

AUTOIMMUNE HEMOLYTIC ANEMIA ASSOCIATED WITH INTESTINAL TUBERCULOSIS

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Tuberculosis, a common disease in the developing world and a resurging problem in the developed world, is associated with numerous hematological manifestations. The most common manifestation is normochromic normocytic anemia of chronic disease. Hemolytic anemia is rare, and there are only a few previously reported cases. We report a case of autoimmune hemolytic anemia (AIHA) associated with intestinal tuberculosis which responded to antituberculous therapy alone. To our knowledge, this is the fourth case to be reported in the literature.

Case Report

A 21-year-old Indonesian housemaid presented to the Emergency Department with a one-week history of vomiting and vague abdominal pain. She had a 4-week history of diarrhea and weight loss of about 3 kg associated with intermittent fever but no night sweats. Two weeks prior to presentation, she had had an upper respiratory tract infection, which resolved spontaneously. She had not been receiving any medications on presentation, and a review of her systems had been unremarkable.

On examination, the patient was found to be pale, febrile (temp. 38.5°C) and mildly jaundiced. Examination of the abdomen revealed mild tenderness in the right iliac fossa but no palpable masses. The remainder of her examination was within normal limits.

Laboratory results were significant for the following (Table 1): WBC 9.8x10⁹/L (59% neutrophils, 31% lymphocytes, 7% monocytes, 3% eosinophils); Hb 5.1 g/dL; platelets 314x10³; MCV 110 fL; MCH 36.2 pg; reticulocyte count 15.4%, and erythrocyte sedimentation rate (ESR) 150 mm/hr. Antiglobulin tests (both direct and indirect) were strongly positive. Cold agglutinins were detected as the responsible antibodies. Unfortunately, the thermal amplitudes of the cold agglutinin could not be determined. Liver function tests (LFT) revealed total bilirubin of 50 µmol/L (normal range up to 17 µmol/L),

indirect bilirubin 40 µmol/L, and lactate dehydrogenase levels of 1480 m/L (normal range 230-460 m/L). The rest of the LFT, urea and electrolytes were normal. Peripheral blood smear showed moderate polychromasia and macrocytosis.

Serology for mycoplasma, respiratory viruses, human immunodeficiency virus and cytomegalovirus were negative, as was the result of Paul-Bunnell test. Antinuclear antibody and anti-DNA antibody tests were also negative. Hemoglobin electrophoresis was normal (A 97.5% AI, 2.5% A2), and serum iron, TIBC, folate and B₁₂ levels were within normal limits. Bone marrow examination revealed normal bone marrow with normoblastic hyperplasia.

Blood, urine and stool cultures were all negative. Mantoux test with 5 IU of PPD was strongly positive (30 mm induration). Upper gastrointestinal tract endoscopy was normal. Ultrasound scan of the abdomen revealed hypoechoic nodules adjacent to the lower one-third of the inferior vena cava (IVC), suggesting enlarged lymph nodes. CT scan of the abdomen confirmed the presence of enlarged lymph nodes (2x3 cm) adjacent to the lower one-third of the IVC, in addition to thickening of the walls of the cecum and terminal ileum. Colonoscopy showed areas of superficial ulceration in the region of the hepatic flexure and gross narrowing of the terminal ileum precluding entry of the endoscope. Biopsies taken from the involved areas showed caseating granuloma without acid fast bacilli (AFB) on staining. Culture of the biopsied material, however, grew *M. tuberculosis*, which was sensitive to the first-line drugs. The patient was started on four anti-TB drugs (rifampicin 450 mg, isoniazid 300 mg, ethambutol 800 mg and pyrazinamide 1 g orally daily). There was remarkable response as her symptoms of abdominal pain, vomiting and diarrhea resolved within two weeks. She gained 5 kg over a three-month follow-up period, and the hematological features resolved (Table 2).

Discussion

On the basis of clinical, colonoscopic and histopathologic features, our patient was treated as a case of intestinal tuberculosis. Although hematological features were of autoimmune hemolytic anemia, steroids were not given, as we believed hemolysis was secondary to

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TABLE 1. Hematological indices before treatment.

| Hospital day | Hb (g/dL) | MCV (fL) | Retic. count (%) | ESR (mm/hr) | Coomb's test |
|--------------|-----------|----------|------------------|-------------|--------------|
| 1st | 5.1 | 110 | 15 | 150 | +++ |
| 5th | 8.9 (PT) | 100.8 | 10.5 | N/A | +++ |
| 10th | 6.8 | 114.8 | 15.6 | 121 | +++ |

NA=not available; PT=post-transfusion.

TABLE 2. Hematological indices on treatment

| Treatment day | Hb (g/dL) | MCV (fL) | Retic. count (%) | ESR (mm/hr) | Coomb's test |
|---------------|-----------|----------|------------------|-------------|--------------|
| 3rd | 8.2 | 118.9 | 22 | 95 | ++ |
| 30th | 11.5 | 98.0 | 8 | 40 | ++ |
| 60th | 13.9 | 90.5 | 1.6 | 5 | NEG |
| 100th | 13.4 | 88.4 | 1.0 | 2 | NEG |

tuberculosis. This responded to antituberculosis therapy alone.

Coburn et al.¹ described an incidence of active tuberculosis infection of 4% -6% in patients with hematological disorders, compared with 0.2% in all other hospital admissions. Similarly, many of the anti-TB drugs have been associated with various hematological complications.²

The most common hematological abnormality associated with tuberculosis is normocytic normochromic anemia of chronic disease. Various abnormalities affecting blood elements have previously been described,³ however, hemolytic anemia has only been reported in three previous reports.⁴⁻⁶ Our case demonstrated hemolysis (increased reticulocyte count, lactic dehydrogenase and indirect bilirubin) of an autoimmune nature (positive antiglobulin test). The diagnosis of *M. tuberculosis* was established by the identification of caseating granuloma, positive TB culture and complete response to anti-TB drugs.

Autoimmune hemolytic anemia is most often of a primary nature, but it can also be secondary. A secondary cause can be considered when autoimmune hemolytic anemia and the underlying disease occur together with greater frequency than can be accounted for by chance alone; or when it reverses simultaneously with the correction of the associated disease; or when AIHA and the associated disease are related by the evidence of immunologic aberration. Our case falls into the second category. A prior upper respiratory tract infection in our patient may implicate other organisms, particularly viruses and mycoplasma. The prolonged course and the negative serology for the common viruses and mycoplasma, however, make these organisms less likely as causative agents. Moreover, the response after commencing anti-tuberculous therapy makes it the most likely cause.

A large number of organisms are known to cause hemolytic anemia. The mechanisms involved vary from direct invasion (e.g., malaria) to release of potent toxins (e.g., *Clostridium welchii*) to AIHA (e.g., *Mycoplasma pneumonia* – the most commonly recognized). Various mechanisms of AIHA have been postulated, including

absorption of immune complexes and complement cross-reacting antigen and a true autoimmune state with possible loss of tolerance secondary to the infectious organism.⁸ Our case, similar to the case reported by Siribaddana and Wijesundera,⁶ who described a case of tuberculous lymphadenitis with positive direct and indirect antiglobulin tests, was due to cold agglutinins. The two earlier cases,^{4,5} however, only demonstrated evidence of hemolysis with a positive antiglobulin test in patients with genitourinary and pulmonary tuberculosis, respectively, who responded to anti-tuberculous therapy. Boots et al.⁹ have demonstrated the presence of platelet surface membrane IgG in a patient with ITP and tuberculosis. Probably the same immune mechanism is responsible for the AIHA in this case.

With the resurgence of TB in the developed world and increase in the number of cases from the developing countries, more cases of TB-associated AIHA should be anticipated. The main treatment of AIHA, whether primary or secondary, is steroids. The inadvertent use of steroids in an undiagnosed and untreated case of tuberculosis with AIHA, however, can have deleterious consequences. For this reason, we advocate the exclusion of tuberculosis as a cause of AIHA before commencing steroids, especially in areas such as Saudi Arabia, where the disease is common. Whether steroids should be used or not in an individual case of secondary AIHA depends on the severity of the case and the state of the patient. Our patient had a limited disease, was young, and had no symptoms attributable to anemia. For these reasons, and to confirm the causative role of *M. tuberculosis* in AIHA, steroids were withheld.

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