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Multiple Organ Failure and Septic Shock in Disseminated Tuberculosis

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ABSTRACT

The diagnosis of disseminated tuberculosis should be entertained in all patients with unexplained fever associated with hepatomegaly and/or splenomegaly with or without anomalies in liver function tests and haemogram. It should be considered as a possible cause of septic shock especially in patients with typical risk factors such as advanced age, diabetes, alcoholism or immunosuppression. Prompt therapy could be life saving in an otherwise potentially fatal condition. It is therefore appropriate to initiate anti-tuberculosis treatment as soon as such a diagnosis is suspected and not await final confirmation.

Keywords: multiple organ failure, septic shock, disseminated tuberculosis

INTRODUCTION

Tuberculosis is a classic example of a protean disease that can resemble other illnesses or present in an atypical manner. The condition is certainly not the first diagnosis that comes to mind when a patient presents with an acute illness rapidly complicated by multiple organ failure and septic shock. Under these circumstances the condition can be overlooked even in Malaysia where tuberculosis is common and physicians' awareness of the disease is high.

A middle-aged lady admitted to the University Hospital highlighted this diagnostic dilemma. The diagnosis of disseminated tuberculosis was confirmed only after death.

CASE REPORT

A 37-year-old Indonesian lady was admitted following a one-week illness of high fever with chills, malaise, anorexia and right hypochondrial discomfort. There was no cough, haemoptysis, night sweats nor recent weight loss. Her past medical history was unremarkable and she had no past history of tuberculosis. There was no history of alcohol abuse, intravenous drug use or risk factors for human immunodeficiency virus (HIV) infection.

The patient came to Malaysia from Java five years ago and worked as a domestic helper in Kuala Lumpur. She was married but her husband died in 1988 after an unexplained illness of fever, cough and weight loss.

Physical examination showed an obviously unwell and lethargic patient. Her temperature was 38.8°C, pulse 125/min and blood pressure 114/60 mmHg. She was jaundiced with an enlarged liver, which was felt at 5 cm below the right costal margin. The spleen was palpable at 1.5 cm below the left costal margin. Examination of the lungs as well as the other systems was unremarkable.

Laboratory investigations revealed a haemoglobin of 107g/L, WBC count of 11.9 x 10^9/L with 87% neutrophils, 5% lymphocytes, 6% monocytes and 2% eosinophils, and platelet count of 84 x 10^9/L. The prothrombin ratio was 1.7, partial thromboplastin time of 55.3s (control 33.0s), fibrinogen degradation products were negative. Her ESR was 20 mm/hour. Blood films were repeatedly negative for malaria parasites. Her blood urea was 3.5 mmol/L, creatinine 76 μmol/L, albumin 18g/L, total bilirubin 75 μmol/L (predominantly conjugated), ALP 1194 IU/L, AST 196 IU/L and ALT 148 IU/L.

Urine analysis was unremarkable. A portable chest X-ray showed ill defined mottling in the right base. Abdominal ultrasonography revealed hepatosplenomegaly with no focal lesion. The gallbladder wall appeared thickened but there was no stone and the intrahepatic and extrahepatic ducts were normal.

She was initially treated with intravenous ampicillin and metronidazole but ampicillin was soon changed to ceftazidime and gentamicin as gram-negative sepsis was considered. Over the next 3 days she failed to improve and remained febrile with intermittent spikes of temperature. Thrombocytopenia and coagulopathy persisted and she developed upper gastrointestinal bleeding presumed to be due to stress ulceration. She was transfused with blood products and given H2-antagonist.

Three sets of blood culture taken on admission yielded no organism. Hepatitis A and C antibodies and HBsAg were undetected. An abdominal CT scan failed to detect any localised pus collection. Her antibiotics were switched to ceftriazone as enteric fever was considered. Over the subsequent 3 days, her jaundice deepened, her fever persisted and there was gradual deterioration in her renal function. Penicillin and doxycycline were added.

On the seventh day of hospitalisation, the patient's respiratory function worsened progressively and mechanical ventilation was subsequently instituted. A repeat chest X-ray revealed bilateral small pleural effusions and ill defined basal infiltrates. She became

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hypotensive and was treated with intravenous fluids and dopamine infusion. Empirical anti-tuberculosis treatment with isoniazid and rifampicin was commenced.

Despite maximum effort to improve her circulation with intravenous fluids, dopamine and adrenaline infusion, she became increasingly hypotensive. Oliguric renal failure developed and she died on the eighth day of hospitalisation.

A paired Widal and Weil-Felix test was unremarkable. Antibodies to HIV, dengue and leptospira were undetected. Connective tissue disease screening was negative. A post-mortem liver biopsy revealed multiple small caseating epithelioid granulomata. Acid fast bacilli were noted on Ziehl-Neelsen staining. Extensive microvesicular steatosis was present. A final diagnosis of disseminated tuberculosis was made.

DISCUSSION

This lady presented with an acute fulminant illness that led to multiorgan failure and death in approximately 2 weeks. Disseminated tuberculosis was the final diagnosis based on the findings of post-mortem liver biopsy. All the features of this case can be explained on the basis of disseminated tuberculosis. No other cause of multiorgan failure and shock could be identified in this patient.

Disseminated tuberculosis is an uncommon but serious illness resulting from active haematogenous spread of *Mycobacteria tuberculosis* to several organs in the body. It often occurs in individuals with an underlying illness such as diabetes, alcohol abuse, parenteral drug use or other conditions of immunosuppression[1]. This patient had no such risk factors but it was not unlikely for her to have acquired tuberculosis. She grew up in an area where tuberculosis is endemic and common. Her husband who died in 1988 could well have the infection before his death in view of the history of fever, cough and weight loss.

Disseminated tuberculosis commonly poses diagnostic difficulties as the principal symptoms and clinical findings are often non-specific. Tuberculin skin test is often non-reliable. The chest X-ray appearance may not be characteristic. Appropriate therapy is thus frequently initiated too late[1,2]. Clinical confirmation of the diagnosis of disseminated tuberculosis is established by bacteriological and/or histological materials. However sputum or gastric aspirate smears frequently (up to 55%) fail to detect acid fast bacilli. Cultures are also not always rewarding and they are too time consuming in critical situations[3]. In these circumstances, a biopsy of palpable lymph nodes, bone marrow, liver, serosal surfaces or pulmonary tissue can be of tremendous help. In a series of 109 patients with miliary tuberculosis, the diagnosis was made by transbronchial biopsy in 44 of 51 patients, bone marrow examination in 19 of 22 patients and liver biopsy in all 10 patients in whom it was undertaken[4]. For this lady who had thrombocytopenia, coagulopathy and was probably too ill to allow for an invasive diagnostic procedure, a bone marrow biopsy would have been an appropriate and the safest procedure. The diagnostic yield for tuberculosis would have been high in the presence of haematological abnormalities.

The history of this patient's illness though short is compatible with the diagnosis of disseminated tuberculosis. In the retrospective survey of 109 patients treated for miliary tuberculosis, the median symptom duration was 4 weeks with a range of 1 to 52 weeks[4]. Hepatomegaly is not uncommon in disseminated tuberculosis. It has been noted in more than one third of patients with miliary tuberculosis[2]. Abnormal findings in liver function test are often reported and are a result of granulomatous response to the infection[4].

A variety of abnormal haematological pictures have also been described in disseminated tuberculosis[5]. In the same series of 109 patients, lymphopenia was noted in 87% of the patients, leucopenia in 15%, thrombocytopenia in 83%, pancytopenia in 5% and disseminated intravascular coagulation occurred in 4 patients[4]. The haematological abnormalities are usually associated with granulomatous inflammation of the bone marrow. Bone marrow necrosis has also been described[6].

Disseminated tuberculosis leading to multiorgan failure and septic shock has been reported in both non-HIV as well as HIV infected individuals[7-11]. In humans, the presence of circulating tumour necrotic factor (TNF) after the administration of endotoxin suggests that this cytokine may mediate, in part, the haemodynamic disturbances of septic shock[12]. In vitro, lipoarabinomannan from *Mycobacteria tuberculosis* has been noted to stimulate the release on TNF from human blood monocytes and activated macrophages[13]. It has been postulated that in vivo lipoarabinomannan or other mycobacterial products may behave in the same manner as bacterial lipopolysaccharide[7].

With regards to the prognosis, disseminated tuberculosis carries significant mortality. A fatality rate of 36% was reported resulting from delayed diagnosis and failure to initiate immediate antituberculous chemotherapy[1]. An age of above 60 years, lymphopenia, thrombocytopenia, hypoalbuminemia, elevated transaminase levels, and treatment delay were identified as the independent predictors of mortality in another study[4]. In our patient, 5 of the 6 unfavourable predictors were present.

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