CASE REPORT

Haemophagocytic syndrome with disseminated intravascular coagulation associated with tuberculosis

Eya Cherif, Nabil Bel Feki, Lamia Ben Hassine, Narjess Khalfallah

Department of Internal Medicine, Charles Nicolle's Hospital, Tunis, Tunisia

Correspondence to

Dr Eya Cherif,
eyacherif@yahoo.fr

SUMMARY

Haemophagocytic syndrome (HPS) is a clinical entity that combines non-specific clinical and biological features. The diagnosis is usually confirmed by a bone marrow examination. HPS may be primary or secondary to a malignancy or to an infectious or autoimmune disease. Early aggressive survey of the aetiology and optimal treatment of the underlying disease improve the outcome of life-threatening HPS. Infection-associated HPS occurs predominantly in immunocompromised patients and is usually fatal. Leading trigger agents are viruses, especially the Epstein-Barr virus and cytomegalovirus. Mycobacterial infections associated with HPS are rare but should be considered in those patients where there is associated fever of unknown origin. We present a case of disseminated tuberculosis-associated HPS.

BACKGROUND

Various haematological abnormalities are seen in tuberculosis. Disseminated intravascular coagulation (DIC) and pancytopenia has been long recognised.^{1 2} But only rare cases of *Mycobacterium* infections triggering haemophagocytosis have been reported.^{3 4} Antituberculous therapy should be initiated early to improve prognosis. We report a rare case of tuberculosis with haemophagocytic syndrome (HPS) and DIC.

CASE PRESENTATION

An 18-year-old Tunisian girl without medical history was admitted for a deterioration of the general state with prolonged fever of 2 months and abdominal pain. She complained of anorexia and weight loss and reported chronic headache. The physical examination at admission revealed an impaired general condition, drowsiness with meningeal stiffness. Kernig's sign was positive. Rectal temperature was 39°C. She had a body mass index of 16 kg/m. Urine sticks were negative. Blood pressure was 100/40 mm Hg and pulse rate was 130 bpm. The respiratory rate was 22 cycles/min and there were decreased breath sounds and crepitations at both lungs' bases at pulmonary auscultation. There was a diffuse tenderness of the abdomen. Examination of the other systems revealed no abnormalities.

INVESTIGATIONS

The laboratory investigations upon admission revealed a DIC with prothrombin time of 9%, D-dimer level of 4 mg/ml, fibrinogenemia of 1 g/l, activated cephalin time of 59 s (control 30 s). Blood count showed a pancytopenia with a

normocytic anaemia (haemoglobin of 4.9 g/dl), leucopenia (leucocytes 2320 cells/mm³, neutrophils 1070 cells/mm³, lymphocytes 860 cells/mm³) and thrombocytopenia (platelet count 8000 cells/mm³). The erythrocyte sedimentation rate was 26 mm/h and C reactive protein was normal. Biochemical analysis revealed alanine transaminase 124 IU/l, aspartate transaminase 167 IU/l, glutamyl transpeptidase 462 IU/l and alkaline phosphatase 533 IU/l. The serum triglyceride level was 256 mg/dl, ferritin was 2575 ng/ml and lactate dehydrogenase was 1059 IU/l. Other biochemical findings were within normal limits. Bone marrow aspiration revealed a massive proliferation of mature histiocytes phagocytosing blood cells. Given the constellation of pancytopenia, hyperferritinaemia and the presence of haemophagocytosis within the bone marrow, an HPS was diagnosed. The patient was admitted in the intensive care unit.

DIFFERENTIAL DIAGNOSIS

Secondary HPS, associated with infection, malignancy and autoimmune disease was evoked. The infectious investigations including blood, urinary, cerebrospinal fluid and marrow cultures were negative. Further microbiological investigations, including brucellosis, leishmaniasis, toxoplasmosis and viral serology (hepatitis A, B, C, Epstein-Barr virus, cytomegalovirus, parvovirus B19, HIV) were all negative. Antinuclear antibody titre was within normal limits. The chest x-ray demonstrated a bilateral interstitial syndrome associated to a slight pleural effusion. Thoracic CT scan showed bilateral lung infiltrates with scattered subcentimetre pulmonary nodules and a moderate pleuritis (figure 1). Abdominal CT revealed a hepatosplenomegaly. Lumbar puncture revealed lymphocytic meningitis. Cranial CT was normal.

TREATMENT

Since the patient's condition rapidly deteriorated, treatment was initiated with an empiric administration of cefotaxime, teicoplanin, acyclovir, corticosteroids, catecholamines and blood transfusions. The patient's neurological symptoms, fever and pancytopenia persisted. Given the overall clinical picture and radiological images, these findings were felt to be most consistent with miliary tuberculosis. Tuberculin skin testing was non-reactive. Acid-fast bacilli in sputum and urine were also negative. Owing to the coagulation defects and the severe inflammation, biopsies were not obtained. But because tuberculosis is a common infection in Tunisia, antituberculosis

To cite: Cherif E, Bel Feki N, Ben Hassine L, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-008743

Figure 1 CT of the chest demonstrates bilateral diffuse infiltrates of lungs.

medications including isoniazid, rifampin, ethambutol and ofloxacin were prescribed.

OUTCOME AND FOLLOW-UP

Evolution 1 week later was marked by a haemodynamic stabilisation, blood cell count improvement, haemostatic parameters normalisation. One month later, she was doing well with an improvement of the general state. Liver enzymes were completely normalised after 8 weeks of treatment. The diagnosis of DIC associated with haemophagocytosis complicating tuberculosis was retained.

DISCUSSION

We reported a case of disseminated tuberculosis revealed by HPS. HPS also called haemophagocytic lymphohistiocytosis represents a severe hyperinflammatory condition with hypercytokinemia owing to a highly stimulated but ineffective immune response. It is a life-threatening clinicopathological entity leading to cellular damage and multiorgan dysfunction.⁵ This disorder is characterised by fever and worsening general status, spleen and liver enlargement with lymphadenopathy. Laboratory abnormalities include cytopenia and serum ferritin elevation. Hepatic cholestasis and/or cytolytic are found in three-quarters of patients and lactate dehydrogenase and triglyceride elevation in two-thirds of patients. Other laboratory abnormalities may include a decrease in serum fibrinogen with or without disseminated intravascular coagulation.⁵ But none of the clinical or laboratory manifestations is specific for HPS. The same manifestations can be caused by the disorders that trigger HPS. Histological specimens of bone marrow showing haemophagocytic macrophages remain the diagnostic reference standard.⁵ Once a diagnosis of HPS is established, searches for an underlying causes should be undertaken. Early aggressive screening of the aetiology and optimal treatment of the underlying disease improve the outcome of life-threatening HPS. Infection-associated HPS occurs predominantly in immunocompromised patients and is usually fatal.^{6,7} Leading trigger agents are viruses, especially the Epstein-Barr virus and cytomegalovirus. Other infections, including typhoid fever, brucellosis, toxoplasmosis and leishmaniasis, have also been described.⁸ A few cases of tuberculosis-associated haemophagocytosis have been reported. Diagnosis may be difficult owing to the absence of specific clinical symptoms, negative initial

radiological examination, as well as delayed and often negative bacterial isolation.^{9,10} In this case, the diagnosis of disseminated tuberculosis was difficult because the sputum for acid-fast stain was negative and non-caseating granulomas were not found in bone marrow biopsies. Tuberculosis was considered because of fever, lymphocytic meningitis and bilateral miliary lung nodules in an endemic zone patient. Among 36 cases of tuberculosis-associated HPS, 29 patients had extrapulmonary tuberculosis.³ Half the patients had underlying comorbidities. The mortality was approximately 50%, but antituberculous therapy and immunomodulatory therapy (steroids, plasma exchanges, intravenous immunoglobulins and epipodophylotoxin) may be associated with improved outcomes. Therefore, an early diagnosis and timely implementation of antituberculous medication is critical.^{11–13} Our patient was successfully treated by antituberculous therapy and prednisone.

Learning point

Mycobacterial infections associated with haemophagocytic syndrome are rare but should be considered in patients with fever of unknown origin, especially in endemic regions. Antituberculous therapy should be initiated early upon diagnosis to improve prognosis.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Glasser RM, Walker RI, Herion JC. The significance of hematologic abnormalities in patients with tuberculosis. *Arch Intern Med* 1970;125:691–5.
- 2 Fujita M, Kunitake R, Nagano Y, *et al.* Disseminated intravascular coagulation associated with pulmonary tuberculosis. *Intern Med* 1997;36:218–20.
- 3 Brastianos PK, Swanson JW, Torbenson M, *et al.* Tuberculosis-associated hemophagocytic syndrome. *Lancet Infect Dis* 2006;6:447–54.
- 4 Lee SW, Wang CY, Lee BJ, *et al.* Hemophagocytic syndrome in miliary tuberculosis presenting with noncaseating granulomas in bone marrow and liver. *J Formos Med Assoc* 2008;107:495–9.
- 5 Larroche C. Hemophagocytic lymphohistiocytosis in adults: Diagnosis and treatment. *Joint Bone Spine* 2012;79:356–61.
- 6 Fisman DN. Hemophagocytic syndromes and infection. *Emerg Infect Dis* 2000;6:601–8.
- 7 Rouphael NG, Talati NJ, Vaughan C, *et al.* Infections associated with hemophagocytic syndrome. *Lancet Infect Dis* 2007;7:814–22.
- 8 Tseng YT, Sheng WH, Lin BH, *et al.* Causes, clinical symptoms, and outcomes of infectious diseases associated with hemophagocytic lymphohistiocytosis in Taiwanese adults. *J Microbiol Immunol Infect* 2011;44:191–7.
- 9 Mazloum W, Marion A, Ferron C, *et al.* Tuberculous tuberculosis: case report and review of literature. *Med Mal Infect* 2002;32:439–48.
- 10 Sandrini J, Beucher AB, Rousselet MC, *et al.* Tuberculosis with a hemophagocytic syndrome. *Med Mal Infect* 2010;40:476–9.
- 11 Subhash HS, Sowmya S, Sitaram U, *et al.* Tuberculosis associated hemophagocytic syndrome. *J Postgrad Med* 2001;47:220–1.
- 12 Khan FY, Fawzy Z, Siddiqui I. Hemophagocytosis and miliary tuberculosis in a patient in the intensive care unit. *Indian J Crit Care Med* 2006;10:112–14.
- 13 Su NW, Chen CK, Chen GS, *et al.* A case of tuberculosis-induced hemophagocytic lymphohistiocytosis in a patient under hemodialysis. *Int J Hematol* 2009;89:298–301.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow