Disseminated Tuberculosis in an Immunocompetent Patient Associated With the Use of Contaminated Bone Matrix Graft in Spine Surgery

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Abstract: Miliary tuberculosis (TB) is a rare and potentially fatal form of disseminated TB. Disseminated TB involving the central nervous system (CNS) may be seen in up to nearly a third of miliary TB cases. We describe a case of miliary TB with CNS involvement and suspected hepatobiliary involvement in an immunocompetent patient after an elective spine surgery. Given the patient's unusual presentation in the absence of risk factors for TB, diagnosis was delayed. We were later informed that the bone graft he received during spine surgery, FiberCel ("FiberCel") Fiber Viable Bone Matrix (Aziyo Biologics, Inc, Richmond, Calif), was contaminated with TB. This patient is 1 of almost 2 dozens reported to be affected. This case represents a novel presentation of TB due to contaminated cadaveric bone allograft matrix implantation, with notable rapid dissemination and CNS involvement.

Key Words: miliary tuberculosis, CNS tuberculosis, FiberCel, bone graft, immunocompetent host

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The primary entry point of most *Mycobacterium tuberculosis* (Mtb) infections is the respiratory system; however, disseminated tuberculosis (TB), including miliary TB, can result from lymphohematogenous spread from a primary site of Mtb infection.[1] Miliary TB represents fewer than 2% of all TB cases, but it can be associated with central nervous system (CNS) involvement in 10% to 30% of cases and can be fatal if untreated.[1] Comorbidities associated with disseminated TB include disease states associated with immunosuppression, including uncontrolled diabetes, malnutrition, coinfection with HIV, and use of immunosuppressant agents such as tumor necrosis factor α antagonists.[1]

Disseminated TB rarely occurs in immunocompetent individuals. However, we present a case of disseminated TB in an immunocompetent patient acquired iatrogenically from a bone matrix graft that was later discovered to be contaminated with Mtb. We also briefly describe the ongoing investigation of an TB outbreak in multiple states all traced back to this contaminated bone graft product lot.

CASE PRESENTATION

This is a 63-year-old man who presented to an outside hospital with 2 weeks of intermittent fever and a syncopal episode. Documented temperature reached 38.3 to 41.1°C. He had 40 lb of weight loss over the course of 2 months. Other associated symptoms included chills, dyspnea, and gradually worsening confusion. Approximately 4 weeks before symptom onset he underwent posterior lumbar decompression with L5-S1 instrument fusion for degenerative disc disease at the outside hospital. A bone matrix graft was used. His medical history consisted of intermittent asthma, hyperlipidemia, and depression, which were all well controlled.

At initial presentation to outside institution, he was afebrile and hemodynamically stable. Oxygen saturation was 96% on room air. Physical examination was notable for confusion, oriented only to self and year. There were no focal neurological findings. Laboratory workup was pertinent for anemia (hemoglobin, 9.8 g/dL; reference range [ref], 13.9–16.3 g/dL). Total white blood cell count was normal (9.3×10^9/L; ref, 3.6–11.1×10^9/L), and differential showed neutrophilia (8.09×10^9/L; ref, 1.9–7.2×10^9/L), lymphopenia (0.37×10^9/L; ref, 1.1–2.7×10^9/L). Alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase were elevated; 1147 U/L (ref, 45–117 U/L), 185 U/L (ref, 10–50 U/L), and 77 U/L (ref, 15–37 U/L), respectively. Bilirubin was normal. Inflammatory markers were increased with a C-reactive protein of 12.9 mg/dL (ref, 0.0–0.9 mg/dL) and sedimentation rate of 64 mm/h (ref, 0–20 mm/h).

Magnetic resonance image (MRI) of the lumbar spine was obtained for concern of surgical site infection, which showed soft tissue signal extending into left lateral recess of L5/S1 with scattered enhancement possibly representing small abscesses. Intravenous antibiotics with vancomycin and cefepime were started, and the patient had lumbar wound exploration and excision of what seemed to be granulation tissue in the epidural space and within the disc space. No abscesses were seen. Antibiotics were discontinued after 9 days as the patient had no improvement of symptoms.

He continued to do poorly postoperatively with worsening encephalopathy. He remained intermittently febrile and developed hypoxia requiring low-flow oxygen supplementation. Magnetic resonance imaging of the brain without intravenous contrast was unremarkable. This was followed by a lumbar puncture with cerebrospinal fluid (CSF) analysis showing 51 total nucleated cells with lymphocytic predominance (68%; ref, 40%–80%), elevated glucose (82 mg/dL; ref, 40–70 mg/dL), and mildly elevated protein (48 mg/dL; ref, 15–45 mg/dL). Bacterial cultures from CSF, blood, and debrided granulation tissue remained negative. Computed tomography (CT) of the chest, abdomen, and pelvis on day 16 of hospitalization showed bilateral diffuse ground-glass opacities and innumerable micronodules in lung parenchyma and mild-moderate splenomegaly and nonspecific prominent portal hepatic lymph nodes in the abdomen.

On day 19 of hospitalization, the patient was transferred to our hospital for remainder of his care. Review of outside radiographic imaging was concerning for miliary TB (Fig. 1). Repeat CSF analysis showed 13 total nucleated cells (39% neutrophils, 30% lymphocytes, and 31% monocytes), protein (69 mg/dL; ref, 0–35 mg/dL), and glucose (46 mg/dL; no reference range given).

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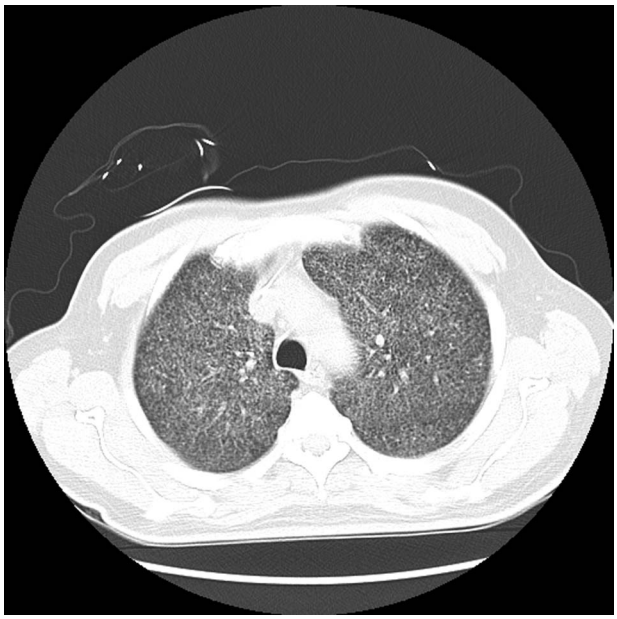

FIGURE 1. Computed tomography scan of the chest without contrast demonstrating innumerable micronodularities consistent with miliary TB. No cavitary lesions were visualized.

On admission to our institution, he had 3 induced sputum samples and a QuantiFERON-TB Gold Plus (QFT-Plus; Qiagen, Germantown, Md) assay. QFT-Plus was positive. All induced sputum samples were acid fast bacilli smear negative. *Mycobacterium tuberculosis*/rifampin resistance polymerase chain reaction testing (Xpert MTB/RIF; Cepheid, Sunnyvale, Calif) was positive. Sputum mycobacterial culture grew acid fast bacilli after 2 weeks of incubation and later confirmed as Mtb complex. The CSF microbiology remained negative including acid fast bacilli smear and mycobacterial culture. Repeat brain MRI with and without contrast was obtained because of persistent encephalopathy and showed innumerable punctate foci of cerebral, cerebellar, and brainstem enhancement, suspicious of TB in the CNS without meningeal involvement (Fig. 2). Repeat spine MRI showed signal abnormality and enhancement within L5, S1, the L5-S1 disc, and minor paravertebral soft tissue changes. Blood mycobacterial culture resulted positive for Mtb complex after 21 days of incubation. Together, with pulmonary micronodules seen on CT chest, enlarged portal hepatic lymph nodes on CT abdomen, and positive Mtb studies, a diagnosis of disseminated miliary TB was made. In addition, given pleocytosis/lymphocytosis seen on CSF analysis, MRI findings of the brain and spine, and cognitive changes, a presumptive diagnosis of CNS-TB was made, specifically tuberculomas without meningitis or arachnoiditis. The standardized microdilution antimicrobial susceptibility testing confirmed that the isolate was susceptible to all 4 first-line anti-TB agents.

Our patient was started on combination therapy with rifampin, isoniazid, ethambutol, and pyrazinamide (RIPE) and experienced gradual resolution of confusion but with persistent mild neurocognitive deficits and clinical improvement during his hospital stay. Given his disseminated TB disease with CNS involvement, the planned duration of therapy was 12 months. Adjunctive corticosteroids were considered, but given improving mentation status and out of concern for worsening disease in setting of high TB organism load, they were not administered. After almost 6 total weeks of hospitalization, he was discharged with arrangements made for him to continue receiving treatment and follow-up assessments through his local county health department under directly observed therapy. At the time of writing, the patient has completed over 3 months of directly observed therapy. He continues to work with a multidisciplinary therapy team with gradual improvement of neurocognitive deficits.

DISCUSSION

We describe a case of rapidly developing disseminated TB in an immunocompetent host acquired iatrogenically from a bone matrix graft contaminated with Mtb. This case is distinctive on multiple counts. First, the patient's diagnosis was challenging—delayed 5 weeks from symptom onset—because of a lack of risk factors for TB. He spent all his life in the United States and denied any contact with someone with known or suspected TB. He was never incarcerated, did not work in a laboratory or healthcare setting, or use illicit drugs. Second, disseminated TB and CNS-TB rarely occur in immunocompetent individuals, and our patient had no history of acquired or congenital immunodeficiency, uncontrolled diabetes, malnutrition, malignancy, or use of immunosuppressive medications.[1,2] His HIV testing was negative, and he was lymphopenic but with CD4 cell count of 272 cells/μL (48% of total T-cell lymphocytes), which can be seen in TB.[3–5] Of note, before infection with TB, the patient had normal lymphocyte counts.

Midway through hospitalization at our institution, the patient was notified by his local hospital, where his spinal surgery was performed, that the product lot for his bone matrix graft was discovered to be contaminated with TB. On May 25, 2021, the Centers of Disease Prevention and Control (CDC) was made aware of a cluster of patients who developed Mtb surgical site infection after spinal surgery at a single facility in another state and had relayed their concern to his local public health department, who communicated this to our team.[6] By June 25, 2021, there were 23 patients identified at this other facility who received bone graft from the same product lot. Nineteen of the 23 patients developed surgical site infections after implantation of this product and had laboratory or imaging evidence of TB in the spine or chest.[6] These infections included surgical site abscess, osteomyelitis, and/or discitis or other manifestations of TB infections such as disseminated TB or TB meningitis.[6–8] The linking factor was a single product lot of FiberCel ("FiberCel") Fiber Viable bone matrix (Aziyo Biologics, Inc, Richmond, CA).[7,8] On June 2, 2021, the manufacturer issued a voluntary nationwide recall of the affected lot.[6,8] The manufacturer reported that 154 total units of this product lot were shipped to more than 30 facilities in 20 different states.[9] At the time of writing, the CDC was working with affected states and health departments to determine the disposition status of units from this lot.[6] The CDC has issued a statement recommending treatment

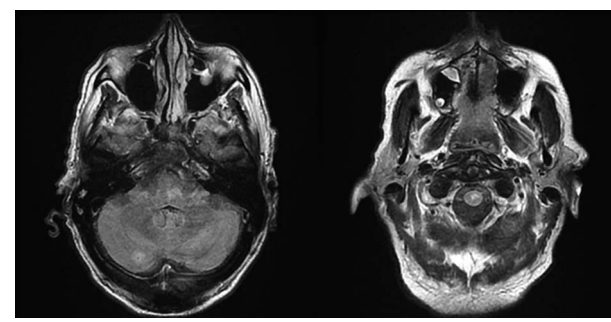

FIGURE 2. Magnetic resonance imaging of the brain (T2 flare image) showing punctate lesion in the right cerebellum and in the pons, representing a tuberculoma.

of all patients who received bone graft from this FiberCel lot regardless of signs or symptoms.[6,10]

CONCLUSIONS

At the time of this report, multiple cases of localized TB surgical site infection were reported by the CDC. However, and to the best of our knowledge, this is the first detailed report of disseminated TB resulting from Mtb transmission from a contaminated bone matrix graft during spine surgery in an immunocompetent host. We hypothesize that our patient developed disseminated infection due to a high inoculum of Mtb, with FiberCel bone matrix serving as a mycobacterium nutrient-rich culture media, placed in a well-vascularized bed. This explains the extensive spread to multiple organs as well as the rapid development of infection within only 4 weeks from initial surgery.

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