


Tuberculosis in the Head and Neck: Changing Trends and Age-Related Patterns

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Objective: To evaluate changing trends in patient collectives, age-related patterns of manifestation, and diagnostic pathways of patients with extrapulmonary head and neck tuberculosis (TB), and to provide strategies to fasten diagnosis in these patients.

Study design: Case control study.

Methods: A 10-year retrospective analysis of 35 patients diagnosed with extrapulmonary TB in the head and neck at a tertiary university institution from 2009 to 2019, with special focus on the influence of the patient's age on consideration of TB and clinical patterns.

Results: The vast majority of patients younger than 40 years had their origin in countries with high TB burden ($P = .0003$), and TB was considered very early as a differential diagnosis ($P = .0068$), while most patients older than 40 years were domestic citizens initially suspected for a malignancy, who more often had an underlying immunosuppressive condition (0.0472). Most frequent manifestations in both groups were the lymph nodes, larynx, and oropharynx. Surprisingly, no differences in the rates of open TB or history of TB infection in the family anamnesis were found.

Conclusion: The two groups of patients found most often are younger patients migrating from regions with high TB burden and elderly domestic patients suffering from immunosuppressive conditions, with the latter often being misdiagnosed as malignancies. TB remains an important but difficult differential diagnosis, due to the initially unspecific symptoms and the great variety in the presentation of manifestations in the head and neck.

Key Words: Tuberculosis, head and neck, extrapulmonary tuberculosis, laryngeal tuberculosis, lymph node tuberculosis.

Level of Evidence: 4

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INTRODUCTION

Accounting for roughly 10 million new cases and 1.4 million deaths in 2018, tuberculosis (TB) remains the leading cause of death among infectious diseases worldwide.¹ The burden of disease varies among countries, from fewer than five to more than 500 new cases per 100,000 population per year.¹ The majority of cases is situated in the regions of Southeast Asia (44%), Africa (24%), and the Western Pacific (18%), but relevant numbers occur in almost every country worldwide.¹ Although the increase in numbers in high prevalence regions since 1985 is largely related to the increase in HIV-positive and multiple drug-resistant TB patients,² the slow but steady increase in low prevalence regions can be attributed to an aging population with higher rates of underlying immunosuppressive conditions like malignancies or

diabetes,³ as well as increased migration in the last decades.⁴ Thus, TB is getting more important as a differential diagnosis even in low prevalence regions.⁵

Extrapulmonary manifestations make up for 20% of all cases of TB,⁶ with head and neck TB accounting for 10% of all patients.^{7,8} TB in the head and neck most frequently affects the lymph nodes,⁹ but is also found in larynx, middle ear, oropharyngeal mucosa, salivary glands, paranasal sinuses, or the prevertebral space,^{3,10,11} since most of these organs are areas of first contact with pathogens in the human body. Consecutively, besides systemic immunosuppression, a local break in the natural barrier of the mucosa such as trauma, inflammation, or poor oral hygiene increases the risk for infection with TB.¹² Nonetheless, extrapulmonary TB can not only be attributed to direct inoculation, as there are studies pointing at a hematogenous spread as the origin of tuberculous manifestations, for example, in larynx or skin as well.¹³

Because manifestations of TB in the head and neck are clinically similar to inflammation or neoplasms, and because of its rarity in low prevalence regions, clinical consideration of TB as a differential diagnosis often occurs quite lately^{14,15} and has not decreased in the past few decades.¹⁶ In this regard, an origin in a region with high prevalence of TB in the population or family members with a known or suspected history of TB can lead to an earlier diagnostic suspicion.⁴ Although some presentations of lymph node TB have a few characteristics in computed tomography, which may lead at least to an earlier

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suspicion of TB as a diagnosis, they are very unspecific and not suited to base a therapy upon; manifestations in larynx, oropharyngeal mucosa, or middle ear cannot be differentiated from malignancies or chronic inflammation radiologically.¹⁷ Even when suspected, attaining diagnostic proof is difficult because of either low sensitivity (PCR, culture) or specificity (interferon-gamma-release-assay [IGRA], histopathology) of the diagnostic procedures.^{18–20} Hence, early consideration of a mycobacterial infection is of great importance to fasten the diagnostic pathway and to reduce exposure to an untreated and possibly infectious patient for their personal environment as well as the medical staff involved.

Although there are known differences between young and elderly patients with TB,¹ to the best of our knowledge no study so far has evaluated the influence of the patient's age on clinical patterns and diagnostic pathways when first being diagnosed in a low prevalence region. To answer that question via a retrospective analysis is the aim of the present study.

MATERIALS AND METHODS

Data Collection and Study Population

Approval of the Würzburg University's Hospital Institutional Review Board and local ethics committee was obtained before data acquisition. The charts of all patients diagnosed with an extrapulmonary TB at our institution between January 2009 and June 2020 were reviewed. Patients with an already known TB being treated for other reasons were excluded. Thereby, 35 patients matching the inclusion criteria could be identified. The cutoff between younger and older patients was set at 40 years.

Among the baseline patient's characteristics investigated were age, gender, region of origin, and the prevalence of TB there, family members with known or suspected TB, and a medical history of immunosuppressive condition. Clinical parameters analyzed included the localization of TB, the initially considered diagnosis, the presence of an "open" TB (i.e., infectious), initial leukocytes and C-reactive protein (CRP), and surgical complications like wound healing disorder after biopsy. It was also examined what kind of and how many radiological diagnostics were conducted. Routine laboratory diagnostic was conducted in every patient.

In most patients, confirmation of TB was done via biopsy, only in a few cases a fine-needle punctate was done instead. Effectiveness of diagnostic methods such as IGRA, PCR, microbiological culture, and histologic examination was analyzed. Only a positive result in culture or in PCR was seen as confirmation of TB according to recent international guidelines. All patients' samples were also investigated histopathologically to exclude malignancy or other infectious or immunological diseases.

Statistical Analysis

The data collected were transferred to standard spreadsheets and statistically analyzed using GraphPad Prism software (version 6.0e; GraphPad Software, Inc., San Diego, CA, USA). Data are presented as mean, unless otherwise stated. Gaussian distribution was verified using the D'Agostino-Pearson omnibus normality test for every item analyzed. Therefore, the *t*-test was used for analysis of two groups with continuous variables.

Categorical data were analyzed with Fisher's exact test or chi-squared test if applied for more than two variables. Odds ratio analysis was calculated for categorical items and stated with 95% confidence interval. A value of $P < .05$ was considered statistically significant. When testing multiple comparisons, a Bonferroni correction was applied to each group of tests.

RESULTS

Overall, the data of 35 patients who matched the inclusion criteria could be evaluated. Table I demonstrates the patient characteristics and clinical data for all patients. Fourteen patients (40.00%) came from low prevalence regions, all of them in Germany. Twenty patients (60.00%) had an origin in high prevalence regions, specifically Africa (10 patients, 28.57%), East Asia (5 patients, 14.29%), Russia (3 patients, 8.57%), and the Middle East (2 patients, 5.71%). When analyzed regarding the patient's age, 15 patients (93.75%) of the younger group had a history of migration from countries with high TB burden, while only 6 (31.58%) of the older patients did ($P = .0003$, OR 0.031 [0.003–0.290]). This was highly significant even after Bonferroni correction. Male-to-female ratio was 50/50% for younger patients versus 73.68/26.32% for older patients ($P = .1789$, OR 0.357 [0.087–1.471]). In both groups, most manifestations of TB were located in the lymph nodes (both 11 patients, 68.75% vs. 57.89%) and only few in other organs (5 patients, 31.25% vs. 8 patients, 42.11%), with no significant difference between the groups ($P = .7271$, OR 1.600 [0.396–6.460]). Other manifestations included prevertebral space (2 patients), middle ear (1), parotid gland (1), and oropharyngeal mucosa (1) in the younger group compared to larynx (4), oropharyngeal mucosa (2), intraorbital tissue (1), and middle ear (1) in the older group.

No difference was found between both groups regarding family members with a known or suspected history of TB (18.75 vs. 42.11%, $P = .1667$, OR 3.152 [0.668–14.87]). However, seven (36.84%) patients from the older group had preexisting immunosuppressive conditions such as cancer or immunosuppressive therapy for other reasons, but only 6.25% of the patients from the younger group ($P = .0472$, OR 8.750 [0.942–81.30]). No difference was found when comparing the initial leukocyte count (6.563 vs. $5.911 \times 1000/\mu\text{l}$, $P = .4513$) and initial CRP (2.699 vs. 1.820 mg/dl, $P = .4722$) between both groups.

Patients of 40 years and older most often were diagnosed with cancer (57.89%), followed by chronic inflammation (21.05%) and then TB (21.05%). In patients younger than 40 years, however, TB was the first suspected diagnosis in 68.75%, while malignancy (12.50%) and chronic inflammation (18.75%) were suspected less frequent. These differences between the two groups ($P = .0068$, OR 8.250 [1.790–38.03]) regarding the correct initial diagnosis were highly significant even after Bonferroni correction.

When presenting with lymph node pathology, all patients received a sonography, while an initial computed tomography was only conducted in 13 of 35 patients (37.14%), primarily when malignancy was suspected. In all patients with manifestations other than lymph nodes,

TABLE I.
Patient Characteristics.

	Age Younger Than 40 Yr	Age 40 Yr or Higher	P-Value	OR (95% CI)
Total patients	16 (45.71%)	19 (54.29%)		
Gender			.1789	0.357 (0.087–1.471)
Male	8 (50.00%)	14 (73.68%)		
Female	8 (50.00%)	5 (26.32%)		
Region of origin			.0003***	0.031 (0.003–0.290)
low TB burden	1 (6.25%)	13 (68.42%)		
high TB burden	15 (93.75%)	6 (31.58%)		
Localization			.7271	1.600 (0.396–6.460)
Lymph node	11 (68.75%)	11 (57.89%)		
Other	5 (31.25%)	8 (42.11%)		
Initial diagnosis			.0068***	8.250 (1.790–38.03)
Tuberculosis	11 (68.75%)	4 (21.05%)		
Malignoma	2 (12.50%)	11 (57.89%)		
Chronic inflammation	3 (18.75%)	4 (21.05%)		
Open TB	3 (18.75%)	8 (42.11%)	.1667	3.152 (0.668–14.87)
TB in family members	5 (31.25%)	5 (26.32%)	1.0000	0.787 (0.181–3.418)
Immunosuppression	1 (6.25%)	7 (36.84%)	.0472	8.750 (0.942–81.30)
Initial leukocytes in 1000/ μ l	6.563	5.911	.4513	
Initial CRP in mg/dl	2.699	1.820	.4722	
Postoperative wound healing disorder	7 (43.75%)	3 (15.79%)	.1316	0.241 (0.050–1.171)

Patient characteristics in relation to their respective age.

***Indicate statistical significance after Bonferroni correction.

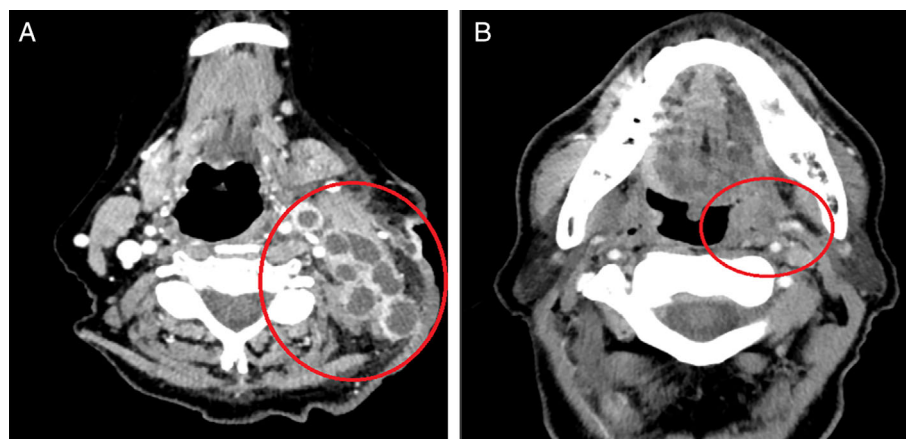


Fig. 1. (A) CT-scan of cervical lymph node TB on the left side. The radiological aspect of enlarged lymph nodes with necrotic liquefaction is suspicious for a manifestation of TB rather than a malignoma or a cervical abscess. (B) CT-scan of a TB manifestation in the tonsillar region on the left side. Unspecific, unilateral thickening of the tonsillar tissue on the left side allows no specific diagnostic association to TB. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

a CT scan of the respective region (neck, temporal bone, parotid gland) was conducted. Only in the two cases with prevertebral TB, an additional magnetic resonance imaging was performed. After verification of TB, pulmonary CT scans were added to diagnostic. While at least in CT scans of lymph node TB patients the diagnosis was suspected by the radiologists in 12 of 23 patients (52.17%, example shown in Fig. 1A), no patient with non-lymph node manifestation had been suspected of having TB radiologically (example shown in Fig. 1B).

The results of pathological and microbiological diagnostics are presented in Figure 2. All but one patients had a positive result in IGRA (97.14%). Acid-fast bacilli were found in half of all patients (51.43%), while the histopathological proof of necrotizing granulomas was possible in 80.00%. Both the PCR and the bacterial culture had the same percentage of positive results (65.71%), but were not correlated with each other, so that a positive result in PCR did not always had a positive result in culture and vice versa. In all patients though, either culture

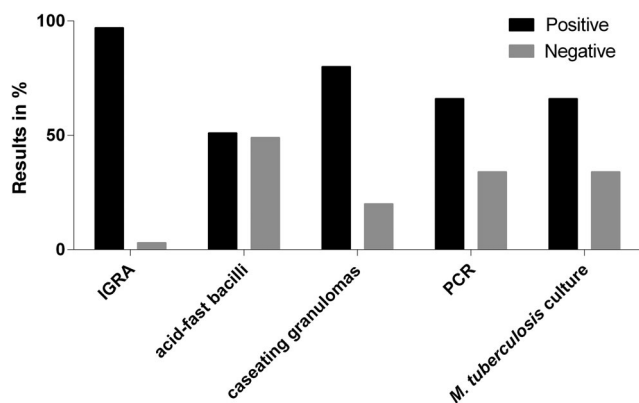


Fig. 2. Analysis of the TB-specific diagnostic results.

or PCR was positive, thereby verifying the diagnosis. Only 2 of 35 (5.72%) patients had proof of drug-resistant TB, one against isoniazid (INH) and another against isoniazid and rifampicin (RIF), which could be diagnosed with both culture and PCR.

Since in all patients investigated, the specimens were obtained via surgical biopsy, there were a few wound healing disorders associated with it, with no differences between both groups (43.75 vs. 15.79%, $P = .1316$, OR 0.241 [0.050–1.171]). All of them could be treated conservatively without additional surgery. No other complications were reported in this collective. Medical treatment followed and was completed in all patients at our institutions department for infectiology.

DISCUSSION

TB remains the leading cause of mortality among infectious diseases worldwide, and its incidence has not declined significantly in the last decades.¹ While in regions of high prevalence HIV-positive patients are the major concern,² the moderate rise in low prevalence regions is attributed to aged patients with immunosuppressive comorbidities^{3,6} and increased migration from high prevalence regions.⁴ 20% to 25% of these patients suffer from extrapulmonary TB, and 8% to 12% have manifestations in the head and neck.¹⁰ Hence, diagnosis and treatment of TB is becoming increasingly important in low prevalence regions as well, especially for ENT specialists.

In the present study, 40% were patients from low prevalence regions in Western Europe and 60% came from high prevalence regions, mainly Africa, East Asia, and Russia. For low prevalence regions, Penfold et al. reported on similar ratios in the United Kingdom.²¹ Most studies published regarding head and neck TB, however, are either case series with small collectives or larger investigations from high prevalence regions. Among younger patients, however, more than 90% migrated from a region with high TB burden, whereas only 31.58% of the older patients did. In larger studies from high prevalence regions, the mean age of the patients is 20 to 30 years.^{22,23} In low prevalence regions, on the other

hand, many had much older patient collectives.^{3,11,24} Reasons therefore typically are a much older general population and, as also shown in the present study, higher rates of immunosuppressive diseases or medications in low prevalence regions.²⁵ Although cancer or immunosuppressive medication are the major reasons for immunosuppression in low prevalence regions,²⁶ mostly affecting elderly patients, simultaneous infection with HIV is the main reason for immunosuppressive conditions in high prevalence regions,^{27,28} which often affects a younger part of the population. Therefore, two groups account for the majority of newly diagnosed TB patients in low prevalence countries: Younger, otherwise healthy patients who migrated from regions with high TB burden and older patients who might have had an infection decades ago, when the prevalence of TB was higher in all regions, and now suffer from an activation of the infection caused by an immunosuppression. In the present study, older patients consecutively more often had an immunosuppressive condition than younger ones.

The present study also revealed that TB as the primary diagnosis was considered significantly more often at the initial admission in younger patients with a background of migration from high prevalence regions than in older patients. In countries with a low burden of TB in the population, the origin of patients in a high prevalence country has already been shown to be one of the most helpful hints to make the correct diagnosis.^{4,29} Moreover, older patients were mostly suspected to suffer from a malignoma in the present study. This has been reported especially for laryngeal TB, which clinically resembles a laryngeal carcinoma being a lot more common in patients older than 40 years.^{3,30} Manifestations of TB in lymph nodes have some features that may allow at least a diagnostic suspicion via radiological examinations like computed tomography,¹⁷ which was possible in almost half of the patients who received a CT scan in the present study, yet is way to unspecific to exclude other differential diagnoses. Manifestations in middle ear,^{31,32} larynx,^{11,30} or intranasal mucosa,³³ however, are rarely ever suspected to be related to TB due to their unspecific characteristics.¹⁷ In literature as well as in our analysis, lymph node TB is by far the most common head and neck manifestation.^{11,23,24,34}

In the present study, male-to-female ratio did not differ significantly between both age-related groups, although there were more male patients among the older group. Since the male-to-female ratios reported in the literature are also varying highly, with ratios ranging from 1:4 to 5:1,^{10,11,34} there does not seem to be a predominance for a certain gender in TB patients.

Surprisingly, there was no difference between the two groups regarding suspected or known TB in family members, situated between 26% and 31%, respectively. Then again, even in regions with high TB burden, the rates of contact history with a diagnosed TB case are reported to be low with 6% to 40%.^{22,35} Infectiousness by means of a simultaneous open TB was found in 18.75% of the younger and 42.11% of the older patients. This is relatively high compared to literature with about 3% to 20% of simultaneous open TB in patients with

extrapulmonary head and neck TB.^{3,11,35} Since in the present study most of the open TB patients were from the older patient's group, the higher numbers of immunosuppressive conditions in this group, and the fact that all of the laryngeal manifestations were found in older patients, might be explanations for that.

In the present study, histopathological examination, IGRA, PCR, and microbiological culture were conducted for all patients. As expected, IGRA was positive in almost all cases due to its high sensitivity, which is in accordance with literature³⁶; it has a very low specificity, though, and gives no information about the activity of the infection. It can therefore only stand at the beginning of the diagnostic process. Histopathological finding of necrotizing granuloma consistent with TB was possible in 80% of the patients, and therefore was the examination with the highest positive result rate in this study. That is why it was long considered it to be the most reliable test.³⁷ Acid-fast bacilli could be identified in microbiological or histopathological samples in about 50% of the patients, which is a bit higher than the results reported in the literature.^{3,38} Mycobacterial culture was successful in 67% of samples, while most authors describe positive results in 20% to 50%.^{11,34,35} PCR also had a success rate of 67% in the present study and is reported as positive in 35% to 50% in the literature available.^{3,11,34} It has to be noted, however, that positive results in PCR did not automatically correspond to a successful culture in the same patients. Since either a positive result in culture or PCR is needed for a verification of the diagnosis, we recommend to conduct all mentioned examinations if possible to increase diagnostic security.

CONCLUSION

We conclude that TB of the head and neck remains an important, but difficult differential diagnosis. Two major age-related groups of patients could be identified, namely younger patients with a history of migration from high prevalence regions and older, mostly domestic patients with an immunosuppressive condition. This last group is often diagnosed very lately due to the rareness of TB in their countries and the clinical aspect of malignomas or other chronic infections. Therefore, anamnesis regarding origin, known TB contacts and underlying immunosuppressive diseases, remains one of the most important tools in fastening the diagnostic pathway in TB patients.

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