Case report

Not all lytic bone lesions are malignant: A report of syphilitic osteitis presenting with multiple lytic skull lesions

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ABSTRACT

Syphilitic osteitis is one of the rare and often under-reported complications of early syphilis. Recognizing this entity is important as it may mimic other conditions like multiple myeloma, lymphoma, or metastatic malignancies. Misdiagnosis and delayed management can lead to irreversible destructive lesions. We herein report a case of calvaria syphilitic osteitis that was initially investigated for possible lymphoma and later diagnosed as secondary syphilis.

Introduction

The sexually transmitted infection, syphilis caused by the organism Treponema pallidum has re-emerged on the global stage as public health concern with a rising incidence in many high-income countries [1]. This chronic multisystemic disease is characterized by periods of clinically active disease and latency as the disease progresses through overlapping phases of primary, secondary, latent and tertiary disease [2]. Bone disease is not uncommon in untreated syphilis with gummatous lesions and periostitis occurring in tertiary syphilis [3]. However, bone involvement is seldom encountered in primary or secondary syphilis [4]. Osteitis (bone inflammation) is a consequence of bone seeding by Treponema pallidum with a resulting intense inflammatory reaction that leads to destruction of the bone tissue. Left untreated, osteitis may lead to bone destruction and long-term morbidity. We herein report the case of 45-year old female who was evaluated for multiple cranial lytic lesions.

Case presentation

A 45-year-old female with no significant past medical history or comorbidities presented to the emergency department with a two-week history of throbbing headaches and temporal swelling. In addition, the patient reported nausea, fatigue, weakness, and subjective low-grade fevers. She denied any recent travel, drug use or exposure to an infectious disease, although she endorsed multiple unprotected sexual encounters. Her physical examination was notable for periauricular, axillary, and inguinal lymphadenopathy. No hepatosplenomegaly, cardiac murmurs, or skin rashes was found on examination. The rest of the physical exam was unremarkable.

CT scan of the head showed multiple cranial bone lytic lesions (Fig. 1A-E). Labs were significant for elevated alkaline phosphatase. Differentials at the time included: multiple myeloma, metastatic or primary malignancy, and endocrine abnormalities. The patient's hemoglobin, hematocrit, white cell count, platelet count, serum calcium, serum phosphorus, parathyroid hormone, and vitamin D levels were all within normal limits. Her renal function was normal with no evidence of proteinuria. Serum protein electrophoresis and free light chain were normal. Patient was evaluated for possible underlying infectious conditions. Sputum culture was negative, oropharyngeal swab and cultures were negative. HIV, hepatitis B and C screening were negative. Chlamydia, Gonorrhea and trichomonas polymerase chain reaction (PCR) screening were negative. Bartonella henselae, Bartonella quintana, Toxoplasma and Francisella tularensis IgG/IgM were negative. In addition, Epstein Barr virus viral capsid antigen (VCA) IgM and Cytomegalovirus PCR were negative. Monospot test was negative. TB screening by Quantiferon gold plus was negative. Due to concern about metastatic cancer, a positron emission tomography (PET) scan was performed that showed increased avidity in the lung (Fig. 1F). Inguinal lymph node biopsy was performed and returned negative for malignancy, and patient was discharged to follow up in outpatient pulmonary

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medicine clinic for bronchoscopy and an excisional biopsy. Bronchoscopy and fine needle aspiration (FNA) of the mediastinal and hilar lymph nodes were performed and the pathology report returned negative for malignancy.

Patient was subsequently scheduled for further workup with an axillary excisional lymph node biopsy. Pathological examination of the resected sample showed paracortical and interfollicular hyperplasia, which can be seen in dermatopathic lymphadenitis, viral infections, in response to malignancy, or as part of an autoimmune process; however, a morphologically atypical T-cell population was also found. A small CD-10 positive T-cell population was detected on flow cytometry. While this can be seen in angioimmunoblastic T-cell lymphoma, it was noted that there can be significant morphological overlap with reactive paracortical hyperplasia. The sample was nonreactive to EBV antibodies. Overall, the pathological impression was an abnormal reactive process with expansion of the normal population of follicular T-helper cells. Close follow-up and clinical correlation were recommended.

A few weeks later, the patient returned to the emergency department with complaints of worsening headache, body aches, hoarseness, and low-grade fevers. Patient denied any weight loss or night sweats. Repeat PET CT showed a mass at the gastroesophageal junction. EGD (esophagogastroduodenoscopy) showed esophageal ulcers with candida and HSV. Acyclovir and fluconazole were started. During the admission, further work up revealed the patient was positive for syphilis IgG and IgM. Rapid plasma regain (RPR) was reactive at 1:64 titers. Immunohistochemical staining for *Treponema* was ordered on the previous axillary lymph node biopsy and was found to be positive. Lumbar puncture was performed and was significant for WBC of 23 cells/μL, with 79% of those cells being lymphocytes, protein ~55 mg/dL, and positive CSF VDRL.

As a result, the patient was diagnosed with neurosyphilis and syphilitic osteitis. Notably, the patient was HIV-negative (per ELISA done at admission and repeated at 1 week after admission and at 3 month follow-up) and was found negative for syphilis a year prior during a routine screening test. The patient was treated with a two-week course of IV penicillin G 24 million units and two weeks of benzathine penicillin G given as 2.4 million units weekly. Patient followed up with the infectious disease clinic later and was found to be clinically improving.

Discussion

Bone involvement has been described as an uncommon feature of early syphilis based on the findings of early studies on syphilis. In the largest case series on syphilis patients, only 15 patients with destructive bone lesions were found in 10,000 cases of early syphilis from 1919 to 1940 (0.15%) [5]. Another series published in 1989 reported 2 cases of osteitis in 854 patients with early syphilis [6]. Improvements and availability of imaging studies means bone lesions are now easier to detect and bone involvement in early syphilis is likely much higher than the 0.15% reported in the earlier study. A study of 11 patients with early syphilis reported all the patients had focal osteitis on scintigraphy [7]. The bones most often affected are long bones of the limbs followed by the skull, as in this case and bone lesions are more likely to be multifocal and osteolytic [4].

The clinical manifestation of syphilis is widely variable, often mimicking that of other pathologies. The typical disease course involves the presence of a chancre and regional lymphadenopathy in primary syphilis, followed by systemic manifestations in a secondary disease which disappears during the latent phase and could reemerge as tertiary syphilis with cardiovascular involvement, neurosyphilis and gummatous lesions [8]. While it is easier to entertain syphilis as a diagnosis in individuals who has a history of chancre or mucocutaneous eruptions, a high index of suspicion is required for diagnosis in individuals without these 'classic' findings as the disease manifestations are highly variable. An earlier systematic review on syphilis reported 68% of patients with osteitis had concomitant mucocutaneous involvement [4]. Our patient had no preceding chancre or mucocutaneous lesions.

A finding of lytic bone lesions arouses the suspicion of a possible malignancy often prompting a search for the underlying primary. However, other non-malignant pathological conditions could present with this abnormality and syphilis should be considered as one of the differentials [9]. This would promote early diagnosis and prompt
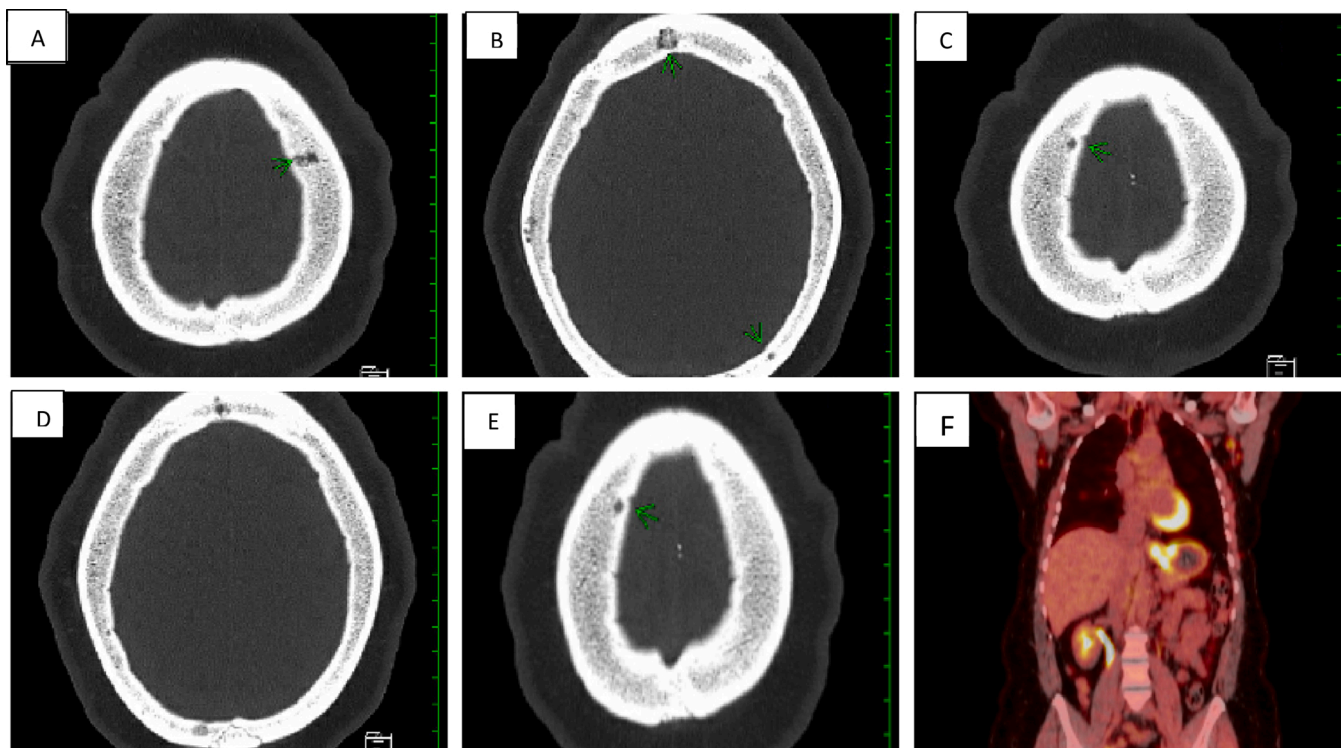

Fig. 1. A-E- CT scan of the head showing multiple cranial bone lytic lesions. F- PET scan showing increased avidity in the lung.

initiation of treatment. Two broad approaches are often used in the diagnosis of syphilis [10]. The first is a traditional testing algorithm which involve an initial screening with a non-treponemal serologic testing (Venereal Disease Research Laboratory and rapid plasma reagin antibody tests) and if positive, a confirmatory test is performed using treponemal tests (fluorescent treponemal antibody absorption assay, enzyme-linked immunoassays, chemiluminescence immunoassays or direct visualization of the organism in tissue samples by dark-field microscopy) [10]. The reverse algorithm involves an initial screening with treponemal tests with reactive samples undergoing a non-treponemal test. If the results are discordant, a different second treponemal test should be performed [10,11]. A positive treponema and non-treponemal test is highly predictive of an active treponemal infection for which treatment should be initiated [11].

Given the rarity of syphilitic bone lesions, the appropriate treatment has not been determined in clinical trials [12]. However, parenteral benzathine penicillin G is the treatment of choice in all stages of syphilis. Dosage depends on the disease stage, presence of neurosyphilis, ocular- and otosyphilis. For patients with primary and secondary syphilis, current CDC guideline recommend single dose benzathine penicillin G 2.4 million units given intramuscularly (CDC). In the presence of neurosyphilis, 18–24 million units of intravenous aqueous crystalline penicillin G daily given in divided doses every 3–4 h for a total of 14 days followed by weekly benzathine penicillin injection for 1–3 weeks is recommended (CDC). Our patient received this regimen with a good outcome.

Conclusion

This case highlights the importance of considering syphilitic osteitis in the differential evaluation of osteolytic lesions. Familiarity with the clinical and histopathologic diversity of syphilis, and its rare manifestations, by both clinicians and pathologists is crucial for timely diagnosis and treatment.

Conflict of interest

The authors declare no conflict of interest.

Informed Consent

Informed consent was obtained from the patient for publication of this case report and the accompanying images.

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