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CLINICAL COMMUNICATIONS TO THE EDITOR

Severe Tuberculosis Sepsis in an Immunocompetent Patient

To the Editor:

A rare complication of *Mycobacterium tuberculosis* infection, severe tuberculosis sepsis, is associated with septic shock with multi-organ dysfunction. It has been reported almost exclusively among immunocompromised hosts, especially patients infected with human immunodeficiency virus (HIV). We report a case of sepsis tuberculosis gravissima in an immunocompetent host, review the literature, and highlight the practical difficulties of treating tuberculosis in an intensive care unit (ICU) patient.

Fulminant infections associated with hematogenous dissemination of *Mycobacterium tuberculosis* (MTB) can occur with or without formation of miliary tubercles. The former type results in miliary tuberculosis. The later, much less common and less well known, is referred to as *sepsis tuberculosa acutissima*.[1] Either can progress to septic shock with multiple organ failure termed *sepsis tuberculosa gravissima*. Features associated with this entity include hematologic abnormalities such as DIC, altered mental status, renal insufficiency, refractory hypotension, and respiratory failure/adult respiratory distress syndrome.[2] In one report, acute empyema was also part of this syndrome.[3]

CASE REPORT

A 50-year-old African-American male with no known previous illnesses presented to the Emergency Department with complaints of watery diarrhea for 1 month, odynophagia and weight loss, and feeling weak for several days. He denied melena or hematochezia. He had developed a sore throat over the previous 2 days. He also admitted to unrelenting chronic cough producing mild amount of clear sputum but denied chest pain or fever. He admitted to moderate-to-heavy tobacco and alcohol consumption. Social history also was remarkable for multiple sexual partners and incarceration 20 years prior. He denied intravenous drug use. He was afebrile; blood pressure was 101/80. Examination was unremarkable.

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Labs showed: hematocrit 19.7, white blood cell count 16.7, platelets 441, and mean corpuscular volume 77.6; iron saturation 4%, ferritin 243, Transferrin: 218, Na 121, K 3.3, Cl 91, CO_2 15, BUN 43, Cr 4.1, alb 2.1, HIV negative, and AST, ALT, AP: all normal.

Chest radiograph showed cavitary lesion L hilar area (Figure 1). Chest computed tomography (CT) scan showed a large multilocular cavitary lesion in the superior segment of the left lower lobe and multiple other smaller cavitary lesions, bilateral pleural effusions, and mediastinal lymphadenopathy (Figure 2).

The patient was promptly started empirically on antituberculous therapy, with isoniazid, rifampin, ethambutol, and pyrazinamide. His clinical status, however, quickly deteriorated with worsening hypotension and respiratory failure requiring intubation and initiation of pressors. His sputum stained positive (4+) for acid-fast bacilli and later grew Mycobacteria tuberculosis. No other source of infection was identified.

He gradually improved on antituberculous therapy and was successfully extubated and taken off pressors. He did, however, have residual renal insufficiency requiring dialysis, necrotic fingers likely secondary to prolonged use of pressors, and blindness, probably due to ethambutol.

DISCUSSION

Tuberculosis sepsis is a rare complication of disseminated tuberculosis. It's been mostly reported in severely immunosuppressed individuals, especially with advanced HIV. Gachot et al reviewed a series of 12 patients with HIV or acquired immunodeficiency syndrome (AIDS) and TB requiring ICU admission. Four of the 12 patients required inotropic support, and 3 of those 4 had blood cultures positive for *M. tuberculosis*.[4] HIV patients have an increased risk of mycobacterial infection and, when severely immunosuppressed, an atypical presentation and more rapid progression of disease. Atypical features may include loss of tuberculin reactivity, loss of granuloma formation, diffuse lung involvement, and extrapulmonary dissemination.[5] This condition has been misdiagnosed early in its course because of these atypical features. In addition, co-infection with TB and PCP has been reported. Characteristic intrathoracic lymphadenopathy of TB seen on chest radiograph may help differentiate TB from other diagnoses. Also hyponatremia, although an unusual feature of PCP pneumonia, is quite common in HIV-associated TB.[6] Other etiologies that

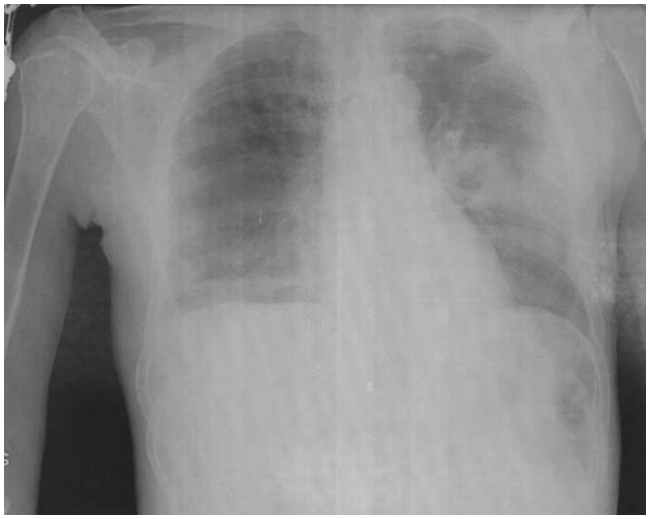

Figure 1 CXR showing L hilar cavitary lesion.

must be considered in AIDS patients include mycobacterium avium complex and CMV.

Respiratory distress and septic shock attributable to *Mycobacterium tuberculosis* in pediatric patients has also been reviewed. Mazade et al reported a 34-day-old infant born at 36 weeks gestation to a mother with miliary TB. They also describe 4 premature infants requiring mechanical ventilation and 6 term infants with either cardiovascular collapse or respiratory failure requiring intubation, all attributable to TB. In infants, progressive respiratory distress, apnea, and hepatomegaly are common but cardiovascular collapse, respiratory failure, DIC, and leukopenia are uncommon.[7]

Sepsis tuberculosis is extremely rare in immunocompetent individuals. Among these, it has been exclusively reported in the setting of miliary tuberculosis, which is itself immunosuppressive. Ours is the first reported case of severe tuberculosis sepsis in an immunocompetent individual without miliary or other evidence of systemic tuberculous infection. It also highlights the practical difficulties of treating tuberculosis in an unconscious patient as well as in the setting of acute renal failure.

Hadad et al reported MTB bacteremia and ultimately death in a 34-year-old male, but the patient never had hypotension or respiratory failure.[8] Pene et al described a 69-year-old Vietnamese/Malagasy female with fever, abdominal pain, diarrhea, cough, mild renal insufficiency, and recurrent autoimmune anemia and thrombocytopenia. On broad spectrum antibiotic coverage her condition deteriorated to nephrotic range proteinuria with anasarca, acute renal failure, DIC, hypotension, and tachycardia, and she expired. Her sputum and ascitic fluid cultures subsequently grew *Mycobacterium tuberculosis*.[9] Finally, Kindler et al described a case of fatal sepsis from MTB in a bone marrow transplant patient.[10]

Septic shock is normally associated with gram-negative bacteria, toxin production from gram-positive bacteria, or fungal infections. In Mycobacterial disease, it is thought to be secondary to tumor necrosis factor production stimulated by lipoarabinomannan from MTB.[1] In vitro studies show that Lipoarabinomannan from MTB stimulates release of TNF from human monocytes and activated peritoneal macrophages.[2]

Recommendations for treatment of all manifestations of pulmonary and extra-pulmonary tuberculosis including sepsis consist of 4-drug therapy with isoniazid, rifampin, pyrazinamide, and either streptomycin or ethambutol for 2-3

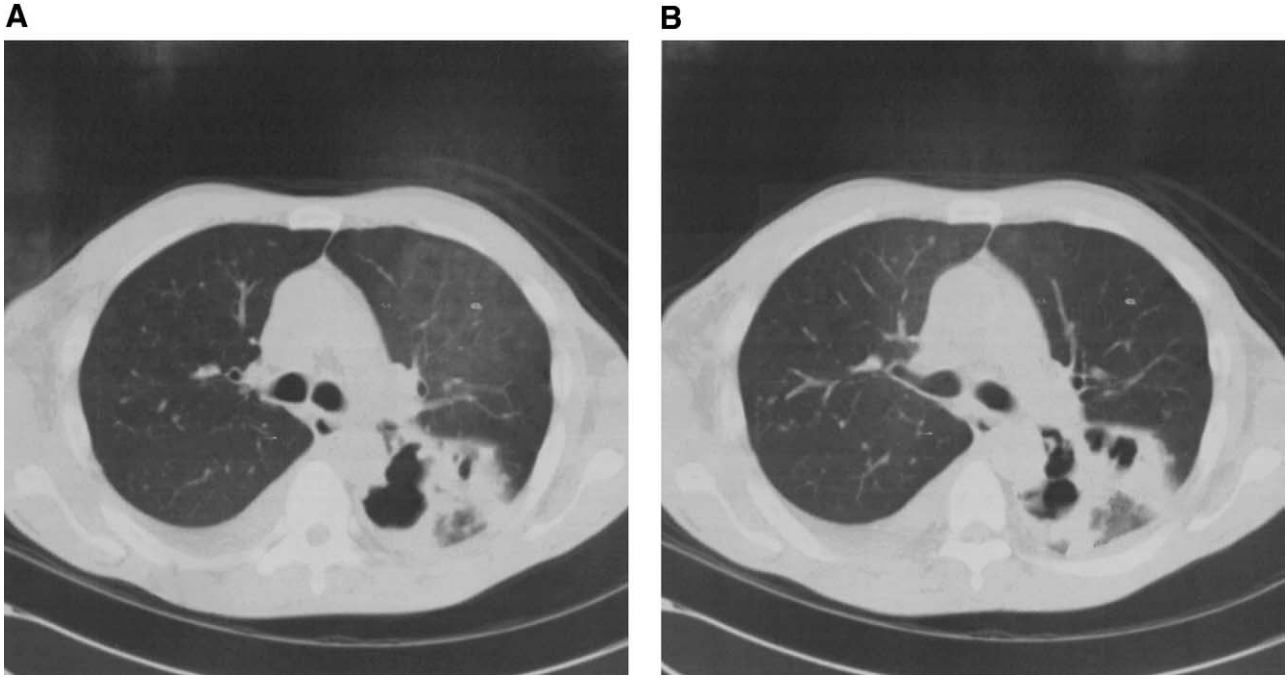

Figure 2 CT chest showing large multilocular cavitary lesion.

Table 1 Dosage Recommendations for Ethambutol, Pyrazinamide and Cycloserine in Patients with Renal Failure*

CL_{CR} (mL/min)	Ethambutol	Pyrazinamide	Cycloserine
≥30	15-25 mg/kg q24h	25-35 mg/kg q24h	250 mg q12h
<30	15-25 mg/kg TIW	25-35 mg/kg TIW	250 mg q24h or 500 mg TIW
Hemodialysis†	15-25 mg/kg TIW	30 mg/kg TIW	250 mg q24h or 500 mg TIW
CAPD	15-25 mg/kg TIW	30 mg/kg TIW	NA

CL_{CR} = creatinine clearance; TIW = three times weekly; CAPD = continuous ambulatory peritoneal dialysis; qxh = every x hours.
*Reproduced with permission from Launay-Vacher et al.[11]
†Drug should be administered after the session on hemodialysis days.

Table 2 Dosage Recommendations for Ethambutol, Isoniazid, Rifampicin and Rifapentine in Patients with Renal Failure*

CL_{CR} (mL/min)	Isoniazid (mg/kg q24h)	Rifabutin (mg q24h)	Rifampin (mg/kg q24h)	Rifapentine (mg/kg BIW)
>50	3-5	600	10 (max. 600 mg/day)	10 (max. 600 mg per dose)
10-50	3-5	300	10 (max. 600 mg/day)	10 (max. 600 mg per dose)
<10	3-5	150-300	10 (max. 600 mg/day)	10 (max. 600 mg per dose)
Hemodialysis†	3-5	150-300	10 (max. 600 mg/day)	10 (max. 600 mg per dose)
CAPD	3-5	150-300	10 (max. 600 mg/day)	10 (max. 600 mg per dose)

CL_{CR} = creatinine clearance; BIW = twice weekly; max. = maximum; CAPD = continuous ambulatory peritoneal dialysis; q24h = every 24 hours.
*Adapted with permission from Launay-Vacher et al.[11]
†Drug should be administered after the session on hemodialysis days.

months, dropping to isoniazid and rifampin alone for an additional 3-4 months. Tuberculous meningitis should be treated for 12 months.

Special considerations in treating ICU patients for tuberculosis include: inability to monitor some side effects of antituberculous medicines, dosing in renal and liver failure, and worsening of renal and liver failure. It is difficult to monitor for peripheral neuropathy and ocular toxicity caused by isoniazid and ethambutol in the comatose patient. For these reasons, caution must be used and the administration of daily pyridoxine is especially important. Streptomycin can cause tinnitus and vertigo, which may go unrecognized. Rifampin and streptomycin can contribute to renal failure. Rifampin can also cause shock and thrombocytopenic purpura, potentially complicating the ICU patient's course. These side effects are more common in intermittently dosed patients (ie, QOD dosing). In renal failure, standard doses of rifampin, isoniazid, and pyrazinoic acid can be given. However, there is some concern about accumulation of pyrazinoic acid metabolites (pyrazinoic acid and 5-hydroxy-pyrazinamide) in dialysis. Tables 1 and 2, adapted from Launay-Vacher et al,[11] present antituberculous drugs dosage recommendations in patients with renal failure. Isoniazid, rifampin, and pyrazinoic acid are all potentially hepatotoxic, but studies have shown that the addition of pyrazinoic acid to 2-drug therapy does not increase mortality. Kimmoun and Samuel[12] recommended starting with half a dose of rifampin and using low dose (3 mg/kg/day) of isoniazid in pre-existing liver failure. Also, streptomycin or ofloxacin can be used as first-line treatment in this instance, and pyrazinoic acid is considered contraindicated.[12] Drug delivery and problems with drug interactions can also be a challenge in treating ICU patients with TB. Drug delivery can be accomplished by using the syrup forms of isoniazid, rifampin, and pyrazinoic acid via nasogastric tube. Pyrazinoic acid can also be given by crushed tablets. Intravenous dosage forms are available for rifampin and isoniazid. Streptomycin and isoniazid can both be given IM. Absorption can be monitored by evaluating urine color change generated by rifampin use and by serum drug levels. Another option would be addition or substitution with intravenous quinolone or macrolide as part of the regimen. However, these second-line drugs are considered less potent. Isoniazid increases levels of some benzodiazepines that may be used for sedation, whereas rifampin can decrease diazepam levels.

Administration of corticosteroids as part of the treatment for TB requiring ICU admission has been suggested if the patient is severely hypoxic or has involvement of their central nervous system, peritoneum, or pericardium.[5] Again, drug interactions can be a problem. Isoniazid can increase the level of prednisone, whereas rifampin can decrease it.[13]

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