Case Report

Unusual presentations and pitfalls of secondary syphilis: Periosteitis, tenosynovitis and hepatic abnormalities

Diana Rosa-Gonçalves*, Miguel Bernardes y Lúcia Costa

Rheumatology Department of Centro Hospitalar Sã o João (CHSJ), Oporto, Portugal

ABSTRACT

We herein describe two cases of secondary syphilis in patients with human immunodeficiency virus (HIV) infection with an unusual presentation, a diffuse polyostotic periosteitis. Patients referred mainly to intense bone pain. Other relevant aspects of the clinical pictures were flexor tenosynovitis and hepatic abnormalities. Given the persistence of symptoms, the treatment performed was different from most described in literature. However, although more slowly than expected, both obtained a favorable clinical response after treatment with benzathine penicillin G.

Keywords:
Syphilis infection
Periosteitis
Bone pain
Tenosynovitis

Introduction

Syphilis is a sexually transmitted disease caused by the spirochete Treponema pallidum and remains a global problem, with an estimated 12 million people infected every year. Given that the beginning of the 21st century, syphilis incidence has started to rise in high-income settings, in part driven by increases in cases among men who have sex with men, although more recent increases among heterosexual people have also been reported.

Most cases of venereal syphilis are acquired through direct sexual contact with lesions of an individual who has active primary or secondary syphilis, and transmission occurs in approximately half of such contacts.

Musculoskeletal manifestations can be associated with congenital, secondary, and tertiary syphilis and can mimic a wide variety of rheumatic and systemic diseases of worse prognosis. Bone involvement is common in treponemal infections and is a usual finding in congenital syphilis. However, bone disease is considered rare, although well known, in acquired syphilis.

We report two cases of secondary syphilis in patients with human immunodeficiency virus (HIV) infection that is presented as polyostotic periosteitis.
Case report

The first case, a 40-year-old caucasian man without any significant past medical history, was initially observed due to a two months history of persistent pain at the anterior aspect of the left shin and forearm, which worsens at night. He also reported loss of appetite, weight loss, malaise and fever. Subsequently pain involved additional locations. Patient denied risk behaviors, recent travel or any sick contacts. Was under maximum dose of paracetamol 500 mg + codeine 30 mg without any improvement.

On physical examination, he exhibited a generalized macular and maculopapular skin rash, including palms and soles (Fig. 1). Significant pain on palpation of the left shin and ulnar bone was found. Multiple lymph nodes could be palpated around his neck and inguinal region. No other relevant changes were found.

Laboratory tests results were significant for a normal complete blood count and raised values of: erythrocyte sedimentation rate (ESR) (113 mm, 1st hour); C-reactive protein (CRP) (56.3 mg/L); gamma-glutamyl transferase (GGT) (501 U/L), alkaline phosphatase (AP) (321 U/L), aspartate aminotransferase (AST) (99 U/L); gamma globulins 4.24 g/L (42%); IgG (5040 mg/dl) and β2-microglobulin (4657 μg/l). Serum levels of creatinine, calcium and uric acid levels were normal, as was the routine urinalysis. Bone X-rays revealed periosteal reaction of the tibiae, fibulae and ulnar bones. Bone scintigraphy was impressive for bilateral, extensive polyostotic uptake within the skull, and humeral, ulnar, tibiae and fibulae diaphysis (Fig. 2). Patient was admitted to our service with suspicion of multiple myeloma. Other tumor markers were negative and urine light-chain concentrations were undetectable. Several febrile peaks (max. 39.1 °C) were registered. No pain relief was observed under buprenorphine 52.5 mcg/h and fentanyl 200 mcg in SOS. Computed tomography (CT) cervico-thoraco-abdominal-pelvic showed hepatomegaly and multiple cervical, thoracic, abdominal, pelvic and inguinal adenopathy suggestive of a lymphoproliferative disorder. Cranial radiography revealed changes suggestive of lytic lesions, subsequently excluded by CT scanning. Biopsy of lymph node and bronchoscopy revealed no significant changes. Serum immunofixation showed polyclonal gammopathy and myelogram was not compatible with lymphoproliferative disease. Serology results were as follows: reactive treponema pallidum particle agglutination assay (TPPA) with a venereal diseases research laboratory (VDRL) titer of 1/128; positive HIV (CD4: 444/mm<sup>3</sup>) and serology compatible with cured hepatitis B. A diagnosis of secondary syphilis with polyostotic periostitis was assumed. He started treatment with penicillin G benzathine 2.4 million units intramuscularly (IM) each at weekly intervals for 3 weeks. After the first dose of penicillin we observed resolution of the rash. Only at this time, the patient revealed his homosexual behavior. After discharge and at 6 months of follow-up he showed significant improvement in pain complaints. The VDRL titer was down to 1/4 and CRP, GGT and AP values returned to normal. Bone scintigraphy showed periostitis in subacute phase at tibiae diaphysis and chronic phase in other locations (Fig. 3). At 12 months, patient was practically asymptomatic and all bone scintigraphy abnormalities were in chronic phase.

The second case refers to a 58-years-old caucasian, homosexual man, with known HIV infection for the past 23 years (viral load undetectable; CD4: 657/mm<sup>3</sup>) on antiretroviral therapy. It was
admitted to the Infectious Diseases service by severe pain in the shins and forearms with five months of evolution. Pain worse at night and was accompanied by daily episodes of throbbing holo-
craneal headache, asthenia, loss of appetite and weight loss. He 
was under maximum dose of tramadol 37.5 mg + acetaminophen 325 mg without any improvement. No other relevant epidemiolo-
gical data.

Initial analytic workup was significant for raised values of: ESR
(46 mm, 1st hour); CRP (5.1 mg/L), GGT (991 U/L), AP (310 U/L) and
β2-microglobulin (5035 μg/l). Bacteriological and mycological exa-
namination of cerebrospinal fluid (CSF) were negative; fluorescent
treponemal antibody absorption (FTA-ABS) test in CSF was positive 
but VDRL in CSF was negative (had previous diagnosis of syphilis 
and appropriate response to therapy). The last serum screening was
performed about 10 months earlier, which showed reactive TPHA 
with negative VDRL.

Skeletal X-rays showed changes consistent with lytic lesion in 
the left frontal cranial bone. CT scan of the lower limbs revealed
permeative pattern lesion in the cortical of tibiae diaphysis and 
middle third of the left fibula. Bone scintigraphy showed hyperemia and bone uptake in the skull (more at left), upper orbital 
margin (intense), clavicles, 7th–9th left ribs (intense), lower half of 
the left femur, tibiae diaphysis (intense) and middle third of left 
fibula (intense). On suspicion of lymphoma, he held a first bone
 marrow biopsy that showed very suggestive alterations of clas-
tical Hodgkin lymphoma although the sample has been scarce 
and poorly processed. Thoraco-abdominal-pelvic CT scan showed only hepatomegaly. A percutaneous liver biopsy was performed and 
revealed poorly formed granulomatous reaction without necro-
sis or multinucleated giant cells; plasma cells in the lymphocytic 
cuff was observed. Blood cultures and mycobacterium tuberculosis

research in liver fragment and gastric lavage were negative. Bone
biopsy was repeated, which did not corroborate the previous
findings.

The patient was discharged; no significant pain improvement 
has been achieved. At 4 months of follow-up, he remained very
symptomatic, mainly at the level of the forearms and shins, 
although under transdermal and sublingual fentanyl and pregabalin.
We requested bone scan and new analytical study including syphi-
lis serology. The same relevant laboratory changes were observed 
however, TPPA was reactive and VDRL 1/128. Bone scintigraphy 
shows overlapping changes but with greater extension and in-
creased intensity of uptake.

Diagnosis of reinfection secondary syphilis with periostitis was
assumed and benzathine penicillin G was administered as 2.4
million units IM each at weekly intervals for 3 weeks. Four months
later, patient denied bone pain but referred inflammatory arthral-
gia with 2 months of evolution. On physical examination showed
fingers flexors tenosynovitis of the hand. Analytical study revealed:
ESR 30 mm/1 h; CRP 22.4 mg/L; GGT 127 U/L, AP 128 U/L and VDRL
titer was down to 1/16. Bone scintigraphy exhibited decrease of
osteoclastic activity and abnormalities were already in subacute 
(leg bones) and chronic phase (skull). Magnetic resonance imaging 
(MRI) of hands not showed arthritis but confirmed tenosynovitis
of 4th–5th digits flexors, abductor pollicis longus, extensor pollicis
brevis and minor changes in other tendons.

We prescribed benzathine penicillin G again (1.2 million units
IM/week, 6 weeks), and we also started acemetacin 150 mg/day and
prednisolone 10 mg/day. A month later, patient was practica-

ly asymptomatic with normalization of acute phase reactants, GGT 
and AP. Corticosteroid therapy was stopped in about 1 year. After
3 months of its discontinuation, the patient restarts prolonged nos-
The window of the hands as well as bone pain in the lower limbs.
Analytical study remained normal. Bone scintigraphy showed only
osteoblastic lesions (lower activity) with mild hyperemia in the 
bones of the legs and osteoblastic lesion (lower activity) without
hyperemia in upper orbital margin. At this time, a similar scheme of
benzathine penicillin G was prescribed and started hydroxychloro-
quine 400 mg/day. Patient’s pain symptoms resolved completely
in about 2 months and VDRL titer was now 1/8.

Discussion

When the skeletal structures become involved during early syphi-
lis, the involvement is usually proliferative periostitis and more
rarely destructive osteitis and osteomyelitis occur. The mechanism
of injury, in this stage, is considered to involve spherioidal invasion 
of periosteal vascular beds, leading to inflammation and granula-
tion tissue formation. The extension of this inflammation into the
haversian canals causes osteitis and osteomyelitis, most commonly
in the tibia and skull, in which there were multiple lytic and scler-
rotic lesions. Relatively constant symptoms are the worsening of
bone pain at night and febrile accesses; examination may reveal
tenderness over the involved bones, which is sharply localized and 
may be accompanied with local edema.2

Early stage syphilitic bone involvement may be an underdiagno-
sed manifestation of this protein disease. The most comprehensive
study on bone-destructive involvement in early syphilis was 
carried out by Reynolds and Wasserman between the years of
1919 and 1940. This study reported only 0.15% of bone-destructive
lesions out of a total of 10,000 cases of early syphilis, suggest-
ing that bone lesions are extremely rare in early-stage syphilis
(primary and secondary). However, a 1952 study by Thompson 
and Preston reported that 9% of patients with secondary syphilis
had cranial lesions. This difference in percentages may be attrib-
uted to the fact that until the 1932 there had been no recorded

Fig. 3. Scintigraphy at presentation (a) and at 6-month (b) blood pool phase.
X-ray observations and early bone-involvement syphilis may not have been identified. Even the introduction of X-ray examinations could not compare with the imaging modalities subsequently developed, which acted to detecting previously unrecognized bony involvement. Thus, there have been more frequent reports regarding skeletal involvement in early syphilis and this may imply that the true incidence of bone involvement in early-stage syphilis may be higher than had previously been appreciated.\[^3\]

Documentation of syphilis periostitis has remained confined mainly to case reports and review articles.

The efficacy of penicillin for the treatment of syphilis has been well established through over 50 years of clinical experience. Almost all treatment recommendations are based on expert opinions and benzylpenicillin (penicillin G), administered parenterally, is the preferred drug. The preparations used, the dosage, and the length of treatment depend on the stage and clinical manifestations of disease and by geographical region. Although there has been some debate on the theoretical benefit of prolonged exposure to therapeutic doses of penicillin, limited data suggest that there is no difference between standard and prolonged regimens.\[^1,2,4\]

An infection with *Treponema pallidum* does not confer solid immunity to reinfection. The secondary stage lasts for several weeks or months and may reoccur in approximately 25% of untreated patients.\[^1\] The titers of antibody during reinfection were usually higher than those during the first infection, and the clinical and serologic responses to treatment were always slower.\[^2\]

The relation of syphilis with arthralgia and tenosynovitis is not so obvious. There are few reports in the literature to describe this rheumalolgical complications and those that exist have reported a rapid improvement after penicillin institution.\[^3\]

There have been reported cases in the literature of hepatitis attributed to syphilis in HIV-infected individuals.\[^7\] The most prominent laboratory abnormality at the time of presentation was a marked cholestatic pattern with milder elevations in liver transaminase levels. The clinical manifestations of syphilitic hepatitis are thus attributable to the perifocal inflammatory response accompanying treponemal invasion. Syphilis should be entertained as a potential etiology of abnormal liver enzyme levels in the proper clinical setting, and the condition is reversible with appropriate antimicrobial therapy.\[^7\]

In conclusion, we present two cases of extensive lytic bone lesions and one of them, curiously, also presented tenosynovitis as part of the presenting symptoms of syphilis. While these presentations, including its appearance on imaging, is not usually considered a typical part of the clinical spectrum of early syphilitic infection, dogma on this point may be dated and indeed outdated. Even in the 21st century, syphilis continues to be a great imitator, and a high index of suspicion must be kept for this classical (and highly treatable) diagnosis in the appropriate clinical set-up.

**Ethical disclosures**

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

**Author disclosure**

All authors make substantial contributions to acquisition, analysis and interpretation of data. All critically revise it for important critical content and give final approval of the version of the article accepted for publication.

**Conflicts of interest**

All authors declare no conflict of interest.

**Sources of support in the form of grants or industrial support**

Not applicable.

**Bibliografia**