers is not acceptable.

Data Fabrication: It is the addition of data that never occurred during the gathering of data or the experiments. Results and their interpretation must be based on the complete data sets and reported accordingly.

Data Manipulation/Falsification: It means manipulating research data with the intention of giving a false impression. This includes manipulating images (e.g. micrographs, gels, radiological images), removing outliers or 'inconvenient' results, changing data points, etc…

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act according to COPE flowcharts.

Preprint

Turkish Archives of Otorhinolaryngology does not consider preprint publications as prior publication. In other words, authors are allowed to present and discuss their findings on a non-commercial preprint server before submission to a journal.

Authors must provide the journal with the preprint server deposition of their article accompanying its DOI during initial submission. If the article is published in the Turkish Archives of Otorhinolaryngology, it is the responsibility of the authors to update the archived preprint and link it to the published version of the article.

AUTHORSHIP

Each person listed as an author should fulfil the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org). The ICMJE recommends that authorship is based on the following four criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. Also, the authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

Author Affiliations

Authors are expected to state the institutions which they affiliated in the time of the study. Their current affiliation can be added to the article as the corresponding address. Change of affiliation requests will not be implemented after submission.

The Turkish Archives of Otorhinolaryngology requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through www.turkarchotolaryngol.net) during the initial submission process to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

Change of Authorship

The Turkish Archives of Otorhinolaryngology reviews the authorship according to the author's declaration in the Title Page; thus it is the authors responsibility to send the final order of the complete author names. Requests in the change of authorship (e.g. removal/addition of the authors, change in the order etc.) after submission are subject to editorial approval. Editorial Board will investigate this kind of cases and act following COPE flowcharts.

Change of authorship requests should be submitted to the Editorial Office with an official letter stating the change's reasons. The letter must be signed by all authors and include their approval on the change in authorship. If the request is approved by the Editorial Board, authors need to submit a new Copyright Agreement Form according to the final order list.

DECLARATION OF INTEREST

The Turkish Archives of Otorhinolaryngology requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of

interests, including financial, consultant, and institutional, that might lead to potential bias or a conflict of interest. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. The journal's Editorial Board resolves cases of a potential conflict of interest of the editors, authors, or reviewers within the scope of COPE and ICMJE guidelines.

APPEAL AND COMPLAINT

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to resolve claims that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

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SUBMISSION REQUIREMENTS

- Cover Letter,
- "ICMJE Conflict of Interest Statement Form" (http://www.icmje.org/conflicts-of-interest/) for all contributing authors,
- A separate title page (Title Page should be submitted with all manuscripts and should include the title of the manuscript, name(s), affiliation(s), major degree(s) and ORCID ID of the author(s). The name, address, telephone (including the mobile phone number) and fax numbers and e-mail address of the corresponding author should be clearly listed. Grant information and other sources of support should also be included. Individuals who contributed to the preparation of the manuscript but did not fulfil the authorship criteria should also be acknowledged in the title page),
- Abstract divided into appropriate sections,
- Keywords (For indexing purposes, a list of 4–8 key words in English is essential),
- Article divided into appropriate sections,
- List of references styled according to "journal requirements",
- A blinded main text (Please exclude all information that may indicate an individual or institution from the main document to ensure a blinded review process),
- The Copyright Agreement and Acknowledgement of Authorship form (Please submit a wet-signed and scanned copy of the Copyright Transfer Form with your submission),
- Upload your title page and forms in the system to Potential Conflict of Interest category to ensure a blinded review process,
- Figures (Figures should be submitted as standalone images through the submission system in .JPG or .TIFF format),
- Ethics Committee Approval Statement (with decision/file no, date and name of the institution, for original articles).

MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2019 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behaviour.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.turkarchotolaryngol.net. Manuscripts submitted via any other medium and submissions by anyone other than one of the authors will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

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Instructions to Authors

Authors are required to submit the following:

- Copyright Agreement and Acknowledgement of Authorship Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors) during the initial submission. These forms are available for download at www.turkarchotolaryngol.net.

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions, and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, highest academic degree(s), and ORCID IDs of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number), and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfil the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of four to a maximum of eight keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Main Points: All submissions except letters to the editor and clinical images should be accompanied by 3 to 5 "main points" which should emphasize the most noteworthy results of the study and underline the principle message that is addressed to the reader. This section should be structured as itemized to give a general overview of the article. Since "Main Points" targeting the experts and specialists of the field, each item should be written as plain and straightforward as possible.

Manuscript Types

Original Articles: This is the most essential type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Methods, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Clinical Trials

Turkish Archives of Otorhinolaryngology adopts the ICMJE's clinical trial registration policy, which requires that clinical trials must be registered in a publicly accessible registry that is a primary register of the WHO International Trials Registry Platform (ICTRP) or in ClinicalTrials.gov.

Instructions for the clinical trials are listed below.

- Clinical trial registry is only required for the prospective research projects that study the relationship between a health-related intervention and an outcome by assigning people.
- To have their manuscript evaluated in the journal, author should register their research to a public registry at or before the time of first patient enrollment.
- Based on most up to date ICMJE recommendations, Turkish Archives of Otorhinolaryngology accepts public registries that include minimum acceptable 24-item trial registration dataset.
- Authors are required to state a data sharing plan for the clinical trial registration. Please see details under "Data Sharing" section.
- For further details, please check ICMJE Clinical Trial Policy at

http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

Data Sharing

As of 1 January 2019, a data-sharing statement is required for the registration of clinical trials. Authors are required to provide a data sharing statement for the articles that reports the results of a clinical trial. The data sharing statement should indicate the items below according to the ICMJE data sharing policy:

- Whether individual de-identified participant data will be shared
- What data in particular will be shared
- Whether additional, related documents will be available

- When the data will be available and for how long
- By what access criteria will be shared

Authors are recommended to check the ICMJE data sharing examples at

http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

While submitting a clinical trial to Turkish Archives of Otorhinolaryngology;

- Authors are required to make registration to a publicly accessible registry according to ICMJE recommendations and the instructions above.
- The name of the registry and the registration number should be provided in the Title Page during the initial submission.
- Data sharing statement should also be stated in the Title Page even the authors do not plan to share it.

Clinical trial and data sharing policy of the journal will be valid for the articles submitted from 1 January 2021.

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Clinical Images: This type of submissions should present a striking image that may challenge and inform readers and contribute to their education. Submissions can include high-quality clinical images, radiology results or surgical images. Please check Table 1 for the limitations for Clinical Images.

Please note that there are author limitations for some article types. Authors should provide a reason for the manuscripts that exceed author limitations. The exception of the articles that are above the author limits is subject to Editorial decision.

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software, and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Table 1. Limitations for each manuscript type

Type of manuscript	Author limit	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	N/A	3500	250 (Structured)	30	6	5 or total of 10 images
Review Article	4	5000	250	50	6	10 or total of 15 images
Case Report	6	1000	200	10	No tables	4 or total of 8 images
Letter to the Editor	3	500	No abstract	5	No tables	No media
Clinical Images	3	500	No abstract	5	No tables	3 or total of 7 images

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Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labelled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

Both in-text citations and the references must be prepared according to the Vancouver style.

While citing publications, preference should be given to the latest, most up-to-date publications. Authors are responsible for the accuracy of references. If an ahead-of-print publication is cited, the DOI number should be provided. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Turkish Archives of Otorhinolaryngology does not acknowledge citations to preprints since preprints yet have not passed the reviewers' evaluation process and verified by experts in the field.

Journal Article: Erkul E, Cekin İE, Kurt O, Gungor A, Babayigit MA. Evaluation of patients with unilateral endoscopic sinus surgery. Turk Arch Otorhinolaryngol 2012; 50: 41-5.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the complete drug reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92.

Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki öğrencilerin beslenme durumları, fiziksel aktiviteleri ve beden kitle indeksleri kan lipidleri arasındaki ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author, and their publication approval is requested within two days of their receipt of the proof.

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Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

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Editorial

Dear Colleagues,

Here we are with our first issue of 2022, as we hopefully approach the end of the two-year long COVID-19 nightmare. In 2021 we enjoyed a significant increase in our impact factor; but we still need to improve our position in the Emerging Sources Citation Index in order to achieve a better ranking. And, to that end, we need to work harder. We would like to thank our authors, reviewers, the Turkish Otorhinolaryngology-Head and Neck Surgery Society and our publisher Galenos for the unwavering support they extended.

We strengthened our Editorial Board with the addition of Özlem Önerci Çelebi, MD and Ali Bayram, MD who joined our team in late 2021. We continue to check, for a very low fee, manuscripts before they are uploaded for submission to our journal. Thanks to the AI-based application which examines manuscripts in five different aspects, we observed marked improvement in the writing quality of the submitted manuscripts. Another novel application which we will launch as of our next issue is the possibility to submit video articles. Presenting scientific data and findings to readers with visual materials is a fairly new concept in journal publishing and we hope that this novelty will bring added value to our readers.

We surely also anticipate your contributions. We plan to include more systematic reviews in our journal this year and look forward to receiving your manuscripts in this category. We also need more reviewers. We would like to invite our colleagues who wish to become a reviewer to contact us.

We wish our otorhinolaryngology community good health and success in 2022.

Sincerely,

Taner Kemal Erdağ, MD
Editor-in-Chief

Treatment Results and Postoperative Complications of Single-Stage Tracheal Resection in Adolescent Patients with Post-Intubation Tracheal Stenosis, Compared to Adults

Original Investigation

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Abstract

Objective: The purpose of this study was to analyze the treatment outcomes and postoperative complications of tracheal resection in patients under the age of 19 years with post-intubation tracheal stenosis, and to compare the results with those of adults.

Methods: Data were retrospectively retrieved from the medical records, including demographic characteristics, perioperative features, any postoperative complications and follow-up statuses of the patients. Treatment results and postoperative complications were compared between adolescent and adult groups.

Results: Overall, anastomotic and non-anastomotic complication rates in the adolescent group and the adult group were 40%, 40%, 10% and 63%, 44.4%, 33.3%, respectively. Overall treatment success rates based on tracheostomy tube and tracheal stent free status were 90% and 92.6% in adolescent and adults, respectively.

Conclusion: Treatment success rates and incidence of anastomotic complications were found similar in patients under the age of 19 years and adult patients who underwent single-stage tracheal resection and end to end anastomosis for treatment of post-intubation tracheal stenosis.

Keywords: General otorhinolaryngology, head and neck surgery, intubation, laryngology, pediatric otorhinolaryngology, surgery, trachea, tracheal stenosis

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Introduction

Intubation trauma with mucosal injury from endotracheal tubes or their cuffs is the most common cause of benign acquired tracheal stenosis (1-3). Endoscopic airway procedures such as excision of the granulation tissue and balloon dilation are usually sufficient for successful results when the scar tissue is incipient and fragile at the early stage (4). Mature cicatricial stenosis can occur over time if etiological factors persist. Dilation, laser and/or tracheal stent placement are usually preferred and appropriate for the treatment of web-type short mature

cicatricial stenosis. However, long mature cicatricial or high-grade tracheal stenosis can pose a therapeutic challenge for surgeons.

Patients with long segment and/or high grade mature tracheal stenosis, or cartilaginous structural problems like tracheomalacia, may need more comprehensive open surgical interventions (4). Three types of open surgical methods, 'tracheal resection', 'slide tracheoplasty' and 'expansion tracheoplasty', have been defined for treating tracheal stenosis (1). Tracheal resection procedure is the complete excision of the stenotic segment and end-to-end anastomosis of the remaining healthy stumps of trachea as cricotracheal or tracheotracheal reconstruction. In contrast, expansion tracheoplasty increases the diameter of the tracheal airway lumen by using a graft without performing a circumferential tracheal resection (1). Slide tracheoplasty, is a surgical method that is generally preferred in the treatment of long segment congenital tracheal stenosis.

Circumferential tracheal resection with end-to-end anastomosis for the treatment of high grade mature tracheal stenosis has been frequently performed with high success rates in achieving decannulation of the adult patients with prolonged intubation (4, 5). Although surgical techniques and postoperative complications are well described in many studies, until quite recently, surgeons have been concerned about the potential adverse effects of tracheal and cricotracheal resection on upper aerodigestive tract growth process in the pediatric population (6). There are very few studies in the literature with a relatively small number of patients under the age of 19 years, in surgical outcomes and complications of tracheal resection for the treatment of acquired tracheal stenosis.

In this study we determined the overall, anastomotic and non-anastomotic postoperative complication rates, the incidence of need for adjunctive procedures after resection and treatment success rates of tracheal resection and end-to-end anastomosis in patients under the age of 19 years with post-intubation tracheal stenosis and compared the results with those of adult patients. Additionally, we did an analysis to define the predictive preoperative and perioperative factors that might be related to treatment outcomes.

Methods

This retrospective cohort study was approved by the Ethics Committee of the Bursa Uludağ University Faculty of Medicine (decision number: 2020-7/19 and date: 29.04.2020).

Study Groups

The medical records of 37 consecutive patients who were treated with single-stage circumferential tracheal resection and end-to-end anastomosis due to post-intubation tracheal stenosis at the Otolaryngology Clinic of Bursa Uludağ University between January 2005 and December 2019 were retrospectively reviewed. Patients who underwent tracheal resection due to congenital tracheal stenosis, tracheoesophageal fistula or neoplastic tumors of trachea were excluded. Patients with laryngotracheal stenosis (with glottic involvement) that required partial cricotracheal resection with thyrotracheal anastomosis and patients with tracheal stenosis extending below the thoracic trachea that required thoracotomy were excluded as well. Patients under the age of 19 years comprised the adolescent group and those aged ≥19 years the adult group. Since we did not have any patients who had undergone tracheal resection due to post-intubation tracheal stenosis before the age of nine, patients were classified as the adolescent group, and not the pediatric group.

Surgical Technique

We used the surgical approach that was described by Grillo and Donahue (7). The main steps of the surgical technique have been described in detail in some previously published studies (8-10). Adult patients were extubated at the end of the surgery in the operating room if there were no comorbidities that required postoperative intensive care or mechanical ventilation. Adolescent patients, however, were followed under intubation in the intensive care unit for three postoperative days for effective neck stabilization, and chin-to-chest sutures were placed in all patients.

Study Variables

The independent variables were age, gender, presence of comorbidity, duration of intubation, presence of pre-existing tracheotomy, Cotton–Myer grading, prior treatment procedures, length of resection, type of anastomosis (cricotracheal or tracheotracheal), use of laryngeal and tracheal releasing maneuvers. Preoperative features and Cotton-Myer grading of the patients were assessed from the rigid endoscopic examination records which were performed under general anesthesia before the tracheal resection surgery.

The dependent variables were the presence of postoperative complications (anastomotic, non-anastomotic and overall) and treatment outcomes (treatment success after tracheal resection, need for adjunctive procedures, treatment success after adjunctive procedures and mortality).

Age, gender, duration of intubation, presence of preoperative tracheostomy, presence of prior treatment, Cotton—Myer grading, type of resection, length of resection, number of resected tracheal rings and use of laryngeal release at the stage of reconstruction were analyzed as predictive factors for treatment success.

Statistical Analysis

Statistical analyses were performed for comparisons of postoperative complications (anastomotic, non-anastomotic

and overall) and treatment outcomes between adolescent and adult patients. The preoperative and perioperative predictive factors potentially associated with treatment success without requiring any adjunctive procedures were analyzed by univariate analysis. Categorical variables were analyzed by Fisher's exact test and continuous variables with the Mann–Whitney U test. Commercially available software (SPSS Version 23.0, IBM, Armonk, NY) was used for the analyses and level of statistical significance was assumed as $p<0.05$.

Results

Patient Characteristics and Preoperative Findings

A total of 37 (21 male and 16 female) patients with a mean age of 36.97 (range: 9 to 73) years were included in the study. There were 10 (27%) patients in the adolescent group and 27 (73%) patients in the adult group. Mean duration of intubation was 15.93 (range: 1 to 60) days. Thirty-one (83.8%) patients had pre-existing tracheotomy and 26 (70.3%) had prior treatment before tracheal resection. Based on the Cotton–Myer grading system, 8 (21.6%) patients were classified as grade II, 22 (59.5%) as grade III, and 7 (18.9%) patients were classified as grade IV. Mean follow-up time after surgery was 20.8 (range: 3 to 84) months.

There were no significant differences between the adolescent and adult groups in terms of gender, duration of intubation, pre-existing tracheotomy, prior treatment before tracheal resection, Cotton–Myer grading and duration of follow-up according to the statistical analysis (p=1.000, p=0.302, p=0.653, p=1.000, p=0.906 and p=0.674 respectively). Patient characteristics and preoperative findings are summarized in Table 1.

Table 1. Patient characteristics and surgical features

	Adolescent group (n=10)	Adult group (n=27)	Total study group (n=37)	p-value
Age (years)				
Min	9	19	9	-
Max	18	73	73	
Mean	14.20	45.41	36.97	
SD	3.910	15.741	19.499	
Gender				
Male	6 (60%)	15 (55.6%)	21 (56.8%)	1.000*
Female	4 (40%)	12 (44.4%)	16 (43.2%)	
Duration of intubation (days)				
Min	7	1	1	
Max	35	60	60	
Mean	12.20	21.56	19.03	0.302**
SD	8.176	17.425	15.930	
Pre-existing tracheotomy	8 (80%)	23 (85.2%)	31 (83.8%)	0.653*
Prior Treatment	7 (70%)	19 (70.4%)	26 (70.3%)	1.000*
Cotton–Myer grading				
Grade 2	2 (20%)	6 (22.2%)	8 (21.6%)	
Grade 3	6 (60%)	16 (59.3%)	22 (59.5%)	0.906**
Grade 4	2 (20%)	5 (18.5%)	7 (18.9%)	
Duration of follow-up (months)				
Min	3	4	3	
Max	33	84	84	
Mean	16.90	26.222	23.70	0.674**
SD	8.647	23.474	20.839	
Length of resection (cm)				
Min	1	1	1	
Max	3.5	4.5	4.5	
Mean	2.200	2.222	2.216	0.933**
SD	0.788	0.933	0.886	
Number of resected tracheal rings				
Min	3	2	2	
Max	7	8	8	0.229**
Mean	5.00	4.33	4.51	
SD	1.414	1.797	1.710	
Laryngeal release	4 (40%)	12 (44.4%)	16 (43.2%)	1.000*
Type of anastomosis				
Tracheal	6 (60%)	21 (77.8%)	27 (73%)	0.407*
Cricotracheal	4 (40%)	6 (22.2%)	10 (27%)	

*Fisher's Exact test, **Mann–Whitney U test, Min: Minimum, Max: Maximum, SD: Standard deviation, n: Number

Perioperative Findings

The mean length of tracheal resection was 2.21 (range: 1 to 4.5) cm, 2.2 (range: 1 to 3.5) cm and 2.22 (range: 1 to 4.5) cm in overall, adolescent and adult groups, respectively (p=0.933). The mean number of tracheal rings resected during surgery was 4.51 (range: 2 to 8) in overall and five (range: 3 to 7) and 4.33 (range: 2 to 8) in the adolescent and adult groups, respectively (p=0.229). Laryngeal release was performed in 16 (43.2%) of the patients; namely, four (40%) and 12 (44.4%) patients in adolescent and adult groups, respectively (p=1.000).

Tracheotracheal anastomosis was performed in 27 (73%) patients and cricotracheal anastomosis was performed in 10 (27%) patients for reconstruction. Tracheotracheal anastomosis was performed in six (60%) patients in the adolescent group and in 21 (77.8%) patients in the adult group. Cricotracheal anastomosis was performed in four (40%) patients in the adolescent group and in six (22.2%) patients in the adult group. There were no significant differences between adolescent and adult groups in terms of the type of anastomosis (p=0.407). Table 1 shows the summary of perioperative findings according to patient groups.

Postoperative Complications

Postoperative complications occurred in 21 (56.8%) patients. Of these, 16 (43.2%) were anastomotic and 10 (27%) were non-anastomotic. The incidences of total complications in adolescent and adult patients were 40% (n=4) and 63% (n=17), respectively. The most frequent complications were restenosis (n=8, 21.6%), anastomotic dehiscence (n=5, 13.5%), pneumonia (n=4, 10.8%) and granulation tissue formation (n=3, 8.1%). Other complications were hematoma (n=2, 5.4%), unilateral cord vocal immobility (n=2, 5.4%), wound site infection (n=1, 2.7%) and keloid (n=1, 2.7%).

The incidences of anastomotic complications in adolescent and adult patients were 40% (n=4) and 44.4% (n=12), respectively. Restenosis was the most frequent anastomotic complication in both groups and occurred in two (20%) of the adolescent patients and six (22.2%) of the adult patients. The incidences of non-anastomotic complications in adolescent and adult patients were 10% (n=1) and 33.3% (n=9), respectively. The solely non-anastomotic complication of the one adolescent patient was cord vocal immobility. In the adult group, pneumonia (n=4, 14.8%) was the most frequent non-anastomotic complication. A summary of the postoperative complications according to patient groups is given in Table 2.

Treatment Outcomes and Mortality

The overall success rate after initial surgery was 64.9% (n=24). There were no differences between the success rates of the adolescent and the adult patients (p=0.716), and properly functioning anastomosis was achieved in six (60%) of the adolescents and 18 (66.7%) of the adults without the need for any adjunctive treatment. After the initial surgery, adjunctive procedures were performed in three (30%) adolescents and eight (29.6%) adults (p=1.000). Final treatment success, based on decannulation and tracheal stent-free status, was accomplished in 34 (91.9%) of the patients; namely, nine (90%) adolescents and 25 (92.6%) adults (p=1.000). Overall mortality rate was 5.4% (n=2): major anastomotic dehiscence occurred in one patient from each group, as a result of which both patients died from respiratory arrest before any surgical intervention could be done. Table 2 shows the summary of treatment outcomes and mortality rates.

Results of Univariate Analysis

None of the predictive factors (age, gender, duration of intubation, preoperative tracheotomy, prior treatment, Cotton-Myer grading, type of resection, length of resection, number of resected tracheal rings and laryngeal release) were related to the success of the treatment after initial surgery (p>0.05). The results of the univariate analysis are given in Table 3.

Discussion

Table 2. Postoperative complications and treatment results

	Adolescent group (n=10)	Adult group (n=27)	Total study group (n=37)	p-value
Total complications	4 (40%)	17 (63%)	21 (56.8%)	0.274*
Anastomotic complications				
Total	4 (40%)	12 (44.4%)	16 (43.2%)	1.000*
Restenosis	2 (20%)	6 (22.2%)	8 (21.6%)	1.000*
Dehiscence	1 (10%)	4 (14.8%)	5 (13.5%)	1.000*
Granulation tissue	1 (10%)	2 (7.4%)	3 (8.1%)	1.000*
Non-anastomotic complications				
Total	1 (10%)	9 (33.3%)	10 (27.0%)	0.229*
Pneumonia	None	4 (14.8%)	4 (10.8%)	
Hematoma	None	2 (7.4%)	2 (5.4%)	
Vocal cord paralysis	1 (10%)	1 (3.7%)	2 (5.4%)	
Wound site infection	None	1 (3.7%)	1 (2.7%)	
Keloid	None	1 (3.7%)	1 (2.7%)	
Successful treatment after initial surgery	6 (60%)	18 (66.7%)	24 (64.9%)	0.716*
Adjunctive procedures needed after initial surgery	3 (30%)	8 (29.6%)	11 (29.7%)	1.000*
Successful treatment after adjunctive procedures	9 (90%)	25 (92.6%)	34 (91.9%)	1.000*
With tracheotomy at last control	None	1 (3.7%)	1 (2.7%)	1.000*
Mortality	1 (10%)	1 (3.7%)	2 (5.4%)	0.473*

*Fisher's Exact test, n: Number

Table 3. Results of univariate analysis

	Successful treatment result after initial surgery		
	Yes (n=24) (64.9%)	No (n=13) (35.1%)	p-value
Age (years)			
Min	9	11	
Max	73	61	0.987***
Mean	36.75	37.38	
SD	20.659	17.952	
Adolescent group			
Yes	6 (16.2%)	4 (10.8%)	0.716*
No	18 (48.6)	9 (24.3%)	
Gender			
Male	16 (43.2%)	5 (13.5%)	
Female	8 (21.6%)	8 (21.6%)	0.192**
Duration of intubation (days)			
Min	4	1	
Max	60	58	
Mean	19.92	17.38	0.236***
SD	15.388	17.405	
Preoperative tracheotomy			
Yes	19 (51.4%)	12 (32.4%)	0.394*
No	5 (13.5%)	1 (2.7%)	
Prior treatment			
Yes	18 (48.6%)	8 (21.6%)	0.465*
No	6 (16.2%)	5 (13.5%)	
Cotton–Myer grading			
Grade 2	3	5	
Grade 3	17	5	0.441***
Grade 4	4	3	
Type of resection			
Tracheal	16 (43.2%)	11 (29.7%)	0.440*
Cricotracheal	8 (21.6%)	2 (5.4%)	
Length of resection (cm)			
Min	1	1	
Max	4.5	4	
Mean	2.292	2.077	0.519***
SD	0.954	0.759	
Number of resected tracheal rings			
Min	2	2	
Max	8	8	
Mean	4.67	4.23	0.499***
SD	1.810	1.536	
Laryngeal release			
Yes	10 (27%)	6 (16.2%)	
No	14 (37.8%)	7 (18.9%)	1.000**

*Fisher's Exact test, **Chi-square test (continuity correction), *** Mann–Whitney U test, Min: Minimum, Max: Maximum, SD: Standard deviation, n: Number

Circumferential tracheal resection and end-to-end anastomosis has been successfully described for the definitive treatment of acquired mature benign tracheal stenosis, with reports of high decannulation rates greater than 90% in adult patients (1-3, 5, 11). However, the management of pediatric airway disorders can be challenging for surgeons and major tracheal procedures are uncommon. There are very few articles in the literature that report about the treatment results and the postoperative complications of tracheal resection in pediatric patients with acquired benign tracheal stenosis (non-congenital) (8, 12, 13). To the best of our knowledge, this is the first report analyzing the incidence of anastomotic complications after single stage tracheal resection together with end-to-end anastomosis indicated for treating post-intubation tracheal stenosis in patients under the age of 19 years and adult patients comparatively.

The incidences of postoperative complications after tracheal resection and end-to-end anastomosis are reported between 5% to 46% in the literature (3, 14-16). Some authors defined the postoperative complications as anastomotic and non-anastomotic (14, 17). Anastomotic complications are generally more common and closely associated with surgical success, and rates even mortality. Formation of granulation tissue at the site of the anastomosis was the most common anastomotic complication of tracheal resection before the suture materials (used for anastomosis) were changed from non-absorbable to absorbable sutures (18, 19). Recent studies show restenosis to be more common than granulation tissue formation with reported incidences of 30%–40% (2, 8, 10, 16, 17). Anastomotic separation is rare, yet the most devastating complication following tracheal resection. Minor separation can occur in some cases and only with subcutaneous emphysema; however, can occasionally require surgical intervention as a major complication and may result in death unless the airway is immediately stabilized. The rate of anastomotic separation after tracheal resection ranges from 4% to 14% and its related mortality can reach 7.8% (14, 20). The 5.4% mortality rate we found in our study was similar to those reported in the literature. In two of our patients, progressive extensive subcutaneous emphysema in the neck and upper chest region developed and sudden respiratory distress emerged in the postoperative period (7th and 9th days). Respiratory arrest occurred within a short time and the patients expired due to major anastomotic dehiscence before any surgical intervention could be done.

Few studies in the literature report a high number of patients with anastomotic complications of tracheal resection. Wright et al. (14) reported the rate of anastomotic complications as 9% (37 separation of anastomosis, 37 restenosis and 7 granulation tissue) among 901 patients, of whom 62 were younger than 17 years of age. They indicated that age was a negative predictive factor for anastomotic separation. Bibas et al. (17) observed anastomotic complications in 20 out

of 94 adult patients (21.3%). Restenosis, granulation tissue formation and anastomotic separation in anastomotic line occurred in 15 (%16), four and one patients, respectively, in their study population. Piazza et al. (20) reported the rate of anastomotic complications as 46% (40 patients) among their 87 patients who underwent cricotracheal/tracheal resection due to benign tracheal stenosis. Anastomotic separation and restenosis occurred in seven (8%) and six (7%) of their patients, respectively. In a recent study including 166 adult patients at three different otorhinolaryngology departments, Fiz et al. (21) reported the overall surgical complication rate as 46%. Laryngeal edema requiring treatment was the most common complication seen in 10 (13.3%), followed by anastomotic separation in eight (10.8%) and granulation tissue formation in seven (9%) of their patients. In another study, Fiz et al. (13) reported the treatment results of 191 pediatric patients who underwent tracheal or laryngotracheal resections due to congenital or acquired laryngotracheal stenosis in four different hospitals. Single stage tracheal surgery was performed in 106 (%55.5) patients. The surgeons performed four different types of cricotracheal resections that were previously classified by Piazza et al. (13, 20). Type A resection was performed in eight patients, Type B in 31 patients, Type C in 113 patients and Type D resection in 39 patients. They determined the decannulation rate as 76% without the need for additional treatment and the final decannulation rate as 88%. Their mean overall complication rate was 24.1%. Laryngeal edema was the most common (8.9%) complication. Anastomotic separation, restenosis and granulation tissue formation occurred in 6.3%, 3.7% and 3.7% of their patients, respectively. Revision surgery was required in 74 patients (38.7%). Stenosis extending to 3–4 subsites of laryngotracheal unit, patients with airway comorbidities and patients with high European Laryngotracheal Society Score were described as risk factors of complications. If we compare the two studies by Fiz et al. (13, 21) the most common complication was laryngeal edema in both adult and pediatric patients. The overall complication rate was higher in adult patients (46% to 24.1%).

In our study, the incidences of overall and anastomotic complication rates after tracheal resection were comparable to those of the previous studies (40% in adolescents and 44.4% in adults). We found restenosis as the most common anastomotic complication. There were no significant differences between the adolescent and adult groups in terms of treatment success and the need for adjunctive procedures. We achieved 90% successful treatment results after tracheal resection +/- adjunctive procedures in the adolescent group with similar complication rates compared to adults.

A tension-free anastomotic line is essential for avoiding such anastomotic complications. The elasticity of the intercartilaginous ligaments is sufficient for low anastomosis tension in limited resections. Many researchers noted that resection less than four cm was safe and adequate (9, 14, 19). If the length of the resection was more than four cm, adjunctive surgical interventions were usually needed. Laryngeal and tracheal release techniques have been used for decreasing the tension at the anastomotic site. However, excessive release procedures may prevent the elevation of the larynx during swallowing and thereby cause dysphagia and aspiration pneumonia (22). Determining the margins of a safe resection is more complicated since the total length of the trachea differs by age in pediatric patients. Previous studies recommend that short segment stenosis on less than 30% of the trachea should be safely resected in pediatric patients (23, 24). In our study, the length of the stenotic segment resected in all adolescent patients was relatively short and not more than 30% of the tracheal length. The most extensive resection was 3.5 cm in two patients aged 17 years in the adolescent group. Resections of one to two cm were performed in four patients aged under 12 years. Therefore, in our study group, laryngeal release was needed in only four patients who were older than 16 years. We did not apply any laryngeal release procedure in patients aged under 16 years.

Based on the results of previous studies, young age, diabetes mellitus, smoking, high grade stenosis, previous history of tracheal surgery, preoperative tracheostomy, laryngotracheal resection, long segment resection greater than four cm and the need for laryngeal release are defined as risk factors for the failure of treatment and/or for complications (2, 17, 25). Our study was limited by a relatively small number of patients, this small size prevented the use of multivariate analysis to define the predictive factors for treatment outcomes. However, according to the results of the univariate analysis, age, gender, duration of intubation, presence of preoperative tracheostomy, presence of initial treatment, grade of stenosis, type of resection, length of resection, number of resected tracheal rings and presence of laryngeal release were not related to treatment success.

Conclusion

The rates of anastomotic complications after tracheal resection and end-to-end anastomosis were similar between patients under the age of 19 and adult patients. Treatment success rates in adolescents were also as high as in adult patients. Basing on these results we can suggest that this surgery can be performed safely in patients aged younger than 19 years with high success rates and low complication risks.

Ethics Committee Approval: This retrospective cohort study was approved by the Ethics Committee of the Bursa Uludağ University Faculty of Medicine (decision number: 2020-7/19, date: 29.04.2020).

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: M.A., H.C., Concept: M.A., H.C., Design: H.C., Data Collection and/or Processing: M.A., M.F.Y., Analysis and/or Interpretation: M.A., M.F.Y., Literature Search: M.A., M.F.Y., Writing: M.A., H.C.

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Main Points

- Frequency of anastomotic complications after tracheal resection and end-to-end anastomosis is similar in patients under the age of 19 years and adults.
- According to the results of univariate analysis, age, gender, duration of intubation, presence of preoperative tracheostomy, presence of initial treatment, grade of stenosis, type of resection, length of resection, amount of resected tracheal rings and presence of laryngeal release are not related with treatment success.
- Treatment success rates in adolescents are also as high as in adult patients.
- Tracheal resection and end-to-end anastomosis can be performed safely in patients under the age of 19 years with high success rates and low risk of complications.

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Original Investigation

Management of Basal Cell Carcinomas: Clinical Experience

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Abstract

Objective: Basal cell carcinomas (BCC) mostly originate from the head and neck region. Main goal in BCC treatment is to achieve both aesthetic and functional results while observing the principles of tumor surgery. We report our experience regarding the clinical, histopathological features and surgical treatment results of head and neck basal cell carcinomas in the light of the literature.

Methods: Files of patients with head and neck BCCs treated surgically in two university hospitals were retrospectively analyzed. Sociodemographic variables, location and size of tumor, pathological subtype, recurrence ratio, complications and technique of reconstruction were evaluated.

Results: We analyzed 119 tumoral lesions in 105 patients of whom 55 (52.4%) were male and 50 (47.6%) were female. Their mean age was 67.3±12 years. The nasal region was the most common location area (n=42, 35.3%). Mean tumor size was 12.6 mm and tumor size range was 2–85 mm. The most commonly used reconstruction techniques were flap surgery, followed by primary closure, and skin grafts.

Conclusion: It is important to remove the tumor with a clear surgical margin at least 4 mm and evaluate the five surgical margins with frozen sections intraoperatively. Operations are often performed under local anesthesia and are well tolerated by patients. The most common flaps used in the reconstruction are not only easy to learn but also sufficient in most cases. Skin grafts are good choices in defects located in the cavum concha and the external meatus.

Keywords: Basal cell carcinoma, skin cancer, pedicled flap, reconstructive surgical procedure

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Introduction

Basal cell carcinoma (BCC) is the most common skin tumor, representing 70% to 80% of all skin tumors (1). It is commonly known that ultraviolet (UV) radiation plays a dominant role as a carcinogenic agent in its development (2). The most common location for BCC are the face and the neck (80%) and the

region most commonly affected in the face is perinasal area (30%) (3). Inspection, dermatoscopic examination and histopathological examination are sufficient for the diagnosis of this tumor. While typical lesions are mostly identified by direct inspection based on common clinical findings, dermatoscopic examination may be required in suspicious cases for diagnosis (4). Numerous histopathological subtypes are known for BCC, which are primarily classified according to their clinical and histopathological characteristics as nodular, superficial, cystic, morpheaform, basosquamous, infiltrative, and fibroepithelioma of Pinkus. The most commonly encountered subtypes are nodular BCCs (2). The morpheaform, infiltrative and basosquamous subtypes of BCC are rare and more aggressive (5). Although mortality related to BCC is low, it still is a significant and costly health problem due to high recurrence rates and destructive local spread may cause significant morbidity (6, 7). The main objectives in BCC treatment are tumor removal with clear surgical margins, thus preventing recurrence, preservation of function and optimal aesthetic outcome (8). BCC treatment mostly involves surgical methods. These methods include surgical excision, micrographically oriented histographic surgery (MOHS) surgery, electrodessication, and curettage. Some low-risk BCC cases can also be managed with topical treatments. If surgery cannot be performed for any reason, radiotherapy is also an option (6).

In this study, the surgical management of the head and neck BCC is discussed based on our 105 patients and in the light of the literature.

Methods

Files of patients with head and neck BCC who were surgically treated between 2015 and 2020 were retrospectively analyzed. Patient data were collected from the two otolaryngology clinics. The study was approved by Kahramanmaraş Sütçü İmam University Faculty of Medicine Clinical Research Ethics Committee (date: 09.09.2020, decision number: 15). Informed consent was obtained from all patients. Sociodemographic variables, location and size of tumor, technique of anesthesia, pathological subtype, recurrence ratio, complications and technique of reconstruction were evaluated. Incisional biopsy samples were obtained for suspicious skin lesions or lesions larger than two centimeters. Local injection anesthesia was the primary anesthesia method used. However, the procedure was performed under general anesthesia (GA) for patients who could not tolerate the procedure under local anesthesia, for patients who preferred GA, and for patients who would recieve GA for another reason. All procedures were performed in the operating room. Surgical excision with 4 mm clean surgical margins was planned after the perimeter of the tumor was defined (9-11). Frozen sections were obtained to verify that all five surgical margins (upper, lower, two sides and base) were clean. If the eyelid was compromised by the tumoral invasion, only three surgical margins (medial, lateral and base) were examined by frozen section. The reconstruction was done simultaneously with tumor resection. Decision for the construction method, namely primary closure, full thickness skin graft or local flap techniques, was based on patient's age, size and location of the tumor, tissue elasticity and patient's preference. The supraclavicular region was the first choice for donor area in the skin graft method. Patients were discharged with oral antibiotics and analgesics on the same or the following day. Sutures were removed on the fifth or seventh postoperative day. The Ophthalmology department was consulted for tumors with periocular location. For patients treated with a flap reconstruction technique, the flap separation procedure was made in the third week for paramedian forehead flap and fourth or sixth week for Hughes flap. Canthotomy and cantholysis were also performed in primary closure for eyelid defects when necessary.

Results

One hundred and five patients who adhered to their follow-up schedules were included in study. Of these 105 patients 50 (47.6%) were female and 55 (52.4%) were male and their ages ranged from 42 to 95 years. Mean patient age was 67.4±10.8 years, male/female ratio was 1.1. Concomitant BCC excision for secondary tumor was done in eight patients, while new BCC was detected in six patients during the follow-up period. One hundred and nineteen tumors were resected from 105 patients. Tumor sizes ranged from 2 to 85 mm with a mean of 12.6±10.86 mm. The nasal region was the most common site (42 lesions, 35.3%), followed by the periocular region (22 lesions, 18.5%), the cheeks and zygoma (22 lesions, 18.5%), the periauricular area (17 lesions,14.3%), the forehead-glabella (6 lesions, 5%) and the scalp (6 lesions, 5%) and others (4 lesions, 3,4 %). Regarding the reconstruction technique, primary closure was used in 45 (37.8%) defects, while local flaps and full thickness skin grafts were used in 53 (44.5%) and 21 (17.6%) defects, respectively. Skin grafts were harvested mostly from the supraclavicular area (Table 1).

Rhomboid flap was commonly used in the cheek and zygomatic region, while the bilobed flap was the technique of choice for nasal area defects. For medial canthal region defects, our preferred method was the glabellar flap. While three different flap techniques (paramedian forehead flap, bilobed flap, nasolabial flap) were used in the nasal area, the glabellar flap, the Hughes flap, and the upper eyelid rotation flap techniques were the flap techniques used in periorbital area defects (Figures 1–6). Of the 119 tumors, 26 (21.84%) were in the low-risk group, and 93 (79.16%) were in the high-risk group (Table 2).

We used general anesthesia (GA) in 22 (21%) and local anesthesia in 83 (79%) patients. Of those operated on under

Table 1. Tumor location and used reconstruction techniques

Tumor location	n	Reconstruction technique	n
Nasal region	42	Primary closure	12
		Skin graft	11
		Bilobed flap	12
		Nasolabial flap	5
		Paramedian forehead flap	2
Cheek-zygomatic region	22	Primary closure	7
		Skin graft	-
		Rhomboid flap	11
		V-Y advancement flap	2
		Rotation flap	2
Periauricular region	17	Primary closure	10
		Skin graft	6
		Local flap	1
Periocular region	22	Primary closure	8
		Skin graft	1
		Glabellar V-Y flap	5
		Hughes flap	7
		Rotation flap (from upper eyelid)	1
Scalp	6	Primary closure	4
		Skin graft	1
		Rotation flap	1
Forehead-glabella	6	Primary closure	4
		Skin graft	-
		Rhomboid flap	2
Temporal-occipital region, chin	4	Primary closure	1
		Skin graft	1
		Rhomboid flap	2

n: Number

GA 19 (86.3%) had high-risk tumors, and the remaining three had other concomitant conditions (thyroidectomy, parotidectomy etc.) that required GA, and BCC excisions were performed simultaneously in these patients. Six patients (5%) had post-operative complications: one had hematoma and was reoperated on for drainage and the flap was resutured. One patient who was treated with a rotation flap for scalp defect had flap necrosis and was allowed to heal by secondary intention. Ectropion developed in one patient with Hughes flap and was managed with lateral strip tarsoraphy. Conservative methods were used for a patient with symblepharon after reconstruction with glabellar flap after removal of a medial canthal region BCC. Skin graft necrosis was seen in two patients with auricular BCC that healed secondarily. Incisional biopsy was performed when the tumor was larger than two cm or there were further suspicions. We performed 26 (21.8%) incisional biopsies in 25 patients preoperatively; tumor size was larger than two cm in 19 of these patients and the remaining patients had suspicious skin lesions. Our pathological specimens revealed

Figure 1. Forehead BCC and rhomboid flap design
BCC: Basal cell carcinoma

Figure 2. View after flap suturation

that our most common subtype was nodular BCC (77 lesions, 65%). Postoperative follow-up period ranged from three to 70 months, with a mean of 35.6±18.3 months. There were no recurrences in any of the patients in the follow-up period.

Discussion

BCCs are the most common cancers in the fair-skinned population (12). Essentially BCC is a tumor of the elderly

Figure 3. View on postoperative day 14

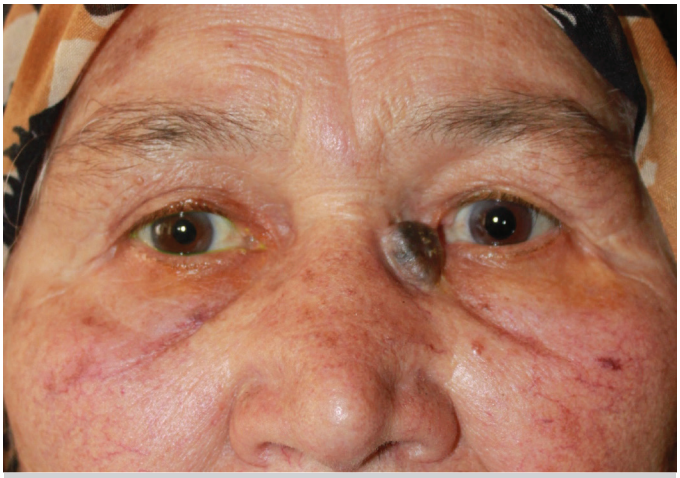

Figure 4. View of medial canthal BCC
BCC: Basal cell carcinoma

and more than 50% of the cases are seen in patients aged 50 to 80 years (3). In our study, mean patient age was 67.4±10.8. Recurrence risk of BCC increases with tumor size when larger than two cm (3). Fifteen percent of our patients had tumors larger than two cm, but none had recurrent disease during the follow-up period. The most common BCC subtype is the nodular ulcerative form and generally affects the head and neck primarily as an isolated lesion (3). According to recent studies, the incidence of nodular BCC varies between 45%–80% (2, 6, 13). In our study, 65% of the tumors of known subtype were nodular type BCC.

Nose, cheek, forehead, ears and periocular regions have the greatest UV exposure in the human body and BCC is most commonly seen in these anatomical areas (14). The nose is the most frequently affected region according to the literature

Figure 5. After tumor excision, intraoperative view

Figure 6. Glabellar V-Y flap, post-operative view

(15-18). In our study, the most affected sites were the nasal, periocular, buccal, and zygomatic, periauricular regions and the forehead. The differences between our study and those in the literature may be related to the fact that we also involved periocular tumors in our study.

Table 2. Risk factors for recurrence (9)

History and physical examination	Low risk	High risk
Location/size	Area M <10 mm	Area M ≥10 mm
	Area H <6 mm	Area H ≥6 mm
Margins	Well defined	Poorly defined
Primary vs. recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior RT	(-)	(+)
Subtype	Nodular, superficial	Aggressive-growth pattern
Perineural involvement	(-)	(+)

Area M: cheeks, forehead, scalp, and neck, Area H: "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, chin, mandible, preauricular and postauricular skin/sulci, temple, ear), RT: Radiotherapy

Overtreating low risk BCC causes avoidable morbidity for the patient and increased health system expenditures, whereas undertreating aggressive high-risk BCC paves the way for recurrence, metastases and further unnecessary highly morbid treatments (19). Therefore, clinicians must distinguish high-risk lesions from low-risk lesions. Of the lesions in our study, 26 (21.84%) were in the low-risk group, and 93 (79.16%) were in the high-risk group. BCC can be easily treated with surgery, especially, when diagnosed early. Local invasion and destruction constitute the main morbidity, when BCCs are located in the face and neck where aesthetic and functional features are crucial (19).

Surgical excision is less effective for BCCs in the H zone, presumably due to its aggressive histology, increased subclinical dissemination and the restricted margins available for removal of the lesion (20). In our study, 85 lesions were in the H zone (area of mask), and none presented with recurrence during follow-up after surgical treatment. The gold standard treatment for non-melanoma skin tumors (NMSTs) is surgical resection. For patients who are not suitable for surgery or do not want to undergo surgery, however, radiotherapy, cryotherapy, topical immunomodulators or photodynamic therapy can be alternative options (5). Radiotherapy is also a treatment option for patients who are unsuitable for surgery or refuse surgery. It is also used as adjuvant treatment in patients with postoperative surgical margin positivity or perineural invasion (21).

Essentially, three methods are used in the evaluation of surgical margins in BCC treatment: histological analysis with frozen sections, micrographic MOHS surgery, and staged-surgery with permanent pathology (5). The recurrence rate after traditional surgical excision can vary between 3 to 42%. Considering that BCC can extend farther than it appears clinically, normal appearing skin should also be removed at tumor excision (22). In our clinic, we routinely evaluate margins from four quadrants and base with frozen sections during the surgical procedure. Although the accuracy of frozen sections is controversial, multiple studies have confirmed its utility (23). When immediate surgical margin assessment is not possible, staged excision with delayed reconstruction should be the choice (23). The National Comprehensive Cancer Network (NCCN) recommends that clean surgical margins of four mm should be obtained for low-risk tumors (9). Wolf and Zitelli (10) reported that in 95% of their patients a clean surgical margin of at least four mm had to be obtained in the removal of tumors smaller than two cm to achieve tumor eradication. In another study, it was recommended to obtain a three mm clean surgical margin for tumors smaller than 10 mm, and a five mm clear surgical margin for tumors sized 10–20 mm for superficial and nodular BCCs on the face (24). Most cases referred to our clinic were < 2 cm and we routinely excised the tumor with a surgical margin of at least four mm. In larger tumors and for aggressive subtypes, the tumor is excised with wider surgical margins after biopsy. Recurrence is rare (<2%) in non-melanoma skin cancers where clear surgical margins are obtained (5). In our study none of the patients had recurrent disease.

Mohs micrographic surgery is also an appropriate surgical option for high-risk BCCs, as it allows for surgical margin analysis during surgery (9). As an alternative to this technique, all circumferential surgical margins and the base can be examined with frozen sections during surgery after excision (9). Before reconstructing the surgical defect, clinicians must ensure that the tumor has been excised completely and with clear surgical margins (19). In our clinic, we routinely work frozen sections from the four quadrants and with deep margins after excision. After ensuring clear surgical margins, the defect is repaired with primary closure, skin graft, or local flaps in the same session. Lack of good communication and cooperation between surgeons and pathologists can impact the success of the operation.

The surgical defect after tumor excision can be reconstructed with regional, local or free flaps, or skin grafts (25). In a study by Bertozzi et al. (16) on head and neck BCCs, 72.5% of the defects were repaired with primary closure and 26.1% with local flap. In our study, the most commonly used closure method was local flap (n=53, 44%) followed by primary closure (n=45, 37.8%), and skin graft (n=21, 17.6%). We believe that these differences could be related to the location of the tumor, the surgeon's preference, and the size of the tumor.

We most commonly used a rhomboid flap in the cheek area, and a bilobed flap in the nasal region. The bilobed flap is easy to plan, aesthetically acceptable and a one-step procedure. The paramedian forehead flap was our technique of choice whenever the bilobed flap and the nasolabial flap were insufficient to repair nasal defects. The most common

repair methods used in eyelid defects are the Hughes flap and primary closure. In the medial canthal region defects, the glabellar v-y flap was the most preferred technique. Skin grafting was mostly preferred when local flaps were not suitable or in the presence of large defects; however, grafts were used as the first choice in defects located in the cavum concha and the external meatus.

Because of the slow growth of BCCs, patients with recurrent disease are usually diagnosed after five years (26). This information shows that unlike conventional head and neck SCCs, relapses occur after a long time. This suggests that we should follow-up patients for longer periods. In our study, new tumor was identified outside the primary region and excised in six patients during the follow-up period. So far, we had no relapsing patients during their follow-up period. This may be related to the shortness of the average follow-up period. Additionally, we believe that removing the tumor with clear surgical margins of at least four mm and evaluating the surgical margins with frozen section may have contributed to this outcome.

Conclusion

It is important to remove the tumor with clear surgical margins of at least four mm and to intraoperatively evaluate the five surgical margins with frozen sections. Procedures are often performed under local anesthesia and well tolerated by patients. The most common flaps used in the reconstruction are not only easy to learn but also sufficient in most cases. Skin grafts are a good choice in defects located in the cavum concha and the external meatus.

Ethics Committee Approval: The study was approved by Kahramanmaraş Sütçü İmam University Faculty of Medicine Clinical Research Ethics Committee (date: 09.09.2020, decision number: 15).

Informed Consent: Informed consent was obtained from all patients.

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Authorship Contributions

Concept: İ.K., Design: İ.K., Supervision: A.V., M.Ü., Data Collection and/or Processing: G.B.G., Analysis and/or Interpretation: F.Ş., Literature Search: F.Ş., Writing: İ.K., F.Ş., Critical Review: İ.K., A.V., M.Ü., M.G.Y.

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Main Points

- It is safe to remove the tumor with clear surgical margins of 4 mm and evaluate the surgical margins with frozen sections.
- Local anesthesia is well tolerated by patients.
- Skin grafts are a good choice in defects located in the cavum concha and the external meatus.
- Local flaps used in head and neck defect reconstruction are easy to learn and apply.

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Instantaneous Gain in Video Head Impulse Test: A Reliability Study

Original Investigation

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Abstract

Objective: Vestibulo-ocular reflex gain at 40, 60, and 80 ms following the head movement start is calculated as the instantaneous gain. The purpose of this study was to investigate the reliability of instantaneous gain values at 40, 60, and 80 ms with testing and retesting in healthy adults.

Methods: The study was conducted with Interacoustics EyeSeeCam vHIT (Interacoustics, Denmark), and 42 healthy adults were evaluated twice at half-hour intervals (test and retest) by the same practitioner. Agreement of mean gain, gain asymmetry, and instantaneous gain was evaluated using a paired samples t-test.

Results: Mean age of the participants was 33.62±11.17; 38.1% were male and 61.9% were female. In the degree of the agreement, paired sample correlation (r) between test and retest results of the horizontal semicircular canals was found to be higher than those of the vertical semicircular canals. Moreover, the highest correlation between test and retest for instantaneous gain, calculated for only horizontal semicircular canals, was found at 80 ms on each side (0.791; 0.838, right and left, respectively), while the lowest correlation between these parameters was found between the gain asymmetry values.

Conclusion: The video head impulse test used in studies calculates the mean gain in approximately at 60 ms. However, the higher correlation between mean gain values at 80 ms in our findings indicates that gain calculation strategies and techniques for latencies should be discussed. Additionally, the low correlation of vertical semicircular canals for mean gain and gain asymmetry between semicircular canal pairs, which clearly shows that more standard and more reliable methods should be developed.

Keywords: Vestibular system, vestibulo ocular reflex, vestibular function tests, video head impulse test, reliability

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Introduction

The vestibular system is a vital structure made up of simple and complex reflex arcs connecting the semicircular canals to the cognitive regions and is related to various senses. One of the most important reflex arcs, the vestibulo-ocular reflex (VOR), is essential for maintaining a

stable gaze during head movement. It consists of a structure that extends from the semicircular canals (SSCs), which are stimulated by the head movement, to the vestibular nuclei, which is a junction point in the brainstem, and to the extra ocular muscles and the oculomotor nuclei (1, 2). VOR is one of the several emerging structures of ocular responses, occurring about 100 seconds after the initiation of the head movement. VOR latency is the shortest time defined for the entire development of VOR in humans, which is 70–80 ms. The gain of the SSCs, the asymmetry between SSC pairs, and the gain-latency relationship of the SSCs are almost all assessed by the video head impulse test (vHIT), which has already been referenced in both clinical practice and in the literature (3, 4).

vHIT is a clinical test that evaluates the dynamic function of six SSCs to detect peripheral vestibular impairments. The clinician performs a high acceleration head rotation in the yawn plane of each SSC while the patient's eyes are fixed on a target. With a compact, light, and high-speed digital camera, vHIT measurements are taken to record eye movements. The camera, which is designed to not slip during head movements, is placed at the supraorbital level tightly around the eyes. Infrared light is cast onto the eyes and the image of the pupilla is projected onto the camera via a mirror. The inertia measuring device, which consists of a two-dimensional gyroscope and a three-dimensional accelerometer mounted on the goggles, measures the head speed (5, 6). Assessment parameters include the gain value for each SSC (main gain: MG), the gain difference between each pair of SSCs (gain asymmetry: GA), and gain values at 40, 60, and 80 ms of horizontal SSCs (instantaneous VOR gain: INSG), which is only a parameter for the device used in this study. Figure 1 shows the above-mentioned parameters on the interface screen. The device estimates the MG of each SSC administered in around 60 ms, indicating that the head movement has reached its maximal point at this time, according to the computation method. Furthermore, unlike the caloric test, the GA between SSCs shows the difference or directional preponderance of gain between horizontal SSC pairs, and gives this information for vertical SSC (7, 8).

vHIT is widely used in vestibular clinics, although despite its benefits, the method's reliability is highly controversial due to various factors such as examiner experience, fitting of goggles, the testing environment, and distance and size of the target point. Furthermore, it should be emphasized that the EyeSeeCam device accepts a gain of about 60 ms during VOR gain and presenting this number as the MG value of horizontal SSCs reduces the test's reliability.

The primary aim of our study was to investigate the reliability of instantaneous gain values at 40, 60 and 80 ms by test and retest method in healthy adults. The secondary aim was to investigate the reliability of the main VOR gain and VOR gain asymmetries of horizontal and vertical SSCs in healthy adults.

Methods

Participants

A total of 42 participants (16 males, 26 females) with a mean age of 33.62±11.17 years and a range of 18–55 years were recruited for the study (Table 1). All were healthy adults with no complaints of hearing, no history of any vestibular problems or surgical operations, and no complaints of dizziness or vertigo. The study was carried out at Gazi University's Hearing, Speech, Voice, and Balance Center. Individuals that accepted to participate in the study signed a written consent form. The study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975. The study was approved by the Human Ethics Committee of Clinical Research of Gazi University Ethics Committee with protocol number 73633 (date: 28/05/2015).

Table1. Demographics

Participants		**n**	**%**	**Age ($\bar{x}$ ± SD)**
Gender		42	100.00%	33.62±11.17
	F	26	61.9%	33.42±12.30
	M	16	38.1%	33.94±9.33
Age groups	18–30	19	45.24%	23.47±3.48
	31–45	15	35.71%	37.27±4.07
	46–55	8	19.05%	50.88±3.44

n: Number of participants, F: Female, M: Male, $\bar{x}$: Mean, SD: Standard deviation

Test Procedure

The test was done with the EyeSeeCam vHIT (Interacoustics, Denmark). The device consists of 40-gram goggles with a flexible, bendable frame which is secured to the head with an elastic strap, a mono ocular camera which can be switched between the right and left sides of the glasses. In our study, the camera was placed on the right side of the goggles. There is also a laser mounted at the center of the goggles. A USB 2.0 cable connects the camera to the computer for data transfer. Each participant was asked to sit in an upright position at a distance of 150 cm from a target on the wall. The device was calibrated before each test, according to the manufacturer's guidelines (9).

Testing consisted of three sections: Lateral (Horizontal vHIT: HvHIT) for assessing horizontal SSCs (HSSC); RALP (Right Anterior SSC and Left Posterior SSC); and LARP (Left Anterior SSC and Right Posterior SSC) for assessing vertical SSCs (Vertical vHIT: VvHIT). The examiner stood behind the participant, placed hands on the participant's chin, and delivered randomized (duration and direction) 20 head impulses to the right and left sides (15°) in the plane of the horizontal SSCs (head flexed 30°

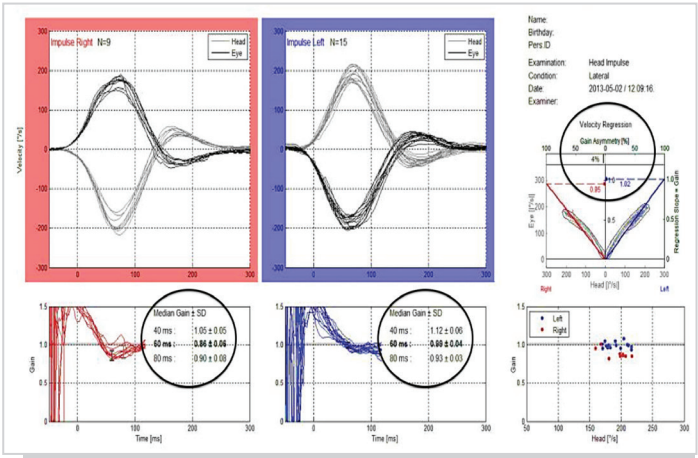

Figure 1. Interface of the vHIT software. INSG of the right and left HSSC at 40, 60, and 80 ms are shown by the left and middle black circles, and mean gain and gain asymmetry between the right and left HSSC are shown by the upper right black circle.
vHIT: Video head impulse test, INSG: Instantaneous gain, HSSC: Horizontal semicircular canal

and eyes fixed) in HvHIT. In VvHIT, participant's head was rotated 40–45 degrees to the right of the fixation point and asked to fix their gaze on the fixation point in this position to test the LARP pair of SSC. The left anterior SSC (LA-SSC) is activated in forward diagonal head movements (a head pitch forward), whereas the right posterior SSC (RP-SSC) is activated in backward diagonal head movements (a head pitch backward) (a head pitch back). Similarly, in the RALP test, the participant was asked to fix their gaze on the target while the head was rotated 40–45 degrees to the left. While forward diagonal head movements activate the right anterior SSC (RA-SSC), backward diagonal head movement activate the left posterior SSC (LP-SSC). The same clinician performed a total of 120 head thrusts to each participant, with 20 for each SSC according to the manufacturer's specifications; i.e., head acceleration had to exceed 1,000/sec2, peak angular head velocity had to be reached within the first 150 ms after initiation of head impulse and must exceed 70°/s, and the maximum difference between eye and head velocity before onset of the head impulse does not exceed 20°/s (9). Retesting was done 30 minutes after testing, using the exact same method.

Statistical Analysis

IBM SPSS version 22 was used to analyze the data (IBM Corp, Armonk, NY, USA). Figures (histograms and probability graphs) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests) were used to assess the normality of the data distribution. The categorical variables were shown as percentage (%), whereas the continuous variables were shown as mean ($\bar{x}$) and standard deviations (SD). The differences among demographic categories such as gender and age were analyzed using the student's t-test and the one-way ANOVA test. Furthermore, the paired samples t-test was used to analyze whether there was 0.05 significant difference between the test and retest results, and the paired samples correlations value (r) value was computed to investigate the association between repeated tests.

Results

The mean age of the 42 (38.1% male, %61.9 female) adult participants was 33.62 years. To evaluate the age effect, participants were divided into three age groups of 18–30 years, 31–45 years, and 46–55 years. Demographic details of the participants are given in Table 1.

Mean Gain and Gain Asymmetry

The values for MG and GA in HvHIT ranged between 0.76–1.20 and 0%–8%, respectively, in test and retest. In VvHIT, ASSC and PSSC MG values were 0.77–1.35 and 0.76–1.29, respectively, and the asymmetry between ASSCs and PSSCs were between 0% and 12%. In HvHIT minimum and maximum INSG values were 0.77–1.87, 0.77–1.45, and 0.64–1.27, respectively, at 40, 60, and 80 ms. The values of the gain parameters of the SSCs in test and retest are shown in Table 2.

Table 2. The gain parameter values for SSCs in test and retest

SSCs MG $\bar{x}$ ± SD		Test		Retest	
		GA $\bar{x}$ ± SD	MG $\bar{x}$ ± SD	GA $\bar{x}$ ± SD	
Horizontal	R-HSSC	0.96±0.10	0.03±0,03	0.96±0.09	0.03±0.02
	L-HSSC	1.00±0.10		0.99±0.10	
RALP	RA-SSC	0.96±0.13	0.03±0.02	0.95±0.11	0.03±0.02
	LP-SSC	0.95±0.11		0.98±0.11	
LARP	LA-SSC	1.03±0.16	0.03±0.01	0.95±0.18	0.03±0.02
	RP-SSC	1.03±0.14		0.97±0.20	

GA values were shown in decimal numbers. These numbers can also be presented as the mean (e.g., 0.03=3%).

SSCs: Semicircular canals, MG: Mean gain, GA: Gain asymmetry, RA-SSC: Right anterior semicircular canal, LP-SSC: Left posterior semicircular canals, LA-SSC: Left anterior semicircular canal, RP-SSC: Right posterior semicircular canal, R-HSSC: Right horizontal semicircular canal, L-HSSC: Left horizontal semicircular canal, $\bar{x}$: Mean, SD: Standard deviation, RALP: Right anterior-left posterior, LARP: Left anterior-right posterior

In the one-way ANOVA test of two sections, there was no statistically significant difference in MG, INSG, and GA values according to age groups ($p>0.05$). Only R-HSSC in MG for the two sections exhibited a statistically significant difference by gender ($p<0.05$) in the student's t-test, although no statistically significant difference was found in others ($p>0.05$).

There was no statistically significant difference between anterior and posterior SSCs and the two sides ($p>0.05$), but there was a statistically significant difference between the VSSCs and the HSSCs ($p<0.05$). The p values of differences

between the SSCs as found in the paired sample t-test are shown in Table 3.

Table 3. P-values of the student's t-test for the pairwise comparisons of the semicircular canals

P-value	R-HSSC	L-HSSC	RA-SSC	LP-SSC	LA-SSC	RP-SSC
R-HSSC	1.000	0.212	0.001**	0.008**	0.018*	0.002**
L-HSSC	0.212	1.000	0.006**	0.001**	0.003**	0.001**
RA-SSC	0.001**	0.006**	1.000	0.531	0.233	0.401
LP-SSC	0.008**	0.001**	0.531	1.000	0.226	0.301
LA-SSC	0.018*	0.003**	0.233	0.226	1.000	0.839
RP-SSC	0.002**	0.001**	0.401	0.301	0.839	1.000

p<0.05:*; p<0.01:**; Statistically significant, R-SSC: Right semicircular canal, L-SSC: Left semicircular canal, RA-SSC: Right anterior semicircular canal, LP-SSC: Left posterior semicircular canals, LA-SSC: Left anterior semicircular canal, RP-SSC: Right posterior semicircular canal, R-HSSC: Right horizontal semicircular canal, L-HSSC: Left horizontal semicircular canal

Reliability Analysis

For each SSC, t and r correlation values were computed for the reliability analysis of the vHIT parameters between test and retest. t and r values between MG and GA of horizontal and vertical SSCs are detailed in Table 4. According to the results, the r value between horizontal SSC measurements was greater than that between vertical canals, and the agreement of the right horizontal SSC was slightly higher than that of the left horizontal SSC. In the case of GA, all canal pairs with the same plane had low r values. All of the r values were statistically significant (p<0.05).

The INSG relevant to horizontal SSCs is only shown in the gain parameters of the EyeSeeCam device used in this study, but it is not available for vertical SSCs. Figure. 2 illustrates the r value of INSG at 40, 60, and 80 ms of the right and left horizontal SSCs in a scatterplot graph with two variances. According to the graph, the most statistically significant agreement (right, left; r: 0.791; 0.838, respectively) was found at 80 ms (p<0.01). Also, the lowest correlation on each side was found at 40 ms, and the r value at 60 ms was higher than the 40 ms values. Furthermore, there were no statistically significant differences between test and retest measures of any semicircular canals (p>0.05).

Discussion

vHIT, with its capacity to assess six SSC functions, is a valuable and effective method in the diagnosis, evaluation, and rehabilitation of peripheral vestibular disorders such as labyrinthitis and neuronitis (10, 11). There are many recent studies in the literature that have assessed hearing loss and the effects of medication on the semicircular canals with vHIT (12, 13). VOR is generated by the eye moving at the same speed as the head but in the opposite direction during a head movement to gaze at an object, and the ratio of eye speed to head velocity is called gain and is "1" in healthy people (14, 15). Normative studies, on the other hand, indicate that the gain between 0.7 and 0.8, and anything less is regarded abnormal (16). Having studied only HCCSs in their study, Bansal and Sinha (17) reported MG to be about 0.96. In their review of the literature, Alhabib and Saliba (18) reported the minimum gain value as 0.79 on using EyeSeeCam vHIT system. In our study, MG values for L-HSSC were found as 1.00±0.10 and 0.96±0.10 for R-HSSC. As a result, physiologically normal responses were symmetrical responses and gain values close toone. Although a controversial subject, there are very few normative and

Table 4. Paired samples t-test and paired samples correlations value (r)

Paired sample t-test			r	t	p#
HSSC		R-HSSC	0.810**	-0.309	>0.05
L-HSSC		0.759**	1.486	>0.05	
GA		0.450**	2.387	>0.05	
VSSC	RALP	RA-SSC	0.768**	1.029	>0.05
		LP-SSC	0.624**	-1.921	>0.05
		GA	0.235*	0.047	>0.05
	LARP	LA-SSC	0.511**	1.156	>0.05
		RP-SSC	0.599**	1.012	>0.05
		GA	0.466**	-0.397	>0.05

p<0.05=*, p<0.01=**, r: Paired samples correlation value, vHIT: Video head impulse test, GA: Gain asymmetry, RA-SSC: Right anterior semicircular canal, LP-SSC: Left posterior semicircular canals, LA-SSC: Left anterior semicircular canal, RP-SSC: Right posterior semicircular canal, RALP: Right anterior-left posterior, LARP: Left anterior-right posterior p#: Paired sample t-test

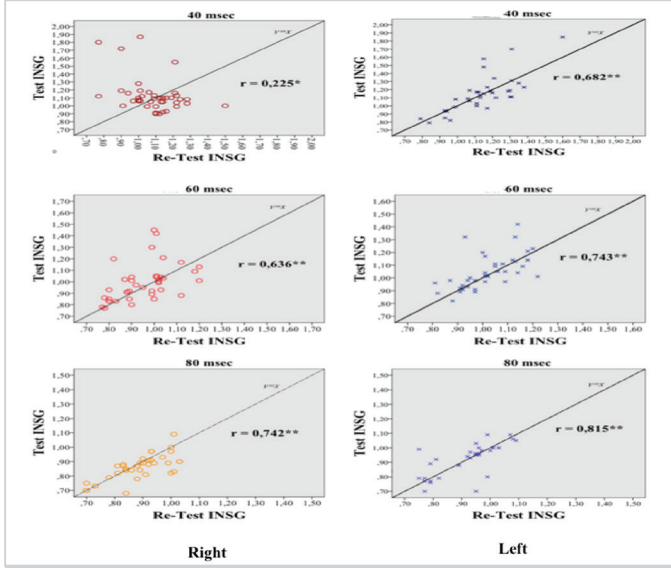

Figure 2. For test and retest, scatter plot graphs of INSG values at 40, 60, and 80 ms on the right and left sides. The right side is represented by red circle, and the left side by blue cross.
p<0.05=*, p<0.01=**, r: Paired sample correlation value, INSG: Instantaneous gain

reliability studies on VSSCs. Bansal and Sinha (17) reported the MG of the VSSC to be 0.87 on the average. The average VOR gain for all VSSCs in our study was 0.99, which is consistent with the literature and physiologically similar to our HSSC results.

INSG (instantaneous gain) is a gain parameter available by Interacoustics EyeSeeCam vHIT only for HSSC. There are few studies on this subject, and no reliability studies have been reported. Janky et al. (19) reported MG values of 0.91, 0.97, and 1.01 at 40, 60, and 80 ms, respectively, and indicated that gain increased with time. In contrast to this, INSG values in our study were 1.14, 1.01, and 0.89, respectively. As a result, unlike the referred study, we found that gain had reduced as latency increased. Mossman et al. (20) only investigating the VOR values at 60 and 80 ms, found the highest and lowest gain values to be 0.76–1.18 and 0.65–1.17, respectively. In our study these values were 0.77–1.45 and 0.70–1.25, respectively.

There are numerous studies that compared the caloric test in healthy individuals and patients, but how vHIT should be used and interpreted are still a matter of discussion. Some studies focus on the benefits of the caloric test, while others highlight the benefits of vHIT (21-24). According to these studies, the most essential advantage of vHIT is the rapid stimulation of the six semicircular canals, yet the caloric test has a greater reliability than vHIT. Singh et al. (25) reported a significant relation in intraclass correlation coefficient values (ICC) of 0.76, 0.86, and 0.77 for HSSCs, A-SSCs, and P-SSCs, respectively. Macdougall et al. (26) found a statistically significant correlation between the scleral coil measuring method and VvHIT in their patient group, with r=0.98. Although there was a statistically significant and strong agreement for HSSCs on the right and left sides, r=0.810 and 0.759, respectively ($p<0.01$), statistically significant correlation was found for VSSCs, RA, LP, LA, and RP-SSC, respectively, r=0.718, 0.624, 0.511, 0.599. The most crucial reason why VSSC demonstrated a worse correlation than HSSCs was assumed to be related to the practitioner's reliability and patient compliance during the test. According to Abrahamsen et al. (27), the effects of the inter-examiner were greater than the effects of the intra-examiner in one test system, but the opposite was true in another. Another factor which contributed to the difference in the correlation was the difficulty of holding the goggles in place during head movement. Suh et al. (28) reported that, the tightness of the strap of the googles affected VOR gains, therefore the strap should be tightened to at least 45 cm/Hg. In our study, our approach was to make sure that the goggles were positioned comfortably on the participants' heads since the device for measuring tightness was not included in the test equipment.

Finally, we believe that using the head movement technique in horizontal semicircular canals is easier than in vertical semicircular canals, and that the head movement angle may be easily altered.

As previously stated, 40, 60, and 80 ms gain values for HSSCs are calculated only on EyeSeeCam while INSG-related head movement continues. The value is computed by generating a regression of the head and eye speeds in these ms, and the device outputs a gain of about 60 ms as MG. There are only a few reports on this topic in the literature. Jacobsen et al. (29) compared the instantaneous gain values to the average gain value and evaluated its repeatability in a study with 60 patients without a vestibular history. According to the authors, the standard deviation of the VOR gain reported at 40 ms was significant, and while it was statistically different from the average gain value, there was no statistical difference at 60 and 80 ms. This study differs from ours in terms of statistical analysis and findings. We found that the correlation findings at 80 ms were slightly better than those at 40 and 60 ms, as well as the HSSC MG correlation findings (Table 4 and Figure 2). As a result, the reliability of the MG parameter produced by this device at 60 ms is controversial.

The caloric test, like the vHIT, calculates asymmetry between pairs of HSSCs. vHIT, on the other hand, calculates GA between pairs of VSSCs in addition to HSSCs.

According to Yang et al. (30), the mean GA of HSSCs was about 2.4, with a minimum value of zero and a maximum value of seven. The mean GA for HSSCs in our study was around 3% [minimum (min)–maximum (max): 0%–8%], while the mean GA for VSSCs was three (min-max: 0%–12%). As a result, it is clear that these findings are consistent with the literature. There are only few studies on the GA values of vertical SSC pairs and the GA reliability of all SSC pairs. Our study revealed that the correlation between GA values was lower than the correlation between MG values (Table 4). We believe that this could be due to the result of the MG-affecting aspects mentioned before. MG can also be affected by the distance and the size of the target. According to Judge et al. (31), gain increases as the target size increases, and it declines as the target distance decreases. In our study, measurements were taken using the manufacturer's recommended distance (150 cm) and target point types.

We believe that our study will contribute to the literature on this topic as GA is a diagnostic criterion, especially in patients with unilateral VOR insufficiency, and important in rehabilitation follow-up of patients with vestibular dysfunction.

Vestibular hypofunction can be revealed by corrective saccades (11). vHIT can be used to measure the frequency, amplitude, and latency of saccades, and several studies have been conducted on this topic. In their study with 25

participants who had undergone cochlear implant surgery, Korsager et al. (32), using EyeSeeCam vHIT, concluded that the occurrence of saccades, not the gain value, should be used to evaluate vHIT outcomes. Janky et al. (33) reported that corrective saccade frequency analysis provided good diagnosis accuracy in 49 patients with bilateral and unilateral vestibular abnormalities, with an 81.9% agreement rate on repeated measures. The reliability of VOR gains was assessed in healthy adults at three separate times (40, 60, and 80 ms) in our study, with varying accuracy findings at each period. We expect that studying the diagnostic accuracy of instantaneous gain values in various vestibular diseases will make a substantial contribution to the literature.

There is clear evidence that the degradation of primary efferent nerves and vestibular cells is associated with ageing. Each semicircular canal in a healthy young adult has a significant number of receptor cells. However, it has been demonstrated that the number of these receptor cells reduce with age (34). McGarvie et al. (15) and Mossman et al. (20) found that MG decreased with age in the function of horizontal semicircular canals, but that this decrease was not statistically significant. To evaluate the effect of age on VOR gain, we divided the participants into three age groups (Table 1). No statistically significant differences were found among these three age groups.

Conclusion

In our study we examined INSG and gain values of VOR. In the literature, there are just a few studies on this topic. The gain at 80 ms was significantly higher than the gains at 40 and 60 ms. Because the device accepts the main VOR gain value at 40 and 60 ms, measurement inconsistency is likely. Furthermore, in terms of agreement, VOR gain values in vertical canals were lower than horizontal canals in our study. The agreement between the RALP and LARP test phases, which are evaluated in the vertical canals, is a subject of controversy. Different strategies should be devised to improve the vertical evaluation's reliability. Finally, the results of the presented study can be used as a norm in vestibular clinics and studies.

Ethics Committee Approval: The procedure was approved by the Human Ethics Gazi University Committee of Clinical Research (protocol number: 73633, date: 28/05/2015).

Informed Consent: Individuals that accepted to participate in the study signed a written consent form.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.K., H.T., B.G., Design: B.K., H.T., B.G., Supervision: H.T., B.G., Data Collection and/or Processing: B.K., Analysis and/or Interpretation: B.K., H.T., B.G., S.A., Literature Search: B.K., S.A., Writing: B.K., Critical Review: B.G., S.A.

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Main Points

- We report the findings of the study on the reliability of instantaneous gain.
- The gain at 80 milliseconds was found to be more reliable than the gains at 40 and 60 milliseconds.
- The gain asymmetry between semisircular canal pairs and the normative values of the gain for all semicircular canals were reported.
- VOR gains in horizontal semicircular canals were shown to be more reliable than VOR gains in vertical semicircular canals.
- The findings indicate that standard vHIT implementation methods should be developed.

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Paranasal Sinus Fungus Ball, Anatomical Variations and Dental Pathologies: Is There Any Relation?

Original Investigation

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Abstract

Objective: The purpose of this study was to investigate the relationship between anatomical variations and the fungus ball (FB), and the association between odontogenic etiologies and the maxillary sinus FB.

Methods: We analyzed the clinical records of 66 patients who underwent endoscopic sinus surgery for FB. The anatomical variations determined were nasal septal deviation (NSD) and direction, presence of Onodi and Haller cell, concha bullosa and lateral recess of the sphenoid sinus. Further, dental X-ray records were reviewed to detect any possible odontogenic etiologies in patients with maxillary sinus FBs.

Results: There were 41 female and 25 male patients. Positive fungal culture was found in 60 patients (91%) and the causative fungus was Aspergillus species in all cases. The correlation between NSD and localization of the maxillary sinus FB was statistically significant (p=0.0409). Maxillary sinus FB was more common on the concave side of the NSD. Presence of dental pathologies was significantly associated with maxillary sinus FB compared to the healthy side (p=0.0011). For sphenoid sinus FB, NSD was detected in a similar number for both the affected and unaffected side and there were no significant correlations (p>0.05). However, the relationship between sphenoid sinus FB and presence of lateral recess was significant (p=0.0262).

Conclusion: Our study revealed that the maxillary sinus FB was more common on the concave side of the deviated septum. Also, dental pathologies or a presence of dental treatment history were associated with maxillary sinus FB.

Keywords: Fungus ball, endoscopic sinus surgery, dental pathology, lateral recess, paranasal sinuses, nasal septum

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Introduction

Fungus balls (FBs) are chronic non-invasive accumulations of fungal elements in the sinus cavity of healthy subjects. They usually affect a single sinus and are most commonly caused by Aspergillus species (1, 2). FBs are frequently localized within the maxillary sinus, followed by the sphenoid sinus. Clinical presentation of FBs are not specific, and patients may complain of various rhinological symptoms. FBs can thereby lead to a diagnostic dilemma for clinicians and most cases are incidentally discovered by computerized tomography (CT) and/or magnetic resonance imaging (MRI) (3).

The pathophysiological mechanism underlying FB is not completely understood. Stammberger (4) hypothesized that nourishment of the fungus by purulent secretions from bacterial and viral superinfections initiated the pathogenesis of fungal sinusitis, followed by the growth of fungal hyphae in a low-pH environment provided by the stenosis of the ostiomeatal complex. Eloy et al. (5) proposed that sinus hypoventilation due to ostial stenosis played a significant role both in the accumulation of fungal spores and in providing anaerobic conditions for the growth of FB. On the other hand, Tsai et al. (6) argued against this hypothesis. They examined Lund-McKay scores in CT images and indicated that ostiomeatal complex dysfunction was not clearly verifiable in the appearance of FBs.

In the presented study, we aimed to investigate the possible relationships between the occurrence of FBs and the presence of different anatomical variations, and the association between odontogenic etiologies and maxillary sinus FBs.

Methods

We retrospectively reviewed the clinical records of patients affected by paranasal sinus (PNS) FB who underwent surgery at a tertiary reference center between 2008 and 2018. The definitive diagnosis was based on histopathological evaluation and/or fungal culture of the surgical specimens. Patients with chronic rhinosinusitis, invasive fungal sinusitis, or allergic fungal sinusitis or who had undergone any previous sinonasal surgery were excluded. Immunocompromised patients were also excluded. The Ethics Committee of İstanbul University İstanbul Faculty of Medicine reviewed and approved the study (project no: 1174/2019).

Preoperative endoscopic examination records, CT and MRI scans of all patients were retrieved from the medical records and reviewed retrospectively. In our clinical practice, patients with maxillary sinus FBs are evaluated with dental X-ray in term of possible odontogenic etiologies such as endodontic treatment history, periodontal disease, tooth extraction, dental implant presence, and communication between tooth apex and maxillary sinus. Therefore, dental X-rays of the patients with maxillary sinus FB were also reviewed. Accordingly, patients with dental pathology and related complaints were consulted to the oral and maxillofacial surgery department.

The anatomical variations determined were nasal septal deviation (NSD) and direction, presence of Onodi and Haller cell, concha bullosa and lateral recess of the sphenoid sinus. NSD of 10 degrees or more was accepted as a separate risk factor. NSD angle was also examined and calculated from coronal CT scans as the angle between the most deviated portion of the septum and the midline (Figure 1).

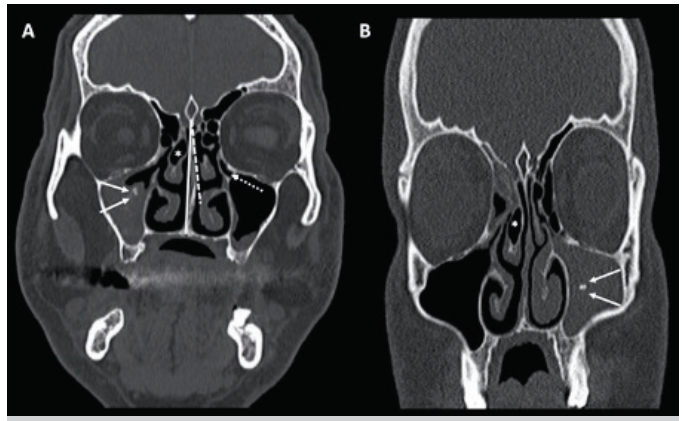

Figure 1. Anatomical variations examples with maxillary sinus fungus balls: (a) Determination of the nasal septal deviation side (straight white arrows: iron-like opacity; dashed white arrow: Haller cell; asterisk: concha bullosa); (b) (straight white arrows: iron-like opacity; asterisk: concha bullosa)

Endoscopic sinus surgery was performed under general anesthesia in all patients. Abundant sinus irrigation was done with saline solution during surgery until all fungal remains were removed. At the end of the surgery nasal packing was applied, and the packing was removed on the second postoperative day. Topical or systemic antifungal therapy were not prescribed. All patients were followed with nasal endoscopy every three months during the first postoperative year.

Statistical Analysis

Descriptive statistics were used to describe continuous variables (average, standard deviation, minimum, median and maximum). We determined significant differences by chi-square test and, if suitable, Fisher's exact test. P-values of <0.05 were assumed to be statistically significant. Statistical analyses were performed with GraphPad Prism (version 8.2.0 for Windows, GraphPad Software, La Jolla, CA, USA).

Results

There were 41 (62.1%) females and 25 (37.9%) male patients, with an age range of 10–84 years (mean: 45.63±17.14). Positive fungal culture was found in 60 patients (91%). The causative fungus was Aspergillus species in all cases.

The localizations of PNS FBs are summarized in Table 1. The most commonly affected sinus was the maxillary sinus (53%) followed by the sphenoid sinus (33.3%). A total of 66 patients had 70 FBs and all patients were unilateral, except for three patients (4.5%). Of these, one had bilateral maxillary sinus FB, one had bilateral sphenoid sinus FB, and one had right maxillary FB and left frontal sinus FB simultaneously.

Table 1. Localization of fungus balls

	n	(%)
Maxillary sinus (unilateral)	35	(53)
Sphenoid sinus (unilateral)	22	(33.3)
Frontal sinus	5	(7.6)
Maxillary sinus (left) and sphenoid sinus (left)	1	(1.5)
Maxillary sinus (left) and frontal sinus (right)	1	(1.5)
Maxillary sinus (bilateral)	1	(1.5)
Sphenoid sinus (bilateral)	1	(1.5)
Total	**66**	**100**

The analysis of anatomical variations is shown in Table 2. In maxillary sinus FB, both NSD and severe NSD (≥10 degrees) were more common on the unaffected side. In other words, the concave side of the deviated septum and the direction of maxillary sinus involvement were the same. However, the relationship between severe NSD and the localization of the maxillary sinus FB was not significant (p>0.05). The maxillary sinus FB was significantly more common on the concave side of the NSD compared to the unaffected side (p=0.0409). Haller cell was detected in both the affected and the unaffected sides in maxillary sinus FB, and a statistically significant difference was not found (p>0.05). Concha bullosa was more common on the affected side in maxillary sinus FB, but this association was not statistically significant (p>0.05).

In sphenoid sinus FB, NSD and severe NSD (≥ 10°) were detected in similar numbers on both the affected and the unaffected sides and there were no significant correlations (p>0.05). Haller cell was more common on the affected side, although Onodi cell was more common on the unaffected side. However, there were no significant differences (p>0.05). Lateral recess was found in 14 of the 24 sphenoid sinuses. Eleven of these were on the same side as FB and this association was significant (Figure 2, p=0.0262).

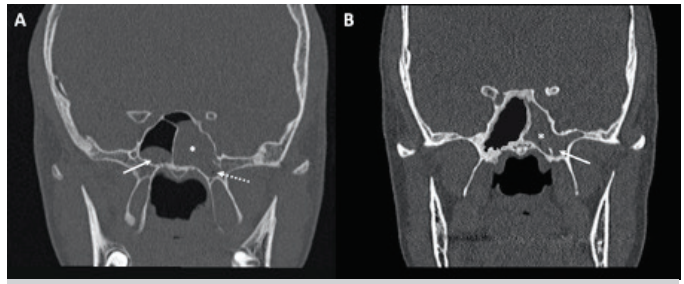

Figure 2. Fungus ball in the left sphenoid sinus (asterisk): (a) Straight white arrow shows mucous retention cyst in the right sphenoid while dashed white arrow shows lateral recess; (b) Straight white arrow shows lateral recess

In 35 of 38 patients who had maxillary sinus FB, 74 dental pathologies were identified on the affected sides. There were 51 dental pathologies on the unaffected sides. In three patients (3/38) with maxillary sinus FB on the affected side and 16 patients (16/38) on the unaffected side, CT scans revealed no dental pathology. Some examples of the dental pathologies are shown in Figure 3. The presence of dental pathologies on the affected side was significantly associated with FB compared to the unaffected side (p=0.0011, Fisher's exact test) (Table 3). The most common pathologies were dental extraction (30/74, 40.5%) followed by endodontic treatment (18/74, 24.3%) and dental root in the maxillary sinus (10/74, 13.5%). The correlation between single dental pathology and FB was not significant.

Discussion

The presented study investigated the possible relationship between FBs and different anatomical variations that can

Table 2. Distribution of anatomical variations according to sinuses

	Nasal septum deviated to	Nasal septum severely deviated to	Haller cell	Onodi cell	Concha bullosa	Lateral recess
Maxillary sinus						
Affected side	11	5	5	2	10	2
Unaffected side	24*	13	4	1	6	1
Sphenoid sinus						
Affected side	4	1	1	7	2	11*
Unaffected side	6	2	5	2	1	3
Frontal sinus						
Affected side	-	-	1	1	1	-
Unaffected side	1	-	-	-	-	1

NSD: Nasal septal deviation, *: p<0.05

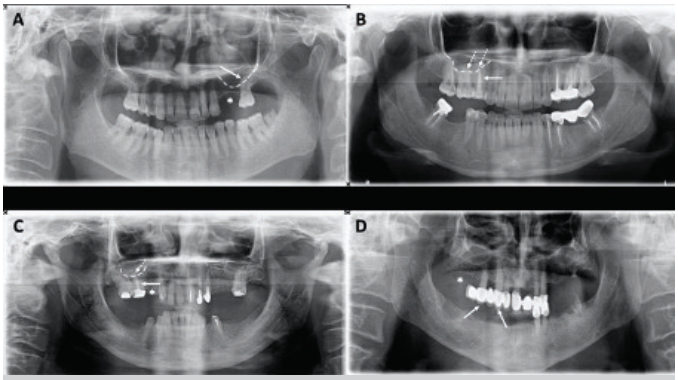

Figure 3. Dental pathologies examples: (a) Dental extractions (asterisk, numbers 24 and 25) and dental root in the maxillary sinus (white arrow: dental apex; dashed line: level of the maxillary sinus floor); (b) Endodontic treatment (straight white arrow) and dental root in the maxillary sinus (dashed white arrows: dental apex; dashed line: level of the maxillary sinus floor); (c) Dental extractions (asterisk, numbers 14 and 15), endodontic treatment (white arrow) and dental root in the maxillary sinus (dashed white arrow: dental apex; dashed line: level of the maxillary sinus floor); (d) Dental extractions (asterisk, numbers 16–18) and dental bridge (white arrows, numbers 13–15)

Table 3. Distribution of dental pathologies according to affected and unaffected side

	Affected side	Unaffected side	p-value
Dental extraction	30	22	0.8540
Endodontic treatment	18	8	0.2706
Dental root in the maxillary sinus	10	7	>0.9999
Apical periodontitis	8	3	0.5228
Implant	4	4	0.7148
Bony dehiscence at the sinus base	3	2	>0.9999
Dental bridge	1	5	0.0509
Dental pathology presence	35	22	0.0011

cause narrowing of the sinus drainage pathway or have a negative effect on mucociliary clearance. We also evaluated dental X-rays of the patients to see whether there were any associations between odontogenic etiology and maxillary sinus FB.

NSD is a well-known anatomical variation that may lead to recurrent rhinosinusitis. Deviation of the septum to one side of the nasal cavity causes chronic influences in nasal airflow. The nasal airflow increases in the contralateral side and decreases in the ipsilateral side. Comprehensive analysis of previous studies showed that an increased angle of NSD was markedly associated with increased frequency of rhinosinusitis, especially with a NSD of 10° or more (7). Oshima et al. (8) found a significant correlation between maxillary sinus FB and NSD in male patients. They discovered that maxillary sinus FB was markedly common on the concave side of the NSD in male patients. Why this association was observed only in males is not clear, but the authors speculated that the relatively larger size of the male nasal cavity could be more sensitive to nasal airflow and its negative effects. Hwang et al. (9) described a statistically positive correlation between larger volume of the middle meatus and maxillary sinus FB. Also, they found no significant relationship between NSD and FB, or the nasal valve area and FB. In our study, a significant correlation between NSD and maxillary sinus FB was observed. Maxillary sinus FB was markedly common on the concave side of the nasal septum. However, the same correlation was not found in patients who had severe NSD. Chen et al. (10) detected increased turbulence and velocity in the middle meatal region on the concave side of the nasal septum. The traumatic effects of turbulent nasal airflow on the concave side can cause ostial stenosis and mucociliary dysfunction due to mucosal injury. Ostial stenosis and decreased mucociliary clearance can result in accumulation of fungal spores and development of FB in the sinus cavity.

Concha bullosa is known as middle turbinate pneumatization, which is associated with recurrent rhinosinusitis due to possible negative effects on both sinus ventilation and mucociliary clearance in the middle meatus (11). However, the role of concha bullosa in maxillary sinusitis development is controversial. In a review study, the presence of concha bullosa in the beginning or the sustaining of rhinosinusitis was not identified as being very important (12). In contrast, Caughey et al. (13) noted a significant association between concha bullosa and maxillary sinusitis. Oshima et al. (8) investigated a possible correlation of different anatomical variations and maxillary sinus FB. Interestingly, they discovered that concha bullosa formation was more prevalent on the healthy side, but this difference was not significant. Tsai et al. (6) reported that there was no structural relationship between concha bullosa and PNS FB. In our study, unlike Oshima et al. (8), concha bullosa was more common on the affected side with maxillary sinus FB. However, a significant correlation was not found between concha bullosa and maxillary sinus FB.

Haller cell is known as infraorbital air cell, which expands from the ethmoid cavity into the maxillary sinus. This air cell may prevent both pneumatization and drainage of the maxillary sinus, hence it can cause recurrent maxillary sinusitis (11). In a review study, Jones (12) noted that Haller cell was not associated with the pathogenesis of maxillary sinusitis. On the other hand, in another study Haller cell was found to be related to both ethmoid and maxillary mucosal disease (13). Oshima et al. (8) examined the relationship of Haller cell and maxillary sinus FB. They reported that FB was present on both the affected and the unaffected sides, but no significant correlation was detected. In the presented study, Haller cell was detected in both the affected side and the healthy side, indicating no significant correlation between Haller cell and maxillary sinus FB.

Onodi cell is the most common anatomical variant of the posterior ethmoidal air cells that pneumatize superiorly and laterally to the sphenoid sinus (14). To our knowledge, there

is no study that investigated the association of Onodi cell and sphenoid sinus FB. In our study, Onodi cell presence was more common on the unaffected sides, but this finding was not significant. However, a significant correlation was present between the lateral recess and FB localization. Sphenoid sinus FB was significantly more common on the same side as the lateral recess. Sphenoid sinus pneumatization can extend into greater wings of the sphenoid bone, resulting in lateral recess. The lateral recess drains into the sphenoethmoidal recess via the sphenoid ostium. The drainage pathway of the lateral recess is against gravity and this situation can lead to difficulty in mucociliary clearance. If suitable environmental conditions are present, the accumulation of fungal spores, which cannot be cleared by the mucosal defense mechanism, can cause FBs.

There are many case reports in the literature that define the association of FB and odontogenic etiologies such as endodontic treatment, dental overfilling, oroantral fistula and dental implant (15-19). Tomazic et al. (20) investigated the association between dentogenic factors and maxillary sinus FB in 102 patients. They reported that the presence of dentogenic factors was significantly associated with FB compared to the healthy side. However, in the referred study, there was no significant relationship between a single dentogenic factor and FB. Mensi et al. (21) reported that patients who underwent endodontic treatment on the upper premolars, molars, and canines, had a 14-fold increased risk for maxillary sinus FB development. Legent et al. (22) investigated dental canal filling and a fungal sinusitis relationship in 85 patients, 85% of whom had dental overfilling of the maxillary sinus. In our study, maxillary sinus FB was found to be markedly frequent in patients who had dental disease or treatment history. Nevertheless, the relationship of a single dental pathology and maxillary FB localization was not statistically significant. Our results support that a combination of dental pathologies should be present in the same patient for maxillary sinus FB development.

Our study focused on both anatomical variations and odontogenic etiologies. The unaffected side was accepted as the negative control group. For this reason, other risk factors such as systemic disease, smoking, air pollution and occupational exposure, which may play a role in fungal sinusitis development, could not be examined. Fungal sinusitis is a multifactorial disease and cannot be explained via a simple cause-effect relationship. Therefore, further prospective randomized controlled trials with a large number of patients are necessary.

Conclusion

Our study revealed that the maxillary sinus FB were more common on the concave side of the nasal septal deviation. This finding may state the outcomes of the traumatic effects caused by wall shear stress of the high-velocity air flow and the increased possibility of the inhalation of fungal spores. Also, dental pathologies or dental treatment history, regardless of type, were significantly associated with maxillary sinus FB. Patients who have dental disease or have undergone dental treatment should be closely monitored and informed about the possible risk of FB development.

Ethics Committee Approval: Ethics committee approval was given by the Clinical Research Ethics Committee of İstanbul University İstanbul Faculty of Medicine (no: 1174/2019).

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Authorship Contributions

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Main Points

- Nasal airflow turbulence and mucociliary clearance dysfunction are extremely important for the pathophysiology of fungal sinusitis.
- Our study revealed that the maxillary sinus FB were more common on the concave side of the nasal septal deviation.
- Dental pathologies or presence of dental treatment history are associated with maxillary sinus FB.

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Estimation of Serum Levels of Heavy Metals in Patients with Chronic Invasive Fungal Rhinosinusitis Before the COVID-19 Era: A Pilot Study

Original Investigation

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Abstract

Objective: Various metals play role in the survival and pathogenesis of the invasive fungal disease. The objectives of this study were to compare the levels of heavy metals in patients with chronic invasive fungal rhinosinusitis (CIFR) and healthy controls, and to analyze their role in disease outcome.

Methods: Twenty-three patients (15 with invasive mucormycosis and 8 with invasive aspergillosis, Group 1), and 14 healthy controls (Group 2) were recruited. Blood samples were collected from each group into ion-free tubes and analyzed for serum levels of Nickel (Ni), Copper (Cu), Zinc (Zn), Gallium (Ga), Arsenic (As), Selenium (Se), Rubidium (Rb), Strontium (Sr), Cadmium (Cd), and Lead (Pb). The final outcome of the patients during their hospital stay was categorized clinico-radiologically as improved or worsened, or death.

Results: The levels of all metals were higher in Group 1 except for As and Pb. However, the differences in Cu (p=0.0026), Ga (p=0.002), Cd (p=0.0027), and Pb (p=0.0075) levels were significant. Higher levels of Zn (p=0.009), Se (p=0.020), and Rb (p=0.016) were seen in the invasive aspergillosis subgroup. Although Zn (p=0.035), As (p=0.022), and Sr (p=0.002) levels were higher in patients with improved outcome, subgroup analysis showed no differences.

Conclusion: The levels of some heavy metals in CIFR significantly differ from those of the general population and also vary with the type of the disease and its outcome. These levels may not have a direct effect on the outcome of the patient, but they do play a role in the pathogenesis of the invading fungus.

Keywords: Chronic invasive fungal rhinosinusitis, invasive mucormycosis, invasive aspergillosis, heavy metals, trace elements

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Introduction

Fungal rhinosinusitis is classified as invasive and non-invasive depending on the potential of the fungal hyphae to invade the superficial epithelium. Invasive fungal sinusitis is further divided into acute, chronic, and chronic granulomatous forms (1). Various micronutrients and metals play an important role in the survival and the pathogenesis of the invasive fungal disease. It has been seen in the pathogenesis of fungal microbes that the host hinders microbial growth and virulence by actively restricting essential metals to fungi, a process known as nutritional immunity. As a result of this, fungi have developed various mechanisms and complex regulatory networks to increase the availability of essential metals such as zinc, copper, and nickel for their survival and virulence. The roles of zinc in the growth of Aspergillus species and of iron in the growth of Mucor species are well-established (2-7). The recent epidemic of invasive mucormycosis in India with the coronavirus disease-2019 (COVID-19) pandemic in the backdrop and the inadvertent use of multivitamins and herbal medicines containing trace or heavy metals (due to the risk to reward ratio in favor of zinc supplementation in COVID-19) may be linked, but to the best of our knowledge, there are no studies available on this topic (8-11). It is also not known whether the levels of these heavy metals are significantly different from those of the general population. We conducted this pilot study in the North Indian population before the COVID-19 era. The primary aim was to compare the levels of various heavy metals between patients diagnosed with chronic invasive fungal rhinosinusitis (CIFR) and healthy controls.

Materials and Methods

A total of 23 adult patients diagnosed with CIFR and 14 healthy controls were included in the study after obtaining ethical clearance from Institute Ethics Committee of All India Institute of Medical Sciences, New Delhi, India (reference number: IEC-436/02.07.2021). Informed and written consent was taken from each of the patients and healthy controls.

The 23 patients included in the study were treatment-naive adult patients (aged >18 years) diagnosed with invasive fungal rhinosinusitis either by microbiological examination (potassium hydroxide wet mount preparation of nasal or palatal crust/swab/ tissue biopsy showing aseptate or septate hyphae) or by histopathological examination of tissue biopsy. The 14 age-matched controls had no pre-existing history of fungal disease. Any patient or control with a history of blood transfusion, prior antifungal treatment, metal intake/ poisoning, and not consenting to take part in the study were excluded. Blood samples (10 mL each) were collected from both the patients and the controls into ion-free tubes and sent to the Ecotoxicology laboratory for the estimation of serum levels of Nickel (Ni), Copper (Cu), Zinc (Zn), Gallium (Ga), Arsenic (As), Selenium (Se), Rubidium (Rb), Strontium (Sr), Cadmium (Cd), and Lead (Pb). The levels of these metals were also compared for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), glycosylated haemoglobin (HbA1c), grade of the disease, and final outcome of the patient during hospital stay.

The results were classified as improved, worsened, or death as per the following definitions:

1. Improved: Both clinical and radiological improvement.

• Clinical improvement: No clinical evidence of residual disease (necrotic tissue or bone/residual fungal debris/ osteomyelitic bone).

• Radiological improvement: No evidence of residual disease on computed tomography (CT) in all cases or magnetic resonance imaging (MRI) in cases involving orbital apex or those with intracranial extension.

2. Worsened: Either clinical or radiological deterioration.

• Clinical deterioration: Progression of disease (involvement of new regions/progression of necrosis) or no clinical improvement despite giving medical therapy and/or possible surgical intervention.

• Radiological deterioration: Progression of disease (involvement of new regions) or persistent residual disease on CT or MRI despite receiving medical therapy and/or possible surgical intervention.

3. Death: Patients who expired during treatment.

Statistical Analysis

Statistical Analysis was performed using the IBM SPSS (IBM SPSS Statistics for Windows, (Version 25.0. Armonk, New York, USA). The levels of heavy metals in both groups were compared using two-tailed t-test considering $p<0.05$ as significant. The Pearson's correlation coefficient was used to check any correlation between serum levels of heavy metals and ESR, CRP, HbA1c, extent of the disease, and outcome of the patient.

Results and Analysis

There were 23 patients (Group 1) and 14 healthy controls (Group 2). Mean age was 42±5.22 years in Group 1 and 35.6±3.20 years in Group 2. In Group 1, 15 patients were diagnosed with invasive Mucormycosis, and eight patients with invasive Aspergillosis. In both types of invasive fungal disease, unilateral disease was more common than bilateral disease. However, the final outcome was different in the two subgroups. In the invasive Mucormycosis subgroup only 26.6% patients improved, while 26.6% patients worsened, and 46.6% died. In the invasive Aspergillosis subgroup

87.5% of the patients improved and 12.5% worsened, and none died during their hospital stay. The disease extent and final outcome of the patients is given in Table 1.

The levels of all metals analyzed in this study were higher in Group 1 (patients) compared to Group 2 (controls) except for As and Pb; however, statistically significant difference (using two-tailed t-test) was seen only in levels of Cu (p=0.002), Ga (p=0.002), Cd (p=0.002), and Pb (p=0.007) between the two groups as shown in Table 2. Levels were found statistically significantly higher for Zn (p=0.009), Se (p=0.020), and Rb (p=0.016) in the invasive Aspergillosis group compared to the invasive Mucormycosis group as shown in Table 3.

Statistically significant differences were also found for Zn (p=0.035), As (p=0.022), and Sr (p=0.002) levels between the improved and the worsened outcome subgroups in all patients. The levels of these three metals were higher in the improved subgroup as shown in Table 4. On subgroup analysis, there were no significant differences among any of the heavy metal levels in the improved, worsened and death outcome groups of patients with invasive mucormycosis. Subgroup analysis could not be done for comparing heavy metals based on outcome in the invasive aspergillosis group as there were seven patients with improved outcome and only one patient with worsened outcome.

There was statistically significant difference between erythrocyte sedimentation rate (ESR) and CRP in the invasive Mucormycosis and the invasive Aspergillosis groups, but there was no correlation between the serum levels of heavy metals and ESR, CRP, and HbA1c in any of these groups as shown in Tables 4, 5, 6 and 7.

Table 1. Disease extent and outcome of patients

	Extent of disease – number of patients	Outcomes of patients – number of patients
Invasive Mucormycosis	• Unilateral disease – 11/15	Improved – 4
	○ Sino-nasal – 4	Worsened – 4
	○ Sino-orbital – 5	Death – 7
	○ Sino-cranial (extradural) – 1	
	○ Sino-orbito-cranial (extradural) – 1	
	• Bilateral – 4/15	
	○ Sino-nasal – 1	
	○ Sino-cranial (extradural) – 1	
	○ Sino-orbito-cranial – 1 extradural, 1 intradura	
Invasive Aspergillosis	• Unilateral disease – 7/8	Improved – 7
	○ Sino-nasal – 1	Worsened – 1
	○ Sino-orbital – 5	Death – 0
	○ Sino-orbito-cranial (intradural) – 1	
	• Bilateral Sino-cranial (extradural) – 1	

Table 2. Mean levels* of heavy metals in patients and controls

No	Heavy metal	Mean level in patients (Group 1)	Mean level in controls (Group2)	p-value
1.	Nickel	1.26±1.09	0.37±0.34	0.472
2.	Copper	1789.73±161.46	1397.96±129.86	**0.002**
3.	Zinc	1913.37±458.84	1864.52±209.33	0.879
4.	Gallium	1.66±0.24	0.48±0.35	**0.002**
5.	Arsenic	1.83±0.18	1.92±0.83	0.221
6.	Selenium	118.51±19.80	109.88±13.45	0.553
7.	Rubidium	1183.40±769.46	543.98±150.69	0.229
8.	Strontium	134.38±14.45	122.86±31.19	0.477
9.	Cadmium	0.72±0.15	0.24±0.18	**0.002**
10.	Lead	4.43±1.45	6.92±2.45	**0.007**

*Measured as parts per billion (ppb) in 10 mL of serum sample.

Significant p-values are shown in bold.

Table 3. Mean level* of heavy metals in Invasive Mucormycosis vs Aspergillosis

No	Heavy metal	Mean level in patients with Invasive Mucormycosis	Mean level in patients with Invasive Aspergillosis	p-value
1.	Nickel	0.96±0.61	1.82±2.89	0.244
2.	Copper	1762.65±188.57	1840.51±297.61	0.670
3.	Zinc	1481.92±295.68	2722.33±975.20	**0.009**
4.	Gallium	1.85±0.55	1.30±0.86	0.309
5.	Arsenic	1.75±0.15	1.97±0.44	0.296
6.	Selenium	101.54±14.84	150.33±41.48	**0.020**
7.	Rubidium	504.64±149.56	2456.08±1903.30	**0.016**
8.	Strontium	124.17±14.69	153.53±26.41	0.061
9.	Cadmium	0.75±0.21	0.69±0.19	0.739
10.	Lead	4.89±1.80	3.57±2.31	0.419

*Measured as parts per billion (ppb) in 10 mL of serum sample.

Significant p-values are shown in bold.

Table 4. Mean level* of heavy metals in patients with different outcomes

No	Heavy metal	Mean level in patients with improved outcome	Mean level in patients with worsened/expired outcome	p-value
1.	Nickel	1.22±1.10	1.29±0.70	0.951
2.	Copper	1879.74±235.52	1707.23±211.20	0.317
3.	Zinc	2429.01±812.67	1440.69±262.58	**0.035**
4.	Gallium	1.37±0.64	1.93±0.67	0.276
5.	Arsenic	2.06±0.33	1.62±0.08	**0.022**
6.	Selenium	133.52±34.90	104.75±17.03	0.169
7.	Rubidium	1953.67±1467.02	477.32±181.39	0.064
8.	Strontium	156.76±21.97	113.86±8.91	**0.002**
9.	Cadmium	0.78±0.18	0.68±0.24	0.273
10.	Lead	4.40±1.93	4.46±2.14	0.485

*Measured as parts per billion (ppb) in 10 mL of serum sample.

Significant p-values are shown in bold.

Table 5. Mean levels of ESR, CRP and HbA1c in invasive Mucormycosis and invasive Aspergillosis

	Mean level in invasive Mucormycosis group	Mean level in invasive Aspergillosis group	p-value
ESR	52.73	31.8	**0.0033**
CRP	116.89	8.68	**0.00004**
HbA1c	9.3	7.2	0.14

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, HbA1c: Glycosylated haemoglobin.

Significant p-values are shown in bold.

Discussion

Metals play important roles in the pathogenesis of infectious disease as these serve as co-factors in various enzymatic processes. A comprehensive review of the role of various heavy metals in fungal virulence and different homeostatic mechanisms has been given by Gerwien et al. (2). Maintenance of adequate intracellular concentrations of trace metal ions like zinc, selenium and copper is essential for many biologically important cellular functions and they are often involved in the regulation of bacterial and fungal virulence. The sequestration of these metals by host defense mechanisms (nutritional immunity) results in extremes of environment for infections to use these metals for various cellular processes, including respiration, replication, transcription, translation, signal transduction and cell division. However, pathogens have also developed counter-defense mechanisms to overcome this metal ion limitation (2, 3, 12). Changes in the levels of certain metals have been shown to increase or decrease infection susceptibility, and the levels of these metals also increase or decrease in response to infection (12).

Copper is an essential element for various enzymatic processes. Excess copper is toxic to cells, and therapies have

Table 6. Correlation of ESR, CRP, and HbA1c with levels of heavy metals in patients with invasive Mucormycosis

No	Heavy metal	Pearson's correlation coefficient (r) and p-value (p)		
		ESR	CRP	HbA1c
1.	Nickel	r=-0.090, p=0.749	r=0.238, p=0.392	r=0.122, p=0.663
2.	Copper	r=-0.294, p=0.287	r=-0.326, p=0.234	r=0.250, p=0.367
3.	Zinc	r=0.149, p =0.596	r=0.013, p=0.962	r=-0.273, p =0.323
4.	Gallium	r=-0.276, p=0.319	r=0.435, p=0.105	r=0.16, p=0.568
5.	Arsenic	r=-0.015, p=0.957	r=0.086, p=0.759	r=-0.134, p =0.631
6.	Selenium	r=0.192, p=0.493	r=0.133, p=0.636	r=-0.004, p=0.986
7.	Rubidium	r=-0.132, p=0.639	r=0.096, p=0731	r=0.346, p=0.205
8.	Strontium	r=0.020, p=0.942	r=0.113, p=0.687	r=0.011, p=0.966
9.	Cadmium	r=0.077, p=0.783	r=-0.151, p=0.588	r=0.532, p=0.409
10.	Lead	r=-0.115, p=0.681	r=0.019, p=0.944	r=-0.086, p=0.759

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, HbA1c: Glycosylated haemoglobin

Table 7. Correlation of ESR, CRP and HbA1c with levels of heavy metals in patients with invasive Aspergillosis

Serial no.	Heavy metal	Pearson's correlation coefficient (r) and p-value (p)		
		ESR	CRP	HbA1c
1.	Nickel	r=-0.393, p=0.335	r=-0.345, p=0.402	r=-0.247, p=0.555
2.	Copper	r=0.255, p=0.542	r=0.114, p=0.787	r=0.325, p=0.430
3.	Zinc	r=0.425, p=0.293	r=-0.179, p=0.670	r=0.555, p=0.152
4.	Gallium	r=-0.390, p=0.338	r=0.211, p=0.615	r=-0.018, p=0.965
5.	Arsenic	r=0.159, p=0.706	r=0.075, p=0.859	r=-0.086, p=0.839
6.	Selenium	r=-0.100, p=0.812	r=-0.553, p=0.155	r=0.013, p=0.974
7.	Rubidium	r=0.235, p=0.573	r=-0.628, p=0.095	r=0.828, p=0.110
8.	Strontium	r=0.653, p =0.078	r=-0.155, p=0.712	r=0.043, p=0.918
9.	Cadmium	r=0.496, p=0.210	r=-0.434, p=0.281	r=0.261, p=0.531
10.	Lead	r=0.601, p=0.114	r=0.269, p=0.518	r=0.049, p=0.907

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, HbA1c: Glycosylated haemoglobin

been developed that boost copper delivery to pathogens resulting in toxicity and less virulence (4, 21). The significantly high levels of copper found in Group 1 in our study may be the response of the body to combat the infection. Copper deficiency, though rare, makes humans more susceptible to infection (12).

The roles of cadmium and lead are not well-studied in human invasive fungal disease. Animal models studying the pathogenesis of *Aspergillus fumigatus* demonstrated that cadmium induced the expression of proteins which support the virulence of the fungal pathogen (13). In our study, cadmium levels were significantly higher in Group 1, a finding that may imply its role in maintaining virulence of the fungal pathogen, especially in invasive Aspergillosis. Lead levels were significantly lower in Group 1 in our study. Blood lead levels in humans depend on genetic and ethnic variations and on environmental exposure which further varies according to geographical areas and local environment (14, 15). Therefore, in our study, neither higher nor lower lead levels could be linked to disease process or pathogenesis, and we did not find any information in the literature for the same.

Zinc is an essential element for fungal proliferation, and pathogens are still able to thrive in the infected host despite the activities of host nutritional immunity. In animal models, loss of zinc transporters causes *Aspergillus fumigatus* to become avirulent, emphasizing the need for coordinated zinc homeostasis during fungal infection. Fungal growth is known to be inhibited by zinc depletion, and evidence suggests that host cells use zinc sequestration to prevent fungal proliferation. Zinc restriction by host cells is achieved by lowering metal availability via the activity of the host zinc transporters or the expression of zinc-binding proteins which may result in higher levels in serum (2, 3, 5, 16-19). Some

zinc-binding enzymes like superoxide dismutase (SOD) and zinc transporters are also involved in fungal virulence (18-20). *Aspergillus fumigatus* cells lacking SOD1 are more susceptible to reactive oxygen species generated by host defense mechanisms and null mutations in zinc transporters lead to reduced ability of the fungus to grow under zinc deprivation (19). *In vitro* studies on the Mucorales species have also shown that the combination of zinc chelators with antifungal therapy resulted in the synergistic inhibition of the fungus (21). We found higher levels of zinc in Group 1, although not statistically significant perhaps due to small sample size or the habit of taking zinc supplements of healthy adults in the form of multivitamins or alternative medicine without proper consultation even before the emergence of COVID-19. But while comparing the patients in the improved and the worsened subgroups, statistically significant higher levels were found in the improved subgroup, a finding that may reflect that the host defense mechanism had either deprived the infected tissue of zinc or increased the toxicity of zinc. High levels of zinc are also detrimental to fungi and excessive zinc exposure can lead to hyphal growth and change in hyphal morphology. Although fungus develops tolerance and resistance to such toxic levels, it is not well-studied in either Aspergillus or Mucor (18, 19, 22). We also found statistically significant higher levels of zinc in patients with invasive aspergillosis compared to those with invasive Mucormycosis, again a finding which emphasizes the role of zinc in infection by Aspergillus species, but the role of zinc in invasive Mucormycosis is not yet known. The role of other rare metals like nickel, arsenic, selenium, rubidium and strontium in invasive fungal disease is also not fully understood and an area of future research.

Although we found significantly raised levels for some heavy metals, particularly zinc, in patients with improved outcome, we cannot attribute these improved outcomes solely to the higher levels of heavy metal. This is because the outcome of the patient in chronic invasive fungal disease is dependent upon various factors like age, comorbidities, surgical success, residual disease, and tolerance to antifungal treatment. Therefore, the role of heavy metals in deciding the outcome of the patient still remains questionable.

Acute inflammatory markers like ESR and CRP are commonly used parameters for prognostication in invasive fungal sinusitis. In addition to this, poor glycemic control is also one of the risk factors for developing invasive fungal disease (23, 24). We compared the levels of heavy metals based on ESR, CRP, and HbA1c as we expected a positive correlation between these parameters and the levels of those heavy metals which are possibly involved in the pathogenesis of CIFR; however, we did not find any correlation. The statistically significant difference between ESR and CRP between invasive Mucormycosis and invasive Aspergillosis may indicate more severe inflammatory response in Mucormycosis, but larger studies are required to validate these results.

Our study was limited by small sample size and hospital-based data. Large community-based studies are required to study the roles and effects of these heavy metals on disease process and survival.

Conclusion

Heavy metals play important role in the pathogenesis of invasive fungal disease. Our study was the first of its kind which compared heavy metal levels between patients with chronic invasive fungal disease and healthy controls. We found significant differences in the levels of some essential metals not only between the two groups but also among patients in different disease and outcome subgroups. These levels may not have a direct effect on the outcome of the patient, but they do play a role in the disease process and the virulence of the organism.

Ethics Committee Approval: This study was approved by Ethics Committee, All India Institute of Medical Sciences, New Delhi, India (reference number: IEC-436/02.07.2021).

Informed Consent: Informed and written consent was taken from all patients and healthy controls.

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Authorship Contributions

Surgical and Medical Practices: K.S., A.T., H.V., Concept: K.S., A.T., H.V., Design: K.S., A.T., H.V., Data Collection and/or Processing: J.A.Q., P.V., R.T., S.P., Analysis and/or Interpretation: J.A.Q., S.P., Literature Search: S.K., P.V., R.T., Writing: S.K.

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Main Points

- Heavy metals play important role in the pathogenesis and the virulence of chronic invasive fungal rhinosinusitis (CIFR).
- It is not known whether the levels of these metals differ from those of the general population.
- Our pilot study found significant differences among the levels of some metals, not only between CIFR patients and healthy controls but also between the different disease groups (invasive mucormycosis vs invasive aspergillosis) and the different outcomes (improved vs worsened).

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Impact of Functional and Aesthetic Factors on Patient Satisfaction in Septorhinoplasty

Original Investigation

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Abstract

Objective: This study aimed to differentiate the functional or aesthetic factors affecting the result of septorhinoplasty and to determine the most important factor related to patient satisfaction.

Methods: Rhinoplasty Outcome Evaluation (ROE) and Visual Analog Scale (VAS) for obstruction (VAS-O) and for appearance (VAS-A) were administered to fifty-five patients undergoing septorhinoplasty preoperatively and six months after the surgery. VAS scores were evaluated as follows: VAS-O (0: unblocked, 10: completely blocked) and VAS-A (0: worst appearance, 10: best appearance). ROE scores were calculated between 0 and 100. In order to examine the relationship between the measurements and determine the most powerful item that affects the overall ROE score, path analysis was performed, and the path coefficients were calculated.

Results: The mean VAS-O and VAS-A scores before and after surgery were 6.85 and 4.36, and 3.91 and 7.22, respectively ($p<0.001$). The absolute value of mean difference was greater for VAS-A (-3.31) than VAS-O (-2.49), which also means appearance scores were more widely affected. The mean ROE score was increased from 46.36±9.28 to 78.85±11.70. VAS-A score had a significant impact on the overall ROE score ($\beta=0.782$, $p=0.001$), while the VAS-O score had no impact. The least effective item on the overall ROE score was item 2 ($\beta=0.445$), while the other items related to aesthetic outcome had higher Path coefficients.

Conclusion: Although septorhinoplasty provides satisfactory results in both functional and aesthetic aspects, patients are more satisfied with the cosmetic outcomes.

Keywords: Rhinoplasty, cosmetic surgery, patient-reported outcome measures, health-related quality of life, patient satisfaction, visual analog scale

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Introduction

Septorhinoplasty can be regarded as a challenging operation because both functional and aesthetic expectations must be considered. The impact of the social and professional environment, nasal obstruction, and concerns about body image are among the reasons why patients request this surgery. Surgical success in septorhinoplasty previously focused on morbidity, complications,

nasal obstruction, and cosmetic outcomes (1). However, improvements in patient satisfaction and quality of life, in addition to surgical values, are important factors in determining surgeons' performance in cosmetic procedures. In other words, the parameter that measures the success of the surgeon in aesthetic operations is patient satisfaction. Different patient-reported outcome measures (PROM) can be used to evaluate the success of nasal surgery in a patient-oriented manner. Some of these PROMs were created to assess functional outcomes, while others were created to assess artistic outcomes or a combination of both (2, 3).

Alsarraf (4) developed a specific questionnaire, rhinoplasty outcome evaluation (ROE), which allowed us to measure health-related quality of life in social, emotional, and psychological aspects in patients undergoing rhinoplasty. This questionnaire was well adopted and is widely used among rhinoplasty surgeons.

Another well-known and easily applicable measurement reported by the patient is the visual analog scale (VAS). This simple numeric scale is a way to turn a subjective feeling into a number (3). The VAS can provide a simple expression of thoughts about appearance and obstruction after septorhinoplasty.

ROE mostly consists of six questions that measure aesthetic satisfaction. Understanding which problem has the greatest impact on the overall score can reveal what factors have the greatest impact on patient satisfaction with septorhinoplasty. The cosmetic result will be less valuable for a patient whose nasal congestion does not improve in the postoperative period.

The aim of this study is to determine whether the main factor affecting patient satisfaction after septorhinoplasty is the aesthetic or functional result.

Methods

Patient Selection

The current study included 58 patients who underwent primary open septorhinoplasty in a tertiary referral hospital between January 2017 and December 2018. The open septorhinoplasty approach was performed on all patients by the same surgeon. Three patients were excluded due to incomplete surveys and missing information. Patients requiring septorhinoplasty due to nasal trauma, congenital nasal abnormalities, or revision surgery were excluded, as were patients receiving closed method septorhinoplasty, patients with systemic disease, allergic rhinitis, or chronic rhinosinusitis, and smokers. Informed consent was obtained from all patients. Institutional ethics committee approval was obtained from Ondokuz Mayıs University School of Medicine Ethics Committee (decision number: OMUKAEK-2018/423).

Assessment of Septorhinoplasty Outcomes

The ROE questionnaire developed by Alsarraf (4) and validated in Turkish by Celik et al. (5) was completed preoperatively and six months after surgery. ROE is composed of six questions related to appearance and nasal breathing (Table 1). Each question is scored on a scale from zero to four, where "0" is the most negative and "4" the most positive answer. The total score is calculated by adding the scores of the individual questions and therefore ranges from 0 to 24. To facilitate interpretation of the results, the total score can be divided by 24 and multiplied by 100, yielding a calculated value between 0 and 100 where higher values denote greater levels of patient satisfaction. A calculated score was obtained for each of the six items by dividing the score by four and multiplying by 100, yielding a value between 0 and 100.

Additionally, all patients were asked to evaluate nasal obstruction and appearance according to VAS preoperatively and six months after surgery. The patients were asked to rate the nasal obstruction based on the VAS score from zero to 10 (VAS-O; 0: unblocked, 10: completely blocked). Also, they were asked to evaluate the appearance of their nose based on the VAS score from zero to 10 (VAS-A; 0: worst appearance, 10: best appearance).

Statistical Analysis

VAS and ROE scores were collected and registered electronically. Statistical data processing was performed using R-Studio software (6). Parametric tests were used when the variables were normally distributed according to

Table 1. Rinoplasty Outcome Evaluation Questionnaire

Item
Item 1. Do you like the look of your nose?
Absolutely not (0) A little (1) More or less (2) Very much (3) Absolutely yes (4)
Item 2. Can you breathe through your nose?
Absolutely not (0) A little (1) More or less (2) Very much (3) Absolutely yes (4)
Item 3. Do you think your friends and the ones dear to you like your nose?
Absolutely not (0) A little (1) More or less (2) Very much (3) Absolutely yes (4)
Item 4. Do you think the looks of your nose limit your social and professional activities?
Absolutely not (0) A little (1) More or less (2) Very much (3) Absolutely yes (4)
Item 5. Is your nose closer to perfection?
Absolutely not (0) A little (1) More or less (2) Very much (3) Absolutely yes (4)
Item 6. Would you like to surgically correct your nose's function or looks?
Certainly yes (0) Very likely yes (1) Possibly yes (2) Probably no (3) Certainly no (4)

the Kolmogorov–Smirnov and Shapiro–Wilk tests. When exploring the preoperative and postoperative scores, paired-samples t was used.

The relationships between VAS-O, VAS-A, and ROE, as well as the impact of individual ROE items on the overall score, were analyzed using structural equation modeling, and path analysis results were presented. The constructed models were evaluated according to the six well-known goodness-of-fit measures such as chi-square (X2) division degrees of freedom (df), goodness-of-fit index (GFI), comparative fit index (CFI), adjusted GFI (AGFI), normed fit index (NFI), and root mean square error of approximation (RMSEA) (7). Path analysis results were interpreted as the model fit indices were obtained within the required limits.

Path analysis is a statistical method that allows the investigation of the interactions between a set of variables. Path coefficients are standardized linear regression weights (β) that can be used to investigate the potential causal linkage between statistical variables in structural equation modeling. The statistical significance was set at the $p<0.05$ level.

Results

In total, 55 questionnaires were collected. The study included 27 female and 28 male patients with a mean age of 29.5 years [standard deviation (SD): 9.10; minimum;18, maximum: 57].

When the relationship of the preoperative VAS-O, VAS-A, and ROE scores was investigated, it was discovered that both the VAS-O and VAS-A scores had no effect on the ROE. However, when the relationship between the postoperative VAS-O, VAS-A, and ROE scores were analyzed, it was discovered that the VAS-A had a major impact (β=0.782, p=0.001) on the overall ROE score, while the VAS-O score had no effect (Table 2). Aesthetic satisfaction explains 63.6% of patient satisfaction after septorhinoplasty (R^2=0.636). The interactions between preoperative (1A) and postoperative (1B) VAS-A, VAS-O, and ROE scores with standardized path coefficients are illustrated in Figure 1.

The mean ROE score was increased from 46.36±9.28 to 78.85±11.70. The mean VAS-O score was 6.85±1.52 and 4.36±1.52 before and after surgery, respectively. The mean VAS-A score was 3.91±1.71 and 7.22±1.11 before and after surgery, respectively. The mean difference of VAS-O was -2.49 [confidence interval (CI): -3.16, -1.82], and the mean difference of VAS-A was -3.31 (CI: -3.84, -2.77). Appearance scores are more widely affected than obstruction scores after septorhinoplasty since the absolute value of the mean difference was greater for VAS-A ($p<0.001$, paired-samples t-test). The decrease in VAS-O scores indicates a reduction in obstructive symptoms, while the rise in VAS-A scores indicates increased patient satisfaction due to the aesthetic result. Table 3 represents the mean values and mean differences of VAS-O, VAS-A, ROE, and overall, ROE scores before and after septorhinoplasty.

When the impact of each ROE question on the overall score was analyzed, it was discovered that all questions had a statistically significant impact on the overall ROE score. The most effective items on the overall ROE score were item 6 (β=0.874), item 5 (β=0.740) and item 4 (β=0.737) respectively. The least effective question was item 2 (β=0.445). Table 4 shows the impact of each item on the overall ROE score and their path coefficients. The Path diagram which illustrates the effect of the individual items on the overall ROE score can be examined in Figure 2.

Discussion

Septorhinoplasty is a common procedure performed by facial plastic surgeons and otolaryngologists (8). PROM measures are defined as "a report directly reported by subjects without commenting on the clinician's study and results. In procedures conducted for cosmetic purposes, evaluating outcomes from the patient's perspective is important (2, 9). The commonly used measures are Septorhinoplasty Outcome Evaluation (ROE), the Functional Septorhinoplasty Outcome Inventory-17 (FROI-17), the Utrecht Questionnaire for Outcome Assessment in Aesthetic Septorhinoplasty (OAR), FACE Questionnaire (FACE-Q), The 10-item Standardized

Table 2. Comparison of preoperative and postoperative VAS-O, VAS-A, ROE, and ROE scores

		Mean (± SD)	Mean difference	95% confidence interval		p-value*
				Lower	Upper	
VAS-0	preVAS-O	6.85 (±1.52)	-2.49	-3.16	-1.82	< 0.001
	postVAS-O	4.36 (±1.94)				
VAS-A	preVAS-A	3.91 (±1.71)	-3.31	-3.84	-2.77	< 0.001
	postVAS-A	7.22 (±1.11)				
ROE	preROE	46.36 (±9.28)	-33.48	-38.84	-29.13	< 0.001
	postROE	79.85 (±11.70)				

SD: Standard deviation, ROE: Septorhinoplasty outcome evaluation score, VAS: Visual Analogue Scale score; VAS-O: Visual analogue scale score for obstruction, VAS-A: Visual Analogue Scale score for appearance, p*: Paired samples t-test

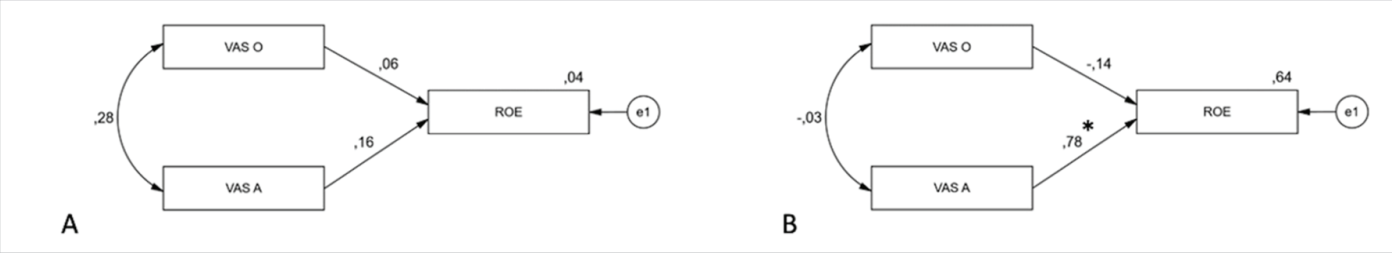

Figure 1.a. Preoperative path coefficients of ROE, VAS-O and VAS-A. b. Postoperative path coefficients of ROE, VAS-O and VAS-A
ROE: Rhinoplasty outcome evaluation, VAS-O: Visual Analog Scale for obstruction, VAS-A: Visual Analog Scale for appearance

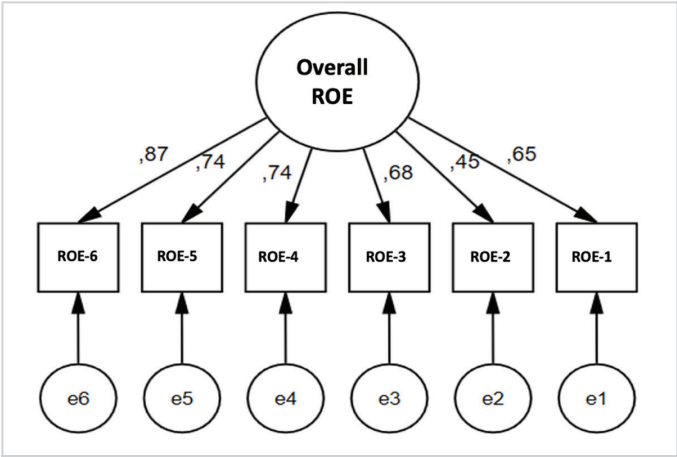

Figure 2. The Path analysis plot with standardized coefficients (β^1) of each item for the postoperative ROE model
ROE: Rhinoplasty outcome evaluation

Cosmesis and Health Nasal Outcomes Survey (SCHNOS), the Sinonasal Outcome Test (SNOT-22), and the Nasal Obstruction and Septoplasty Effectiveness Scale (NOSE) (8, 10, 11). ROE, FROI-17 and SCHNOS are focused on the subjective perception of cosmetic and functional results. OAR and FACE-Q are focused only cosmetic results, while the SNOT-22 and NOSE scales are only concerned with functional symptoms. Alsarraf (4) developed ROE, which has since been validated and translated into Turkish. It is a common PROM with six things that assess physical, social, and emotional factors (4, 5).

Despite the fact that measuring the quality of life after septorhinoplasty has become more common in recent years, the research designs and measurement instruments used in recent studies were remarkably diverse. This variety and heterogeneity create challenges in the literature review. Wahmann et al. (8) conducted a systematic review of 62 post-septorhinoplasty PROM studies published between 2002 and 2017. Only 17 of these met the requirements of being prospective, involving at least 50 participants, using at least one PROM, and collecting full preoperative and postoperative data. We conducted a prospective study with 55 patients using a widely accepted measure (ROE), that is comparable to other research in the literature.

In general, cosmetically unpleasant nasal deformities are associated with functional issues. In addition to reduced nasal breathing, a compromised nasal wall or a severely deviated septum may cause cosmetic deformities. According to our ROE, VAS-O, and VAS-A ratings, our patients had both cosmetic and obstructive symptoms prior to surgery. VAS-O scores decreased, while ROE and VAS-A scores dramatically improved, indicating relief of obstruction-related problems and pleasing aesthetic outcomes. Spiekermann et al. (10) conducted a study in which a VAS was scored between 0 (very ugly) and 10 (very nice). They showed that as the follow-up period increased, aesthetic satisfaction increased from the 1st to the 12th month. In our study, we used final survey scores at the end of the sixth month. Moubayed et al. (11) measured postoperative satisfaction using NOSE, ROE, and VAS in both functional and aesthetic aspects. They found no significant relationship between sex and scores, as in our findings.

The abovementioned studies clearly indicated that patients benefit from septorhinoplasty. However, only before and after surgery scores were compared in these studies. The causal relationship between aesthetics and functionality has not been investigated. Goal of septorhinoplasty is to improve patient satisfaction, it is important to identify the exact factor that has the greatest impact on patient satisfaction. It is obvious that patients benefit from septorhinoplasty both functionally and aesthetically. The question is which factor is more effective on overall satisfaction. Basic statistical work may be insufficient to answer this question. PROMs do not provide us with a measurable value like height or weight. They provide information about the extent of complaint of the patient. If variables related to this type of patient perception are evaluated with structural equation modeling or path analysis, which is a subtype of structural equation modeling, the causality relationship can be revealed more clearly. In our sample, there was no significant interaction between VAS-O, VAS-A, and ROE scores in the preoperative period. This finding may have been obtained during the preoperative phase because patients were dissatisfied with both the shape and function of their noses. While there was an important and strong relationship between VAS-A and ROE in the postoperative period (β=0.782, $p<0.001$). These findings can be interpreted as follows; The main factor affecting patient

Table 3. Preoperative and postoperative path analysis results belonging to ROE. VAS-O. and VAS-A

			β^1	β^2	SE	CR	p-value	r	R^2
Preoperative model									
PreROE	<---	PreVAS-O	0.063	0.387	0.849	0.456	0.648	0.062	0.037
PreROE	<---	PreVAS-A	0.165	0.893	0.754	1.185	0.236	0.159	
Postoperative model									
PostROE	<---	PostVAS- O	-0.138	-0.828	0.493	-1.678	0.093	-0.223	0.636
PostROE	<---	PostVAS- A	0.782	8.185	0.860	9.520	**<0.001**	0.792	

β1: Standardized coefficient (Path coefficient), β2: Unstandardized coefficient, SE: Standart error, CR: Critical ratio, r: Bivariate correlation coefficient, R2: Coefficient of determination, PreROE: Preoperative septorhinoplasty outcome evaluation, PreVAS-O: Preoperative visual analog scale related to obstruction, PreVAS-A: Preoperative visual analog scale related to appearance, PostROE: Postoperative septorhinoplasty outcome evaluation, PostVAS-O: Postoperative visual analog scale related to obstruction, PostVAS-A: Postoperative visual analog scale related to appearance.

<--- decribes the effect of VAS-O and VAS-A scores on overall ROE scores

Table 4. Path analysis results of individual ROE items

			β^1	β^2	SE	CR	p-value
postROE1	<---	postROE	0.648	1.000	-	-	-
postROE2	<---	postROE	0.445	0.737	0.251	2.943	0.003
postROE3	<---	postROE	0.677	0.821	0.194	4.243	<0.001
postROE4	<---	postROE	0.737	0.814	0.179	4.537	<0.001
postROE5	<---	postROE	0.740	0.908	0.199	4.556	<0.001
postROE6	<---	postROE	0.874	1.309	0.258	5.078	<0.001

β^1: Standardized coefficient (Path coefficient), β^2: Unstandardized coefficient, SE: Standart error, CR: Critical ratio.

<--- describes the effect of individual item (e.g. postROE1) on postoperative overall ROE score

satisfaction in the postoperative period is the aesthetic result. Even if the patients' nasal congestion concerns resolve, if the aesthetic outcome is unsatisfactory, they are dissatisfied with the surgical outcome.

The postoperative VAS-O score was significantly lower than the preoperative VAS-O score (less obstruction). Patients are also functionally satisfied with the result, but VAS-A is more successful in affecting patient satisfaction. This situation was confirmed by examining ROE questions.

While item 2 (Do you breathe well through your nose?) had the least impact (β=0.445) on the overall ROE score, the items regarding aesthetic satisfaction were found to be more effective on the overall score. Evaluation of current questionnaires such as SCCHNOS, which evaluates both functional and cosmetic results similar to ROE and has been validated in Turkish (12), with similar statistical methods will clarify the effect of functional results on patient satisfaction after septorhinoplasty. According to our findings, 63.9% of patient satisfaction after septorhinoplasty can be explained by aesthetic factors. To clarify the remaining, additional demographic or psychosocial factors should be furtherly studied in larger patient series.

Path analysis, in addition to being thought of as a form of multiple regression based on causality, can be regarded as a subset of structural equation modeling (SEM). It examines the causality relationship between variables, and as the path coefficient increases, the strength of this causality relationship increases (13). In order to perform a comprehensive analysis about factors affecting patient satisfaction, researchers should additionally perform further statistical analyses. The novelty of our paper is the use of this structural model to order the factors that affect ROE scores. No previous studies have constructed or verified a comprehensive structural model of the relationships among the various factors that may affect the quality of life of patients undergoing septorhinoplasty. Spiekerman et al. (10) published an innovative study about the development of a short and brief questionnaire to identify patients' motivations for septorhinoplasty. According to their study, the questions with the strongest loading on ROE were item 6 and item 1. We also found that item 6 had the highest Path coefficient (β=0.874), where the path coefficient of item 1 was 0.648. Question 6 covers both aesthetic and functional satisfaction. The fact that this is the most effective item on the total ROE score can be interpreted as ROE is successful in measuring both functional and aesthetic satisfaction. Nevertheless, the questions measuring only aesthetic satisfaction (items 1,3, and 5) were found to be more effective in measuring patient satisfaction than the question measuring only functionality (item 2).

One of the limitations of our study is the lack of additional PROMs about nasal obstruction such as NOSE that corroborate with the VAS-O scale. Further studies related to this subject should be enhanced with multiple PROMs. Accompanying factors such as age, sex, socioeconomic

status, and personality were not evaluated in our study. This can be accepted as a limitation; however, it was beyond the objective of this study. This study only presents the results from open septorhinoplasty and may only be applicable to such patients. Another study focusing on other techniques should be planned.

Conclusion

Septorhinoplasty significantly improves patient's quality of life and satisfaction predominantly on cosmetic aspects. More comprehensive analyses should be performed in order to deeply understand factors related to patient satisfaction. There is no universally accepted standardized outcome measure for septorhinoplasty. Further prospective studies should be performed using other validated questionnaires and various statistical analyses to support our study.

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Data Transparency

The data of the study can be shared on-demand, and it was uploaded to "Figshare"

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Main Points

- The main factor affecting patient satisfaction after septorhinoplasty is the aesthetic result.
- Even if the patients' nasal congestion symptoms subside, if the aesthetic outcome is unsatisfactory, they are unsatisfied with the surgical outcome.
- Although ROE is successful in evaluating both functional and aesthetic satisfaction, the questions measuring only aesthetic satisfaction were more effective than the question measuring only functionality in patient satisfaction after septorhinoplasty.

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Ethical Dilemmas in the Management of Head and Neck Cancers in the Era of the COVID-19 Pandemic

Review

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Abstract

Coronavirus disease 2019 (COVID-19) has emerged as an unforeseen challenge for head and neck cancer care providers. A similar challenge is also faced by other oncological fields, but the severity of this challenge is highest in otolaryngology because of the need for additional precautionary measures and curbs on the possibility of aerosol forming interventions related to the upper aerodigestive tract. In this narrative review, provision of ethical and consistent care on moral and professional grounds to head and neck cancer patients during the pandemic are discussed for professionals who provide head and neck oncology care.

Keywords: COVID-19, pandemics, ethics, head and neck cancer, otorhinolaryngology

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has tested the mental and physical tenacity of humanity at multiple levels. During the pandemic, the field of medicine primarily focused on the prevention and management of COVID-19. In these difficult times, the practice of ancillary aspects of the field of medicine and surgery suffered severe polarization and ultimately led to the compromise of a huge subset of our patient population. Head and neck cancer patients partly form this subset. The grim environment of the pandemic delayed and even denied the due care needed for such patients (1). Surveys have showed a pervasive impact of the pandemic on the care of all cancer patients, some attributing it to the lack of preparatory steps and foresight, others calling it a crisis of conscience (2, 3). A recent study estimated 33,890 deaths in excess among the United States (US) cancer survivors over 40 years of age in the current COVID-19 pandemic (4). With the realization that the pandemic is here to stay and one would have to operate in all walks of life with its presence, the field of medicine must be molded if not

transformed in order to ensure effective medical care for all patient subsets. Head and neck cancer care, in order to address the conflicts considering the ongoing ethical issues, needs to standardize the goals of care in the light of the pandemic, and ensure consistency in these principles with apt allocation of the resources. This review intends to highlight the various aspects of head and neck cancer care, including the conflicts of duties for a physician, the balance of clinical ethics and public health ethics, and lastly the goals and the standards of care for such patients while ensuring consistent allocation of resources.

Conflict of Duties

During the pandemic, risks of exposure and contracting the COVID-19 virus have emerged as a great challenge for the clinicians providing care to the patients with head and neck cancers. The risk is higher especially while examining, performing biopsy and treating the diseases of the upper aerodigestive tract. A large number of health professionals were infected in the first cohort (3). Earlier, management, including the head and neck region, and endoscopic examination, biopsy, and surgery were all routinely performed procedures. In the current pandemic, however, the threat of potential aerosol formation of the SARS-CoV-2 virus has created hurdles in performing routine management and requires extra time and a lot of resources. Regularly updated and publishing guidelines and infection control measures confirm the importance of limiting unnecessary exposure of healthcare professionals as well as emphasizing on the protection of the patients (5, 6). For sure, protecting both healthcare workers and patients is our fundamental, professional and ethical responsibility; however, the conditions are yet to be balanced on how to provide the appropriate treatments that patients should receive while protecting healthcare workers.

Healthcare staff providing head and neck oncology care can refer to dynamic online guidelines and resources provided by societies including The American Head and Neck Society, The American Academy of Otolaryngology – Head & Neck Surgery, The American College of Surgeons, The Society of Surgical Oncology and The American Society of Clinical Oncology (3). All these available resources and guidelines emphasize the need to avoid all unnecessary clinical interactions, and to delay or postpone nonessential surgeries and procedures, although, such decisions should be made based on the physician's judgement, the patient's medical condition and the social needs.

While provision of the best standards of care to the patient is the ultimate goal of a healthcare professional, a balance should be maintained between the duty towards the patients and the duty of caring for ourselves and our colleagues. For example, the number of personnel in the operating room should be limited in such a manner that the surgical procedure can be performed with ease and at the same time not all the team members are at risk. Similarly, those patients who are on regular follow-up can be referred to telemedicine clinics rather than physical follow-ups. Head and neck oncology care providers should understand and recognize the stress of the current ongoing pandemic, and practice efficient selfcare which can be achieved by involvement in clinical activity only as long as deemed necessary for the patient and requires urgent intervention.

"Clinical Ethics" vs. "Public Health Ethics"

Medical ethics requires healthcare providers to consider the preferences of patients, providing maximum benefits to the patients while reducing harms and providing fair treatment options (7). Adhering to these principles has become a major challenge due to the lack of resources during the pandemic. There will be instances where we have to overlook the specific needs of an individual patient because of the obligation to protect the larger population and spare the resources for others. Situations like these highlight the increasing conflict between the principles of clinical and public health ethics (7). Clinical ethics emphasizes a healthy relationship between a patient and doctor and encourages the development of a management plan designed to provide the maximum benefit to an individual patient. In comparison, public health ethics is in the best interest of a larger population even if it turns out to be harmful to an individual patient.

Acceptance of this paradigm shift might prove to be difficult and become an increasing challenge for the head and neck cancer caregivers. Institutions should take lead from the front for smooth and swift shift to a public health framework. It should be distinguished by the oncology community that when the needs of a community outweigh the requirements of an individual patient. Which will ultimately lead to delay in treatment and use of nonstandard management protocols (3).

Goals of Care

Although the standard of care varies institutionally, we should deliver a universal benchmark of the most basic and realistic care goals during the pandemic. Any algorithm design has to address two key factors—protect the patient, the healthcare staff, and the community from COVID-19 and allocate resources fairly to prevent undue delay in the care of a cancer patient (8).

The complexities in the management of head and neck cancers stem from the many treatment options available in terms of surgery, radiation, chemotherapy, or a combination of these. Multidisciplinary tumor teams—comprising specialists from each of these domains—discuss individual patients in the light of the disease and patient-specific

factors, and reference rigorous scientific evidence to actualize the treatment pathway (9). These teams' roles of expediting the decision to treat the patient is of utmost importance and typically range from days to weeks. Any further delay can advance the stage and give rise to the need for further imaging and possibly change of treatment modality.

The four pillars of medical ethics—beneficence, nonmaleficence, patient autonomy and justice—place the goal of care to the patient in the center. Thus, individual patients have complete autonomy on deciding their treatment. In an ideal world, this should be unaffected by the availability of healthcare resources, access, and finances. COVID-19 exposed the disparity of these services available to cancer patients—even more strongly in the developing nations. The pandemic turns our perspective to the notion that medicine cannot be practiced in isolation from the world and is a complex interplay between political, economic and social factors influencing medical decisions (10, 11).

Studies today attempt to further characterize molecular level tumor characteristics as targets for therapy; e.g., for immune checkpoint inhibitors such as anti-program death (PD1) Nivolumab was approved by the FDA as a standard of care regimen for patients with platinum refractory recurrent/metastatic head and neck squamous cell carcinoma (12). Although immunotherapy is currently utilized for palliative measures, deeper understanding might extend them to adjuvant or definitive treatment armamentarium as standard goals of care.

Standards of Care

The National Comprehensive Cancer Network (NCCN) guidelines play a very important part in determining the course of treatment for patients with head and neck cancers. These guidelines are updated at least annually. All these guidelines are derived from evidence which is reviewed. The NCCN guidelines were last updated in April 2021. There has not been enough data regarding COVID-19 to determine the risk to healthcare providers and patients with head and neck cancers.

Any form of treatment, whether surgery, radiotherapy or chemotherapy, comes with its own share of risks. The art of decision making is to weigh the benefits of any treatment against its known risks.

Due to the ongoing pandemic, many committees including the NCCN have come up with solutions that cannot be considered the standard of care. These include cancelling the clinic visits and imaging for routine cancer surveillance, conversion to telemedicine and avoiding aerosol generating procedures in the elective setting (13).

Most of these changes that have been proposed cannot be considered standard of care, but are deemed appropriate in these circumstances where minimizing exposure has become a priority (14).

These changes may not directly affect the management plan for patients with head and neck cancers, there is a possibility that early detection or recurrences can be missed. The question remains whether this risk is justified by the need to reduce exposure to COVID-19.

Consistency of Ethical Principles

Management of head and neck cancers requires a multidisciplinary care team including surgeons, radiation and medical oncologists, physiotherapists, psychologists, and nutritionists. Besides these main stakeholders there are many other members of the hospital care staff that are involved in the care of these patients including the nursing staff, healthcare assistants and intensive care specialists. Many factors need to be taken in account while taking decisions in the management of the patients with head and neck cancers, and the safety of both the patients and the healthcare personnel should be considered. When this pandemic first emerged on the world stage, the initial response from many head and neck cancer teams was that the surgeries were delayed indefinitely; however, as the pandemic progressed it became evident that these patients could not be left untreated for indefinite periods of time.

While the risks to the healthcare staff remains as threatening as ever, World Health Organization (WHO) highlighted an alarming rise in reports of verbal harassment, discrimination, and physical violence towards healthcare workers in the wake of COVID-19. WHO has also outlined specific World Patient Safety Day 2020 Goals for healthcare leaders to invest in, measure, and improve healthcare worker safety over the next year. The goals are intended for healthcare facilities to address five areas: preventing sharps injuries; reducing work-related stress and burnout; improving the use of personal protective equipment; promoting zero tolerance to violence against healthcare workers, and reporting and analyzing serious safety related incidents (15).

All patients should still be discussed in multidisciplinary tumor boards; however, these meetings can be held online rather than physically. Free flap reconstructions can be replaced with loco-regional flaps as free flaps require longer operating times and oftentimes require postoperative intensive care including ventilator support—which cannot be spared in an era when ventilators are scarce because of the overburden caused by COVID-19 affected patients (16). Another step that can be taken is that ancillary services can be provided via online channels; for example, nutrition and psychology clinics can monitor patients, and physiotherapy exercises can be taught to patients and families online.

Another important point that needs to be taken into account is that certain populations have been subjected to different treatments on basis of race, geographical and economic status while triaging patients for definitive treatment (17). All efforts should be taken to avoid this from happening and healthcare providers should partner with underrepresented groups to assure that the risks of care disparities are minimized in the face of crisis.

It is also important to take into account the patient's autonomy. It is the patient's right to make a decision about their medical care without their healthcare provider trying to influence their decision. The healthcare provider can help by informing the patient about the pros and cons of a particular management plan but cannot decide for the patient.

Allocation of Resources

The burden of COVID-19 was borne by a number of departments within a state, but hospitals were the real shock absorbers. It created an immense logistic inconvenience for the hospitals that were already rich in resources; however, the hospitals in a developing country like Pakistan were out of the league. Surgical treatment is the mainstay of head and neck cancer management and cannot be performed without having a ventilator, intensive care unit or special care unit on back up. Additionally, the operating team must be provided with an adequate number of personal protective equipment (PPE) and respirators in order to operate on a patient with head and neck cancer, but unfortunately such items are already scarce (8).

This is where the justified allocation of the resources or what we call, rationing, comes to play its part. Rationing has always been a topic of debate among healthcare providers. It can simply be defined as refusing the most beneficial treatment for a patient and providing an alternative treatment because of the scarcity of resources (18). In otolaryngology and head and neck surgery, a number of daycare procedures can be delayed in given circumstances, but the treatment of a patient with squamous cell carcinoma cannot be delayed as it will result in the extension of the disease which can threaten the patient's life. Therefore, in such cases, economic rationing can be achieved by maneuvers like limiting the number of staff involved in the pre-, intra and post-operative care of the patient. This will not only reduce the number of PPEs, masks, gloves, etc. utilized but also will prevent the exposure of a number of staff in the times of pandemic. This will be then a part of rationing to promote public health, where the exposure of an infected patient to the staff and other patients in the hospital is minimized.

COVID-19 and Healthcare Workers

An important consideration to be made is for the healthcare workers who are more vulnerable to dire complications of this disease, i.e., the elderly and those have other systematic diseases. A study from the USA and a systematic review published in BMJ have reported an alarmingly high rate of 37% mortality among healthcare workers who are above the age of 65 years (19, 20). This should prompt the authorities to keep these vulnerable healthcare providers away from taking care of patients with COVID-19 and instead use them in settings such as telemedicine, non-COVID-19 outpatient clinics or administrative positions. This can also be achieved by relocating the younger head and neck staff to the isolation wards if the units are having low number of cases.

Conclusion

During the pandemic there has been a significant risk to patients as well as healthcare professionals. Further, COVID-19 has jolted the true spirits of head and neck oncological care delivery. It has created a hurdle that must be recognized as an ethical dispute between the care of an individual and care of the society.

We recommend provision of consistent and ethical care to the patients with head and neck cancer. All cases should be discussed in multidisciplinary tumor board meetings which can be conducted online. Free flap reconstruction can be replaced by local flap reconstruction where necessary. Head and neck oncology care providers should practice efficient selfcare and justified allocation of resources should be performed. Lastly this epidemic should prompt the authorities to make long term policies regarding ethical considerations in a future pandemic which may well turn to have a much higher morbidity and mortality ratio then the current pandemic.

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Main Points

- During the pandemic, the risks of exposure and contracting the COVID-19 virus have emerged as a great challenge for the clinicians providing care to the patients with head and neck cancer and the risk is higher especially while examining, performing biopsy, and treating diseases of the upper aerodigestive tract.
- Available resources and guidelines emphasize the need of avoiding all unnecessary clinical interactions and delaying or postponing surgeries and procedures which are nonessential.
- A balance should be maintained between the duty towards the patients and the duty of caring for ourselves and our colleagues.

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Primary Laryngeal Tuberculosis Manifesting as Irregular Vocal Fold Lesion

Case Report

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Abstract

Laryngeal tuberculosis is rare despite its close anatomical and physiological proximity to the lungs. It constitutes less than 1% of extrapulmonary tuberculosis. The symptoms of laryngeal tuberculosis are non-specific and mimic other laryngeal pathologies. The recent evolving and atypical endoscopic laryngeal features cause a diagnostic dilemma and delay in treatment. In this report, we presented three patients with distinct age and medical history, and hoarseness. Flexible videolaryngoscopy showed similar findings in the three cases, with irregular mucosa involving the entire length of the vocal fold, unilaterally in two cases and bilaterally in one. Mucosal waves were typically absent on laryngostroboscopy examination. The routine workup for pulmonary tuberculosis was unremarkable. The usage of *Mycobacterium tuberculosis* complex (MTBC) and rifampicin resistance (Xpert MTB/RIF) assay that detects *Mycobacterium tuberculosis* in the tissue biopsy specimens has helped in the rapid diagnosis of primary laryngeal tuberculosis and timely commencement of anti-tuberculous therapy. The clinical course and response to treatment were diverse in which two cases showed good response whilst the third developed disseminated tuberculosis despite optimal therapy.

Keywords: Dysphonia, hoarseness, laryngeal tuberculosis, mycobacterium, stroboscopy, case report

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Introduction

Primary laryngeal tuberculosis (PLTB) without pulmonary involvement is rare and merely constitutes <1% of extrapulmonary tuberculosis cases (1). It is postulated that PLTB occurs as a result of the direct invasion of the larynx by inhaled mycobacteria, rather than ascending infection from the lower airways (1). Other possible routes of laryngeal infection are via hematogenous or lymphatic spread. The morphological appearance of PLTB was described as ulcerative, polypoid, granulomatous, and nonspecific lesions (2). However, in the authors' experience, patients with early PLTB presenting with endoscopic findings of irregular mucosa of the true vocal fold has never been described in the literature. Hereby

the authors present three PLTB cases together with their laryngoscopic images which depicted similar findings but with contrasting clinical outcomes.

Case Presentation

Case 1: A 31-year-old female presented with worsening hoarseness accompanied by voice fatigue and irritative dry cough for one month. Otherwise, she had no shortness of breath, dysphagia, laryngopharyngeal reflux (LPR) or constitutional symptoms. She was not immunocompromised and had no history of close contact with patients who had pulmonary tuberculosis (PTB). On examination, she had hoarseness at a GRBAS score of G2R1B2A1S1 (G, overall dysphonia; R, roughness; B, breathiness; A, asthenia; and S, strain), the main component being breathiness. The maximum phonation time (MPT) was seven seconds. There was no stridor or signs of respiratory distress. Videoendoscopy and laryngostroboscopy (Pentax Medical, Japan & US) examination showed irregular mucosa involving the entire length of the right vocal fold with absent mucosal wave (Figure 1). Otherwise, the mobility of both vocal folds was normal and symmetrical, and the glottic airway was patent. Infective and inflammatory markers such as total white cell count (TWC) and total erythrocyte sedimentation rate (ESR) were normal. Other routine tuberculosis workups such as sputum for acid-fast bacilli (AFB) smear, chest radiograph and Mantoux test (Tuberculin skin test) were unremarkable. Direct laryngoscopy and examination under general anaesthesia (EUA) revealed irregular mucosa with some cobblestone appearance of the right vocal fold. Endolaryngeal microsurgery (ELMS) and subepithelial incisional biopsy of the right vocal fold lesion with a precision technique was performed using microlaryngeal instruments (Figure 2). The lesion was found confined to the epithelial layer of the vocal fold, sparing the vocal ligament. The incised mucosa was friable and it was sent for a rapid molecular biological diagnostic test to detect *Mycobacterium tuberculosis* complex (MTBC) and rifampicin resistance (Xpert MTB/RIF assay). The result that was ready in 24 hours revealed positive for MTBC and negative for rifampicin resistance. Anti-tuberculous therapy was commenced immediately. Histopathologic examination (HPE) of the specimen, which was completed two weeks later, reported chronic granulomatous inflammation with negative Ziehl-Neelsen stain. Her hoarseness improved significantly during the two-month follow-up. Repeat laryngostroboscopy showed a return of mucosal wave and resolved mucosal lesion over the affected vocal fold (Figure 3). She continued to improve and completed the anti-tuberculous treatment.

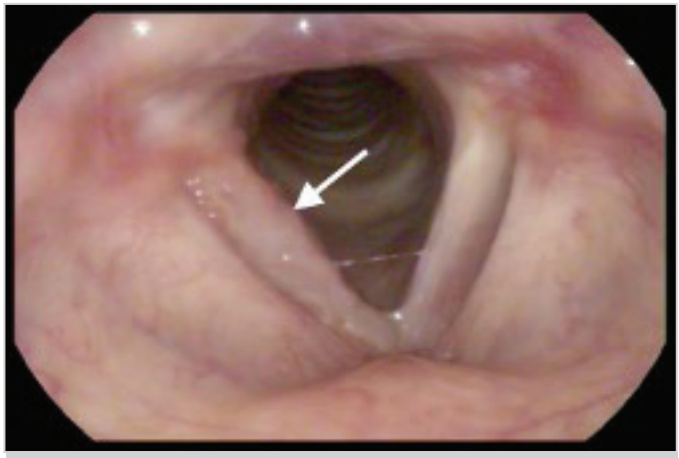

Figure 1. Endoscopic image of Case 1 shows irregular mucosa lesions along the entire length of the right vocal fold with cobblestone appearance (arrow)

Case 2: A 70-year-old male, a chronic ex-smoker with underlying hypertension, diabetes mellitus, presented with persistent hoarseness for one-month and preceding dry cough. For the past two years he had LPR symptoms that were treated medically. There was no constitutional symptom or history of contact with PTB patients. On examination, he was identified to have dysphonia with a score of G3R3B0A1S2, with a main component of roughness. MPT was 16 seconds. There was no stridor or palpable cervical lymphadenopathy. Videoendoscopy and laryngostroboscopy revealed findings almost similar to those of Case 1, in which there was irregular mucosa involving the entire length of the right vocal fold with absent mucosal wave (Figure 4). The vocal folds were mobile and the glottic airway was patent. TWC and ESR were not raised and other PTB investigations such as chest radiograph, sputum examination and Mantoux test were unremarkable. Direct laryngoscopy

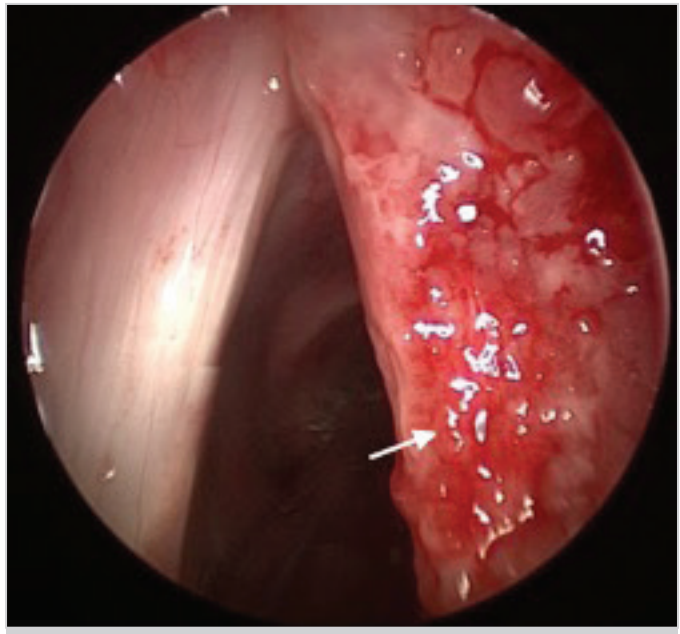

Figure 2. Subepithelial incisional biopsy of the right vocal fold (arrow) was performed under direct laryngoscopy via ELMS, preserving the vocal ligament
ELMS: Endolaryngeal microsurgery

and EUA revealed irregular mucosa with slough on the right vocal fold. Incisional biopsy was taken via ELMS with a precision technique, preserving the vocal ligament (Figure 5). Xpert MTB/RIF assay revealed positive detection of MTBC without rifampicin resistance. He was started on anti-tuberculous therapy right away, but unfortunately developed intolerance to the medication, complicated with acute kidney injury and hepatitis. HPE revealed chronic granulomatous inflammation with necrotic tissue and Langhans type multinucleated giant cells seen (Figure 6). There was no AFB seen on Ziehl-Neelsen stain. Human immunodeficiency virus (HIV) and viral hepatitis screening tests were negative. Two months later the disease progressed and disseminated as he developed PTB with pneumothorax and TB meningitis. He had an acute cardiac event while nursed in the intensive care unit and required tracheostomy due to prolonged ventilation with poor neurological recovery. He was eventually discharged home and dependent on long-term positive pressure ventilation via tracheostomy, making his condition not suitable for reassessment using laryngostroboscopy.

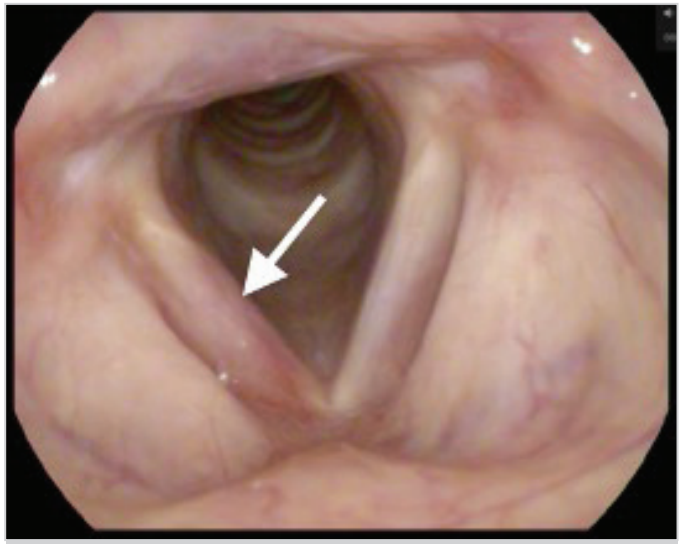

Figure 3. Endoscopic image of Case 1 shows resolved mucosal lesion over the affected vocal fold (arrow) after two months of anti-tuberculous therapy

Figure 4. Endoscopic image of Case 2 shows irregular mucosa lesions along the entire length of the right vocal fold with erythema (arrow)

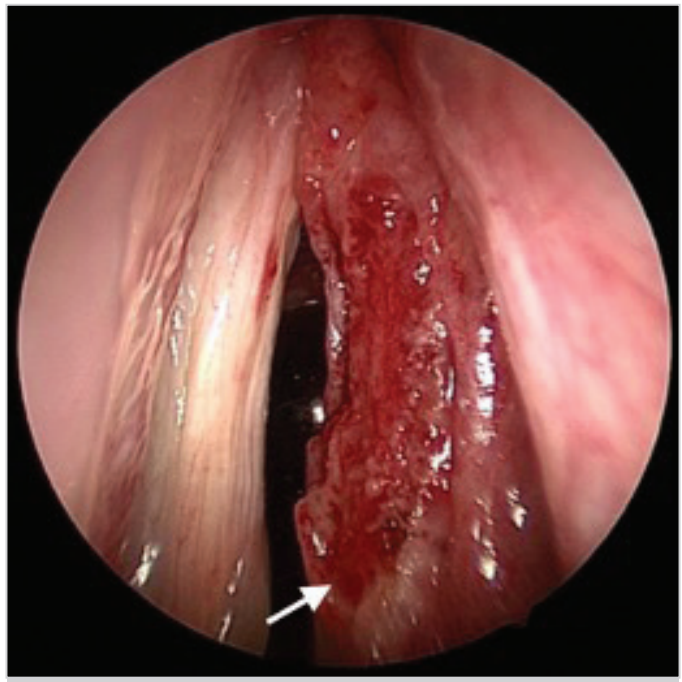

Figure 5. Direct laryngoscopic image shows subepithelial incisional biopsy of the right vocal fold lesion was performed, preserving the vocal ligament

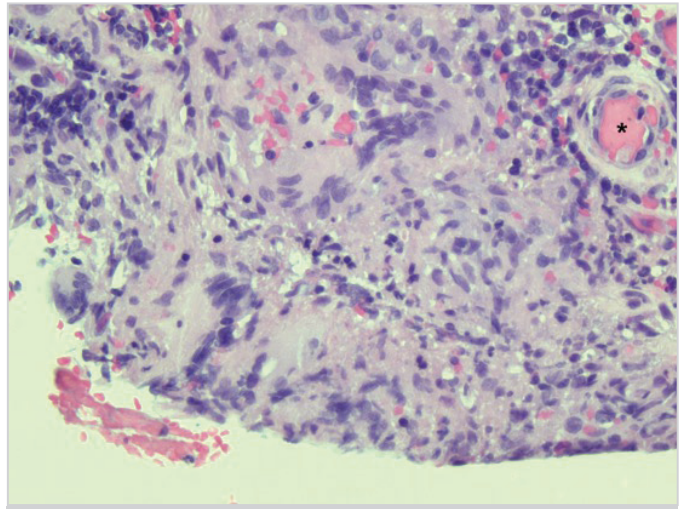

Figure 6. Histopathologic image shows granuloma composed of a collection of epithelioid histiocytes rimmed by lymphocytes and plasma cells with Langhans type multinucleated giant cells (asterisk) (H&E, x400)
H&E: Hematoxylin and eosin stain

Case 3: A 73-year-old male with underlying diabetes mellitus and hypertension, presented with a two-year history of hoarseness worsened over the past six months, associated with poor voice projection. There was no constitutional symptom or history of contact with PTB patients. Examination revealed dysphonia G2R2B0A1S1, with a main component of roughness. MPT was two seconds. There was no stridor or palpable cervical lymph node. Videoendoscopy showed thickened whitish mucosal lesion over the entire length of both vocal folds, without abnormal perpendicular vessels seen. Laryngostroboscopy examination showed an absent mucosal wave bilaterally. Chest radiograph and Mantoux test results were normal. ESR and TWC were not raised. Direct laryngoscopy and EUA showed irregular mucosa and slough on both vocal folds, with cobblestone appearance on its posterior third (Figure 7). Vocal fold lesions were biopsied via ELMS, preserving the vocal ligament. Xpert MTB/RIF assay of the specimen revealed positive detection of MTBC, and treatment was initiated within 24 hours. The result of the histopathologic examination of the biopsy specimen revealed chronic granulomatous inflammation with caseous necrosis. Numerous AFBs were seen on the Ziehl-Neelsen stain (Figure 8). He showed good response to anti-tuberculous therapy. The hoarseness had improved at the one-month follow-up visit. Repeat laryngostroboscopy showed a return of mucosal wave over both vocal folds. Presently he is followed up at another hospital because of logistic reasons.

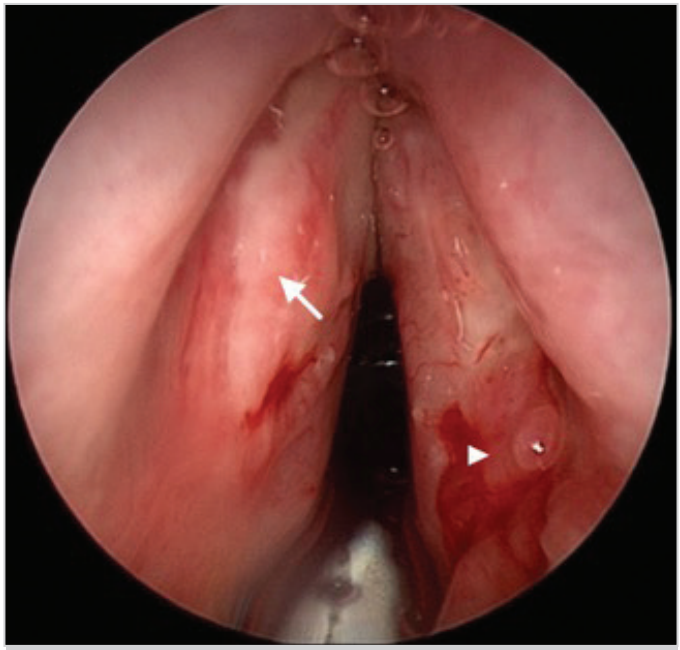

Figure 7. Direct laryngoscopy image of Case 3 shows whitish thickened mucosal lesion over the entire length of left vocal fold (arrow) and cobblestone appearance at the right posterior third (arrowhead)

Discussion

Laryngeal tuberculosis is the most common granulomatous disease of the larynx (1). The incidence of PLTB has increased following the resurgence of tuberculosis globally with a changing trend of clinical manifestations. Primary laryngeal tuberculosis is prevalent in the fifth to sixth decades of life with male predominance. Hoarseness (80%–100%) and odynophagia/dysphagia (55%–100%) are the most common presentations whilst dry cough (11%–45%) and constitutional symptoms are uncommon (3).

The risk factors for PLTB include HIV infection, diabetes mellitus, immunosuppressive therapies, tobacco smoking, alcoholism, drug abuse, malnutrition and poor socioeconomic status (4). In the present case series, the main risk factor was diabetes mellitus, however it was well controlled with medications. None of the three patients had a history of close contact with TB patients or of excessive alcohol use, and their HIV statuses were negative.

PLTB frequently involves the true vocal folds (3, 5, 6). However, the morphological description varies with the preponderance of single exophytic or ulcerative lesion at the vocal fold (67%–73%) (2). Hematogenous spread is associated with polypoid and non-specific lesions. The atypical manifestations that mimic neoplasm, laryngitis and polyp often result in misdiagnosis (3). To the extent of the authors' experience and knowledge, PLTB presenting as an isolated irregular mucosa at the true vocal fold has not been previously described in the literature. In these cases, videoendoscopy and laryngostroboscopy demonstrate reduced or absent mucosal waves at vocal fold with a non-vibrating segment indicating submucosal invasion, which mimic a malignant tumor (7). Therefore, laryngeal biopsy is crucial to ascertain the diagnosis (5, 6). The intraoperative findings of our cases under direct laryngoscopy showed irregular mucosa lesions

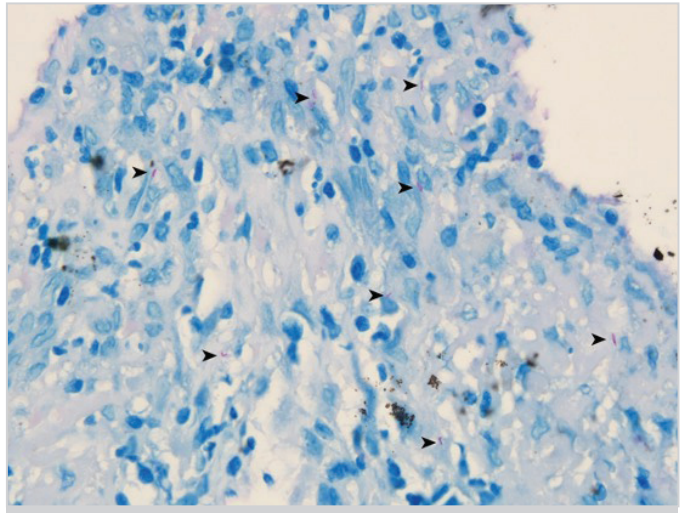

Figure 8. Histopathology image shows acid-fast bacilli (arrowhead) on Ziehl-Neelsen stain (x600)

involving the entire length of the vocal fold, with cobblestone appearance on the posterior third of the vocal fold and ventricle. The incised mucosa was friable with slough seen, which is not typical of a glottic malignant lesion. Chronic inflammatory disorders such as laryngeal tuberculosis therefore must be excluded in such cases since tuberculosis is endemic in this region. Subepithelial incisional biopsy of the vocal fold lesion was performed using microlaryngeal instruments, preserving the vocal ligament underneath. The specimens were sent for histopathological examination and tuberculous investigations including Mycobacterium culture and Xpert MTB/RIF assay.

The routine workup for PTB, such as chest radiography, sputum examination, Mantoux test and serum ESR is unremarkable in PLTB, as demonstrated in our cases. Conventional chest radiograph remains as the initial imaging modality for pulmonary TB screening. Computed tomography of the thorax is not a routine investigation for PLTB if the chest X-ray shows normal findings (8). PLTB was diagnosed essentially based on tissue biopsy specimens that were sent for histopathological examination and mycobacterial culture. However, only 34% of HPE results of PLTB demonstrated chronic granulomatous inflammation with caseous necrosis, which is pathognomonic of TB (3). In two out of three of our cases, the Ziehl-Neelsen stain on histopathology specimen was negative (Table 1). This finding is consistent with the literature where 40%–100% of the PLTB tissue biopsies were negative for AFB on Ziehl-Neelsen stain due to its paucibacillary nature (9). Standard mycobacterium culture has moderate sensitivity and specificity for extrapulmonary TB and it takes up to six weeks for MTBC to grow (10). In all three of our cases, the diagnosis was inconclusive at the initial stage due to the atypical endoscopic laryngeal features and negative PTB investigations. The treatment could be initiated only when confirmatory result was obtained from HPE or mycobacterial culture. In our center, the finalized HPE report turnaround time is usually two weeks. However, the result of positive Xpert MTB/RIF assay that detects MTB DNA in the biopsy tissue within hours has helped for the rapid definitive diagnosis of PLTB. As a result, it helped to avoid delays in diagnosis and enabled timely commencement of the anti-tuberculous therapy.

The Xpert MTB/RIF assay is an automated cartridge-based nucleic acid amplification test for the rapid identification of MTB DNA and rifampicin resistance. The result would be ready in less than two hours using real-time polymerase chain reaction (11). The rapid identification of a drug resistant variant is extremely beneficial as the conventional drug susceptibility test takes longer than two months (12).

Table 1. Summary of patient characteristics, presenting symptoms, video laryngostroboscopic findings, investigation results and treatment outcomes

Case (Age/ gender)	Comorbidities	Presenting symptoms	Video endoscopy and laryngo-stroboscopic findings	HPE result of VF biopsy	AFB on ZN stain	Serum ESR, TWC, CXR, TST	Xpert MTB/ RIF assay	Treatment outcome
Case 1 (31/F)	None	Hoarseness, voice fatigue, dry cough for 1 month	Irregular mucosa and cobblestone appearance of right VF, mucosal wave absent	Chronic granulomatous inflammation	Neg	Normal	MTB detected	Hoarseness improved, VF mucosal wave returned at 2 months
Case 2 (70/M)	DM, HPT, ex-chronic smoker, LPR	Hoarseness and dry cough for 1 month	Irregular mucosa and slough at right VF, mucosal wave absent	Chronic granulomatous inflammation, Langhans multinucleated giant cells seen	Neg	Normal	MTB detected	Disseminated TB (PTB, TB meningitis), ALTE with poor neurological recovery Long-term PPV via tracheostomy
Case 3 (73/M)	DM, HPT	Worsening hoarseness with poor voice projection for 6 months	Whitish mucosal lesion with cobblestone appearance, involving both VF, mucosal wave absent	Chronic granulomatous inflammation with caseous necrosis	Pos	Normal	MTB detected	Hoarseness improved, VF mucosal wave returned at 2 months

F: Female, M: Male, DM: Diabetes mellitus, HPT: Hypertension, LPR: Laryngopharyngeal reflux, VF: Vocal fold, HPE: Histopathology, AFB: Acid fast bacilli, ZN: Ziehl-Neelsen, Neg: Negative, Pos: Positive, ESR: Erythrocyte sedimentation rate, TWC: Total white cell count, CXR: Chest X-ray, TST: Tuberculin skin test, MTB: *Mycobacterium tuberculosis*, TB: Tuberculosis, ALTE: Acute life-threatening event, PPV: Positive pressure ventilation

It was reported that the Xpert MTB/RIF assay has 81.3% sensitivity and 99.8% specificity in detecting MTB in extrapulmonary specimens (12). Current WHO guidelines recommend using Xpert MTB/RIF as a replacement test for specific non-respiratory tissue specimens to diagnose extrapulmonary TB. To the authors' knowledge, there is no study on the diagnostic accuracy of Xpert MTB/RIF in PLTB to date, probably due to this rare clinical entity.

PLTB responds well to anti-tuberculous therapy within 18 weeks (7). However, long-term follow-up is recommended to monitor possible laryngeal and extralaryngeal complications. PLTB may progress into disseminated TB that carries a poor prognosis, as demonstrated in our second case.

Conclusion

In view of the emergence of PLTB with atypical clinical manifestations, otolaryngologists in endemic regions should be more vigilant when treating patients presenting with hoarseness and subtle laryngeal endoscopic findings. PLTB must be considered as a differential diagnosis in a patient with unilateral irregular vocal fold lesion. Employing the Xpert MTB/RIF assay would be exceedingly beneficial in the early detection of the disease with good diagnostic accuracy, which, in turn, contributes to achieve a favorable outcome.

Informed Consent: The patients signed informed consent regarding publishing their data and photographs.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: L.S.G., T.K.J., M.A., M.M.B., Concept: L.S.G., T.K.J., M.A., M.M.B., Design: L.S.G., M.A., M.M.B., Data Collection and/or Processing: L.S.G., T.K.J., Analysis and/or Interpretation: L.S.G., T.K.J., M.A., M.M.B., Literature DSearch: L.S.G., T.K.J., M.A., M.M.B., Writing: L.S.G., T.K.J., M.A., M.M.B.

Main Points

- Primary laryngeal tuberculosis is becoming more common with hoarseness as the chief complaint.
- Irregular vocal fold mucosal lesion, either unilateral or bilateral, can be the early and the only clinical manifestation of primary laryngeal tuberculosis.
- The vocal fold mucosal waves in primary laryngeal tuberculosis were typically absent on laryngostroboscopy examination.
- Biopsy of the vocal fold lesion with precision technique is crucial to confirm the diagnosis.
- Xpert MTB/RIF assay that detects *Mycobacterium tuberculosis* in the tissue biopsy specimens enables the rapid diagnosis of primary laryngeal tuberculosis.
- The vocal fold mucosal lesions can be potentially resolved with return of the mucosal wave by timely commencement of antituberculous therapy.

Conflict of Interest: There is no conflict of interest to disclose.

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A Rare Sinonasal Malignancy: Biphenotypic Sinonasal Sarcoma

Case Report

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Abstract

Biphenotypic sinonasal sarcoma (BSNS), which has been described in the recent years, is a low-grade spindle cell sinonasal sarcoma characterized by rare neural and myogenic features. It has a slow growth pattern; does not metastasize, but local recurrences are common after surgery. Non-specificity of examination findings and symptoms and similarities of its histopathological features with other spindle cell sarcomas, neural tumors, and skeletal muscle-derived tumors involving the nasal cavity make the diagnosis difficult. Therefore, histopathological features should be evaluated together with immunophenotyping and molecular studies for differential diagnosis. There are very few BSNS cases or case series in the literature. In this report, we reported our clinical approach to a case with BSNS in the right nasal cavity and the histopathological features of the disease in the light of the current literature.

Keywords: Biphenotypic sinonasal sarcoma, paranasal sinus, sarcoma, spindle cell tumor, case report

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Introduction

Biphenotypic sinonasal sarcoma (BSNS) is a rare type of locally aggressive sarcoma that originates from the sinonasal region and is characterized by the molecular rearrangements of the *PAX3* gene. As summarized in Stelow et al. (1), the condition was first described by Lewis et al. in 2012 as "low-grade sinonasal sarcoma with neural and myogenic differentiation. In 2017, the condition was included in the updated World Health Organization classification of head and neck tumors.

BSNS can arise from any site in the sinonasal tract; however, it typically involves multiple subregions and often originates from the ethmoid sinuses. It may also spread extra sinonasal sites such as orbit and the skull base via the cribriform plate (2).

Patients usually present with non-specific symptoms related to the mass effect of the

tumor, such as nasal obstruction, nasal congestion, recurrent sinusitis attacks, epistaxis, facial pain, and pressure sensation. Ophthalmologic symptoms such as diplopia, proptosis, and blurred vision can also be observed in patients with orbital spread (2, 3).

Histologically, it is defined as a type of spindle cell neoplasia consisting of uniform, elongated nucleated cells, and showing an infiltrative growth pattern. It is characterized by staining of both nervous and muscular system markers in immunohistochemical examinations. Its immunohistochemical profile reveals S100 and actin expression. The diagnosis is further supported by immunopositivity for B-catenin and immunonegativity for SOX10. Fluorescent *in situ* hybridization (FISH) studies reveal numerous rearrangements in the *PAX3* gene, which is a transcription factor involved in the differentiation of neural and myogenic cells (4).

Histological features of BSNS show varying degrees of overlap with tumors such as fibrosarcoma, monophasic synovial sarcoma, peripheral nerve sheath tumors, glomangiopericytoma, and solitary fibrous tumors. This overlap makes it difficult to diagnose (5).

In this case report, we present our clinical approach in a patient with BSNS. We discuss the clinical, histopathological, immunohistochemical, molecular features of the disease and its differential diagnosis in the light of the current literature.

Case Presentation

A 55-year-old female patient was admitted with complaints of right-sided nasal congestion and a feeling of pressure in the right half of the face for about two years. There was no complaint of epistaxis, rhinorrhea, or anosmia. The patient's anamnesis revealed that she had type 2 diabetes mellitus. There was no history of neurofibromatosis in her family.

Nasal endoscopy revealed a pink-colored, hemorrhagic polypoid mass protruding from the right middle meatus to the choana (Figure 1). Other head and neck examinations revealed no abnormalities. Paranasal sinus computed tomography (CT) showed a massive lesion filling the right middle meatus and the right posterior ethmoid cells, and mucosal thickening in the sphenoid sinus (Figure 2). Contrast-enhanced magnetic resonance imaging (MRI) was planned because of the atypical hemorrhagic appearance of the lesion. A mass lesion with an irregular contour of approximately 4x4x1 cm, hyperintense on T2-weighted sequences, hypointense on T1-weighted sequences, enhancing after intravenous contrast agent, and not diffusion restriction, was observed as a result of MRI (Figures 3a and 3b). There was no orbital or skull base extension of tumor. First, an endoscopic biopsy was planned from the mass in outpatient clinic conditions. After the histopathology results

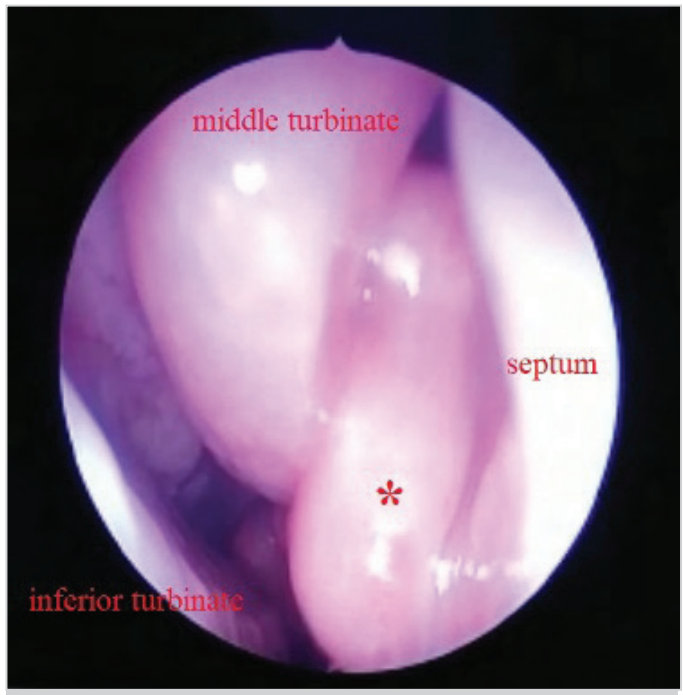

Figure 1. Endoscopic examination revealed a pink-colored hemorrhagic polypoid lesion hanging from the right nasal cavity from the middle meatus

of the biopsies taken twice in a row were reported as nasal polyp, mass resection was planned with transnasal endoscopic sinus surgery in the operating room. During surgery, the mass originating from the sphenoid sinus ostium and posterior ethmoid cells and filling the upper and middle meatus was totally excised. There was no invasion of surrounding tissues. Frozen pathology was studied during the surgery, but a specific diagnosis could not be made. In the final pathology report, this tumor, consisting of infiltrative proliferating spindle cells arranged in fascicles, with low mitotic activity, and without necrosis and atypia, was evaluated as BSNS (Figure 4). The tumor was focal immunopositive for S100 and SMA (smooth muscle antigen). In addition, beta-catenin cytoplasmic and nuclear positive staining and SOX10 negative staining were the other features supporting the diagnosis.

The patient had no complications in the postoperative period. Adjuvant chemotherapy or radiotherapy was not given as there was no extrasinonasal involvement, and the mass was excised with a negative surgical margin. The patient was informed, and the decision was made together with her. Follow up was planned. No recurrence was observed in the 1-year follow-up of the patient.

Discussion

BSNS is a rare tumor characterized by the combination of neural and myogenic histological features. It is more common in females and usually occurs in the fifth decade

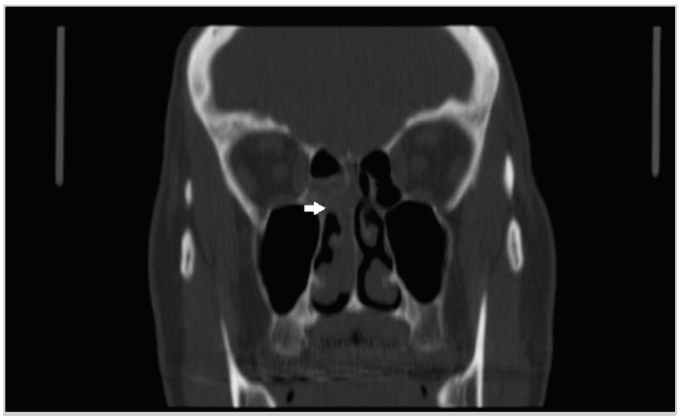

Figure 2. A polypoid mass in the right nasal cavity and mucosal thickening in the sphenoid sinus were observed in the coronal section of paranasal sinus CT
CT: Computed tomography

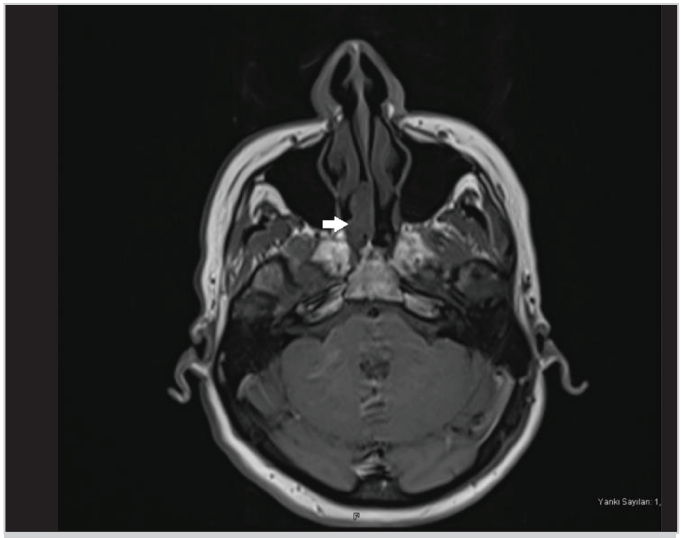

Figure 3.a. A hypointense lesion was observed in the right nasal cavity on T1-weighted sequences of MRI
MRI: Magnetic resonance imaging

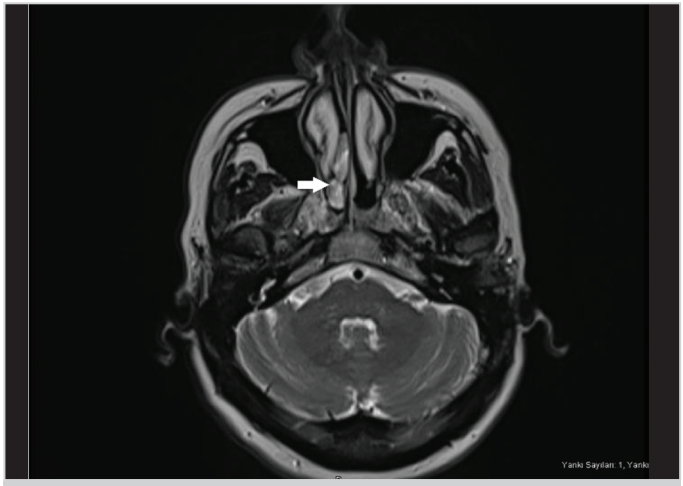

Figure 3.b. A hyperintense lesion was observed in the right nasal cavity on T2-weighted sequences of MRI
MRI: Magnetic resonance imaging

(6). The disease progresses slowly and does not metastasize; however, local recurrences occur in approximately one third of the patients within the first five years after surgery (5). The recurrence rate is approximately 40% to 50%, with recurrence-free intervals ranging from less than one year to more than nine years (7). In the literature, mortality from BSNS is quite rare, with only two reported cases of tumor related death (8, 9).

BSNS typically involves multiple subsites, often from the superior nasal cavity and ethmoid sinuses; less frequently, it may originate from the frontal, maxillary, or sphenoid sinuses (6). Extrasinonasal spread may occur with extension into the orbit in 25% of the cases (requiring orbital exenteration) and through the cribriform plate in 10% of cases (7).

Radiological studies are used to support the diagnosis. Radiological findings are variable and not specific for BSNS. On MRI, T1-weighted images are non-specific, on T2-weighted images the mass appears isointense with cerebral gray matter and is more hypointense than many other sinonasal tumors. This feature is seen in fibrotic and hypercellular tumors and is not specific for BSNS. Bone erosion can be observed on CT, and hyperostosis is frequently detected in areas with erosion (80%) (4, 7).

In our case, the patient's age and sex, the location of the mass in the superior nasal cavity (which originated from the posterior ethmoid cells in front of the sphenoid sinus ostium) was consistent with the general demographic and

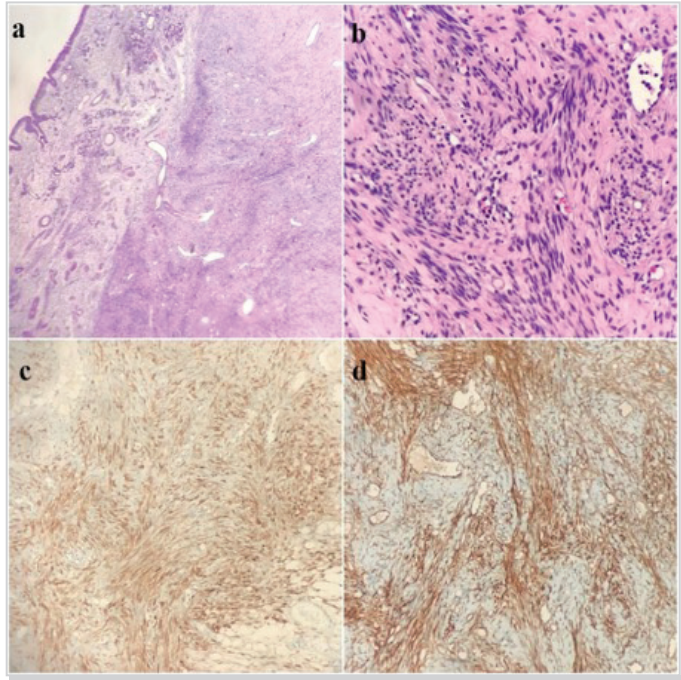

Figure 4. Biphenotypic sinonasal sarcoma a-b) Hematoxylin-eosin staining showing spindle cells arranged in fascicles or in a "herringbone" pattern, and infiltrative proliferation. c) S100 immunopositive staining. d) B-catenin immunopositive staining

typical localization characteristics of BSNS. There was no extrasinonasal (orbital, cribriform plate, and skull base) spread. No bone erosion or hyperostosis was observed on CT. In MRI, it was hyperintense on T2-weighted sequences. These findings supported that CT and MRI were not specific for diagnosis. The key histological features of BSNS are that it is infiltrative, showing an insufficient matrix arranged in fascicles or "herringbone", a hemangiopericytoma-like vascular pattern and a highly cellular uniformity of spindle cell proliferation with benign sinonasal-type glands interspersed with spindle cell proliferation (10). The nuclei are uniform, pale, and thin. It shows hypercellular features, but mitotic figures are rare. Necrosis and atypia are not observed. Foci of invagination of the respiratory epithelium are common and this may mimic inverted papilloma (1).

The "biphenotypic" characteristic of the tumor comes from the presence of both neural and myogenic markers in immunophenotypic studies. The tumor shows immunoreactivity for both S100 (neural marker) and smooth muscle markers [smooth muscle actin (SMA), muscle specific actin (MSA) or calponin], but the intensity and the extent of staining are variable and may be diffuse or patchy. Other myogenic markers such as desmin, myoD1 and myogenin show patchy or focal staining. Nuclear B-catenin is 90% positive. In particular, SOX10 is consistently negative. In addition, H3K27me3 stains at least partially; TLE1, cytokeratin, CD34, epithelial membrane antigen (EMA) are other markers that show focal positivity (6, 7).

Rearrangements in the *PAX3* gene, which is known to be a transcription factor that plays a critical role in neural and skeletal muscle differentiation, are responsible for the dual differentiation pattern (1). *NTRK3* and *pan-TRK* gene expressions were also shown in most of the cases (11).

In molecular analyses, Fluorescent *in situ* hybridization (FISH) studies, the PAX3-MAML3 fusion is present in 79%–96% of the cases and pathognomonic for BSNS. It should also be noted that there are reports of patient groups in which *PAX3* gene fusion was not detected (2, 5). This gene rearrangement can distinguish BSNS from its morphologic mimics with a high sensitivity of 100% (8). The *PAX3* gene expression could not be evaluated in our case as FISH cannot be performed in our hospital.

Peripheral nerve sheath tumors, tumors with skeletal muscle and myoid differentiation, solitary fibrous tumors and synovial sarcoma should be included in the differential diagnosis of BSNS (6). These tumors consist of spindle cells that occupy the nasal cavity and show histopathologically mostly fascicular arrangement. This similarity and the wide variety of parameters for diagnosis and the focal or patchy positivity of these parameters make the diagnosis difficult. A definitive diagnosis cannot be made with frozen biopsies.

Schwannoma and malignant peripheral nerve sheath tumors show varying degrees of S100 positivity, as in BSNS. The well-circumscribed growth pattern in schwannomas is an important distinguishing feature (5, 7). In addition, detection of Verocay bodies, Antoni A and B areas, and SOX10 positivity in schwannoma are helpful. Contrary to BSNS, malignant peripheral nerve sheath tumors (MPNST) are distinguished by their high mitotic activity, cellular atypia, and necrosis, as well as SOX10 positive staining. Neurofibromatosis Type 1 is accompanied by 50% of MPNST. Detection of precursor neurofibroma lesions on physical examination supports the diagnosis. In the differential diagnosis of spindle cell rhabdomyosarcomas, it is important to have S100 negativity, higher mitotic activity, more widespread desmin positivity, and diffuse myoD1 positivity in patients with MYOD1 mutation (2, 7). Sinonasal hemangiopericytomas are histologically composed of eosinophilic cells with paler cytoplasm compared to BSNS. The CTNNB1 mutation is held responsible for tumorigenesis and is characterized by nuclear β-Catenin staining with the negativity of S100 and myogenic markers (5, 7). Solitary fibrous tumors may be located in the sinonasal cavity. The difference from BSNS is that it does not show a fascicular or herringbone cellular arrangement and is characterized by the detection of NAB2-STAT6 fusion (2).

Synovial sarcoma can also show TLE1 expression like BSNS. Presence of SS18 fusions in synovial sarcomas is important in differential diagnosis (5).

The main features that distinguish BSNS from other sinonasal malignancies are summarized in Table 1.

The treatment approach is the surgical excision of the lesion. In a review published by Kominsky et al. (3) in 2021, recurrence rates were found comparable between patients who underwent surgical excision only and patients who received radiotherapy after surgical excision. Therefore, the benefit of radiotherapy can be said to be controversial. The rarity of the disease and the small number of cases described in the literature limit the assessment of treatment efficacy and more data is needed. Postoperative radiotherapy and chemotherapy options should be decided by discussing the risks and possible outcomes with the patient (3).

Conclusion

BSNS is a rare tumor characterized by the combination of the histological features of the neural system and the muscular system. It has a slow and silent course and does not metastasize; however, it can progress with recurrences after surgery.

Symptoms, examination findings, and imaging modalities are not specific to BSNS. Detailed evaluation is required for differential diagnosis with spindle cell neoplasms with

Table 1. Summary of the histopathological features distinguishing BSNS from other sinonasal malignancies

	Histopathology		Immunohistochemistry			Molecular features	Other differential features
	Growth pattern	**Cytology**	**S100**	**SOX10**	**Myogenic markers (desmin, myogenin)**		
Biphenotypic Sinonasal Sarcoma (BSNS)	Infiltrative	Spindle cells arranged in fascicles or in a "herringbone" pattern Low mitosis rate, No necrosis and atypia	+ (patchy or diffuse)	-	Focal +	*PAX3* gene fusion	B-Catenin + (%90) TLE-1 (focal +) Cytokeratin (focal +) CD34(focal +) EMA(focal +)
Schwannom	Circumscribed but unencapsulated	Verocay body Antoni A ve B areas	+ (diffuse)	+	-		
Malignant peripheral nerve sheath tumor (MPNST)	Fusiform	High mitosis rate Necrosis and atypia +	focal + or -	focal + or -	focal + or -	Loss of Histone H3K27 trimethylation (It is seen in 70% of high grade MPNST)	Neurofibromatosis type 1 accompanies 50% of the cases. Detection of the precursor neurofibroma lesion is important in the diagnosis.
MPNST with rhabdomyoblastic differentiation (Triton tumour)	Fusiform	High mitosis rate Necrosis and atypia +	focal + or -	focal + or -	focal +		
Spindle cell rhabdomyosarcoma	Circumscribed	High mitosis rate	-	-	Focal +	MYOD1 mutation	CTNNB1 mutation
Sinonasal hemangiopericytoma	Polypoid and lobulated	Spinde cells with pale eosinophilic cytoplasm Perivascular hyalinization	-	-	-	CTNNB1 mutation	B-Catenin + (CTNNB1 mutation)
Solitary fibrous tumor	Circumscribed	There is no pattern of fascicles.	-	-	-	NAB2-STAT6 fusion	Diffuse or strong CD 34 staining STAT6 immunpositive (typical)
Synovial sarcoma	Circumscribed		focal + or -	focal + or -	-	SS18-SSX fusion	TLE-1, Cytokeratin, EMA

-: Negative, +: Positive, TLE-1: Transducin-like enhancer of split-1, EMA: Epithelial membrane antigen

oncogenic fusions such as peripheral nerve sheath tumors, tumors with skeletal muscle and myoid differentiation, solitary fibrous tumor, and synovial sarcoma. Histopathological findings, immunohistochemical and molecular studies should be evaluated together.

Main Points

- BSNS should be kept in mind in the differential diagnosis of unilateral nasal masses, especially of those with slow growth patterns.
- It is a diagnostic challenge due to its histologic similarities to other sinonasal malignancies.
- Histology, immunohistochemistry, and molecular studies should be evaluated together.
- Surgical excision is recommended for treatment. Radiotherapy and chemotherapy options are controversial.
- Close follow-up is important because it frequently shows local recurrences.

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Challenging Removal of Embedded Fishbone in Tongue: Multimodal Technique, Surgical Approach and Consideration of Migration

Case Report

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Abstract

Fishbone ingestion is a common occurrence and patients present with various symptoms, posing challenges to the attending physicians. Here, we present two unique cases of patients with an unexpected rapidly migrating fishbone in the tongue. The first patient was operated transorally because of a foreign body embedded in the genioglossus muscle. In the second patient, CT scan located a fishbone embedded in the left hyoglossus muscle; however, the fishbone had to be relocated intraoperatively using bedside ultrasound guidance and was eventually found embedded within the mylohyoid muscle. The fishbone was successfully removed via transcervical approach following a failed transoral approach.

Keywords: Foreign bodies, tongue, floor of mouth, foreign-body migration, surgery, computed tomography, case report

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Introduction

In fishbone ingestion cases, most patients present with foreign body sensation in throat, odynophagia, and dysphagia. Embedded fishbone or extraluminal migration should be suspected when patients experience persistent symptoms despite normal clinical findings.

Case Presentation

Case 1: A 72-year-old male presented with persistent foreign body sensation in the throat for five days following fishbone ingestion. He had visited an outpatient clinic several times due to unresolved symptoms before visiting our center. He had been treated with multiple courses of oral antibiotics as oropharyngeal examination findings were normal. He was then referred to our center following a neck computed tomography (CT) scan that revealed a 30.7×1.8 mm linear opaque foreign body embedded in the genioglossus muscle (Figure 1). Otherwise, he was afebrile, and the flexible nasopharyngolaryngoscopy examination

was unremarkable. His white blood cell (WBC), hemoglobin (Hb) and platelet counts were 5.5×10^9/L, 15.8 g/dL and 247×10^9/L, respectively. He underwent examination under anesthesia (EUA) and transorally floor of mouth (FOM) exploration. The tongue was retracted and maintained superiorly with a stay suture. An incision was made at the midline ventral surface of the tongue. The genioglossus muscle was identified, and a blunt dissection was made at the avascular plane of the midline. The fishbone was found embedded in the muscle approximately three cm deep horizontally, crossing the midline and subsequently removed (Figure 2). Postoperatively, intravenous dexamethasone, cefuroxime and metronidazole were initiated. The patient recovered well and was discharged with oral antibiotics on postoperative day three. A two-week follow-up showed good recovery with good FOM (floor of the mouth) wound healing.

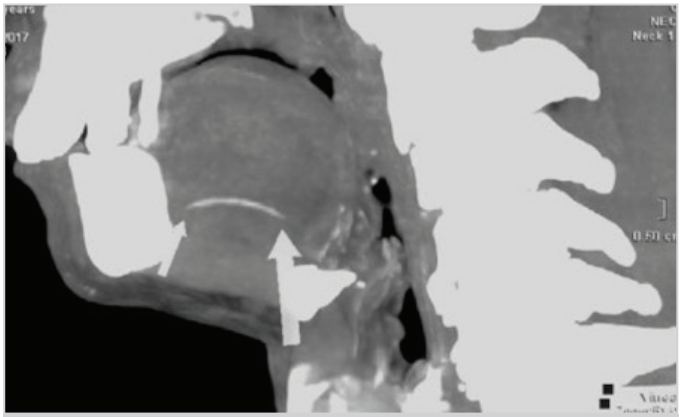

Figure 1. Sagittal computed tomography scan of the neck showing the anterior (small arrow) and posterior ends (large arrow) of the fishbone embedded in the genioglossus muscle

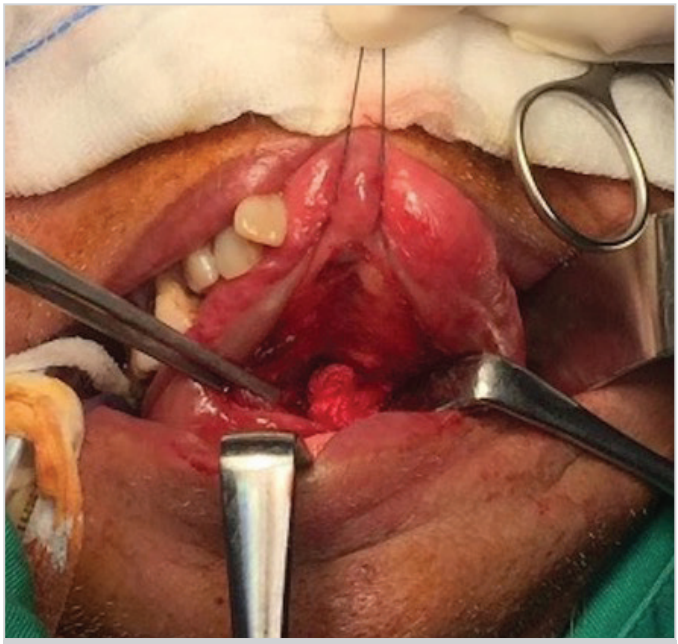

Figure 2. An incision at the midline of the floor of the mouth slightly extended onto the ventral surface of the tongue. The tongue was sutured with silk and retracted superiorly

Case 2: A 41-year-old male presented with a two-week history of persistent odynophagia and dysphagia following fishbone ingestion. Before visiting our center, the patient had sought treatment at another hospital on the day of incidence. He had undergone EUA and tongue exploration twice via a dorsal midline incision, as a CT scan had shown a foreign body embedded in the tongue (Figure 3); but the fishbone could not be localized intraoperatively. The patient's symptoms improved and was sent home after three days of hospitalization with oral antibiotics. The patient presented to our center with a persistent pain on the left side of the tongue for one week following his discharge. Oral examination revealed edema at the FOM and the left base of the tongue. No fishbone or sloughy mucosa was found. Repeat neck CT scan revealed a dense tubular structure in the left hyoglossus muscle measuring 1.7 cm (Figures 4a and 4b). Initially, the fishbone could not be localized during transoral FOM exploration under general anesthesia. Intraoperative ultrasound was then employed, and the foreign body was identified approximately 1.4 cm anterior to the submandibular gland (Figure 5). The transoral approach was then converted to a transcervical approach. The left submandibular space was explored until the fishbone was finally located in the mylohyoid muscle and subsequently removed (Figure 6). Postoperative recovery was uneventful

Figure 3. Sagittal computed tomography scan of the neck (first CT scan) showing a fishbone embedded in the tongue (white arrow)
CT: Computed tomography

and similar medications as Case 1 were administered. He was sent home with oral antibiotics after resuming normal oral intake three days later. A two-week follow-up showed complete resolution of the symptoms, and both the intraoral and cervical wounds healed satisfactorily.

Discussion

Although fishbone ingestion is common, serious sequelae such as deep neck abscess, injury to the common carotid artery, and thyroid gland can occur if not managed properly (1). In few isolated cases, as reported in the literature, the fishbone migrated in the aerodigestive tract and eventually pierced through the skin without complications (2).

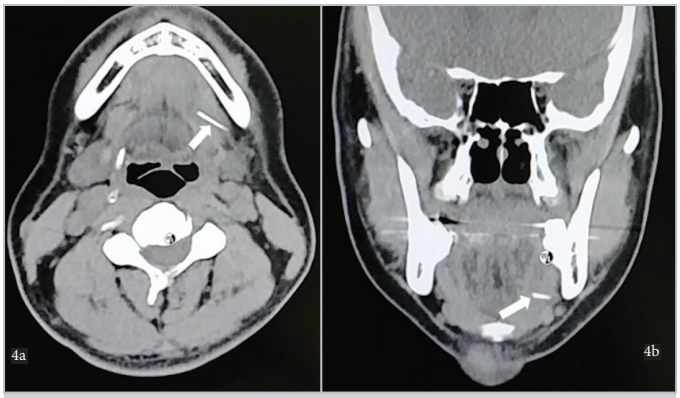

Figure 4. (a) Axial and (b) coronal computed tomography scan of the neck (second CT scan) showing a dense tubular structure in the left hyoglossus muscle (white arrow)
CT: Computed tomography

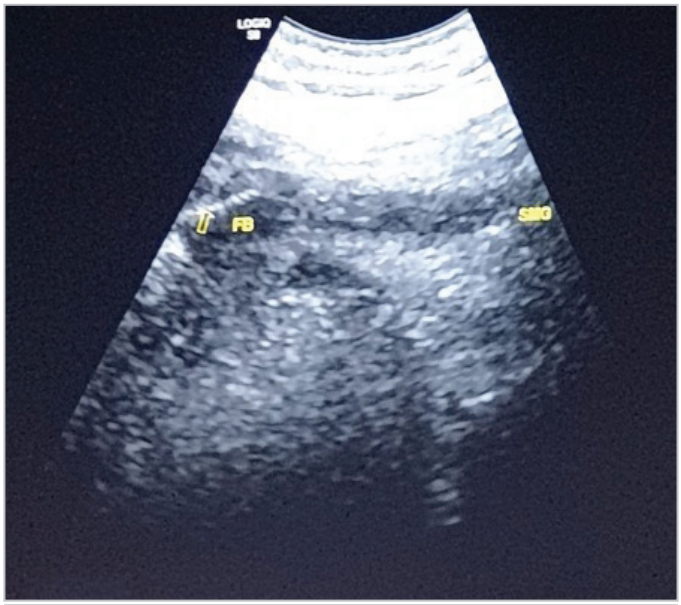

Figure 5. Linear echogenic foreign body (yellow arrow) in the left submandibular space, approximately 1.4 cm anterior to the submandibular gland (labeled as SMG) and embedded in the left mylohyoid muscle

Lateral neck radiography enables early detection, is cost-effective, and provides 90.6% diagnostic accuracy in the presence of both radiopaque density and air column lucency. Increased prevertebral thickness of more than 20 mm at the C6 level is indicated as an alarming finding (3).

CT scan provides accurate anatomical mapping of the fishbone and reveals surrounding changes or structures (4). Additionally, it is helpful in identifying the penetration site, planning for the surgical approach, and determining the direction of exploration.

Ultrasound offers the advantage of soft tissue foreign body detection and an increased ability in identifying radiolucent foreign bodies (5). It is recommended in detecting the location of a migrating fishbone as reported in the case of a rapid migration within 48 hours (2). Intraoperative ultrasound provides a dynamic assessment of fishbone location during operation. The migration is assisted by the physiologic movement of the neck muscles, horizontal

Figure 6. Linear fishbone embedded in the left mylohyoid bone (white arrow) was successfully removed

location, and the sharp and slender shape of the fishbone (2). The ingested fishbones in our cases were more feasible for extraluminal migration as both were horizontally oriented.

For intraluminal foreign bodies, retrieval using an endoscopic approach is less invasive, with rigid instrumentation success rate ranging from 94% to 100%, whereas that of flexible esophagoscopy is between 76% and 98.5% (6). However, open surgery is the best option for migrated foreign bodies (6).

A transoral incision either at the ventral surface of the tongue, the FOM, or lateral border of the tongue are among the common approaches to retrieve the embedded fishbone in the tongue (7-9). Its anatomical location and muscle fiber orientation determine the appropriate surgical approach (2, 7). In Case 1, the best access to the genioglossus muscle was over a transoral median ventral FOM incision, which is an avascular site. However, this surgical technique was unsuccessful in Case 2, as the foreign body had migrated laterally to the genioglossus muscle and was embedded in the mylohyoid muscle. Therefore, the transcervical approach followed by submandibular space exploration provided shorter and better access for bone retrieval. The submandibular gland is a good landmark as the hyoglossus and the mylohyoid muscles are located medially. Our transcervical approach for removing the fishbone embedded in the tongue is a novel surgical technique. Other transcervical access techniques were documented for retrieving a fishbone embedded in distal neck structures such as the thyroid gland, the hypopharynx, and the esophagus (1, 10).

Conclusion

A case of fishbone ingestion with atypical presentation and unexpected migration demands proper management planning and optimum utilization of resources. Both transoral and transcervical approaches with ultrasound assistance should be considered following the failure of fishbone retrieval via endoscopic approach.

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Author Contributions

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Main Points

- Regardless of normal clinical examination findings, computed tomography scanning is strongly recommended for assessing extraluminal migration in patients with persistent symptoms following fishbone ingestion.
- Intraoperative ultrasound provides a dynamic assessment of the fishbone location and is highly useful in cases of suspected migrating fishbones.
- If endoscopic approach fails, open surgery is the best option, and the use of either a transoral or transcervical approach greatly depends on the site of the foreign body.

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