A rare case of concomitant tuberculosis of the nose, paranasal sinuses and larynx: clinical, histological and immunohistochemical aspects. A case report

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Abstract
Extrapulmonary tuberculosis is a rare condition determined by Mycobacterium tuberculosis. It can affect any organ, and has a higher incidence with the increase of HIV infection, or in countries with high pulmonary tuberculosis. Diagnosis is difficult, mostly because of non-specific symptoms and a low rate of presentation for medical consult when symptoms do occur. Complete diagnosis is usually set by histological, immunohistochemical examinations, and also with Polymerase Chain Reaction (PCR) in selected cases. The authors present a case of concomitant tuberculosis of the nose, paranasal sinuses and subglottic larynx, without primary involvement of the lungs. The diagnosis was imposed by histological examination and immunostaining of probes obtained in surgery. The treatment was surgical debridement followed by specific antituberculosis medication.

Keywords: extrapulmonary tuberculosis, maxillary sinus, subglottic larynx.

Introduction
Extrapulmonary tuberculosis is a rare encounter nowadays. It can occur as a primary disease or secondary to pulmonary tuberculosis or disseminated tuberculosis. Virtually any organ can be involved. The most common sites are lymph nodes, followed by pleural effusion [1].

Tuberculosis of the sinuses is rare even in countries with high incidence of this disease. Mycobacterium tuberculosis most frequently involves the lungs. Although the incidence of extrapulmonary tuberculosis has increased due to association with human immunodeficiency virus (HIV) [2] only rare cases with primary sinuses and nasopharynx involvement were described [3].

Tuberculosis of the larynx is a rare entity, its incidence being of less than 1% of tuberculosis cases [4, 5]. It was usually described following pulmonary tuberculosis, but nowadays, the pattern has changed, and most patients present with no history of pulmonary disease [6–8]. Laryngeal tuberculosis has a male predominance of approximately 3:1 according to most authors [9]. In laryngeal tuberculosis, most commonly, the vocal folds are affected, followed by the false vocal folds. The subglottic region is only affected in 10–15% of cases [4, 10].

These atypical involvements appear by blood or lymphatics spread or by direct local extension. The evolution is often slow, with low-grade symptoms.

Diagnosis of extrapulmonary tuberculosis is difficult and is sometimes based on biopsy of the lesion, followed by histological and immunohistochemical examinations. Differential diagnosis is frequently challenging, and is often made with other granulomatous lesions or with neoplastic lesion, due to the various types of lesions, which can appear.

The aim of this paper is to present a very rare case of extra pulmonary tuberculosis affecting the nose and paranasal sinuses, as well as the larynx. We discuss the case presentation, clinical, radiological and especially the histological and immunohistochemical diagnosis, and also the treatment for this disease.

Case report
A 42-year-old patient presented in our clinic complaining of chronic nasal obstruction, purulent rhinorrhea and repetitive minor epistaxis, dysphonia and trouble breathing. The patient had a good socio-economic status and no apparent contact with tuberculosis patients. He underwent prior surgery for a septal deviation, a couple of months before admission.
Nasal endoscopy revealed a large perforation of the nasal septum, with evident crusting on its margins, bilateral purulent secretions in the middle meatus and crusting on both inferior and middle nasal conchae, pale aspect of the nasal mucosa. Laryngeal endoscopy showed a circular lesion, apparently well delimited, which determined partial stenosis of the subglottic region, mobile vocal cords, with no apparent structural lesions.

Chest X-ray was normal, without nodular lesions or pulmonary infiltrates. Acid-fast bacilli from repeated sputum and nasal exudates were negative. Special stains for fungi were negative. Also, cytoplasmic antineutrophil cytoplasmic antibodies (cANCA), perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), human immunodeficiency virus (HIV) and hepatitis markers were negative, normal urine exam. Tuberculin intradermal reaction came positive (16 mm), revealing a positive infection, but in a country with high incidence of tuberculosis this test only orientates the diagnosis. Contrast-enhanced computed-tomography was performed for both sinus and cervical regions (Figure 1).

Figure 1 – Contrast-enhanced computed-tomography of the paranasal sinuses and of the larynx, showing opacity of the ethmoid sinuses with destruction of intercellular bony septa and stenosis of the subglottic larynx.

The patient underwent initial therapy with antibiotics 500 mg Ciprofloxacin twice a day, and 100 mg Hydrocortisone a day, with no improvement of symptoms. Surgical treatment was decided. Tracheostomy was the first step in surgery, due to the obvious stenosis in the subglottic region, followed by intubation on the tracheal stoma. Under general anesthesia, the patient underwent endoscopic endo-nasal bilateral ethmoidectomy, middle antrostomy and debridement of nasal crusting. The same surgery was followed by trans-oral endoscopic examination of the larynx. Biopsies were performed from both nasal cavities and laryngeal tumor and were sent to the pathology lab for further examination. All tissue samples were immediately immersed in 10% buffered formalin and then routinely processed (24 hours fixation, one hour wash, dehydration in three baths with 96% ethanol for 24 hours, then two one-hour baths of absolute ethanol, then clearing with toluene for one hour at 58°C and, finally, three one-hour baths of paraffin at 58°C). The specimens were paraffin embedded and sectioned in 3 μm slices. The slides were stained with Hematoxylin–Eosin (HE). Microscopic examination revealed multiple confluent granulomas, centered by a granular, bright eosinophilic mass with hematoxylinophilic nuclear dust. In periphery there were large sheets composed of large, epithelioid cells, with peripheral, vesicular nuclei with clumped chromatin, visible nucleoli and large amounts of eosinophilic cytoplasm (Figure 2).

Figure 2 – Sheets of epithelioid histiocytes with large, vesicular, yet monomorphous nuclei, admixed with small, reactive lymphocytes and scattered giant Langhans cells (HE staining, 200×).

Admixed there were frequent giant, multinucleated cells with abundant cytoplasm and dark, small nuclei disposed in horseshoe-shaped pattern under the plasma membrane and numerous small, reactive lymphocytes. Also, there were identified quite frequent eosinophil granulocytes and rare neutrophil granulocytes (Figure 3).

Figure 3 – Syncytial conglomerates of epithelioid histiocytes and a couple of characteristic Langhans cells in the periphery of a caseous necrosis mass (HE staining, 400×).

Further special stains were ordered: Periodic Acid–Schiff (PAS) that was positive in necrotic areas, but did not revealed fungal elements or intracellular bacilli; Gomori silver impregnation that highlighted the persistence of reticulin and collagen fibers in the necrosis areas and Ziehl–Neelsen staining that did not identify any acid-fast organisms. For further confirmation, some immunohistochemical tests were performed: CD68 was positive in all histiocytes and, also, in giant cells, CD3 was positive in numerous T-cells intermixed with histiocytes and also placed at the periphery of granulomas, CD20 identified scarce B-cells in the inflammatory infiltrate, AE1/AE3 did not revealed epithelial cells in lesional areas and Ki67 was positive in very few macrophages and in frequent lymphocytes (Figure 4).
The histological and immunohistochemical diagnosis of chronic tuberculous granulomatous inflammation was established from both the nasal cavity and the subglottic region. The patient received antituberculosis treatment with good outcome.

Discussion

Extrapulmonary tuberculosis is rare in most developed countries, and appears as a primary disease especially in immunocompromised patients, or secondary to pulmonary tuberculosis. Modern literature has rare references regarding these types of tuberculosis, but nowadays these affects are more commonly encountered due to frequent association with HIV infection and AIDS (acquired immunodeficiency syndrome) [2].

Primary sinus tuberculosis is a rare entity. Few cases of maxillary sinus tuberculosis were reported. Tuberculosis of the maxillary sinus is usually associated and secondary to another localization of tuberculosis, especially in the lungs [11]. This disease often occurs in males [12]. Due to mild and non-specific symptoms, the diagnosis is often delayed. Common presentation is with discharging sinus and non-healing local lesions [13]. If left untreated it can progress to loss of visual acuity [13], spreading to larynx or lungs, brain abscess [14]. One case report described an association of tuberculosis and malignancy in the maxillary sinus [15]. CT-scan of the paranasal sinuses shows sclerotic or lytic lesion [16]. In our case, the patient presented with chronic nasal obstruction, crusting and purulent rhinorrhea, followed by repeated epistaxis from both nasal fossae. Clinical examination showed non-specific lesions of the nasal mucosa and sinuses, which had a pale aspect, secretions and crusts, as well as a large perforation of the nasal septum. Also, a tendency for bleeding after instrumental palpation was observed. This was also encountered by other authors in patients with tuberculosis of the sinuses [17].

The contrast-enhanced computed-tomography exam performed showed the large perforation f the septum, and opacity of all the sinuses (ethmoid, frontal, maxillary and sphenoid) with clear destruction of bony septa, especially in the ethmoid.

Laryngeal tuberculosis is also a rare clinical encounter and usually appears after contamination from primary tuberculosis of the lungs. Primary tuberculosis of the larynx is rare, and occurs without evidence of pulmonary disease, or disease of other organs [4]. Common presenting symptoms of laryngeal tuberculosis are dysphonia and odynophagia, others including productive cough and throat pain, fever, night sweats and weight loss [4, 6, 18]. Regarding clinical findings, this form of tuberculosis usually affects the supraglottic larynx, especially the vocal folds, false vocal folds, epiglottis, arytenoids and aryepiglottic folds, with rare encounters of posterior commissure or subglottic region [4, 10]. It has multiple appearances, which vary among whitish ulcerative lesions to ulcerating mass lesions [4, 19]. In the case presented by us, the patient had minor dysphonia and trouble breathing, and the lesion was only in the subglottic larynx. It presented as a round, circumferential, well-differentiated lesion determining stenosis of the subglottic region. The contrast-enhanced computed tomography showed the same aspect.

Although it is rare to encounter extrapulmonary tuberculosis, it is even more rare for it to affect both the nose and paranasal sinuses as well as the larynx. Common differential diagnosis of such lesions includes midline granulomas such as Wegener’s granulomatosis, leprosy, sarcoidosis, granulomatous syphilis and other diseases such as rhinoscleroma and Rhinosporidium seeberi [17].

Diagnosis of extrapulmonary tuberculosis is difficult due to non-specific clinical presentation, and is challenging for both clinicians and microbiologists [20, 21]. Many factors contribute to make the diagnosis difficult, such as paucibacillary nature of specimens and lack of adequate sample amounts or volumes [22]. Moreover, usually invasive procedures are necessary to obtain specimens for histological examination [23]. Due to these factors, histological, and sometimes immunohistochemical examinations are necessary for diagnosis confirmation.

In our case, the diagnosis of tuberculous granulomatous inflammation was imposed by the presence of large, confluent granulomas with central caseous necrosis, epithelioid histiocytes and multinuclear giant Langhans cells. We excluded any tumoral lesion due to no epithelial proliferation identified on usual, special and immunohistochemical stains; no lymphoid proliferation since the inflammatory infiltrate was polymorphous including activated T-cells, B-cells, and granulocytes. The most important differential diagnosis was made with other granulomatous inflammatory lesions. Sarcoidosis was excluded because the lesion was made predominant out of confluent granulomas with large areas of typical caseous necrosis. A mycotic inflammation was ruled out since PAS staining failed to identify spores and hyphae. The specific appearance and lack of intracellular bacilli ruled out an infection with Mycobacterium avium-intracellulare.

The presence of granulocytes in this chronic lesion was atypical, but probably due to the superficial localization of lesions in the nose and larynx where they could easily be superinfected with common bacterial strains, especially since they were ulcerated lesions.

The treatment was surgical excision of the lesions and anti-tuberculosis treatment with favorable clinical outcome.

Conclusions

In this paper, the authors present a rare case of extrapulmonary tuberculosis affecting the nose, paranasal sinuses, and the larynx. Extrapulmonary tuberculosis is...
a rare condition, and it is even more rare to affect both these organs. The diagnosis was difficult and histological and immunohistochemical stains were necessary. Treatment in this case was surgical excision of the lesions and long-term anti-tuberculosis treatment. Even tough extrapulmonary tuberculosis is rare, it should be considered as a diagnosis in cases with non-specific granulomatous lesions in the head and neck.

Conflict of interests
The authors declare that they have no conflict of interests.

References

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