Syphilitic osteomyelitis in a patient with headache and lytic lesions

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A 25-year-old man presented to his family physician with a 3-week history of progressive headache. In addition to exploring common causes of headache — including migraine, tension headache, and cluster headache — the patient's family physician completed a review of systems and sexual history. The patient described having had a painless penile chancre 2 months before presentation, and said he was sexually active with men only and used condoms for anal but not oral intercourse. He had no history of sexually transmitted infections (STIs) and had tested negative for syphilis and HIV during routine screening 11 months before presentation. Given this presentation, syphilis serology was sent to Public Health Ontario, and chemiluminescent microparticle immunoassay and *Treponema pallidum* particle agglutination were found to be positive. These positive screening tests automatically prompted testing for a rapid plasma reagin, which returned positive at 1:16, indicating active syphilis infection in this context. At a follow-up visit with his family physician several days later, where the patient was to receive treatment for syphilis, he reported worsening headache despite analgesics and was sent to hospital for evaluation for possible neurosyphilis.

In consultation with our infectious diseases team, we admitted the patient to the general internal medicine service for further investigation and management. He described the headache as localized to the frontotemporal region, with no other associated neurologic symptoms. He had no rashes, constitutional symptoms, alopecia, ocular, or otitic symptoms. On examination, he had bilateral cervical adenopathy, a healing painless penile chancre, and reproducible tenderness on palpation of the vertex of his skull. His neurologic examination was normal. A computed tomography (CT) scan of the head showed a lytic osseous lesion in the left parietal bone measuring 2.3 × 1.4 × 0.8 cm. Multiple small foci of bony destruction in a circular fashion resulted in an irregular tubular appearance, with soft tissue swelling in the overlying scalp, concerning for syphilitic osteomyelitis. Magnetic resonance imaging (MRI) showed corresponding marrow edema and enhancement in the left parietal bone with surrounding enhancing dural and scalp thickening (Figure 1 and Figure 2). We repeated rapid plasma reagin testing; the result was 1:32, indicating progressive untreated infection. A test for HIV antibodies was negative. We performed a lumbar puncture, which showed a leukocyte count of 1 (normal < 5) × 10^9/L, erythrocyte count of 436 (normal 0) × 10^9/L, glucose level of 3.4 mmol/L (serum 5.6; normal is 60% of serum glucose), protein level of 0.32 (normal range 0.15–0.45) g/L, negative Venereal Disease Research Laboratory test, and indeterminate fluorescent treponemal antibody absorption indicating antibodies to syphilis (FTA-ABS). The elevated erythrocyte count was attributed to contamination of the lumbar puncture with blood.

Given the patient's headache and presence of a penile chancre with associated cervical adenopathy, serology, and imaging findings, we made a provisional diagnosis of secondary syphilis with calvarial osteomyelitis. Discussion with the patient resulted in a mutual decision to treat empirically and monitor for improvement of bony lesions, with biopsy reserved in case he did not improve clinically or on serial imaging. Given the indeterminate cerebrospinal fluid FTA-ABS and diagnosis of osteomyelitis, we elected to complete a total of 6 weeks of therapy, with an initial 2 weeks of penicillin G 4 million units administered intravenously (IV) every 4 hours, followed by benzathine penicillin 2.4 million units intramuscularly (IM) weekly for 4 weeks. As part of the initial investigations for STIs, the patient had a positive throat swab for chlamydia and was treated with 1 dose of azithromycin 1 g, administered orally.

After 2 weeks of therapy, the patient's headache had resolved, and repeat head CT showed improvement in surrounding soft tissue swelling. The repeat head CT revealed 3 additional frontal

Key points

- Syphilis should be considered in the differential diagnosis for lytic osseous lesions.
- The diagnosis of syphilitic osteitis can be made based on clinical, radiographic, and serologic findings, and radiographic resolution of lesions can lag behind clinical and serologic improvement after treatment.
- Management of syphilitic osteitis and osteomyelitis is not well established in the existing literature, and should be based on clinical, serologic, and radiographic response to treatment.
- Coinfection with other sexually transmitted infections (STIs) is common, and diagnosis of any STI should prompt further discussion about STI screening and prevention.

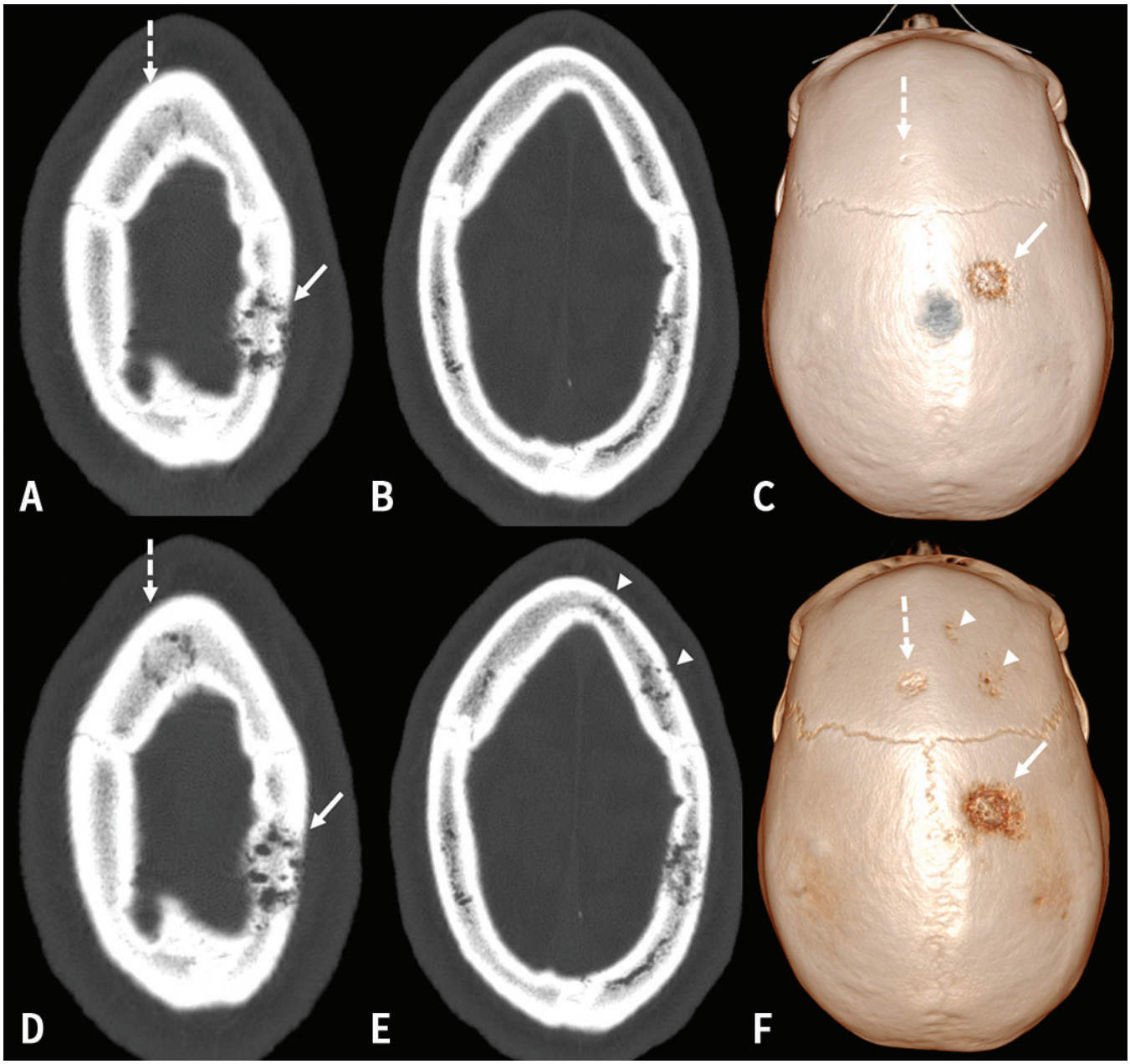

Figure 1: Osseous changes in syphilitic osteomyelitis in a 25-year-old man. (A, B) Axial initial computed tomography (CT) images show a circular area of bone destruction with an irregular tubular (worm-like) appearance (arrow). (C) A 3-D volume-rendered (VR) initial CT image shows this lesion. (D, E) Axial CT images after 2 weeks of treatment show 3 similar additional lesions in the frontal bone, which are subtle (dashed arrows) or not seen (arrowheads) on the initial CT. The dominant lesion also shows minimal progression of osseous destruction (arrows). (F) A 3-D VR image shows these lesions well.

bone lesions and minimal progression of osseous destruction in the parietal bone lesion (Figure 1). Magnetic resonance imaging performed 10 weeks after we initiated therapy showed resolution of soft tissue scalp changes and improved dural thickening with residual marrow edema and enhancement (Figure 2). A repeat rapid plasma reagin test 2 months after the patient's initial presentation was 1:8, and negative after 9 months, indicating successful treatment of infection. In follow-up, he was offered and expressed interest in starting HIV pre-exposure prophylaxis. He remains clinically well and continues to have clinical and radiographic follow-up with our infectious disease clinic.

Discussion

Syphilis, an STI caused by the spirochete *Treponema pallidum*, is often referred to as "the great imitator," given its propensity for causing varied disease manifestations that can mimic other clinical syndromes.[1] Syphilis infection is classically divided into 4 stages: primary, secondary, tertiary, and latent.[2] Primary syphilis can present with a painless, clean-based, well-demarcated ulcer at the site of inoculation, which can include tongue, oral mucosal, vaginal, and penile lesions. It is usually associated with nontender regional adenopathy. Within 3–6 weeks, the

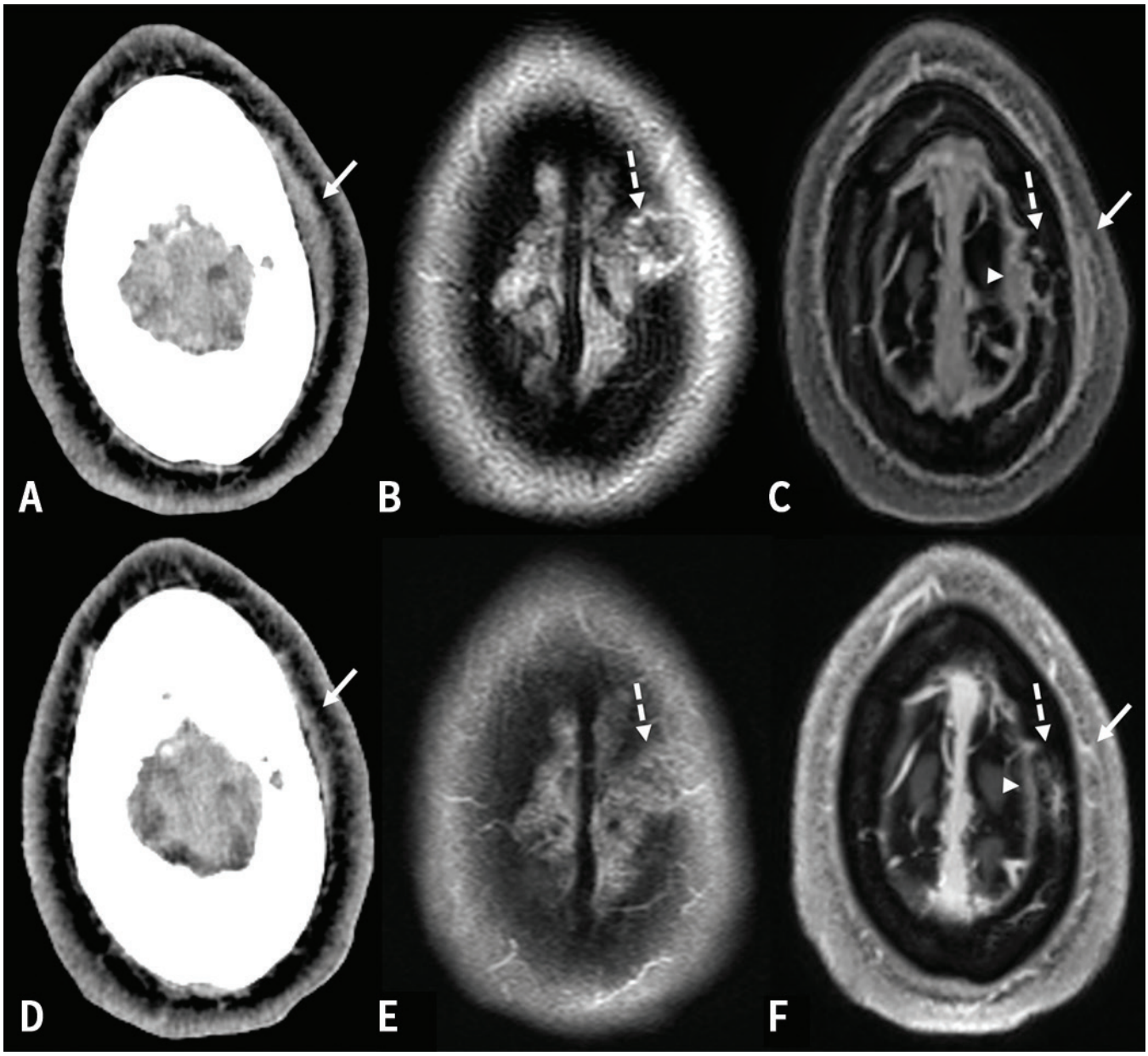

Figure 2: Soft tissue and marrow changes in a 25-year-old patient with syphilitic osteomyelitis. (A) Axial initial computed tomography (CT) and (C) contrast-enhanced, fat-saturated T_1-weighted magnetic resonance images (MRIs) show soft tissue swelling overlying the left parietal osseous lesion (arrow). The CT performed 2 weeks after initiating treatment shows improvement (D), and the contrast-enhanced T_1-weighted MRIs obtained about 10 weeks (F) after treatment was initiated show resolution (solid arrows). (C, F) Underlying dural thickening also shows marked improvement (arrowheads). Evolution of marrow edema and enhancement (dashed arrows) corresponding to the osseous lesion seen on CT is visible in (B, E) axial fluid attenuated inversion recovery (FLAIR) images and (C, F) contrast-enhanced images of MRI performed initially and 10 weeks after treatment initiation, respectively.

spirochete can disseminate to cause secondary syphilis, typically associated with a rash involving the palms and soles. This can be accompanied by mucocutaneous changes, generalized uveitis, and hepatitis; arthralgias and periostitis are less commonly observed. If left untreated, the disease may evolve to tertiary syphilis 1–10 years after initial infection, with cardiac, neurologic, and gummatous lesions. Asymptomatic disease is classified as early or late latent — this distinction is important. Late latent syphilis requires 3 weekly doses of benzathine penicillin, compared with 1 dose for patients with early latent disease. Finally, neurosyphilis (including ocular or otitic manifestations) may occur at any stage and is more likely in people living with HIV.

Syphilitic osteitis and osteomyelitis have historically been rare complications of early (primary and secondary) syphilis and are more commonly described in congenital and tertiary disease.[2] In a previous case series on patients with early syphilis, from 1919 to 1940, only 15 of 10 000 patients had bony lesions.[3] In a more recent systematic review of bony manifestations in secondary syphilis, only 36 cases of secondary syphilis with bone

involvement were identified from 1964 to 2014.[4] An increasing number of case reports of syphilitic osteitis in early syphilis, particularly in people living with HIV, suggests that osteitis may be a more common manifestation of syphilis than previously described.[5–9] The increased relative prevalence is potentially secondary to advanced imaging techniques, as well as the increased number of people living with HIV.

Osteitis, periostitis, and osteomyelitis likely result from hematogenous dissemination of spirochetes during secondary syphilis with deposition into the periosteum, Haversian canal, and bony medulla, leading to an inflammatory reaction with periostitis and subsequent osteolytic lesions.[3,4] The long bones, skull, sternum, and clavicle are the most frequently affected bone sites. Patients with osseous syphilis typically present with localized pain, erythema, or chronic headaches, but can also be asymptomatic.[4] On CT imaging, these osteolytic lesions have typically been described as "worm-eaten bone."[10] Magnetic resonance imaging and nuclear medicine studies are more sensitive for osteomyelitis. Magnetic resonance imaging has the advantage of better delineation of soft tissue, marrow, and intracranial findings.

The diagnosis of syphilitic osteitis is often made through a combination of clinical, serologic, and radiographic findings.[3,4] Bone biopsy can be used to confirm a diagnosis, as spirochetes may be visible, but empiric therapy with monitoring of clinical and radiologic response has been described in the literature.[1,9] When biopsy is performed, pathologic findings show fibrous proliferation with lymphoplasmacytic infiltration. Spirochetes may also be identified using the Warthin–Starry stain but is of low sensitivity, and polymerase chain reaction testing of tissue specimens has also been used to make a microbiologic diagnosis.

In our patient, clinical and ongoing radiographic response to treatment and typical radiologic features supported the diagnosis and obviated the need for an invasive biopsy. However, we observed worsening of osseous changes on CT imaging after treatment was initiated despite simultaneous improvement in the patient's clinical condition and serology. The soft tissue and dural findings on imaging indicated a clinical-radiologic lag. This lag likely reflected ongoing localized inflammation without new bone deposition, and serial imaging out to 2 years showed ongoing improvement. Recognizing that clinical improvement often precedes radiologic improvement may prevent premature discontinuation when treating syphilitic osteitis, periostitis, or osteomyelitis.

Optimal treatment of syphilitic osteitis and osteomyelitis is not well established in the existing literature, and no definitive guidelines exist. Both IM and IV penicillin have been used, and suggestions for duration of therapy are widely variable. These have ranged from 2 to 3 weeks of IV penicillin G when osteitis is associated with early syphilis, to 3 weeks of IM benzathine penicillin, or 6 weeks of IV penicillin or doxycycline when bony changes are found in association with later stages.[1,9] Other variations have included 3 weeks of ceftriaxone, or a combination of IV penicillin for 2 weeks followed by 3 weeks of weekly IM penicillin, similar to the regimen used in our patient, who preferred to avoid prolonged IV therapy.[9] Rapid symptomatic relief is common with treatment, but osseous lesions can persist for as long as 1 year; in some case studies, no substantial radiographic changes in lesions were observed after therapy.[5,10] For treatment monitoring, most patients are followed with serial chemiluminescent microparticle immunoassays to ensure a fourfold decrease within 12–24 months.

The differential diagnosis for calvarial lesions is broad (Box 1).[11] These alternative causes should be considered and evaluated as appropriate, based on a full history, physical examination, and review of systems. Bony involvement of early-stage syphilis should be considered, as incidence may be higher than previously appreciated. This may be related to increased ease of diagnosis based on improved radiologic modalities, along with potential increase in osseous syphilis in people living with HIV. It is important to consider syphilitic osteitis when assessing patients with bony pain, as misdiagnosis and delayed treatment can lead to permanent bony destruction. Frequent screening (i.e., every 3–6 months, considering high-risk encounters, immune status, and sexual practices) for syphilis is also important to identify the disease early on in its clinical course, given that many patients may present asymptomatically, especially as the incidence of syphilis continues to rise in Canada. Lastly, concomitant STIs like gonorrhea, chlamydia, and HIV are common and should be screened for. A diagnosis of syphilis should also prompt discussion of other preventive measures like HIV preexposure prophylaxis.

Box 1: Differential diagnosis for calvarial lesions[11]

Infectious
- Tuberculosis
- Bacterial osteomyelitis (including syphilis)

Malignant neoplasm
- Metastasis
- Myeloma
- Lymphoma
- Sarcoma
- Hemangiopericytoma

Inflammatory
- Sarcoidosis
- Langerhans cell histiocytosis

Metabolic
- Hyperparathyroidism
- Lytic phase of Paget disease

Other
- Meningioma
- Surgical defects
- Arachnoid granulation
- Venous lakes
- Intraosseous venous malformation (hemangioma)
- Fibrous dysplasia
- Epidermoid cyst
- Dermoid cyst
- Gorham disease

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