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ORIGINAL ARTICLE

Head and Neck Tuberculosis: 6-Year Retrospective Study☆

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Abstract
Introduction: Pulmonary involvement exists in 80% of cases of infection with *Mycobacterium tuberculosis*; however, in up to 20% of cases there may be extra-pulmonary involvement. In the ENT area, the most common site is cervical lymphadenitis, affecting approximately 95% of cases.
Materials and methods: This was a retrospective study of patients attending an ENT department in a tertiary hospital for head and neck symptoms that were diagnosed with tuberculosis (TB), between December 2007 and December 2013.
Results: The study included 73 patients, 41 (56.2%) males and 32 (43.8%) females (M/F ratio=1.28), with a mean age of 39.4 years (±26.5 years; Min 1, Max 88). There were 53 (72.6%) cases of cervical lymphadenopathy, 11 (15%) of laryngeal tuberculosis 3 (4.1%) of hypopharyngeal tuberculosis, and six cases in other locations. Of the total, 14 (19.2%) patients were HIV positive and 10 (13.7%) had a history of contact with relatives who had suffered pulmonary tuberculosis. PCR was performed in 51 (69.8%) cases to confirm being positive, of which 47 (92.1%) cases were.
Conclusion: The similarity of tuberculosis to diseases of poor prognosis and the difficulty of its diagnosis make considering tuberculosis necessary when exploring patients with ulcerative or granulomatous ENT lesions. Analysing our results, the incidence of TB according to its ENT area location is similar to that reported in the literature. It is important to make special mention of the use of PCR in our study and the benefits that its implementation means for diagnosis.

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PALABRAS CLAVE
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Tuberculosis de cabeza y cuello: estudio retrospectivo de 6 años

Resumen
Introducción: En el 80% de los casos de infección por *Mycobacterium tuberculosis* existe afectación pulmonar, sin embargo hasta en un 20% de casos puede haber compromiso extrapulmonar. En el área otorrinolaringológica la localización más frecuente es la linfadenitis cervical, que afecta aproximadamente al 95% de los casos.
Materiales y métodos: Estudio retrospectivo en pacientes que acudieron a consulta de ORL en un hospital terciario por sintomatología en cabeza y cuello y que fueron diagnosticados de tuberculosis, entre diciembre del año 2007 y diciembre del año 2013.
Resultados: Un total de 73 pacientes fueron incluidos, 41 (56,2%) hombres y 32 (43,8%) mujeres (ratio H/M = 1,28), con una edad promedio de 39,4 años (±26,5 años; mín: 1/máx 88). Un total de 53 (72,6%) casos correspondieron a linfadenopatía cervical, 11 (15%) a tuberculosis laríngea, 3 (4,1%) a tuberculosis hipofaríngea, y los restantes 6 en otras localizaciones. Del total, 14 (19,2%) pacientes eran VIH positivo y 10 (13,7%) tenían antecedentes de contacto con familiares que habían sufrido tuberculosis pulmonar. En 51 (69,8%) de los casos se realizó una PCR como medida de confirmación, siendo positiva en 47 de estos (92,1%).
Conclusión: La similitud de la tuberculosis con enfermedades de mal pronóstico y la dificultad que entraña su diagnóstico hacen necesario tener en cuenta la tuberculosis a la hora de explorar a pacientes con lesiones granulomatosas o ulcerativas del área ORL. Al analizar nuestros resultados, la incidencia de tuberculosis según su localización en el área ORL es similar a la reportada en la literatura. Es importante hacer mención especial del uso de la PCR en nuestro estudio y las ventajas que su aplicación significa para el diagnóstico.

Introduction

Tuberculosis (TB) is one of the oldest infections known to humanity. Even today, it is still one of the main causes of death from infection in adults.[1] In 2011, the World Health Organisation estimated an incidence of 8.3–9 million cases at global level.[2] Furthermore, 1 of every 3 individuals in the world is thought to be infected with *Mycobacterium tuberculosis*[1,3] (*M. tuberculosis*) or runs the risk of developing the disease.[3]

There is extra-pulmonary infection in 80% of the cases of infection by *M. tuberculosis*, but up to 20% of cases can have extra-pulmonary compromise.[4] In the ear, nose, and throat (ENT) area specifically, the most frequent location is the cervical lymph nodes, involving approximately 95% of the cases. The remaining locations (such as larynx, ear, nostrils, pharynx, tonsils, mastoids, salivary glands or cavum) each represent less than 1% of all the TB cases.[5]

Over the last years, the increase in the cases of human immunodeficiency virus (HIV) has been accompanied by an increase in extrapulmonary manifestations of TB at the level of the head and neck. Up to 25% of the cases of positive HIV in this area of the body occur without pulmonary involvement or wasting syndrome.[2] Yang et al.[6] reported nearly 50% of cases that presented co-infection with extrapulmonary HIV+TB, and this percentage could increase up to 80% in patients with severe immunosuppression. Other factors to consider are the great migrations, the appearance of resistant strains, the increase in poverty and the greater number of patients immunocompromised by other diseases or treatments, which have also accompanied this increase in incidence in the developed countries.

That is why the objective of this study was to describe the cases of head and neck TB referred to the Ear, Nose, and Throat (ENT) Service in a tertiary hospital in the community of Galicia (Spain) over a 6-year period, and to compare these results with those published in the international literature.

Materials and Methods

This was a retrospective analysis of the patients that came to the ENT consultation at our tertiary hospital in the autonomous community of Galicia (Spain) for head and neck symptoms and were diagnosed with TB. The period covered patients seen from December 2007 through December 2013. We identified the cases thanks to a computer search of the registers in our service using the International Classification of Diseases (ICD)-9 and ICD-10 codes. The Ethics Committee at our centre approved this study.

The revision of the clinical histories provided the demographic data (age, nationality, and sex), clinical information, signs, and symptoms at the time of consultation, way disease presented, information on diagnostic tests, *etc.*

Statistical analysis was carried out using the program SPSS for Windows, version 20.0 (SPSS, Inc., IL, USA). Quantitative study variables were expressed as mean±standard deviation and the results were expressed as total plus percentage.

Results

The total patients included were 73, with 41 (56.2%) males and 32 (43.8%) females (M/F ratio=1.28) and a mean age of 39.4 years (±26.5 years; minimum: 1/maximum 88). As for the anatomical location of infection, 53 cases (72.6%) corresponded to cervical lymphadenopathy (Figs. 1 and 2), 11 (15%) to laryngeal TB (10 vocal fold cases and 1 case that involved exclusively the epiglottis), 3 (4.1%) to hypopharyngeal gland TB and 1 case (1.4%) to TB in each of the following respective locations: ear, tongue, submandibular gland, parotid, oropharynx, and nose (Table 1). Another 14 (19.2%) patients were HIV positive, 10 (13.7%) patients presented a history of contact with relatives that had suffered from pulmonary TB and 2 (2.73%) patients were foreigners from developing countries (Table 1).

Table 1 Topographical Location.

Location	Cases	Percentage (%)
Cervical lymph node TB	53	72.6
Larynx	11	15
Hypopharynx	3	4.1
Ear	1	1.4
Tongue	1	1.4
Submandibular gland	1	1.4
Parotid gland	1	1.4
Nasal	1	1.4
Oropharynx	1	1.4
Total	73	100

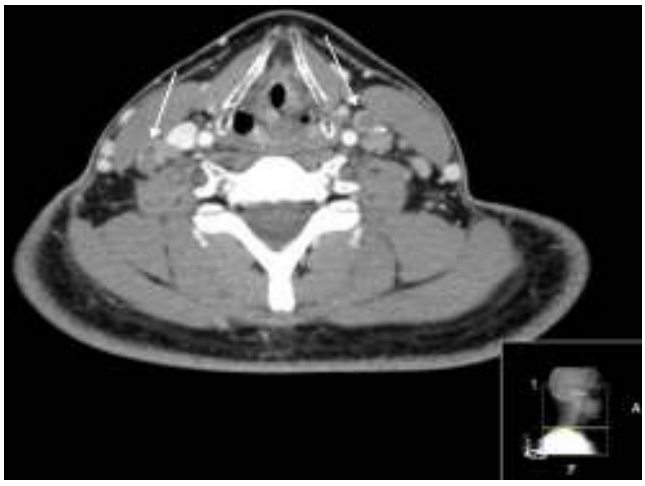

Figure 1 Laterocervical adenopathies (white arrows) in a patient that consulted because of palpable bilateral masses in the cervical lymph node area.

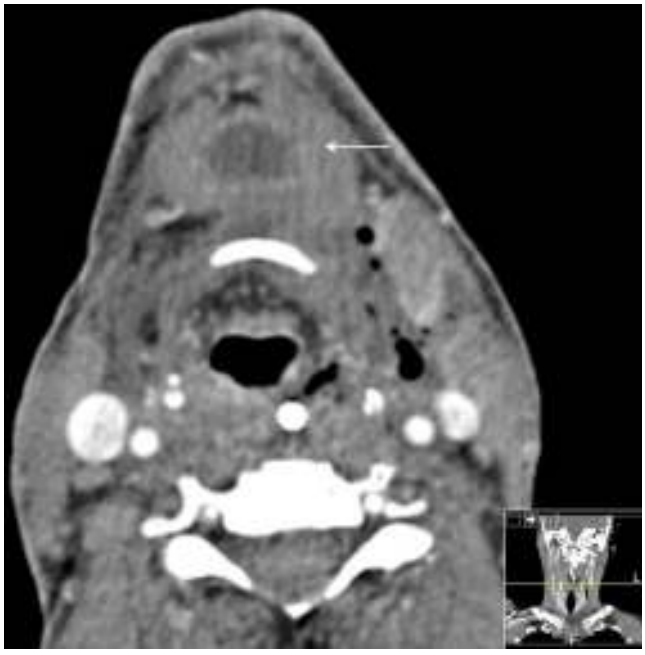

Figure 2 Pre-thyroid adenopathy (white arrow) in a patient with a palpable mass at the anterior cervical lymph node level.

As for Mantoux tuberculin skin test results, 47 (64.4%) patients presented a positive result with a mean diameter of 14.8 cm; the rest of the patients had negative results. A total of 42 (57.5%) patients presented a positive Lowenstëin media result, 46 (63%) of the cases obtained a positive acid-fast bacilli (AFB) smear using the Ziehl-Neelsen staining technique. Polymerase chain reaction (PCR) for detecting *M. tuberculosis* was used in 53 (69.8%) of the cases. At first it was used as a means of confirmation when the result was negative (elevated clinical suspicion) or when there were diagnostic doubts using the classic means. Later on, PCR was routinely used for diagnosis, yielding positive results in 47 of these (92.15%) (Table 2). In all, 9 (12.3%) patients presented some type of complication; the most frequent was miliary TB, present in 5 cases (5.8%) (Table 3). One (1.4%) patient died from miliary TB complications.

With respect to the symptoms, 57 (78.1%) patients presented evening fever; 35 (47.9%) presented asthenia; 22 (30.1%), weight loss; and 7 (9.6%), odynophagia (3 cases with hypopharyngeal involvement, 1 case of oropharyngeal involvement, 1 of laryngeal, 1 of the epiglottis and 1 case with tongue involvement). There were 12 (16.4%) patients that came to the hospital for dysphagia (3 cases with hypopharyngeal involvement, 1 case of oropharyngeal involvement, 6 cases with laryngeal TB, 1 in the epiglottis and 1 in the base of the tongue), while 11 (15.1%) patients came to the hospital due to dysphonia (10 cases con laryngeal TB and 1 case with TB in the epiglottis).

Clinical findings differed according to the area affected. All of the patients con tuberculous cervical adenitis (53=72.6% of the total) consulted for palpable masses. Of the 11 cases of laryngeal TB, 9 (12.3%) presented oedematous, rough and vegetative lesions, while 2 (2.8%) presented ulcerous, vegetative lesions that affected both vocal folds. In the case of TB of the tongue, a vegetative lesion with whitish stippling sticking out over the tongue border could be seen. In the patient with nasal TB, an erythematous, a polypoid-appearing lesion occupied the entire nasal fossa and curved the septum towards the contralateral fossa. The case of TB of the ear showed a subtotal tympanic membrane perforation with lesions of a polypoid appearance in the middle ear.

Fine needle aspiration (FNA) cytology was performed in 44 cases (60.4%). In 29 of these (65% of the FNA performed),

Table 2 Polymerase Chain Reaction (PCR) Results Related to Head and Neck TB Location.

Location	Positive	Negative	Not performed	Total PCRs performed	% PCRs (+) performed
Tuberculous lymphadenitis	35	2	16	37	94.59
Larynx	7	1	3	8	87.5
Hypopharynx	2	0	1	2	100
Tongue	1	0	0	1	100
Parotid gland	1	0	0	1	100
Oropharynx	0	0	1	0	0
Nose	1	0	0	1	100
Submandibular gland	0	0	1	0	0
Ear	0	1	0	1	0
Total	47	4	22	51	92.15

Table 3 TB Complications.

Complication	Cases	%
Miliary TB	5	6.8
Mediastinal-oesophageal fistula	1	1.4
Mastoiditis	1	1.4
Scrofula	1	1.4
Pott's disease	1	1.4
Total	9	12.3

the results were suggestive of TB; and in 14 (19.2%), the sample was insufficient. In the final case (1.4%), the anatomopathological result was lymphoma, which was ruled out once the adenopathy was biopsied by cervicotomy.

The radiological studies performed in most of the patients were chest X-rays (CXR), echography, and computerised tomography (CT) scans of the head and neck. A total of 25 (34.2%) patients presented a CXR suggestive of TB (Table 4), while in 48 (65.8%) the CXR was anodyne or the findings were not suggestive of TB. Echography was used in 37 (69.8%) of the cases of cervical TB and the findings were suggestive of lymph node TB in 13 (35.1%) of the patients.

Table 4 Location by Chest Radiography Suggestive or Non-suggestive of Pulmonary Tuberculosis.

Location	Suggestive chest radiography	Non-suggestive chest radiography	%
Cervical lymph node TB	10	43	18.8
Larynx	10	1	90.9
Ear	0	1	0
Hypopharynx	3	0	100
Tongue	0	1	0
Submandibular gland	1	0	100
Parotid gland	0	1	0
Oropharynx	1	0	100
Nasal	0	1	0
Total	25	48	34.2

Lastly, tomography was used in 58 (79.4%) of the cases, being suggestive in 27 (37%) of these.

All the patients were treated with anti-TB chemotherapy, although biopsy for histological study was required for 16 (21.9%) of them. The drugs used were isoniazid, rifampicin, pyrazinamide, and ethambutol. Only 4 (5.5%) patients presented alterations in hepatic function markers during the drug treatment.

Discussion

With respect to sex, several studies report a disease dominance in males, with a ratio of 1.8:1.[7,8] This ratio was a bit smaller in our study (1.28:1), with the male population being slightly more affected.

As far as reaching a diagnosis, an in-depth history, a detailed physical examination and a chest CXR to rule out lung involvement are essential.[9] Along these lines, we have an arsenal of tests that can help to reach a diagnosis. One of these is FNA, backed by several studies that attribute it a sensitivity of up to 80%.[10,11] However, other authors report lower sensitivities. Memish et al.[12] found sensitivity of 46%, while Mcallister et al.[13] reported sensitivity of 53%. Our results reflect sensitivity that falls in the middle between those of these 2 teams; in 65% of the cases in which an FNA was performed, a TB diagnosis was possible. It is important to emphasise that in their study Mcallister et al. did not manage to demonstrate greater diagnostic profitability by using sonography to locate suspicious adenopathy. In that study, 50% of the adenopathies located using echography were positive, while 54% the adenopathies located without echography were positive; however, this result was unreliable as there were only 26 patients in which adenopathies were located using echography.[14]

As for imaging test, in the cases of tuberculous involvement at the level of the head and neck and depending on location, echography, CT scans, and magnetic resonance images were useful. The most frequent finding was a hypodense centre with peripheral enhancement when using contrast.[15]

In turn, stains can be used in studying histological samples through specific techniques. These are especially useful if there is a suspicion of granulomas in the sample, as it is possible to detect acid-alcohol-resistant bacilli. However, the PCR is currently a highly useful test in cases where there are

still doubts. In aspirated samples of cervical adenopathies, the results generally yield sensibility of 41%–75% and specificity of nearly 97.3%–100%.[16,17] In our study, it was possible to confirm the diagnosis of extrapulmonary TB in 92.15% if all the patients, and up to 94.59% of the adenopathy aspirates. However, the remaining 7.85% presented a negative result (2 cases of adenopathy aspirate, 1 larynx biopsy and 1 ear biopsy), which were considered false negatives due to how suggestive the clinical picture was, the positivity of the rest of the tests and the overall response to treatment. Individually, it should be remember that the PCR specificity in tissue samples from the larynx and ear are not totally clear and that, during preparation of samples for study, there are possible errors that may occur, affecting the final result.

It is important to mention new tests, recently introduced to improve diagnosis of tuberculous infection, whose objective is detecting *in vitro* production of interferon-gamma (IFN-γ) against *M. tuberculosis*. These tests are known as interferon-gamma release assays (IGRA). One of these assays, sold as the QuantiFERON-TB-Gold in Tube® (QFT-IT) test (Cellestis Ltd.; Carnegie, Victoria, Australia), measures the specific antigen production of IFN-γ by the circulating T-cells in whole blood, using an enzyme-linked immunosorbent assay (ELISA). Another is the T-SPOT.TB® (Oxford Immunotec, Oxford, United Kingdom), which measures the IFN-γ producing T-cells using the enzyme-linked immunospot (Elispot) technique. These tests achieve greater specificity on diagnosis.[18]

With respect to the clinical signs and symptoms of head and neck TB, tuberculous lymphadenitis is the main type reported in the literature. It represents approximately 95% of the cases, and is present in more than 25% of patients affected by TB.[9] The results we obtained in this study were similar (although slightly less), with 72.6% of the patients presenting lymph gland involvement. This may be because not all tuberculous patients that come to our centre are referred for specialised ENT evaluation. In addition, as this was a retrospective study, we included only the patients referred to our department for suspicious adenopathies that were then diagnosed as having tuberculous lymphadenitis.

According to our results and coinciding with current literature, laryngeal involvement is the next most frequent location after cervical lymphadenitis. In fact, until the beginnings of the 1900s, it was the most prevalent disease of the larynx.[19] Based on autopsy studies carried out on patients with pulmonary TB, up to 48% of the cadavers presented involvement at the laryngeal level. Currently, after the introduction of anti-TB chemotherapy, the incidence of this location has dropped dramatically, with the reported worldwide incidence being close to 0.8%–1%.[18] However, despite being rare, the importance of laryngeal involvement lies in differential diagnosis with malignant diseases at this level; consequently, it is necessary to biopsy the lesion for study, to avoid complications from a delayed diagnosis.[20]

Pharyngeal involvement is in third place for frequency of locations, again based on the data available in the literature. In our case series, hypopharyngeal involvement was the most common, with 3 (4.1%) cases; this was followed by oropharyngeal location, with a single (1.4%) case. When there is pharyngeal involvement, the literature indicates that it is frequently associated with pulmonary involvement, which was the case in 100% of the cases in our study. As for the type of lesions found, the lesions were ulcerous and painful in 3 of the cases and an ulcerated, erythematous-type lesion in 1. With respect to symptoms, these patients generally present with dysphagia and, less frequently, odynophagia.[21,22]

The other locations involved in our series corresponded to the oral cavity. This could present as primary TB or be a result of extra-thoracic dissemination from a primary pulmonary focus through contaminated sputum or haematogenous dissemination.[23,24] The tongue is usually the structure most often involved at this level.[25] Specifically, the lateral side of the tongue is the most probable site of a lesion.[26]

Ear TB is also a rare form, representing less than 1% of the chronic ear diseases.[27] It can present as a non-painful chronic otorrhea, with a course of several months; it can be accompanied by polypoid formations[27] or involve facial paralysis complications.[28] Cutaneous TB has also been described. This usually manifests as an irregularly shaped, friable skin plaque.[29]

Salivary gland involvement is rare. The method of dissemination seems to be associated with the presence of dental or oral cavity lesions; contamination is generally through contiguity or lymphatic-blood bacterium migration, normally manifesting in a period of immunosuppression.[30] If it is a case of primary TB at this level, the presentation is normally in the form of suppurative sialadenitis or simulating a chronic tumoral lesion. Secondary forms are generally associated with systemic TB, most frequently pulmonary.[31]

There are few published cases at nose level. These usually manifest as nasal obstruction, accompanied by chronic rhinorrhoea. Lesions at this level are generally of a granulomatous or ulcerative type.[32] During the physical examination, they are often confused with neoplastic lesions and, in more advanced states, with Wegener's granulomatosis, which is why early diagnosis is important.[27] Tuberculous infection is also possible in the nasal sinuses, where it can cause bone erosion. If there is local progression, these cases may become complicated with episodes of meningitis, pituitary invasion or skin invasion.[27,33–35]

The drug treatment currently recommended for extrapulmonary TB is the plan based on the combination of 4 drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months, and then isoniazid and rifampicin for another 4 months.[36]

Conclusion

Despite being a rare clinical picture, the similarity of TB with diseases that have a poor prognosis and the difficulty involved in TB diagnosis make it necessary to consider TB when examining patients with granulomatous or ulcerative lesions in the ENT area. As for our results, the incidence of TB according to its ENT location is similar to that reported in the literature. It is important to point out the use of PCR in our study and the advantages that its application represents for diagnosis.

Conflict of Interests

The authors have no conflicts of interest to declare.

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