

An atypical manifestation of lymph node tuberculosis: A case report

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Abstract

Tuberculosis is a chronic granulomatous infection caused by *Mycobacterium tuberculosis*. Since the 80's, new cases have been increasing especially in developed countries because of spreading of HIV-infection, immunodeficiency and immigration phenomenon. Cervical lymphadenitis is the most frequent localization of extrapulmonary tuberculosis. Clinical manifestations consist in a slow growth and painless swelling of a single or multiple neck nodes, generally unilateral, with rare manifestations of fistulization and of systemic symptoms. Diagnosis is performed by fine-needle aspiration cytology (FNAC) or excisional biopsy integrated by Ziehl-Neelsen stain and Mycobacteria culture. A 57-year-old male patient affected by a right-side large laterocervical swelling. The patient referred that almost one month before he noted the onset of the lesion sizing about 1 cm, so he treated it with antibiotic association of amoxicillin and clavulanate acid without any improvement. The lesion quickly doubled its size, became painful and hyperemic the skin above it. Because of the clinical worsening, the patient undergone to neck ultrasonography that showed a neck mass sizing about 50×25 mm. He began a new antibiotic therapy with Ceftriaxone intra muscle, with no modifications of the lesion. Few days later his clinical conditions drastically got worse - increasing pain and skin fistulization. So he practiced a magnetic resonance imaging of the neck that showed a massive suppurated lesion of the neck. The patient was hospital-

ized in our Otolaryngology Unit where he began a diagnostic *iter* in order to clarify the nature of the lesion and differentiate between neoplastic/lymphoproliferative lesion and an infective one. After a biopsy of the lesion, the hysthopatologic examination reported the presence of dense mononuclear cell infiltrate surrounding a set of Langerhans cells, so our diagnostic suspect was addressed to extrapulmonary tuberculosis.

The authors report a case of a healthy man without risk factors for tuberculosis infection, come to our attention with a large and aggressive unilateral tubercular cervical lymphadenitis, skin fistulization and no systemic symptoms. To make diagnosis of tubercular lymphadenitis, we sustain that biopsy is still the gold standard if FNAC is in doubt.

Introduction

Tuberculosis (TBC) is a chronic granulomatous infection principally caused by *Mycobacterium tuberculosis*.¹ During the last five decades the immigrated people, the diffusion of HIV infection, raising-up of multidrug resistant mycobacteria and drug addiction have been resulting in spreading of new cases of pulmonary and extrapulmonary tuberculosis in low-incidence countries.²

Recent studies indicate that extrapulmonary TBC represents approximately 25% of overall tubercular morbidity.³

According to the World Health Organization data report in 2017, 10 millions of people were affected by TBC (higher incidence in Asia and Africa),⁴ and 1,3 millions of patients died of it. In 2006 in the United States the 57% of TBC new cases was diagnosed among foreigners and this rate increased of 9.9 times in 2007.⁵ In Italy TBC incidence was 3.8/100.000 among Italians compared to 52.1/100.000 among foreigners in 2008.⁶

The authors report a case of a middle age man with an aggressive cervical nodal swelling without lung lesions at X-ray of chest and without typical risk factors for TBC infection in order to make a few comments about epidemiology, clinical signs, diagnosis and therapy.

Case Report

A 57-year-old patient affected by a right-side large laterocervical swelling underwent to our attention in July 2016. The patient referred that almost one month

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before he had noted the onset of the lesion sizing about 1 cm, so he treated it with antibiotic association of amoxicillin and clavulanate acid without any improvement. The lesion quickly doubled its size, became painful and hyperemic the skin above it. Because of the clinical worsening, the patient undergone to neck ultrasonography that showed a neck mass sizing about 50×25 mm. He began a new antibiotic therapy with Ceftriaxone intra muscle, with no modifications of the lesion. Few days later his clinical conditions drastically got worse - increasing pain and skin fistulization. So he practiced a magnetic resonance imaging (MRI) of the neck that showed a massive suppurated lesion of the neck.

The patient was hospitalized in our Otolaryngology Unit where he began a diagnostic *iter* in order to clarify the nature of the lesion and differentiate between neoplastic/lymphoproliferative lesion and an infective one. The clinical examination

showed a new formation below the right corner of the jaw, measuring about six centimeters in its maximum diameter, with skin fistulization and surrounded by hyperemic skin (Figure 1).

We began an antibiotic therapy with ampicillin-sulbactam and Gentamicin after taking a sample of the purulent material by skin fistulization for bacterial and mycobacterial culture. Blood analysis did not show signs of immunodeficiency, and HIV test was negative.

He then performed: i) a chest X-ray resulting negative for lung lesions; ii) a neck and thoracic computed tomography (CT) that did not add other information to the MRI performed before (Figure 2); iii) a fine-needle aspiration cytology (FNAC) of the lesion, with poor results because of the excess of necrotic- inflammatory material with several histiocytes in macrophagic activity.

Because of negativity both of the FNAC and of the bacterial culture, we submit the patient to a PET-CT and to a biopsy of the lesion in order to exclude or confirm our strong suspect of neoplasia. PET-CT showed a high glucidic metabolism in the lesion area (SUV max 14.4) while histopathologic examination reported the presence of dense mononuclear cell infiltrate surrounding a set of Langerhans cells, so our diagnostic suspect was addressed to extrapulmonary tuberculosis.

The Mantoux test, the T-SPOT TB test the polymerase chain reaction (PCR) and the culture of necrotic material taken during incisional biopsy confirmed diagnosis of tubercular lesion. Our patient was treated with antitubercular polychemotherapy, according to the following scheme: two months of combination therapy with four drugs (isoniazid: 5 mg/kg/day, rifampicin: 10 mg/kg/day, ethambutol: 15-20 mg/kg/day, and pyrazinamide: 20-25mg/kg/day), and subsequent four months of therapy with two drugs (isoniazid and rifampicin at the same dose). At the end of therapy the lesion was disappeared (Figure 3). Patient agree and gave his consensus for publication of the data.

Discussion

TBC is one of the major cause of mortality worldwide, especially in developing countries, but since spreading of HIV infection and immigration phenomenon TBC cases have been increasing in developed countries.

Tuberculous cervical lymphadenitis is the most common form of extrapulmonary



Figure 1. Tubercular lesion of the neck with skin fistulization and inflammation.

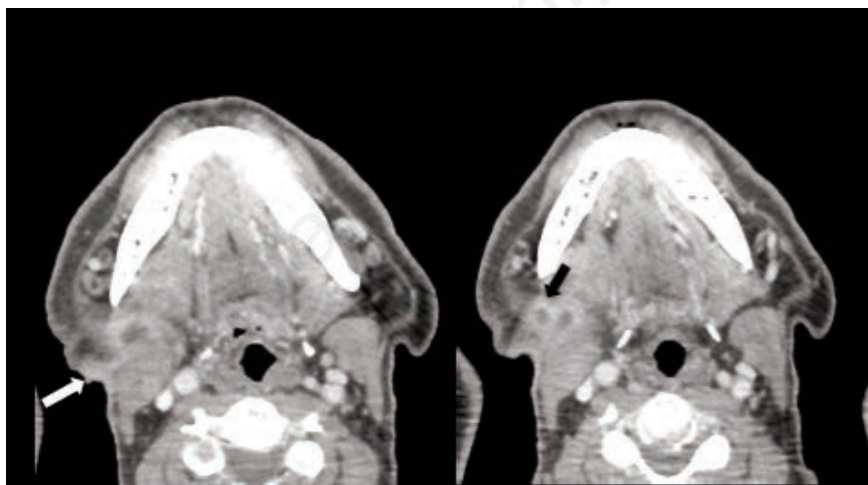


Figure 2. Tubercular cervical lymphadenitis: lateral neck mass with skin fistulization (white arrow on the left side) and colliquation (black arrow on the right side).



Figure 3. Clinical picture at the end of the therapy.

tuberculosis (60-90%).⁷ In patients affected by HIV almost half of cervical node swelling are caused by TBC.⁸ It is more common in females and younger patients, with a peak between 20 and 40 years of age, in contrast to pulmonary tuberculosis that is more frequent in the elderly ones.⁸ The patient object of our study had not any contact with immigrated people, he was HIV free and he didn't suffer of any others comorbidities which may cause immunodeficiency.

In literature, typical clinical manifestations of cervical lymphadenitis are described as a non-tender, painless, small to moderate size (rarely above 2 cm), fixed mass on the neck. Systemic symptoms such as fever, weight loss, fatigue and night sweats are commonly seen in patients also affected by HIV. The majority of these patients had unilateral involvement of the neck with a single group of lymphnodes mostly located in the posterior cervical or supraclavicular region.⁸⁻¹⁰ The disease expressions have been considerably changing during the last few years. At this regard, the classical picture of lymphadenitis with multiple localizations and rapid evolution towards colliquation and fistulization, is actually extremely rare.¹¹ In contrast with these usual clinical characteristics of a tubercular lesion, our patient showed a unilateral laterocervical mass that rapidly and aggressively grew-up after a first asymptomatic phase, and it evolved to skin fistulizations without systemic symptoms. Once suspected extrapulmonary TBC, we reached diagnosis by performing a Mantoux test, a T-Spot TB assay, an incisional biopsy with microscopic research of *M. tuberculosis*, PCR, cultural exam and histopathological examination. The Mantoux test shows delayed type hypersensitivity reactions against mycobacterial antigens and it results positive in about 75% patients with lymphnodal TBC, while it is often non-reactive in patients with Non-Tubercular *Mycobacteria* lymphadenitis. It is only a sign of contact with the MTB. The PCR with specific primers allows rapid identification of the mycobacteria's species and detection of drug resistance.⁸ The T-Spot TB assay searches for T-cells producing INF- γ , in order to integrate the Mantoux Test result. Diagnosis of TBC is made when Ziehl-Neelsen (ZN) staining and PCR are positive. Results by these methods are available in one-two days. When positive they allow to begin therapy without waiting cultural research and typing of the *Mycobacteria* that is available on average after six weeks with Lowenstein-Jensen solid medium and Bactec-*Mycobacterium* Growth Indicator Tube liquid culture.

Anyway, cultural research is the gold standard diagnostic method and it is mandatory in order to test mycobacteria's antibiotic resistance and sensitivity.

Facing an extrapulmonary tuberculous lymphadenitis, the histopathology examination on excisional biopsy was the gold standard in the past. Identification of caseating granulomatous inflammation with Langhans giant cells, surrounded by epithelioid cell aggregates, supports the diagnosis of TB.¹² Nowadays it has been replaced by FNAC that is a diagnostic technique safer than the excisional biopsy.⁸ Incisional biopsy is not recommended because it is associated with sinus tract and fistula formation.¹³ FNAC has excellent sensitivity and specificity for the diagnosis of mycobacterial lymphadenitis and is recommended to be used as the initial diagnostic test in suspected cases. Aspirated material is always subjected to ZN stain for acid fast bacilli (AFB). Sensitivity and specificity of AFB on aspirate smear from lymphnodes was found to be 76.47% and 100% respectively.¹⁴

In our case, we performed a FNAC but it wasn't diriment for diagnosis of lymphnodal pathology. This is in accord with a previous study conducted by Ricciardiello *et al.*,¹⁵ where FNAC wasn't useful in 58.3% of cases, and with another case series by Penfold *et al.*⁹ where diagnosis was reached by excisional biopsy in the 65% of case. We think that excisional biopsy is still preferred, when FNAC is not clear, because it makes available a larger amount of tissue for histopathological and bacteriological examination and it is the most reliable method to not delay the final diagnosis, and to differentiate many other conditions such as adenitis due to other mycobacteria, bacterial adenitis, fungal disease, toxoplasmosis, sarcoidosis, cat-scratch disease, cystic hygroma, nonspecific hyperplasia, and primary or metastatic neoplasms. In our case we performed an incisional biopsy because the dimension of the lesion makes surgery too unsafety and the CT study didn't show a clear dissection plane from neurovascular bundle of the neck.

In our case the chest X-ray was negative, according to the study conducted by Jha *et al.* and Magsi *et al.* which found associated lung lesions only in 16% and 7.5% of cases.^{16,17}

On CT images lymphnodes show as homogeneous lesion in early stages of the pathology and only later demonstrate central necrosis. This one on MRI T1 and T2 weighted images appears respectively as an area of low -T1-and high signal intensity - T2- in the center of the mass with peripheral rim enhancement such as with CT.

Tuberculosis lesions appear on CT as conglomerated nodal masses with central hyperdensity. Images can show thick irregular rim of contrast enhancement, dermal and subcutaneous manifestations of inflammation, thickening of the overlying skin and of the adjacent muscles, and a not clear fascial plane. However, these findings may also be seen in other diseases like lymphoma and metastatic lymphadenopathy. Nodal calcification often develops in late TBC, which may help to distinguish it from squamous cell carcinoma metastases.^{18,19}

In our case we performed a CT, but images weren't useful to differentiate TBC manifestation from a malignant neoplasia.

It is important to discern between tuberculous and nontuberculous cervical lymphadenitis in order to choose the better treatment - medical or surgical respectively. Tuberculous adenitis responds well to anti-tuberculous drugs, and surgery has a limited role in its treatment.

There are two groups of antituberculous drugs. First-line drugs are isoniazid (INH), rifampicin, ethambutol (EMB), pyrazinamide and streptomycin. Second-line drugs, which are less efficacious and more toxic than the first-line drugs, are capreomycin, kanaycin, ethionamide, thiacetazone, para-aminosalicylic acid and cycloserine. Resistance to one or more drugs is seen in 61% of isolated strains with maximum resistance to INH and minimum to EMB.²⁰

In our case the genotype of *M. tuberculosis* resulted sensitive to drugs and the patient was treated with antitubercular polychemotherapy, according to the following scheme: two months of combination therapy with four drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide), and subsequent four months of therapy with two drugs (isoniazid and rifampicin at the same dose). According to the literature,¹² the polychemotherapy ensured good results and a normalization of clinical signs after three months from beginning of treatment.

Conclusions

In developed countries lymphnodal tuberculosis still represents an enormous public health problem, difficult to eradicate for the increase of the phenomenon of immigration, spreading of HIV infections and other causes of immunodeficiency. Clinicians have always to consider tuberculosis in the differential diagnosis of neck masses, even if they don't show typical characteristics of tubercular lesions. To make diagnosis of tubercular lymphadeni-

tis, we sustain that biopsy is still the gold standard if FNAC is doubtful. The Mantoux reaction and study of imaging can increase the suspect on the nature of the lesions but only histological examination and culture test allow differential diagnosis from other forms of adenopathy. Medical therapy has still good results despite a high incidence of multidrug resistant *Mycobacteria*.

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