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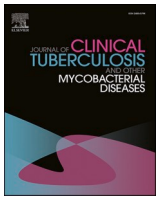

A review of 280 nasopharyngeal tuberculosis cases and the effectiveness of antituberculosis treatments

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ABSTRACT

Objectives: Nasopharyngeal tuberculosis is a rare form of tuberculosis in which Mycobacterium tuberculosis infects the nasopharyngeal tissue. In this study, we analyzed key clinical features to prevent misdiagnosis and to raise awareness of the condition, while recommending suitable treatments. We also report a case of nasopharyngeal tuberculosis presenting with nasal congestion and intermittent ear fullness, contributing valuable educational insight for diagnosis.

Methods: Demographic and clinical data from patients with nasopharyngeal tuberculosis were collected from PubMed, Embase, Web of Science and the Cochrane Central Register of Controlled Trials up to September 2022. In total, 280 patients from 69 studies were analyzed.

Results: Reports indicate that the incidence of nasopharyngeal tuberculosis has doubled every decade, particularly in Asia. Most patients are female, presenting with granulomatous pathology and findings such as masses, lymphoid hyperplasia, polypoid formations, or swelling on endoscopic examination. Common symptoms include nasal obstruction, hearing impairment, sore throat, and dysphagia, usually accompanied by cervical lymphadenopathy. The mean duration from symptom onset to diagnosis is ~2.88 months, and the average time from the start of treatment to resolution of symptoms is ~ 4.90 months. The antituberculosis treatment regimen and duration are significantly associated with the time to resolution ($r = -0.648$, $p = 0.003$ and $r = 0.584$, $p = 0.028$, respectively).

Conclusion: These results suggest that an extended regimen of antituberculosis drugs may expedite symptom relief. However, there is a need for more standardized data on patient outcomes and treatment efficacy due to the current lack of comprehensive data.

1. Introduction

Tuberculosis remains a global epidemic with extrapulmonary manifestations affecting various organs outside the lungs [1], accounting for ~10–46 % tuberculosis cases [2]. Within the head and neck region, extrapulmonary tuberculosis is observed in ~10–35 % of cases, involving structures such as the larynx, oral cavity, pharynx, and lymph nodes [3].

Tuberculosis that targets the nasal cavity or nasopharynx is notably uncommon, and instances of primary nasopharyngeal tuberculosis, defined as an infection solely within the nasopharynx, without pulmonary or other involvement, are particularly rare [4]. The initial symptoms are often nonspecific, complicating the early diagnostic process [2,5]. These symptoms may include a persistent sore throat, dysphagia, hoarseness, nasal congestion, and a sensation of a lump in the throat. Systemic symptoms may include fever, night sweats, weight loss, and fatigue [5].

Historically, primary nasopharyngeal tuberculosis has predominantly been reported in young women with no prior tuberculosis diagnosis [6,7]. We report the case of a 30-year-old female with nasopharyngeal tuberculosis who presented with white discoloration of the nasopharynx, mucosal erosion, and mucopurulent discharge (Fig. 1). The patient suffered from bilateral nasal obstruction, aural fullness, and purulent rhinorrhea for ~3 months. Notably, this case differs from previous reports [1,2,4,5,8,9,11,12,13,17,18,22,23,24] with the unusual presence of a soft palate fistula. Computer tomography revealed

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diffuse necrotic changes extending from the inferior aspect of the left nasopharynx to the posterolateral wall of the left oropharynx. We used a *trans*-nasal endoscope to do a deep tissue biopsy of nasopharyngeal lesion under local anesthesia. A definitive diagnosis was made based on the microscopic findings of inflammation, necrosis, and indistinct granuloma formation.

Irrespective of prior tuberculosis history or pulmonary symptoms, nasal mucosal examinations are necessary for patients with persistent rhinorrhea or nasal obstruction that is unresponsive to conventional treatments [2]. Diagnostic protocols typically involve imaging, such as computed tomography (CT) or magnetic resonance imaging (MRI), and tissue biopsies to detect tuberculosis bacteria and to distinguish the condition from nasopharyngeal carcinoma, where biopsy and diligent assessment are essential [8]. The treatment protocol includes a regimen of antibiotics over several months, supplemented by supportive care to alleviate symptoms and prevent further complications.

Although various cases of nasopharyngeal tuberculosis have been reported, systematic analyses of such cases are lacking. To the best of our knowledge, this literature review is the first to thoroughly investigate endoscopic findings, clinical presentations, and specific treatments for nasopharyngeal tuberculosis. In addition, we report a case of nasopharyngeal tuberculosis presenting with nasal congestion and intermittent ear fullness, contributing valuable information for diagnosis.

2. Materials and methods

2.1. Search methods

We analyzed studies available up to September 2022 from PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials. We used keywords including 'nasopharyngeal tuberculosis,' 'tuberculosis of nasopharynx,' and 'nasopharynx tuberculosis,' along with related terms.

Titles and abstracts were reviewed by two authors to identify studies that directly reported on patients diagnosed with nasopharyngeal tuberculosis. The authors independently reviewed the studies and extracted data regarding patient demographics, diagnosis, and treatment details. In cases of insufficient data, the authors held multiple discussions to review the information thoroughly. Data extracted from the included studies included the year of reporting, patient age and sex, nationality, presence of associated pulmonary tuberculosis, pathological results from nasopharyngeal biopsies, findings from nasopharyngeal endoscopies, cervical lymphadenopathy, rhinologic and otologic symptoms, other clinical presentations, antituberculosis treatment regimens and durations, time from treatment to symptom resolution, time from symptom onset to diagnosis, and diagnostic imaging tools utilized.

Studies not available in English, or lacking abstracts, were excluded. Cases that did not involve nasopharyngeal tuberculosis were also omitted. The process of identifying and screening the included studies is detailed in Fig. 2.

2.2. Statistical analysis

For statistical evaluation, we utilized IBM SPSS Statistics 22.0. Data are presented as means and standard deviations for continuous variables, and as frequencies and percentages for nominal variables. The correlation between the duration from treatment to symptom resolution and other variables was determined through simple correlation analysis. Differences in the duration from treatment to symptom resolution, based on the antituberculosis treatment regimens and durations, were assessed using one-way ANOVA, with the Tukey post hoc test applied for further analysis. p-value <0.05 was considered statistically significant.

3. Results

3.1. Demographic features of nasopharyngeal tuberculosis patients

Our analysis included 280 cases of nasopharyngeal tuberculosis

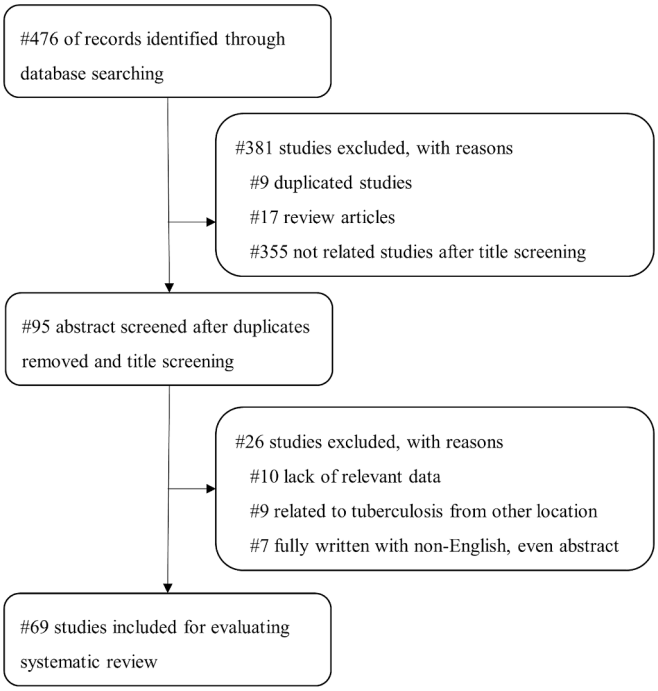

Fig. 2. Flowchart retrieving studies search process and selection.

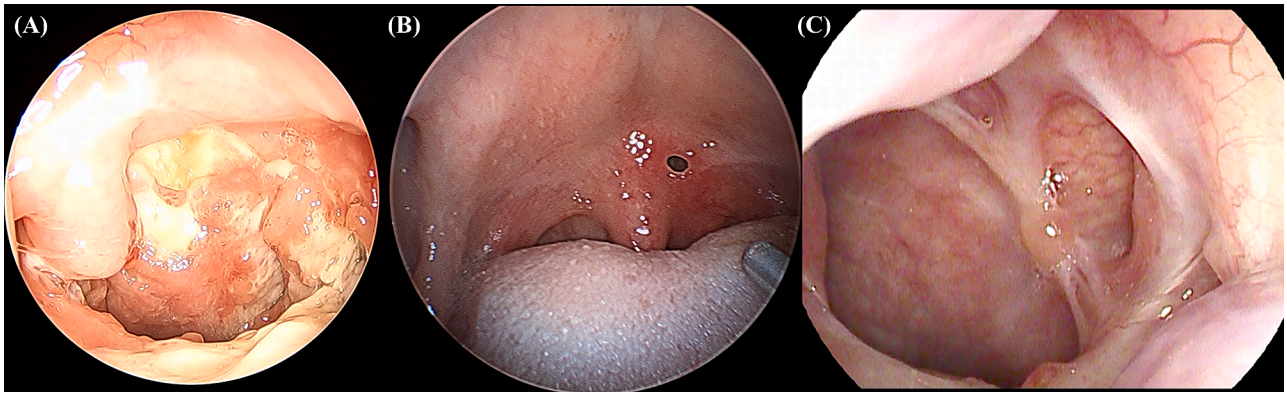

Fig. 1. Endoscopic view of nasopharyngeal tuberculosis patients accompanying palatal fistula: (A) endoscopic view of nasopharynx before anti-tuberculosis treatment, (B) fistula on soft palate of nasopharyngeal tuberculosis patient, and (C) endoscopic view of nasopharynx after anti-tuberculosis treatment.

derived from 69 studies. The number of nasopharyngeal tuberculosis cases has shown an increasing trend since the 1980s, with the majority of reports originating from China, and more broadly, Asia (Fig. 3). Although reports are rare, it has also been documented in the Middle East and European countries. The patient demographic skews slightly towards females, with an average age of ~38.52 years (Table 1).

3.2. Clinical features of nasopharyngeal tuberculosis patients

Associated pulmonary tuberculosis was identified in 19 % of the cases through chest CT scans or patient history. Endoscopic examination of the nasopharynx revealed a variety of lesions, with ~68 % of patients exhibiting a nasopharyngeal mass, lymphoid hyperplasia, polypoid formations, or swelling. Less than 20 % presented with irregularities or ulcers, while necrotic nasopharynx, thickened diffuse mucosa, discharge, white discoloration, and hyperemia were noted in <10 % of cases. Approximately 8 % of patients displayed a normal nasopharynx without specific findings. Pathological examination of nasopharyngeal biopsies predominantly showed granulomatous or necrotic lesions. Not all patients had positive results for acid-fast bacilli, polymerase chain reaction (PCR), or culture tests.

CT generally revealed positive findings in most patients, and ~4 % had abnormal results in positron emission tomography/CT scans. Symptomatology varied widely, with the most common being cervical lymphadenopathy (69 %), followed by rhinologic and auditory symptoms such as nasal obstruction, hearing impairment, and postnasal drip. Sore throat, dysphagia, and systemic symptoms such as fever, night sweats, and weight loss were also reported. Facial pain, skin lesions, and taste or smell disturbances were rare. Symptoms of nasopharyngeal tuberculosis are related to infection of the upper respiratory tract, but systemic symptoms such as lymphadenopathy, fever, night sweat, or weight loss may also be present in pulmonary tuberculosis.

Treatment of nasopharyngeal tuberculosis typically involved a regimen of 3 or 4 antituberculosis drugs, similar to that for pulmonary tuberculosis. A combination of 3 to 4 drugs was administered to 60 % of patients over various durations, with the average treatment lasting 6.72 months. The mean time from symptom onset to the diagnosis was ~2.88 months, indicating a delay of more than 2 months. Symptom improvement was observed at ~4.9 months after treatment initiation. Adjuvant treatments, including isoniazid, rifampicin, and streptomycin solution nasal sprays for 3 months, as well as mastoid surgery [9] or levofloxacin [10], were also considered.

3.3. Simple correlation analysis of factors influencing the duration from treatment to resolution

With no reported cases resulting in death, a simple correlation analysis was performed to identify factors influencing the duration from treatment initiation to recovery. Significant associations were found between the time to resolution and the antituberculosis treatment regimen ($r = -0.648$, $p = 0.003$) and duration ($r = 0.584$, $p = 0.028$)

Table 1
Demographic data of patients from included studies.

	Number of patients or mean ± SD (n = 280)	Percentage
Female (n, %)	114	59 %
Age (years, mean ± SD)	38.52 ± 15.27	
Associated pulmonary tuberculosis (n, %)	35	19 %
Pathologic result from biopsy (n, %)		
Granulomatous lesion	131	92 %
(Caseous) necrotic lesion	45	34 %
Acid-fast bacilli (AFB) positive	22	67 %
Endoscopic finding of nasopharynx (n, %)		
Mass, lymphoid hyperplasia, polypoid or swelling	115	68 %
Irregularity	29	17 %
Ulcer	20	12 %
Necrotic lesion	15	9 %
Diffuse mucosa thickening	10	6 %
Discharge	6	4 %
White discoloration or slough mucosa	4	2 %
Hyperemia	2	1 %
Normal	13	8 %
Positive finding of image (n, %)		
CT	39	52 %
MRI	33	44 %
PET CT	3	4 %
Associated symptoms (n, %)		
Cervical lymphadenopathy	130	69 %
Nasal obstruction	20	14 %
Postnasal drip	8	6 %
Blood tinged nasal discharge or purulent discharge	7	5 %
Snoring	4	3 %
Hearing impairment	18	14 %
Otorrhea	6	5 %
Earfullness	5	4 %
Tinnitus	5	4 %
Otalgia	4	3 %
Sore throat or dysphagia	17	14 %
Fever, night sweat or weight loss	11	9 %
Headache or dizziness	9	7 %
Diplopia or neurologic symptoms (facial palsy, tongue deviation)	3	2 %
Facial pain	1	1 %
Skin lesion	1	1 %
Taste or smell dysfunction	1	1 %
Anti-tuberculosis treatment regimen (n, %)		
Combination	25	60 %
Quadruple anti-tuberculosis regimen	14	33 %
Triple anti-tuberculosis regimen	3	7 %
Anti-tuberculosis treatment periods (months, mean ± SD)	6.72 ± 3.25	
Time from anti-tuberculosis treatment to resolution (months, mean ± SD)	4.90 ± 2.80	
Time from symptom to diagnosis (months, mean ± SD)	2.88 ± 2.16	

SD: standardized deviation.

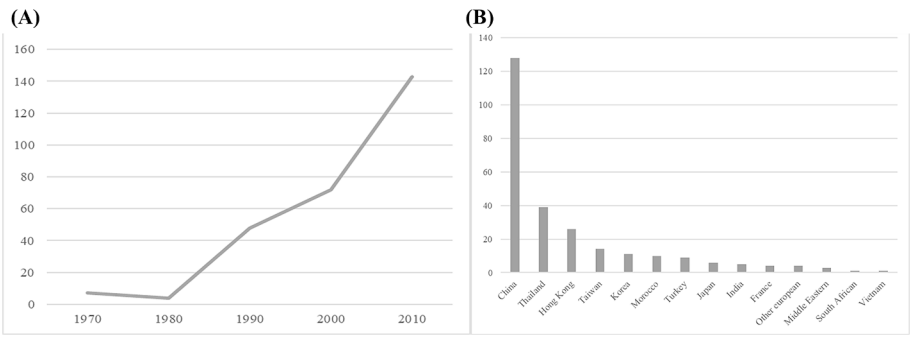

Fig. 3. Reported (A) years and (B) countries of nasopharyngeal tuberculosis.

Table 2
Simple correlation analysis of influencing factors for time from anti-tuberculosis treatment to resolution.

	r	*p*-value
Female	0.071	0.740
Age	0.154	0.473
Associated pulmonary tuberculosis	−0.160	0.45
Pathologic result from biopsy		
Granulomatous lesion	−0.330	0.125
(Caseous) necrotic lesion	−0.006	0.977
Acid-fast bacilli (AFB) positive	0.706	0.501
Endoscopic finding of nasopharynx		
Mass, lymphoid hyperplasia, polypoid or swelling	0.037	0.864
Irregularity	0.097	0.652
Ulcer	0.219	0.304
Diffuse mucosa thickening	−0.160	0.455
Discharge	0.244	0.250
White discoloration or slough mucosa	NA	
Hyperemia	−0.322	0.124
Normal	NA	
Associated symptoms		
Cervical lymphadenopathy	−0.098	0.690
Nasal obstruction	−0.076	0.737
Postnasal drip	0.099	0.663
Blood tinged nasal discharge or purulent discharge	0.262	0.239
Snoring	−0.257	0.249
Hearing impairment	0.233	0.298
Otorrhea	−0.154	0.494
Earfullness	−0.058	0.799
Tinnitus	0.074	0.742
Headache	0.144	0.588
Sore throat or dysphagia	−0.187	0.458
Fever, night sweat or weight loss	−0.055	0.798
Skin lesion	−0.066	0.796
Taste or smell dysfunction	−0.374	0.127
Neurologic symptoms	−0.374	0.127
Anti-tuberculosis treatment regimen	**−0.648****	**0.003**
Anti-tuberculosis treatment periods	**0.584***	**0.028**
Time from symptom to diagnosis	0.459	0.115

NA: not available.

(Table 2). In addition, a significant difference in recovery time was observed among groups treated with combination regimens, three-drug regimens, and four-drug regimens ($p = 0.015$). Further post hoc analysis indicated a significant difference in recovery time between patients treated with combination regimens and those on four-drug regimens ($p = 0.017$) (Supplementary Table 1).

4. Discussion

Nasopharyngeal tuberculosis, initially documented by Morgagni in 1761, presents diagnostic challenges in the early stages for otolaryngologists [2,11,12]. Common clinical symptoms such as neck swelling, hearing loss, ear fullness, nasal obstruction, postnasal drip, epistaxis, and rhinorrhea are often not evident in the initial stages of the disease [13]. Our objective is to provide a more detailed demographic analysis through the clinical examination of nasopharyngeal tuberculosis, which is notably challenging to diagnose early, even for specialists.

Nasopharyngeal tuberculosis can occur through primary or secondary infection [8]. 8 The primary form can occur due to inhalation exposure through the nose [8], while the secondary form may result from infection through the airway, lymphatic, or vascular pathways [14]. There is ongoing debate regarding the prevalence of primary versus secondary nasopharyngeal tuberculosis [15,16]. While we did not specifically analyze the proportion of primary to secondary cases, ~19 % of the cases did have associated pulmonary tuberculosis.

The endoscopic appearance of nasopharyngeal tuberculosis can vary, varying between proliferative and exfoliative phases [12,17]. Although studies differ on the most common endoscopic features [5], we found that masses or swelling were prevalent, with normal nasopharynx observed in ~8 % of patients with nasopharyngeal tuberculosis. Lesions resembling masses, polyps, or swelling require careful consideration to differentiate them from nasopharyngeal carcinoma.

Not all cases exhibit abnormal endoscopic findings; therefore, additional diagnostic methods are required. Histological examination is crucial to diagnose nasopharyngeal tuberculosis, with CT or MRI serving as supplementary diagnostic tools [18]. Necrotic nasopharynx might be detected in CT scans [12], yet it is not a consistent finding. Imaging tests raised suspicions of nasopharyngeal tuberculosis in 52 % of cases via CT and 44 % via MRI, which were later confirmed.

As previously discussed, histological examination is critical for diagnosing nasopharyngeal tuberculosis, typically presenting with granulomatous inflammation, epithelioid giant cells, and caseous necrosis. Granulomatous lesions are also common in other conditions such as infectious diseases, Wegener's granulomatosis, or sarcoidosis, necessitating differential diagnosis [15,19]. In our analysis, granulomatous lesions were the most frequent histologic findings. PCR for Mycobacterium tuberculosis DNA in tissue specimens is considered the most accurate diagnostic method [20], but its utility as a follow-up tool is limited because it can yield positive results even for inactive tuberculosis [21]. Acid-fast staining provides rapid results but has low sensitivity for extrapulmonary tuberculosis diagnosis [2], with a 67 % positivity rate in this study. Culture tests have high sensitivity, yet they can delay diagnosis due to the required minimum culture period of 6 weeks [2].

The increasing rate of resistance to antituberculosis drugs highlights the need for prompt and effective treatment to curb resistance [1]. Treatment protocols align with those for pulmonary tuberculosis [1,5]. While no absolute treatment duration for primary nasopharyngeal tuberculosis has been established, it generally has a favorable prognosis with sufficient treatment period [5,8]. Treatment for extrapulmonary tuberculosis should last at least 6 months, with a triple combination of isoniazid, rifampicin, and ethambutol for 9–18 months, or a quadruple regimen with the addition of pyrazinamide for 9 months [8,22]. Initially, quadruple therapy is administered for 2 months, sometimes followed by triple therapy for 4 months [1]. After the initial 2 months, isoniazid and rifampicin may be continued for 4–7 months [23,24]. Treatment approaches can vary, but nasopharyngeal tuberculosis cases generally have a good prognosis. However, hepatotoxicity, peripheral neuropathy, optic neuritis related to visual disturbances, gastrointestinal disturbances such as nausea, vomiting, and abdominal discomfort have been reported as common complications of a triple or a quadruple combination regimen of antituberculosis drugs, so caution must be taken during treatment. Our literature review suggests that prolonged combination therapy may be more effective than shorter triple or quadruple regimens for rapid clinical improvement.

This study represents an initial understanding of the clinical and demographic patterns of rare nasopharyngeal tuberculosis cases and their optimal treatment. However, our study also had several limitations. First, Only English-language studies were analyzed, with one report included based only on an English abstract. Second, Treatment course details were often unspecified. In addition, this systematic review was based on retrospective data, which may lack comprehensiveness, particularly in case series. The majority of studies were case reports or case series. Third, the simple correlation analysis for treatment resolution time may be affected by multiple confounding factors. Finally, the sample size of 280 patients is insufficient. Future large-scale studies or prospective cohorts for anti-tuberculosis treatment on nasopharyngeal tuberculosis are needed to establish optimal treatment regimens and validate the findings of this study.

In conclusion, nasopharyngeal tuberculosis, once a rare diagnosis, has shown an increasing trend. This study highlights significant clinical features to prevent misdiagnosis and to increase awareness of the condition through precise patient assessment. Pathological results often reveal granulomatous lesions, and endoscopic findings typically show masses, lymphoid hyperplasia, or polypoid swelling. Common symptoms include cervical lymphadenopathy, nasal obstruction, hearing

impairment, sore throat, or dysphagia. Preliminary data indicate that extended combination therapy with antituberculosis drugs may lead to quicker symptomatic improvement compared to shorter triple or quadruple regimens. Due to insufficient data on treatment outcomes, further studies with more standardized patient data are imperative.

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CRediT authorship contribution statement

Yun Jin Kang: Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jin-Hee Cho:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Conceptualization.

Declaration of competing interest

This work was supported by the Soonchunhyang University Research Fund. The sponsor had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. And the authors declare no conflicts of interest.

Data availability

The raw data of individual articles used in this *meta*-analysis are included in the main text or Supplementary Data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2024.100455.

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