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Case Report

Extrapulmonary tuberculosis: mimicking metastases in a patient with melanoma in a high TB-burden country; case report

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ABSTRACT

This is a case report that includes an analysis about extrapulmonary tuberculosis and his singularities, cause can be confused with cancer. Our patient an 83-year-old woman from Pasto-Colombia presents a mimicking metastasis with melanoma. This guides us to understand that extrapulmonary tuberculosis is a rare pathology, but it should be considered as a potential differential diagnosis of any osteolytic lesion. That is the reasons for to be one of the great imitators in medicine, we come up with are totally necessary in a differential diagnosis with malignancies, a high index of suspicion.

Introduction

Extrapulmonary tuberculosis (TBE) is one of the great mimics in medicine, and due to the clinical variability of its presentation can be confused with cancer. Globally, about 20% of all tuberculosis cases occur in extrapulmonary sites, being more incident in women (odds ratio [OR], 1.98; 95% confidence interval [CI], 1.25-3.13), non-Hispanic Afro-descendants (OR, 2.38; 95% CI, 1.42-3.97), and in the HIV-positive population (OR, 4.93; 95% CI, 1.95-12.46) [1]; however, because of the progressive increase in multidrug-resistant (MDR) Mycobacterium tuberculosis strains, an increase in cases of TBE has been seen in immunocompetent individuals.

In Colombia for 2018, the National Health Surveillance System (SIVIGILA) [2] reported 14,338 cases of tuberculosis of all forms, with an incidence rate of 26/100,000 inhabitants, of which 17.3% correspond to the extrapulmonary form.

We present a case of TBE that mimics bone metastatic lesions in a patient with a history of melanoma and whose diagnosis was confirmed by biopsy and microbiology. Our

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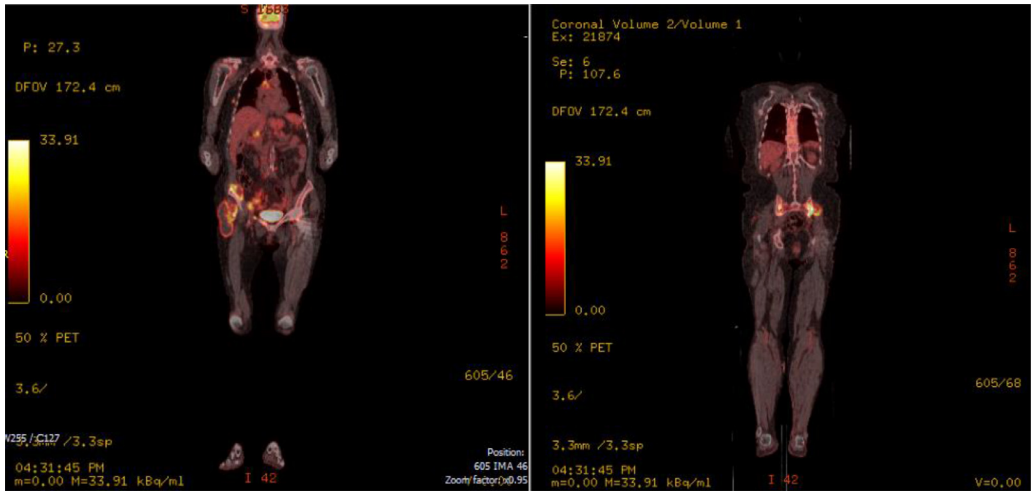


Fig. 1 – PET SCAN positron emission tomography: Shows multiple metastatic hypermetabolic lymphadenopathies at the level of the spleen, pancreas, right intercostal space adjacent to the xiphoid appendix, skin, and subcutaneous cell tissue adjacent to the right deltoid and in the mammary regions. Hypermetabolic compromise in the soft tissues, adjacent to the right hip and another in the supraclavicular region.

objective is to show some of the clinical-radiological characteristics of bone lesions due to TBE and its differential diagnosis with metastases in a high TB-burden country.

Clinical case

An 83-year-old woman from Pasto (Department of Nariño - Colombia), with a history of melanoma in situ on the sole of the left foot resected in 2007, melanotic macula on the palate in 2016, melanoma in situ in the oral mucosa, right palate with free margins in 2018. She has also history of a total left hip replacement due to osteoarthritis. During a medical office visit in 2019, a right clavicular ulcer was evidenced, with a biopsy report for nodular and granulomatous dermatitis; by the same time, she was complaining of progressive pain in both hips for last 6 months, predominantly right, which limited the mobility until total prostration. On physical examination, it was evident palpable cervical and inguinal masses and a new hyperpigmented lesion on the sole of the foot. A biopsy was performed confirming melanoma in situ histology. Positron emission tomography-computed tomography (PET-CT) revealed multiple hypermetabolic lesions with polyostotic involvement, predominantly on the iliacs, with extension to the right hip soft tissues and multiple hypermetabolic lymphadenopathies in the neck, thorax, abdomen, and pelvis (Fig. 1). Chest radiography found no signs of primary or secondary tumor, cavitation or other signs suggestive of lung or pleural infection (Fig. 2); the pelvis radiograph showed changes in the soft tissues of the right hemipelvis (Fig. 3). She remained in hospital care for study and management under the initial suspicion of progression to metastatic melanoma or other occult metastatic neoplasia, performing bone curettage by the oncological orthopedic group for confirmation of differential diagnoses.

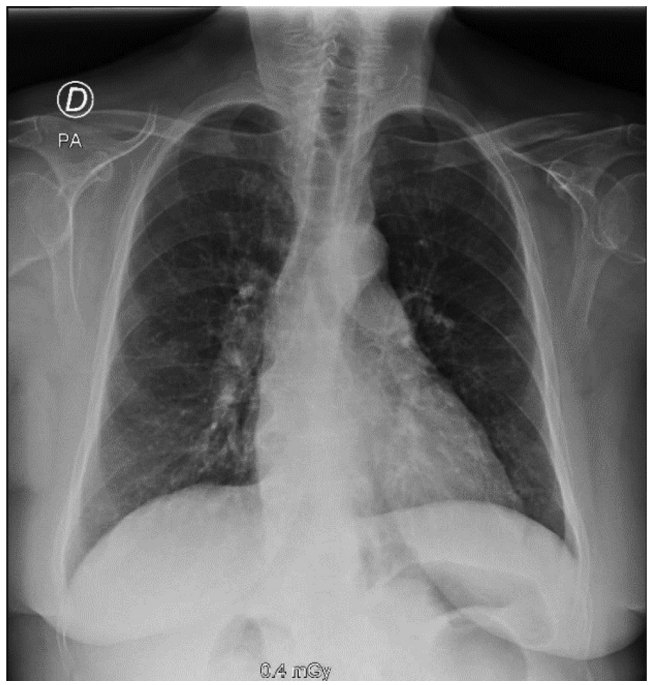


Fig. 2 – Chest radiograph: There are no signs of nodules, masses, consolidation, cavitation in the lung parenchyma or signs of pleural effusion.

An initial contrast-enhanced computed tomography scan revealed lytic lesions at the level of bilateral sacroiliac joints, predominantly right, and collections in the pelvic region. A subsequent contrast-enhanced pelvic resonance reported osteolysis of the right anterior superior iliac spine with collection at the origin of the tensor fascia latae, sartorius, oblique and transverse abdomen, in addition with a small retroperitoneal component, in subcutaneous tissue and in the muscular plane; presence of necrotic adenomegalies in the

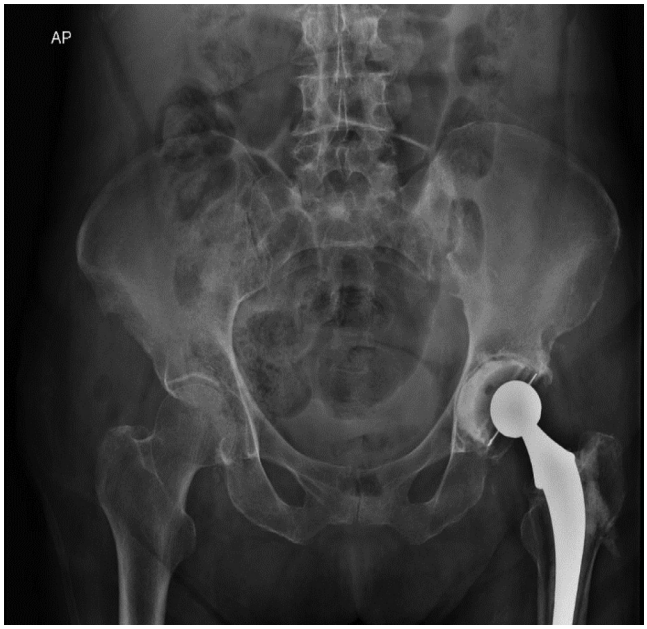


Fig. 3 – X-ray of the pelvis. Reading; left hip arthroplasty: An increase in soft tissue density in the right hemipelvis with radiolucent images suggesting gas bubbles adjacent to the iliac spine.

ipsilateral external iliac chain, sacroiliitis, and osteomyelitis of the left sacroiliac joint (Fig. 4). With these findings, we suspected tuberculosis infection vs tumor liquefaction necrosis, so she was taken to surgical lavages, biopsy and bone curettage, obtaining 200 mL of purulent liquid at right iliac bone which preliminar culture reported Gram positive growth. By the same time, a multiresistant *E. coli* infection of the urinary tract had been diagnosed; therefore, treatment with meropenem and linezolid was started.

In conjunction with the pathology department, samples of iliac bone with hematoxylin eosin staining and Ziehl-Nielsen staining were reviewed, describing the presence of acid-resistant bacilli with morphological characteristics compatible with mycobacteria; Gomori and PAS staining was negative. Right iliac bone curettage histology showed compromise due to chronic granulomatous inflammation with caseifying necrosis, compatible with bone tuberculosis, later confirmed by Real Time Polymerase Chain Reaction multiplex (RT-PCR-multiplex, GeneXpert [TM]). Meropenem and Linezolid were discontinued and initial phase antituberculous therapy was started with a combined daily dose of Rifampicin 150 mg (R)/Isoniazide 75 mg (H)/Pyrazinamide 400 mg (Z)/Ethambutol 275 mg (E), associated to pyridoxine. The patient had a prolonged hospital stay for complications associated with septic soft tissue shock, and was finally discharged with adequate follow-up and adherence to treatment, completing a second phase of the 3-weekly dose of the combination R 300 mg/H 150 mg per 16 weeks for a total of 6 months of supervised tuberculosis treatment. At the moment it is 17 months of follow-up showing complete recovery of mobility.

Discussion

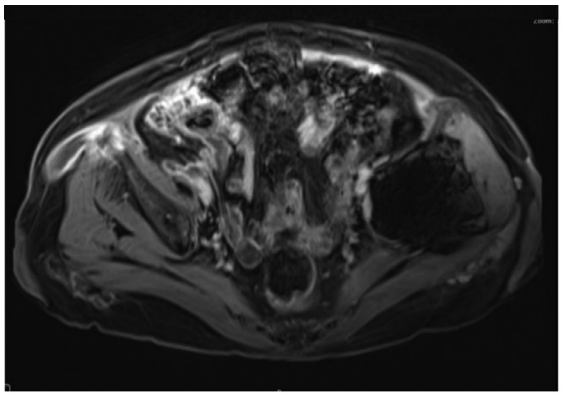
TBE can involve any organ, being more common in the lymph nodes (19%), pleura (7%), osteoarticular (6%), gastrointestinal tract (4%), central nervous system (3%), and genitourinary tract (3%) [3]. Specifically, osteoarticular-compromise TBE is a rare pathology, but it should be considered as a potential differential diagnosis of any osteolytic lesion [4]. The most frequent osteoarticular tuberculosis sites are the spine, hip, and knee. It tends to be unifocal and in rare cases it presents with multifocal involvement up to 10% [4].

CT and magnetic resonance imaging are the radiological studies of choice due to their multiplanar quality that allows differentiating tuberculous arthritis from other commitments due to the disease. CT provides excellent bone, periosteal, and cortical definition, while magnetic resonance imaging is the modality of choice to assess bone marrow extension, effusions, and synovial involvement [5].

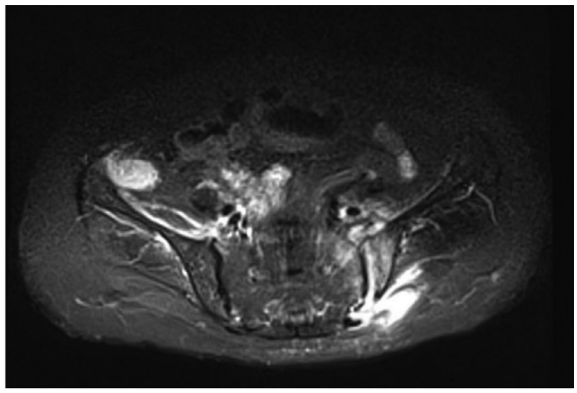
Imaging findings include signs of decreased bone density, osteolytic lesions with poorly defined edges, sclerosis and periostitis in variable range, predominantly of metaphyseal involvement [6], which can be confused with primary tumors such as osteosarcoma or with metastasis of neoplasms, such as prostate, breast, and renal cell carcinoma. However, some signs favor the diagnosis of TBE over neoplasia, such as the presence of juxtacortical abscesses or rings of inflammatory tissue due to the spread of infection to extraosseous tissue [7]. In our case, the hypermetabolic lesions mentioned suggested an osteosarcomatous neoplasm of an advanced clinical stage.

There is no clinical or radiological sign that is pathognomonic of this disease. Some available tests such as the purified protein derivative skin test (PPD, also known as the tuberculin test) and the interferon gamma release test (IGRA) are useful for detecting latent infection due to tuberculosis, they do not have the capacity to differentiate between latent and active infection [8]. A positive PPD in the presence of pulmonary imaging findings can guide the diagnosis; however, the absence of this does not rule it out since in more than 50% of cases TBE occurs without concurrent intrathoracic involvement [5,9].

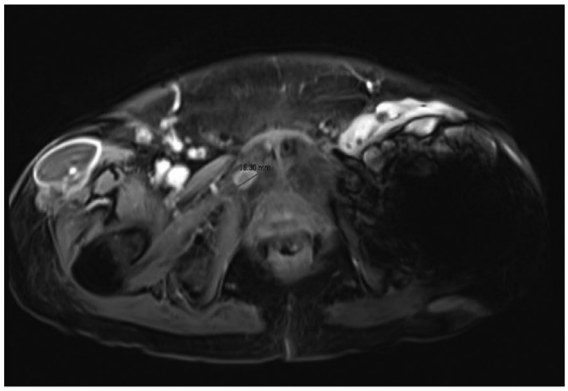
Cytological examination of fine needle aspiration biopsy of lymphadenopathy has a sensitivity of 88% and specificity of 96% for the diagnosis of TB lymphadenitis [10]. Because TBE is a paucibacillary disease, a further study with PCR is very useful, with a variable sensitivity between 43% and 84% and a specificity of 75% and 100%, reducing the need for an open biopsy, particularly in cases where an initial cytology and negative culture are obtained with high clinical suspicion [10,11]. GeneXpert MTB/RIF (TM) is a rapid test that detects in 2 hours the presence of *Mycobacterium tuberculosis* (MTB) DNA and mutations in the rpoB gene responsible for resistance to rifampicin with a specificity of 99%-100% which is similar to that of a culture, and with a sensitivity of 77.3%-95% that varies depending on the type and site of the sample, and that is endorsed for diagnosis in both pulmonary TB and TBE [12]. The culture for mycobacteria and the histopathological study are confirmatory diagnostic tests, but they take several

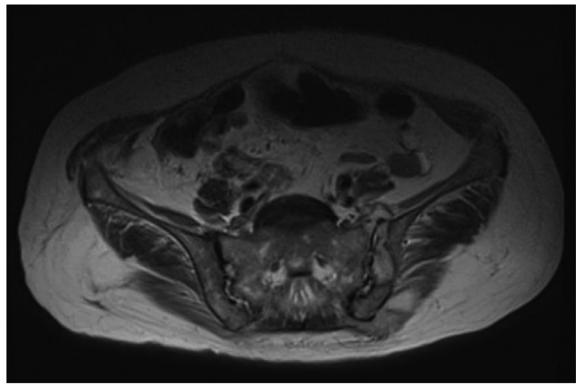


Pelvic MRI with contrast. Axial section(a)

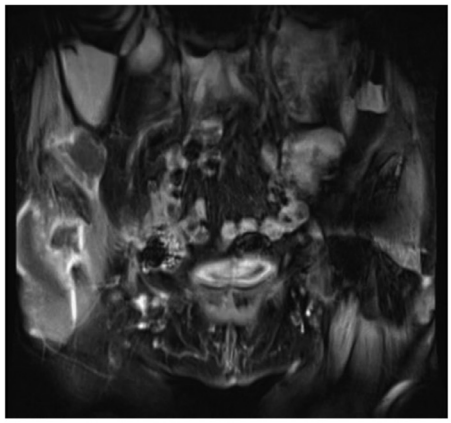


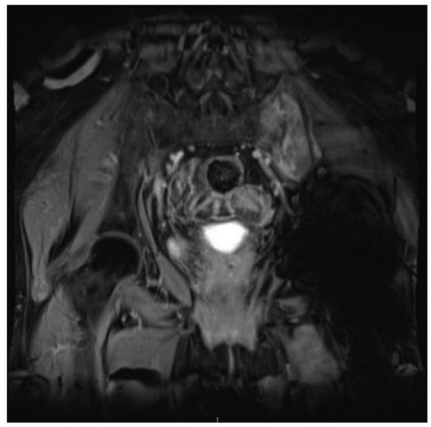
Pelvic MRI with contrast. Axial section(b)





Pelvic MRI with contrast. Axial section (c and d)





Pelvic MRI with contrast. Coronal section (e and f)

Fig. 4 – Contrast-enhanced magnetic resonance imaging of the pelvis: first, images (a) axial T2 with fat suppression: Edema of the bone marrow in the sacrum and the left iliac, fluid collection in the left sacroiliac joint with distension of the capsule in its posterior margin, (b) axial T1: Alteration of the bone marrow signal intensity for edema without evidence of infiltrative tumor injury, (c) and (d) Axial T1 contrasted with fat suppression, (e) and (f) coronal T1 contrasted with fat suppression: Osteolysis of the right anterosuperior iliac spine, with fluid collection at the origin of the tensor fascia latae, sartorius, oblique, and transverse abdomen in subcutaneous tissue and in the muscular plane.

Fig. 4. Contrasting pelvic resonance; Axial and coronal section: Osteolysis of the right anterior superior iliac spine with collection at the origin of the fascia latae tensor, sartorius, oblique, and transverse abdomen with collection (ossifluent abscess). It shows a small retroperitoneal component, in subcutaneous tissue and in the described muscular plane. It is accompanied by necrotic adenomegalies in the ipsilateral external iliac chain, findings may correspond to mycobacterial infection (scrofuloderma). Fluid study is recommended. Sacroiliitis and osteomyelitis of the left sacroiliac joint with small collections (ossifluent abscesses) in the anterior margin and posterior articulation with compromise of the medial margin of the gluteus maximus, could be correspond to mycobacterial infection. Slight right sacroiliitis, small abscess in the upper fibers of the right external obturator.

weeks to provide a result, which reduces the effectiveness of an early start of treatment.

The principles of pulmonary TB therapy apply to TBE with some specific considerations depending on the site it affects. The basic regimen for TBE includes a 2-month initial phase with Isoniazide (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) dosed once a day, followed by a maintenance phase with only the H association and R in sensitive strains, for a time that varies between 6 and 12 months depending on the affected site and according to the health policies in each x country.

Given that resistance rates in Colombia exceed 4%, the best currently available treatment is available by national consensus, due to the efficacy of the association of medications that it uses (four bactericides), of the minimum necessary duration (6 months), of the required supervision, and the facilitation of its use (free, 2 phases, 1 of them intermittent and fixed-dose H/R), with scientific evidence that ensures cure in 99% of cases and prevents relapse in 97% of them [13]. The first phase is an intensive daily regimen of combined therapy with R, H, Z, and E, followed by the second intermittent phase (3 times per week) of the R and H association, for a total of 6 months. The patient has to attend the treatment every day during the first stage, except Sundays, for 8 weeks and the minimum number of doses is 48. During the second phase, the patient must attend twice a week, for 18 weeks, for a minimum total of 36 doses [13].

Randomized controlled studies suggest that a 6-9 months regimen containing H and R is effective for most TBE locations, with the exception of meningeal disease in which different societal guidelines agree to extend therapy to 12 months [14–16]. For osteoarticular and spinal TB, due to the difficulty in evaluating the response, some experts recommend a duration of 9 months, and in people with a requirement for abundant osteosynthesis material, extend the treatment to 12 months. Surgery should be considered in situations where there is a poor response to medical management with evidence of active infection or clinical deterioration; in patients who present with medullary compression and persistent or recurrent neurological deficit, and in case of vertebral instability [14].

There is no international protocol or defined societal guide for monitoring the therapeutic response in TBE; when there is associated lymph node involvement, the response can be evaluated with the decrease in its size, however, it is not a very reliable strategy since it has been observed that the nodes can decrease in size long after completing treatment, and in 11 %-13% of patients can remain with residual nodes in the long term [11]. PET/CT techniques with 18F-fluorodeoxyglucose can help predict response to treatment thanks to the ability of inflammatory cells present in tuberculous lesions to capture and accumulate this marker [11,17].

Conclusions

TBE is one of the great imitators in medicine, its differential diagnosis with malignancies requires a high index of suspicion, and since there are no pathognomonic clinical or radiological data of the disease, it must always be confirmed by histopathological and microbiological study of the lesion.

In developing countries, the incidence of tuberculosis should encourage physicians to be highly suspicious of this type of injury given the importance of timely initiation of targeted antituberculosis treatment (Fig. 4).

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