CASE REPORT

TUBERCULOSIS OR SYSTEMIC LUPUS ERYTHEMATOSUS? A DIAGNOSTIC AND THERAPEUTIC DILEMMA

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Abstract. The diagnosis of patients with fever of unknown origin (FUO) is often problematic because the range of possible differential diagnoses is broad. We report on a case in which a patient presented with FUO and was subsequently found to have both a collagen vascular disease and an intercurrent infection. Treatment for the collagen vascular disease with corticosteroids exacerbated the intercurrent infection. The problems in the diagnosis and management of such cases are discussed.

Fever of unknown origin (FUO) has been defined as a temperature of higher than 38.3ºC (recorded repeatedly) that persists for more than three weeks and that remains undiagnosed despite one week of inpatient investigations (Petersdorf and Beeson, 1961). Making a diagnosis in such cases remains a challenge as the possibilities are numerous. Infections are the commonest cause of FUO, accounting for 22.5-40% of cases; other common causes are collagen vascular diseases (13-21.5%) and neoplasms (7-31%) (Gelfund and Dinarello, 1998). Treatment of such patients is also difficult as patients with collagen vascular diseases require immunosuppression, which can exacerbate occult infections.

We report on a case in which a patient presented with FUO and was subsequently found to have both a collagen vascular disease and an intercurrent infection. The problems in the diagnosis and management of such cases are discussed.

Mr SM, an 18-year-old Indian tile cleaner, presented on the 17th May 2000 with a 6-month history of progressive weakness and lethargy that was associated with myalgia and generalized body pain. He also had an intermittent low grade fever which was not associated with chills, rigors or night sweats. The patient complained of a loss of appetite, weight loss, recurrent lower abdominal pain with frequent loose stools. Stools were not accompanied by passing out of mucous or bleeding per rectum. There was no vomiting. Subsequently, the patient developed painless bilateral ankle swelling.

He had no significant past medical history and systemic enquiry was otherwise normal. His grandfather had a history of pulmonary tuberculosis. He was a non-smoker, did not drink alcohol and denied any history of unprotected sexual intercourse.

On physical examination, the patient was cachectic and dehydrated. He opened his eyes spontaneously but was confused and unable to obey commands. He was febrile, 38ºC. He was pale but free of jaundice and clubbing; there was no lymphadenopathy. Old vasculitic lesions over his palms, soles and digits were noted. On fundoscopy, cytoid bodies were seen bilaterally. He had oral candidiasis. There was bilateral pitting ankle edema. Cardiovascular, respiratory and abdominal examinations were normal. There was no evidence of arthritis, rashes, alopecia or oral ulcers.

Investigations yielded the following results: hemoglobin 6.5 g/dl, MCV 76 fl, MCH 25.4 pg, white cell count (WCC) 6.5 $x10^9$/l (neutrophils 81% and lymphocytes 11%), platelets 281$x10^9$/l,

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erythrocyte sedimentation rate (ESR) 76 mm/hr, serum albumin 18 g/l [normal range (NR) 35-50], alkaline phosphatase 445 IU/l (NR 30-300), alanine aminotransferase (ALT) 126 IU/l (NR 5-35), aspartate aminotransferase (AST) 116 IU/l (NR 5-35), gamma-glutamyl transpeptidase (γGT) 883 IU/l (NR 11-51), total bilirubin 4 μmol/l (NR 3-17), total cholesterol 5.9 mmol/l (NR 3.6-5.2), triglycerides 3.5 mmol/l (NR 0.4-1.5), 24-hour urinary protein excretion 3.19 g/dl (NR < 0.5), serum iron 5.2 μmol/l (NR 9.5-29.9), ferritin 895.2 μg/l (NR 22-322), normal coagulation profile, complement (C) 3 30 mg/dl (NR 86-184), C4 <10 mg/dl (NR 20-59), anti-nuclear antibody (ANA) positive 1:320, double-stranded DNA 1,893 (NR < 200), IgG 2,040 mg/dl, (NR 931-1,916), IgA 438 mg/dl (NR 70-473), IgM 125 mg/dl (NR 34-265). His peripheral blood film showed dimorphic red blood cells. Viral hepatitis serology was negative. Fecal occult blood tests were negative. Urine microscopy showed urine RBC 102/μl (NR 0-1), urine WBC 37/μl (NR 0-3) but no casts or bacteria. Blood, urine and stool cultures were negative. The Weil-Felix test for typhus and the Widal test for *Salmonella typhi* and *S. paratyphi* were negative. Sputum culture showed *Acinetobacter* species. Sputum for acid-fast bacilli (AFB) was negative. He was negative for HIV-1 antibody. The C-reactive protein (CRP) on admission was <0.8 mg/dl (NR 0.0-0.8).

Chest x-ray was normal. Upper gastrointestinal endoscopy showed esophageal candidiasis with no peptic ulcer disease; abdominal ultrasound was normal. An echocardiogram showed normal left ventricular function and no vegetations.

Because of the significant proteinuria and active urine sediments, a renal biopsy was performed on the 8th June 2000; active diffuse proliferative lupus nephritis (WHO Class IV) with segmental glomerulitis was reported and marked tubulointerstitial inflammation and vasculopathy were also found. A diagnosis of systemic lupus erythematosus (SLE) with renal and skin involvement was made.

The patient was started on intravenous ampicillin-sulbactam for his *Acinetobacter* infection; for his lupus nephritis, he was given three days of intravenous (IV) methylprednisolone (500 mg daily) followed by oral prednisolone (40 mg). His esophageal candidiasis was treated with oral fluconazole (400 mg daily).

His general condition improved and his fever settled after a few days. However, five days later, his fever recurred. On this occasion, it was associated with a productive cough and pain and swelling of his left ankle and knee. The patient had not been in contact with tuberculosis patients while he had been in hospital. On examination, he had shotty right anterior cervical lymphadenopathy and coarse crepitations in the lower zone of the right lung. A repeat chest X-ray showed clear lung fields. His left knee and ankle were swollen and tender on palpation.

Aspiration of the left knee recovered blood-stained synovial fluid with RBC 5,680, WCC 600 (polymorphs 80%, lymphocytes 20%); no organisms or crystals were seen. His blood WCC had risen to $20x10^9$/l and the CRP was also elevated (14.4 mg/dl). No bacterial organisms were cultured from blood, sputum, or urine; fungal blood cultures were also negative. A repeat abdominal ultrasound showed no abnormality. However, a repeat echocardiogram showed a small pericardial effusion. A further chest X-ray (21st June) showed mild reticular changes which became more marked after one week. On the 24th June, two samples of sputum were positive for AFB.

He was started on anti-tuberculosis drug therapy: ethambutol 1g daily, ofloxacin 400 mg daily, and clarithromycin 500 mg daily, due to his liver impairment. At the same time, a broad-spectrum antibiotic (imipenam) was given as he remained unwell and febrile. His oral prednisolone was switched to a small dose of IV hydrocortisone for adrenal support.

Despite all these measures, his condition failed to improve. He continued to have a spiking temperature and required ventilatory support on the 25th June 2000. He then developed disseminated intravascular coagulopathy and went into acute hepato-renal failure despite all supportive measures. The patient died on the 27th June 2000. Autopsy showed disseminated TB in the lungs, kidneys, liver and spleen.

This patient illustrates the diagnostic difficulties in FUO. His initial presenting problems

were non-specific, with abdominal symptoms as well as fever. The fever, alopecia, proteinuria and later the immunological tests, suggested a diagnosis of SLE. However, SLE is much more common in females and our patient was male. Fever and weight loss could also be due to TB, especially in a country endemic for TB, such as Malaysia. It has been estimated that the prevalence of TB in Southeast Asia is 524 per 100,000, which is the highest of any region of the world (Dye *et al*, 1999). Infections, especially extra-pulmonary TB, remain a leading cause of FUO (Gelfund and Dinarello, 1998). Therefore, in this patient, a thorough search for TB was made when he was first admitted: all the initial investigations were negative. However, the diagnosis of extra-pulmonary TB is difficult: miliary or disseminated TB can often present with fever, night sweats, anorexia, weakness and weight loss without any respiratory symtoms or sign (Raviglione and O'Brien, 1998). In addition, SLE patients have an increased susceptibility to infection due to many abnormalities in their immune system, such as immunoglobulin deficiency, acquired and inherited complement deficiencies, defects in chemotaxis and phagocytic activity and delayed hypersensitivity and abnormalities of cellular immunity (Ginzler, 1997). Therefore, both problems can co-exist in the same patient.

Several investigations for TB were unhelpful in this patient. The chest X-ray is frequently abnormal in patients with disseminated TB (Raviglione and O'Brien, 1998) but this was not the case in our patient until nearly a month after he was admitted. Initial sputum samples for AFB were negative; his Mantoux test was negative. It is well-known that false-negative reactions on PPD skin testing are common in patients with overwhelming TB (Raviglione and O'Brien, 1998). Interestingly, a study from Malaysia suggested that 86% of patients with active TB had a positive Mantoux test, and those cases with a positive Mantoux test but no evidence of active TB had evidence of past infection with TB. The study concluded that the Mantoux test in Malaysian patients was a sensitive but non-specific test in the diagnosis of active TB (Yaacob and Ahmad, 1990).

The measurement of autoantibodies for the diagnosis of collagen vascular diseases is generally useful, but it is known that chronic infections such as TB can also give rise to elevated autoantibody levels. Up to 40% of TB patients can have a positive ANA. However, antibodies to double-stranded DNA are said to occur rarely (< 5%) in patients with TB (Adebajo and Isenberg, 1995). Our patient's markedly elevated double-stranded DNA titer was probably due to his SLE. The American College of Rheumatology has published criteria for the identification of patients with SLE (Tan *et al*, 1982): a person is said to have SLE if four of the following eleven criteria are present, namely, malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder or presence of ANA. Strictly speaking, this patient did not fulfill these criteria for the diagnosis of SLE: he had only three of the eleven criteria: renal disease, positive ANA and positive double-stranded DNA (immunologic disorder) in a high titer only. Nevertheless, based on his renal biopsy findings, we decided to treat him for SLE.

There is no doubt that high-dose corticosteroids, including pulsed IV methylprednisolone and other immunosuppressants, are the treatment of choice in proliferative lupus nephritis (Austin and Barlow, 2000). The use of corticosteroids in patients with TB is unclear: it has been recommended that adjunctive corticosteroid treatment be considered in patients with tuberculous meningitis, pericarditis (Joint Tuberculosis Committee, 1998), or peritonitis (Alrajhi *et al*, 1998). There have been no studies to show that the use of corticosteroids increases the risk of developing new TB or reactivating old TB (Cline and Davis, 1997). However, in the absence of effective anti-tuberculosis therapy, corticosteroids enhance the virulence of *Mycobacterium tuberculosis* (Varon and Marik, 2000). Our patient, two weeks following his IV methylprednisolone, developed respiratory symptoms and shadowing on his chest X-ray. We postulate that his pre-existing disseminated TB spread following the corticosteroid therapy; it would be unlikely that he developed TB *de novo* during his four-week hospitalization given that he had had no obvious close contact with TB patients.

It has been shown that the use of prophylactic isoniazid in SLE patients starting long-term corticosteroids in a country endemic for TB (India) reduces the incidence of future TB (Gaitonde *et al*, 2002). However, in this case, the use of just one anti-tuberculosis drug would not have stopped the development of disseminated TB. Another course of action may have been to stop his oral prednisolone as soon as his fever recurred, shortly after the IV methylprednisolone. However, this may have led to an exacerbation of his lupus nephritis.

In conclusion, in patients with prolonged fever and an atypical presentation of connective tissue disease, the possibility of TB should always be borne in mind.

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