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CASE REPORT

# Miliary tuberculosis and acquired immunodeficiency syndrome – 'a cursed duet'

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Tuberculous osteomyelitis is rare and usually involves the vertebrae but is seldom found in the foot. The uncommon site and ability to mimic other disorders clinically and radiographically leads to diagnostic and therapeutic delays. We report a case of a 40-year-old man who initially presented to his podiatrist with intermittent pain and swelling of his right ankle and foot that lasted for a year. He also started to exhibit significant weight loss and unexplained fevers and was subsequently hospitalized for cellulitis of his right foot. On further workup, patient was found to have miliary tuberculosis (TB) and acquired immunodeficiency syndrome (AIDS). Patient was treated with anti-TB therapy for 9 months and highly active anti-retroviral therapy. Our patient presented with ongoing chronic right foot and ankle pain that was proven to be secondary to TB osteomyelitis of cuneiform bones of the right ankle in the setting of AIDS. The patient's clinical presentation was unusual due to symptom duration and lack of systemic characteristics. Like our case, reported incidence of osteomyelitis of bone/joint in extrapulmonary TB is estimated to be 10%, and out of all bones/joint TB cases, only 1% are found to be in the foot.

Keywords: *AIDS*; *osteomyelitis*; *miliary tuberculosis*

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Tuberculosis (TB) infection, clinical disease, radiographic presentation, diagnosis, treatment, and prognosis are all deeply affected by the presence of human immunodeficiency virus (HIV) co-infection. Patients with advanced HIV infection who develop TB are more likely to manifest with extrapulmonary and disseminated disease. TB and HIV epidemics are closely connected, and often seen as a deadly associated, or the 'cursed duet'. Our HIV-positive patient presented with chronic right foot and ankle pain that proved to be secondary to disseminated tuberculosis resulting in TB osteomyelitis of the cuneiform bones of the right ankle.

## Case report

A 40-year-old Hispanic man from Mexico presented with pain and swelling of the right foot for 1 year. His medical history was only remarkable for latent TB diagnosed 9 months prior to presentation and was prescribed isoniazid for 9 months, but only 2 months was completed by the patient for unknown reasons. The pain in his right foot had been increasing in intensity and began to hinder his ambulation, thus leading to a visit to the emergency room. The pain was throbbing in nature, localized to the right foot, and was exacerbated by walking and movement of the ankle. The patient was unable to bear weight on his ankle. He denied any trauma, insect bites, or recent travels. Review of systems was negative for dyspnea, cough, sputum production, chest pain, pleurisy, fevers, chills, or night sweats. He did, however, report a 20-pound weight loss over the past 6 months.

On physical examination, inspection of the right foot showed no erythema, pallor, lesions, or discharge. The right foot was warm to touch and tender, especially along the lateral portion of the dorsum of foot. There was decreased range of motion secondary to pain and edema that extended from the mid-foot up to the ankle. Pedal





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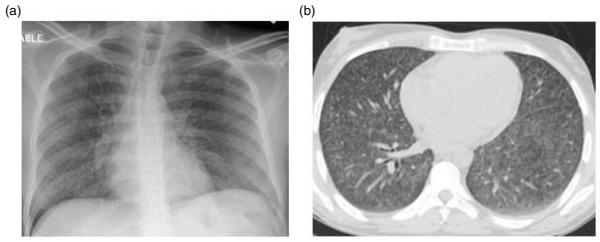

*Fig. 1.* Imaging of chest (a) x-ray and (b) CT scan during initial hospitalization depicting miliary TB pattern.

pulses were intact, and there were no signs of trauma or infection. The remainder of his physical examination, including the lungs, was unremarkable. Initial laboratory studies revealed the following values: white blood cell (WBC) count 10.8 (normal 4.8–10.8 thousands/mL); hemoglobin 10.5 (normal 14–18 g/dL); hematocrit 31 (normal 42–52%); platelets 172,000 (normal 130,000–400,000); serum sodium 130 (normal 135–145 mmol/L); serum potassium 4.6 (normal 3.5–5.1 mmol/L); serum chloride 94 (normal 98–107 mmol/L); serum bicarbonate 25 (normal 22–29 mmol/L); Blood Urea Nitrogen (BUN) 17 (normal 6–20 mg/dL); serum creatinine 0.96 (normal 0.7–1.2 mg/dL). Liver function tests were all within normal limits, except for elevated alkaline phosphatase of 584 (normal 40–129 u/L). On admission, HIV screening was positive which was confirmed with western blot assay. HIV viral load was found to be 76,168 copies (normal $<175$) and CD4 count was 89 (normal 490–1,740 cells/μL). Admission chest x-ray was suggestive of miliary TB (Fig. 1a).

The patient was admitted and placed in respiratory isolation. CT demonstrated a diffuse pattern of nodules throughout both lungs, also suggestive of military TB (Fig. 1b). Radiography and magnetic resonance imaging (MRI) of the right foot and ankle revealed significant destruction of the navicular cuneiform joints with associated osteomyelitis compared to initial imaging 1 year prior (Fig. 2a and b). Differential diagnosis at the time of admission included septic arthritis, inflammatory arthritis, aseptic necrosis, and TB osteomyelitis. Serological investigations revealed the following: C Reactive Protein (CRP) 5.24 (normal $<0.5$ mg/dL); Erythrocyte Sedimentation Rate (ESR) 100 (normal 20 mm/h); uric acid 6.4 (normal 3.4–7.0 mg/dL); Lactate Dehydrogenase (LDH) 248 (normal 135–225 units/L); Anti-Nuclear Antibodies (ANA) negative; anti-Cyclic Citrullinated Peptide (CCP) $<16$ (normal $<20$); Rheumatoid Factor negative; and Quantiferon-TB Gold positive. Acid-fast bacilli (AFB) sputum smears and cultures were negative. On discussion with an infectious disease consultant regarding initiation of anti-TB chemotherapy, it was recommended that treatment be started after a tissue diagnosis has been obtained. A fluoroscopy guided bone biopsy of the right first cuneiform was performed which revealed severe acute and chronic mycobacterial osteomyelitis with numerous AFB (Fig. 3). Furthermore, cultures were positive for mycobacterium TB and it was sensitive to all anti-TB drugs. Anti-tubercular chemotherapy was initiated after tissue diagnosis was obtained. Highly active anti-retroviral therapy (HAART) was started 2 weeks later due to the increased risk of immune reconstitution syndrome (IRIS). The patient was found to have iron deficiency anemia and subsequently started on iron supplementation. During the course of the hospital stay, he started having fevers with a T-max of 102.7°F along with watery diarrhea associated with non-specific abdominal pain and oral thrush. He was empirically started on vancomycin, cefepime, bactrim, and fluconazole for possible septic arthritis, pneumonia, *Pneumocystis* pneumonia infection, and oral candidiasis. CT of the abdomen and pelvis with oral contrast revealed diffuse colitis and metronidazole was added to therapy. All blood, sputum, and urine cultures were negative, including toxins for *Clostridium difficile*. Eventually the fevers and diarrhea resolved; however, his renal function began to deteriorate. Vancomycin was discontinued and trimethoprim–sulfamethoxazole was switched to atovaquone. Renal function quickly improved with hydration and the change in drug regimen.

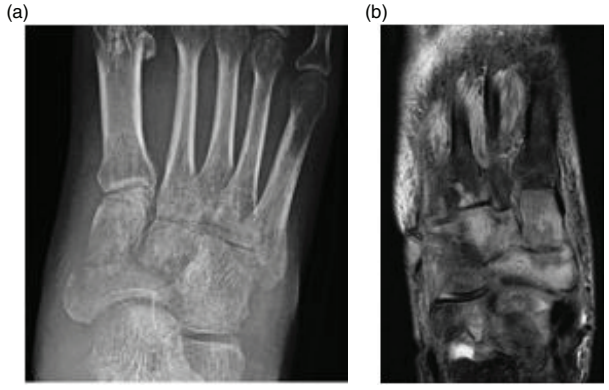

*Fig. 2.* Imaging of the right foot (a) x-ray and (b) MRI from initial hospitalization depicting the destruction of the navicular cuneiform bones as well as the joints.

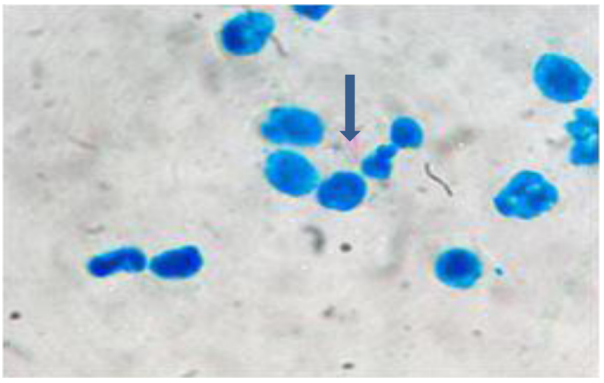

*Fig. 3.* Acid-fast bacilli (beaded red stained mycobacterial rods, as marked with arrow) with inflammatory debris from right ankle fine needle aspiration (Ziehl Neelsen 1500 ×).


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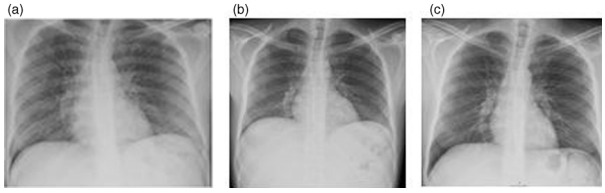


*Fig. 4.* Imaging of chest comparing (a) pre-treatment, (b) 3 months post-treatment, and (c) 1 year post-treatment. Note the improvement of miliary TB pattern with treatment.

Our patient had a positive clinical response to medical therapy with a decrease in the pain and swelling of his right foot and ankle in 2 weeks time. Upon discharge, his ambulatory dysfunction resolved and he was walking with the assistance of a cane. Follow-up with 3 months of anti-TB treatment, repeat chest x-ray showed significant improvement from the previously seen miliary TB pattern (Fig. 4). His viral load was undetectable and CD4 trended up. One year after discharge the patient was ambulating without any assistance. Follow-up chest x-ray and MRI of his right foot showed no pulmonary abnormalities and significant improvement of the navicular and first and second cuneiforms of the right foot, with the bones appearing relatively normal (Fig. 5). His total anti-TB therapy duration was 9 months of rifabutin, which was used instead of rifamycin during his therapy. After HRZE therapy (isoniazid, rifabutin, pyrazinamide, and ethambutol) for 2 months, patient received 7 months of isoniazid (INH)/rifabutin treatment. His HAART treatment consisted of protease inhibitor (PI)-based therapy.

## Discussion

TB and HIV epidemics are closely connected, and often seen as a deadly association, or the 'cursed duet'. TB remains a major cause of morbidity and mortality in HIV-infected individuals, especially in countries where TB is highly prevalent. HIV on the other hand has changed the epidemiology, natural history, and pathogenesis of TB infection. TB infection, clinical disease, radiographic presentation, diagnosis, treatment, and prognosis are all deeply affected by the presence of HIV co-infection. In general, people living with HIV are 20–40 times more likely to develop TB disease during their lifetimes as compared with HIV-infected uninfected individuals (1, 2).

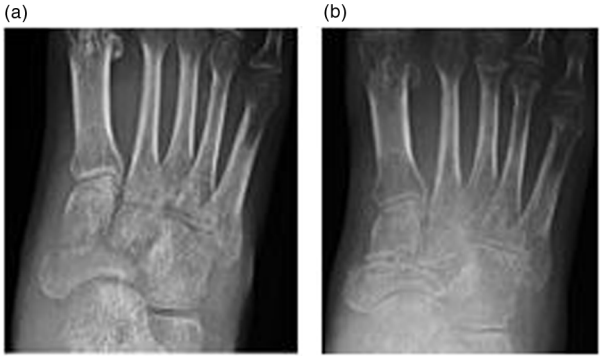


*Fig. 5.* Imaging of right foot comparing (a) prior treatment and (b) 1 year post-treatment. Note the marked improvement of the navicular and cuneiform bones.

Patients with advanced HIV disease who develop TB are more likely to manifest with extrapulmonary and disseminated disease. The diagnosis of TB in HIV patients is often more difficult and treatment is complicated with drug interactions and cumulative toxicities.

We are presenting a case of disseminated TB disease in an HIV-positive patient who presented with ongoing chronic right foot and ankle pain that was proven to be secondary TB osteomyelitis of cuneiform bones of the right ankle. The patient's clinical presentation was unusual due to its duration of symptoms and lack of systemic symptoms characteristic of disseminated TB disease. Other than a 20-pound weight loss, the patient did not have any constitutional symptoms such as fever, cough, or shortness of breath until a few days after his hospitalization for presumed ankle osteomyelitis when he spiked temperatures.

Like in our case, reported cases of osteomyelitis of bone/joint (2) in extrapulmonary TB cases are estimated to be 10% and all bones/joint TB cases only 1% are found to be in foot bones (3, 4). The diagnosis of TB osteomyelitis requires a high degree of suspicion for accurate and timely diagnosis and treatment. Challenges in the workup of TB bone disease include lack of familiarity with the spectrum of TB osteomyelitis and the lack of inclusion in the differential early on (5). Reports of hand, calvarium, sternum, mandibular, scapular, and foot–ankle TB osteomyelitis cases are all indicators that diagnostic delays were secondary to lack of inclusion of TB in the differential early on in the disease process (6–14).

In our case, early bone biopsy and consideration of TB bone disease in the presence of abnormal chest x-ray and HIV serology were paramount for timely diagnosis. The miliary TB refers to TB infections involving many different organ systems, including the lungs. The name is related to the small size of lesions, which are usually $<2$ mm in diameters, resembling millet seeds. Eight percent of extrapulmonary TB reports in 1990 were miliary and more common in older age and in acquired immunodeficiency syndrome (AIDS) patients (15, 16). Although our patient did well and continues to do well after more than 18 months of follow-up, his case has unique features that deserve further discussion.

His bone infection was diagnosed late due to a delay in obtaining a tissue diagnosis that could have helped in early treatment of TB bone disease as well as possible early diagnosis of his HIV infection along with earlier HIV treatment. The delay in diagnosis of what is believed to be reactivation of his TB along with hematogenous spread to bone in this case became worse with ongoing

HIV infection and vice versa. Progressive weight loss in the past 6 months prior to his admission was secondary to further dissemination of TB and worsening of his HIV status. Since at the time of presentation to the emergency room for severe foot/ankle pain, he also had pulmonary radiographic findings of diffuse TB. We believe his disseminated TB was a late effect since his clinical findings were not consistent or compatible with ongoing pulmonary disease for 12 months or more. In addition, public health concerns for transmission of TB due to undiagnosed, untreated TB pulmonary involvement are extremely disconcerting in the years 2014–2015. Failure of latent TB treatment in this patient is not unique nor is his entry to HIV care with CD4 count below 100 and AIDS diagnosis. It remains a huge public health policy task for implementation of infection control practices that safeguard public and infected individuals alike (in this case co-infected patients).

This case strengthens the argument that both HIV and TB remain as a 'cursed duet'. Aggressive efforts in screening for both conditions remain as an important educational goal for healthcare providers. Since miliary TB usually presents with fever, weight loss, night sweats, and minimal or absent pulmonary symptoms or signs, one should always keep TB disease in the differential of HIV-infected individuals.

The world experts believe TB should be treated with the same regimen as pulmonary TB. Some experts believe TB meningitis should be treated for 12 months due to the seriousness of disability and mortality. Nine months of treatment for bone/joint disease should be given due to difficulties of assessing the treatment response (17). In our case, we have treated our patient for 9 months for TB disease and a clinical decision of early HAART treatment was made despite his CD4 count being greater than 50 cell/mm$^3$. In addition, he was treated with INH, rifabutin, pyrazinamide (PZA), and ethambutol for 2 months and was continued with INH and rifabutin for an additional 7 months. The choice for rifabutin instead of rifamycin in this patient was due to PI-based HAART therapy, and the patient did well clinically and radiographically with excellent viral load reduction and response.

Finally, immigrants who reside from areas where the burden of TB disease/infection is high, clinicians should consider TB as a potential diagnosis. The screening and appropriate treatment of latent tuberculosis infection or TB disease in these populations is paramount for decreasing the TB incidence in the developed world and decreasing the morbidity and mortality across the globe where 1/3 of the HIV population is believed to be co-infected with TB. Of 9.4 million TB cases, 1.1 million had HIV infection (12%) in 2009 (2). Therefore either one of the diagnoses should prompt investigation and screening of the other infection as in our case. Both clinical and public health benefits of such efforts will have long-lasting impact against two major epidemics that feed each other.

## Conflict of interest and funding

The authors reported no conflict of interest and no funding was received on this work. All authors reviewed and approved the final version of the manuscript.

## References

1. Chretien J. Tuberculosis and HIV. The cursed duet. Bull Int Union Tuberc Lung Dis 1990; 65(1): 25–8.
2. World Health Organization (2010). Global tuberculosis control. WHO/HTM/TB/2010.7. Geneva:WHO.
3. Davidson PT, Fernandez E. Bone and spine tuberculosis. In: Schlossinberg ed. Tuberculosis. 2nd ed. New York: Springer-Verlag; 1983, pp. 119–32.
4. Bozkurt M, Dogan M, Sesen H, Turanli S, Basbozkurt M. Isolated medial cuneiform tuberculosis: A case report. J Foot Ankle Surg 2005; 44(1): 60–3.
5. Mannepalli S, Mitchell-Samon L, Guzman N, Relan M, McCarter YS. Mycobacterium tuberculosis osteomyelitis in a patient with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS): A case report. Cases J 2010; 3(67): 1–4.
6. Brew CJ, Rao V, Shanker J. Tuberculosis infection of the talonavicular joint. Foot 2010; 20(4): 146–8.
7. Singh G, Kumar S, Singh DP, Verma V, Mohammad A. A rare case of primary tuberculosis osteomyelitis of skull vault. Indian J Tuberc 2014; 61(1): 79–83.
8. Hegazi A, Dragovic B. Tuberculosis osteomyelitis of the sternum in a patient with well controlled HIV infection and undetectable vitamin D levels. HIV &AIDS Review 2012; 11: 71–2.
9. Al-Qattan MM, Al-Namia A, Al-Thunayan A, Al-Omawi M. Tuberculosis of the hand. J Hand Surg Am 2011; 36(8): 1413–21.
10. Khullar SM, Tvedt D, Chapman K, Herlofson BB. Sixty cases of extreme osteonecrosis and osteomyelitis of the mandible and mailla in a West African population. Int J Oral Macillofac Surg 2012; 41(8): 978–85.
11. Saifundheen K, Anoop TM, Mini PN, Ramachandran M, Jabbar PK, Jayaprakash R. Primary tubercular osteomyelitis of the sternum. Int J Infect Dis 2010; 14: e164–6.
12. Kannaperuman J, Natarajarathinam G, Rao AV, Palanimuthu S. Primary tuberculosis osteomyelitis of the mandible: A rare case report. Dent Res J (Isfahan) 2013; 10(2): 283–6.
13. Jagtap S, Sonawane D, Saraogi A. Isolated tuberculosis of scapula in a young adult. Int J Mycobacteriol 2013; 2: 114–7.
14. Upadhaya GK, Jain VK, Sinha S, Naik AK. Isolated calcaneocuboid joint tuberculosis: A rare case report. Foot 2013; 23(4): 169–71.
15. Wein MR, Thoroutin GF. Extrapulmonary tuberculosis: Experience of community hospital and review of literature. Am J Med 1985; 79: 467–78.
16. Shafer RW, Kim DS, Weiss JP, Quale JM. Extrapulmonary tuberculosis in patients with human immunodeficiency virus infection. Medicine 1991; 70: 384–97.
17. Azis L, Jones-Lopez EC, Ellher JJ. HIV associated tuberculosis. In Volberding PA, et al. eds. Sande's HIV/AIDS Medicine. 2nd ed. China: Elsevier; 2013, pp. 325–47.