CASE REPORT

Surprising pathological and clinical manifestations of miliary tuberculosis

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Accepted 1 April 2018

SUMMARY

We report a surprising pathological finding of miliary tuberculosis (TB) in a 49-year-old Chuukese, immunocompetent woman who was initially admitted to the hospital for a 1-month duration of chronic abdominal pain and intermittent fevers. Her clinical symptoms did not improve despite treatment with vancomycin and piperacillin–tazobactam. Based on the primary abdominal CT findings suggesting advanced ovarian cancer with omental metastatic disease, further workup with omental core biopsy was performed and demonstrated acute neutrophilic necrosis without malignant cells or granulomata. Within the omental tissue, however, many organisms stained positive for acid-fast bacilli despite lack of typical granulomata. The diagnosis of genitourinary TB was confirmed by urine *Mycobacterium tuberculosis*/rifampin automated molecular rapid nucleic acid amplification test. The chest CT showed a millet seed pattern of infiltration which is a hallmark for miliary TB. After initiation of multidrug TB therapy, her fever and abdominal pain drastically improved.

BACKGROUND

Despite growth of new diagnostic methods for tuberculosis (TB) over the past decade, diagnosing TB, especially extrapulmonary, is still very difficult and challenging due to protean clinical presentations. Maintaining a high index of suspicion is very important in patients with fever of unclear origin regardless of immune status, particularly in foreign-born individuals who are originally from endemic countries. In our case, the patient was originally from Chuuk (a member of the Federated States of Micronesia) which had an incidence of TB of 127 cases per 100 000 in 2007, 30 times higher than the incidence of TB in the USA.¹ The typical pathological findings of caseating granulomata may not always be present in miliary TB.² Acid-fast bacilli (AFB) stain and nucleic acid amplification test (NAAT) can be used to increase sensitivity and specificity to diagnose TB in high-risk patients even with the lack of typical caseating granulomata.^{3,4}

CASE PRESENTATION

The patient is a 49-year-old Chuukese HIV-negative woman with no medical history who presented to a hospital in Chuuk with 1-month duration of abdominal pain and intermittent fevers. The abdominal pain was localised to the left lower quadrant, cramping in nature, non-radiating, 4/10 in severity

and associated with low-grade fevers, decreased appetite, weight loss, nausea and vomiting. She denied sick or TB contacts, changes in bowel habits, vaginal bleeding or vaginal discharge. She was a housewife who mostly stayed at home. History of prior BCG vaccine was uncertain. She was not sexually active. She took no medications regularly. She has never had a tuberculin skin test (TST) performed in the past. Gynaecological history was remarkable only for five normal vaginal deliveries. Family history was unremarkable. She denied the use of tobacco, alcohol or illicit substances.

During her hospitalisation in Chuuk, the patient was treated for suspected intra-abdominal infection with a lengthy course of unknown antibiotics without improvement. The patient's family therefore decided to bring her to Hawaii for further medical evaluation and treatment. Her medical records from Chuuk were not available. She was initially brought to a community hospital in Hawaii, where she was initially hypotensive and tachycardic. Laboratory analysis was remarkable for leucocytosis, hyperlactatemia and elevated creatinine. Her initial chest X-ray was unremarkable for infiltrates. She was transferred to our centre for further management.

When she arrived at our institution, she was lethargic and had left lower abdominal pain. Blood pressure was 102/65 mm Hg, pulse was 112 beats/min, respiratory rate was 18 breaths/min and oxygen saturation was 97% on ambient air. Initial temperature was 36.8°C, but she spiked a fever (38.7°C) within the first 24 hours. On physical examination, she had dry oral mucosa, temporal muscle wasting and abdominal tenderness in all four quadrants, especially at the left lower quadrant. There was no rebound tenderness, guarding or rigidity. Gynaecological examination was limited by patient's discomfort. The remainder of the physical examination was unremarkable, including no lymphadenopathy, abdominal mass, hepatosplenomegaly or skin rashes.

LABORATORY RESULTS

On arrival at the community hospital, the initial notable laboratory results were haemoglobin 7.8 g/dL, white cell count $11.6 \times 10^9/L$ with neutrophil 88% (no bands), blood Urea Nitrogen (BUN) 57 mg/dL, creatinine 2.5 mg/dL (no baseline), HCO_3^- 19 mg/dL, alkaline phosphatase 220 mg/dL, albumin 1.3 g/dL, *Lactate dehydrogenase* (LDH) 308 mg/dL and lactic acid 5.2 mg/dL. The CT abdomen and pelvis without contrast showed bilateral ovarian masses,

To cite: Wirunsawanya K, Bolger Jr DT. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223360

Figure 1 Peritoneal and omental nodularity on abdominal CT.

loculated free fluid and multiple soft tissue nodules in the omentum and peritoneum, suggesting peritoneal carcinomatosis (figure 1). The liver, pancreas, intestines, adrenal glands and kidneys appeared unremarkable.

During the hospitalisation at our facility, a transvaginal pelvic ultrasound (US) revealed a 6.8×5.3×7.3 cm complex left ovarian mass with free fluid at Morrison's pouch. Blood cultures were negative for 5 days. Urinalysis was relatively unremarkable except for trace proteinuria and blood without red blood cells. Creatine kinase was normal. Fractional excretion of sodium was 1.7%. Renal US showed normal-sized kidneys without evidence of hydronephrosis, mass or abnormal parenchymal echogenicity.

DIFFERENTIAL DIAGNOSIS

Because of the patient's fever of unclear origin, lower abdominal pain, left complex cyst on transvaginal US and the aforementioned CT findings, our working diagnosis was advanced ovarian cancer with peritoneal carcinomatosis. Tubo-ovarian abscess and intra-abdominal abscess were also suspected. Genitourinary and abdominal TB were also considered, given the high prevalence of TB infection in Chuuk, as well as the patient's persistent fevers despite treatment with broad-spectrum antibiotics. Additionally, metastatic cancer with unknown primary and lymphoma were entertained.

FURTHER INVESTIGATION

Gynaecological oncology service was consulted and recommended an omental biopsy due to a high suspicion of advanced ovarian cancer with omental and peritoneal metastases. The CT-guided omental core biopsy revealed acute neutrophilic necrosis, without malignant cells. AFB staining on tissue and urine samples was 4+ and 2+, respectively (figure 2). A TST was negative. The urine NAAT was also positive for *Mycobacterium tuberculosis* and negative for rifampicin resistance gene mutation. Subsequently, urine culture was positive for *M. tuberculosis* without drug resistance.

After abdominal and genitourinary TB infection was diagnosed, CT chest without contrast was performed and showed innumerable bilateral and small reticulonodular opacities (figure 3). Sputum AFB stains were not obtained because our patient did not have productive cough, even after attempts to induce sputum production with hypertonic saline. HIV 1 and 2 antibodies were negative. Tumour markers including *carcinoembryonic antigen* (CEA) and cancer antigen 125 (CA-125) were normal but CA 19-9 was 104 U/mL (normal range <35 U/mL). Haemoglobin A1c was 5.3 g/dL. Creatinine gradually decreased to 0.7 mg/dL after volume replenishment and initiation of anti-TB

Figure 2 Acid-fast bacillus smears in the omental core biopsy.

medication. In addition, a tissue culture was not obtained in our case, (due to an ordering error) which could have provided accurate microbiological susceptibility.

FINAL DIAGNOSIS

Miliary TB (abdominal, genitourinary and pulmonary TB).

TREATMENT

After the diagnosis of miliary TB was confirmed, our patient received a standard multiple anti-TB regimen of isoniazid, rifampicin, pyrazinamide and ethambutol as the induction phase per Infectious Disease Society of America and the Centers for Disease Control and Prevention (CDC) guidelines.^{5 6} Although tissue culture was not obtained, and urine mycobacterial culture was pending, urine NAAT showed no gene mutation for rifampicin resistance which suggested low likelihood of multidrug resistant TB.^{7 8} Her persistent fevers and abdominal pain improved significantly after 5 days of treatment.

Figure 3 Radiological hallmark for miliary tuberculosis on chest CT.

OUTCOME AND FOLLOW-UP

After hospital discharge, our patient reported to the Department of Health clinic in Hawaii to receive her anti-TB medications and to monitor treatment response. Unfortunately, she was readmitted to the hospital 2 days after the hospital discharge for stress-induced cardiomyopathy and mildly elevated transaminases. Her anti-TB medications were held due to suspected drug-induced hepatitis. She was discharged home and 1 week later, her liver function tests returned to normal. She followed up with an infectious disease specialist, who rechallenged her with the initial medications and thought that pyrazinamide was the culprit. Urine culture eventually grew *M. tuberculosis* with no resistance to medications. Her final regimen of anti-TB medications was isoniazid, ethambutol, rifampicin and levofloxacin. At 6 months of follow-up, she was without symptoms, and imaging showed complete resolution of infection.

DISCUSSION

Miliary TB is a potentially lethal and uncommon form of TB infection which can affect multiple organs, including the lungs and extrapulmonary sites through lymphohaematogenous spread.⁹ In adult immunocompetent hosts with TB infection, the incidence of miliary TB and extrapulmonary TB is approximately 2% and 20%, respectively.^{9 10} There should be heightened clinical suspicion of miliary TB among foreign-born individuals from high-risk countries regardless of immune status.⁹ Early diagnosis is imperative as prolonged delays can lead to increased morbidity and mortality.

The development of miliary TB in our case was most likely due to reactivation of latent TB infection and less likely due to progressive primary TB infection given a protracted clinical course and adult age of the patient.^{9 11} Our patient had no clear risk factors for miliary TB such as HIV infection or AIDS, diabetes mellitus and underlying malignancy.⁹ However, her premorbid nutritional status was difficult to truly determine. Additionally, crowded living conditions and sanitation are concerns for many people living in Chuuk. Our case also featured anergic pathology without a concomitant immunodeficiency disease. The histopathological findings of caseating granulomata are expected in TB infection. Sometimes, typical caseating granulomata are not found in patients who have anergic TB infection, similar to our case. The immunological mechanism of anergic TB infection may involve reduced number and/or responsiveness of circulating T-lymphocytes and dysregulation of cytokines, especially interleukin (IL) 4 and IL-10.^{9 12 13} Additionally, it has been reported that serum immunoglobulins and antibodies specific for *M. tuberculosis* antigen are significantly increased among patients with miliary TB.^{14 15} The inhibition of an effective cell-mediated response by these antibodies or circulating antigen-antibody complexes could result in an anergic immune response.^{14 15}

Miliary TB can present with pulmonary symptoms and extrapulmonary disease.⁹ Extrapulmonary disease can be the initial presentation and be more pronounced than pulmonary symptoms in miliary TB, especially in patients with HIV infection.⁹ According to recent surveillance data of 9421 patients with TB from the CDC in 2014, extrapulmonary TB was reported to be about 21%.¹⁶ Lymph nodes (38.2%) and pleura (16.3%) were the most commonly affected sites in extrapulmonary TB.¹⁶ Once the diagnosis of extrapulmonary TB is established, the exclusion of pulmonary TB is necessary in order to prevent the transmission of the disease.

To diagnose miliary or extrapulmonary TB, mycobacterial culture of blood, tissue or body fluids is required because cultures provide the identification of species and drug susceptibilities. While the mycobacterial culture is pending, body fluids or tissue AFB stains and NAAT can be used to preliminarily diagnose TB infection. Currently, NAAT has been recommended by WHO to use as an adjunctive method for diagnosis because of its rapid turnaround time and better sensitivity compared with traditional AFB culture and stains, respectively.³ In addition, NAAT facilitates the preliminary result of drug susceptibilities. Xpert *M. tuberculosis* /rifampin (MTB/RIF) has been shown to have overall sensitivity of 83.1% and a pooled specificity of 98.7% for the diagnosis of extrapulmonary TB in a recent meta-analysis.^{17 18} Notably, NAAT must be interpreted with AFB stains given the possibility of false negative and positive results of NAAT. Positive results of AFB stains and NAAT are supportive of the diagnosis of TB because the positive predictive value for Food and Drug Administration-approved NAATs for TB is >95% in AFB stain-positive cases.¹⁰ However, TB infection cannot be excluded by a negative result of NAAT or AFB stains if the clinical suspicion of TB is high.⁴ Our patient's diagnosis of miliary TB (abdominal, genitourinary and pulmonary TB) was confirmed by positive AFB stain in omental tissue and urine, positive urine NAAT for *M. tuberculosis*, and the radiological hallmark of millet seed pattern on chest CT. MTB/RIF automated molecular rapid NAAT was used to guide the diagnosis and treatment in our case.

We report a novel case of miliary TB without typical caseating granulomata in an immunocompetent host. Omental sampling showed only frank necrosis with neutrophils. It is very important to understand that anergic pathology can be found in tissue samples of patients with miliary TB regardless of the immune status. TB infection should always be suspected in foreign-born individuals from high-risk countries who present with fever of unknown origin. Successful treatment and cure from TB infection, including miliary TB, is likely when diagnosis is timely and appropriate treatment is initiated.

Learning points

- ▶ Miliary tuberculosis (TB) can present with protean clinical manifestations and unexpected pathological findings, such as abscesses.
- ▶ TB, in all its forms, should be considered in patients from endemic areas and within impoverished populations regardless of immune status.
- ▶ Pulmonary TB must be excluded to prevent the transmission of disease once the diagnosis of extrapulmonary TB is established.
- ▶ Rapid and effective molecular DNA-based tests can be used to confirm the diagnosis of *Mycobacterium tuberculosis* and provide the preliminary results of susceptibility which enables timely and appropriate therapy.

Acknowledgements We would like to express our appreciation to Dr. Aaron Hoo for assistance with pre-submission reviews that greatly improved the manuscript, and to the patient who kindly gave consent for this case report.

Contributors KW wrote the manuscript under the guidance of DTBJ who edited and revised the manuscript. Both authors cared for the patient and determined the education areas in which to focus.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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