CASE REPORT

Brucellosis accompanied by haemophagocytic lymphohistiocytosis and multiple splenic abscesses in a patient with depression

Fatehi E Elzein,¹ Nisreen Al Sherbini,² Mohammed M Alotaibi,² Wassiem M Al-Hassan¹

¹Department of Medicine, Prince Sultan Military Medical City, Riyadh, Saudi Arabia
²Department of Medicine-ID, Prince Sultan Military Medical City, Riyadh, Saudi Arabia

Correspondence to
 Dr Fatehi E Elzein,
 fatehielzein@gmail.com

Accepted 9 February 2018

SUMMARY

A 39-year-old woman was being treated for depression in our clinic. She subsequently developed a fever and was diagnosed with pancytopenia and moderate splenomegaly. Laboratory and bone marrow results, including markedly increased serum ferritin levels, suggested haemophagocytic lymphohistiocytosis. CT showed multiple splenic abscesses and ovarian vein thrombosis. All laboratory values returned to normal after treatment for culture-positive brucellosis.

BACKGROUND

Brucellosis is a systemic disease endemic to the Middle East.¹ It has several presentations and serious complications (eg, endocarditis, neurobrucellosis and disabilities) and is sometimes misdiagnosed as a haematological malignancy.² Among the 787 patients with brucellosis in a previous study, 14% had thrombocytopenia, 12% had leucopenia, 5% had pancytopenia and 4% had bicytopenia.³ In a large study performed in Turkey, pancytopenia was more common in acute cases (8.8%) than subacute (1.4%) and chronic (0.1%) cases.² Although pancytopenia is associated with hypersplenism, the concomitant occurrence of hepatosplenomegaly and pancytopenia raises the possibility of Brucella-induced haemophagocytic lymphohistiocytosis (HLH).⁴ Infections contribute to 41.1% of HLH cases, while 28.8% of cases have an associated malignancy and 17% have no identifiable underlying cause.⁵ A marked release

of inflammatory cytokines, lymphocyte activation and multiorgan (eg, liver, spleen and brain) histiocyte infiltration account, in part, for the signs and symptoms of HLH. Triglyceride levels also increase owing to a tumour necrosis factor α -mediated inhibition of lipoprotein lipase activity. Additional diagnostic criteria for HLH are based on secretions of ferritin and plasminogen activator that contribute to fibrinolysis, by activated macrophages.⁶ Brucella-induced (unlike malignancy induced) histiocytic haemophagocytosis is usually treatable.

We report this case to remind practitioners in endemic areas to consider brucellosis when patients present with acutely depressed mood, particularly if accompanied by fever. Unexplained haemophagocytosis and multiple splenic abscesses also warrant consideration of brucellosis in endemic areas.

CASE PRESENTATION

A 39-year-old woman was seen in the clinic with generalised fatigability, anorexia, lassitude and mood disturbance. She was diagnosed with depression and started on citalopram 10 mg once daily. One week later, she experienced fever, chills and rigors and headache. Her temperature on admission was 36.7°C and her blood pressure, pulse and respiratory rates were normal. The general examination was unremarkable apart from splenomegaly, identified by the splenic edge measured at 4 cm below the left costal margin. Laboratory investigations revealed pancytopenia and an extremely elevated serum ferritin of

Figure 1 CT scan of the abdomen (liver view) showing multiple splenic abscesses.

To cite: Elzein FE, Al Sherbini N, Alotaibi MM, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-224018

Table 1 Investigations before and after treatment

Item	Before treatment	Normal values	Follow-up values
White cell count	$2.2 \times 10^9/L$	$4.0\text{--}11.0 \times 10^9/L$	$8.0 \times 10^9/L$
Neutrophils	$1.0 \times 10^9/L$		
Haemoglobin	10.3 g/dL	11.5–16.5 g/dL	14.0 g/dL
Platelets	$45 \times 10^9/L$	$150\text{--}450 \times 10^9/L$	$259 \times 10^9/L$
Urea	12.7 mmol/L	2.0–6.7 mmol/L	3.4 mmol/L
Creatinine	134 $\mu\text{mol/L}$	45–84 $\mu\text{mol/L}$	63 $\mu\text{mol/L}$
Potassium	3.1 mmol/L	3.2–5.0 mmol/L	3.6 mmol/L
Ferritin	78 777 ng/mL	13–150 ng/mL	94 ng/mL
Cholesterol	6.00 mmol/L		4.94 mmol/L
Triglyceride	3.0 mmol/L		2.11 mmol/L
Low-density lipoprotein cholesterol	3.85 mmol/L		3.34 mmol/L
Lactate dehydrogenase	616 U/L	135–214 U/L	
Total bilirubin	17 $\mu\text{mol/L}$	2–21 $\mu\text{mol/L}$	10 $\mu\text{mol/L}$
Albumin	24 g/L	36–51 g/L	35 g/L
Alkaline phosphatase	371 U/L	35–104 U/L	138 U/L
Alanine transaminase	84 U/L	2–40 U/L	22 U/L
CA-125	150 U/mL	0–35 U/mL	
CA15-3	72 U/mL	0–25 U/mL	
C-reactive protein	89 mg/L	0–6 mg/L	21 mg/L

78 777 ng/mL (normal range: 13–150 ng/mL). Both liver function tests and renal profiles were abnormal on admission but reverted to normal prior to discharge (table 1). Leukaemia, systemic lupus erythematosus (SLE), HIV and aplastic anaemia were suspected initially. Ultrasound of the abdomen showed moderate hepatomegaly and splenomegaly measuring 20 cm in craniocaudal dimensions. A repeat CT scan confirmed a moderate splenomegaly showing innumerable small hypodense lesions (figure 1). In addition, right ovarian vein thrombosis was noted (figure 2). No vegetations were detected on echocardiogram. Serum tests for HIV, hepatitis B surface antigen, hepatitis C virus, Epstein-Barr virus and cytomegalovirus were all negative. Antinuclear antibodies, antineutrophil cytoplasmic antibodies and antiphospholipid antibodies were negative. Bone marrow aspiration showed that some of the erythroid precursors had degrees of dysplasia. Myeloid precursors were also present, along with cells in all stages of maturation, but there was no increase in blast cells, and megakaryocytes were occasionally seen. Prominent phagocytic activity was noted (figure 3). A blood culture grew gram-negative coccobacillus which was further identified to be a fully

Figure 3 Bone marrow aspirate showing hemophagocytosis (erythroid precursors and platelets are engulfed by macrophage).

sensitive *Brucella* species with a high minimum inhibitory concentration to rifampicin of 3.0. She received intravenous gentamicin 5 mg/kg/day for 10 days and doxycycline 100 mg twice daily for 12 weeks. In addition, she was anticoagulated with heparin then warfarin for 6 months.

DIFFERENTIAL DIAGNOSIS

For our differential diagnosis, we suggested brucellosis, with or without endocarditis, leading to splenic abscesses, hypersplenism or HLH causing pancytopenia. Miliary tuberculosis can present with varied haematological changes including pancytopenia, splenomegaly and HLH. Further, SLE should be considered in a female with psychiatric symptoms, thrombocytopenia, splenomegaly and pancytopenia as well as HLH. Haematological malignancies including leukaemia and lymphoma can also present with pancytopenia, splenomegaly and HLH.

TREATMENT

1. Intravenous gentamicin 5 mg/kg per day for 1 week.
2. Doxycycline 100 mg orally twice daily for 3 months.
3. Enoxaparin sodium followed by warfarin (initiated and adjusted based on the international normalised ratio) for a total of 6 months.

Figure 2 CT scan of the abdomen showing right (R) ovarian vein thrombosis (arrow).

OUTCOME AND FOLLOW-UP

The patient's condition and mood improved on treatment. C-reactive protein and ferritin levels and blood counts returned to normal (Table 1).

DISCUSSION

This case highlights several recognised, although uncommon, complications of brucellosis. The patient in our case presented with only vague symptoms of depression and fatigue. In a pooled analysis of 35 studies performed in Turkey, depression was detected in 5% of 187 neurobrucellosis cases.⁷ Importantly, brucellosis treatment alleviates cognitive and emotional disturbances in infected patients, as seen in our case, without additional antidepressant therapy.⁸

Diagnostic criteria for HLH include fever, splenomegaly, cytopenias affecting ≥ 2 of 3 lineages in the peripheral blood, hypertriglyceridaemia and/or hypofibrinogenaemia, haemophagocytosis in bone marrow or spleen or lymph nodes, low or absent natural killer cell activity, ferritin $\geq 500 \mu\text{g/L}$ and soluble CD25 (ie, soluble interleukin-2 receptor) $\geq 2400 \text{ U/mL}$. Five of these eight criteria need to be present to establish the diagnosis.⁹ In our case, *Brucella*-induced haemophagocytic syndrome was suggested by the presence of six of these criteria including fever, splenomegaly, cytopenia (neutropaenia, thrombocytopenia and anaemia), bone marrow haemophagocytosis, hypertriglyceridaemia and hyperferritinaemia exceeding 70 000. HLH was identified in 48.9% of children and 14.2% of adults with ferritin $>10\,000 \mu\text{g/L}$.¹⁰ Other factors associated with this syndrome were not examined in our case. Early reports of *Brucella*-induced HLH were described by Zuazu in 1979.¹¹ Mild haemophagocytosis was observed in the bone marrows of nine (1.4%) patients of 622 children with brucellosis. On the other hand, mild to moderate haemophagocytosis on the bone marrow smear was detected in 8% (18/233) of cases.¹² Unlike malignancy-induced HLH, *Brucella*-induced HLH is potentially curable by treating the brucellosis alone.¹³

Ovarian vein thrombosis (OVT) is a relatively rare disorder that classically occurs in postpartum women.¹⁴ Most (70%–90%) OVT cases involve the right ovarian vein owing to lengthy antegrade flow and the presence of dysfunctional valves in this vein. Although there are no previous reports of OVT in brucellosis, numerous thrombotic disorders, including thromboses of the cerebral venous system, portal vein and inferior vena cava, have been described.¹⁵ Vascular complications in brucellosis occur in less than 1.0% of cases, with only 14 cases of *Brucella*-related thrombosis reported so far.¹⁶ The exact pathogenesis of *Brucella*-related deep vein thrombosis is unclear. Suggested causes include endothelial infection and induction of inflammation, granulomatous endophlebitis, a transient hypercoagulable state and an immune reaction to a *Brucella* antigen.¹⁷

In our study, the abdominal CT showed multiple hypodense lesions distributed in almost a 'miliary' pattern. Such lesions are characteristic of miliary tuberculosis, which is also endemic to the Middle East; however, chest imaging (CT and X-ray) and the bone marrow examination did not support this diagnosis. Moreover, an echocardiogram appeared to rule out *Brucella*-induced endocarditis, as no vegetations were revealed.

In a previous study, approximately 0.4% of patients with brucellosis ($n=2475$) had splenic abscesses and only 1.2% had hepatosplenic lesions.¹⁸ Abscesses occur mainly in the liver, less frequently in the spleen (28%) and rarely in both organs (2%). Solitary abscesses with central calcifications occur most commonly in the liver and are indicative of brucellosis. Less indicative are multiple

small abscesses, which tend to occur in the spleen. Splenic abscesses with calcifications are less common than liver abscesses with calcifications and occur in 24%–25% of brucellosis splenic abscesses, irrespective of their number.¹⁸

Learning points

1. Depression is a potential, but often overlooked, presenting symptom of brucellosis.
2. Pancytopenia, splenomegaly and high ferritin should raise the possibility of haemophagocytic lymphohistiocytosis in patients with brucellosis.
3. 'Miliary-like' splenic abscesses characteristic of disseminated tuberculosis can accompany brucellosis.
4. Venous thrombosis and arterial thrombosis are recognised features of brucellosis.

Contributors FEE had substantial contributions to the conception or design of the work and drafting the manuscript. MMA prepared the figures and revised the manuscript. WMA-H did the follow-up of the patient in the hospital. All the authors contributed to the critical review of the manuscript, final approval of the version published and agreed to be accountable for all aspects of the work

Funding This research received no specific grant 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.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Pappas G, Papadimitriou P, Akritidis N, *et al*. The new global map of human brucellosis. *Lancet Infect Dis* 2006;6:91–9.
- 2 Guler S, Kokoglu OF, Ucmak H, *et al*. Human brucellosis in Turkey: different clinical presentations. *J Infect Dev Ctries* 2014;8:581–8.
- 3 Dilek I, Durmuş A, Karahocagil MK, *et al*. Hematological complications in 787 cases of acute brucellosis in eastern Turkey. *Turk J Med Sci* 2008;38:421–4.
- 4 Aysha MH, Shayib MA. Pancytopenia and other haematological findings in brucellosis. *Scand J Haematol* 1986;36:335–8.
- 5 Otroek ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. *Am J Hematol* 2015;90:220–4.
- 6 Janka GE. Hemophagocytic syndromes. *Blood Rev* 2007;21:245–53.
- 7 Gul HC, Erdem H, Bek S. Overview of neurobrucellosis: a pooled analysis of 187 cases. *Int J Infect Dis* 2009;13:e339–e343.
- 8 Eren S, Bayam G, Ergönül O, *et al*. Cognitive and emotional changes in neurobrucellosis. *J Infect* 2006;53:184–9.
- 9 Henter JL, Horne A, Aricó M, *et al*. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007;48:124–31.
- 10 Otroek ZK, Hock KG, Riley SB, *et al*. Elevated serum ferritin is not specific for hemophagocytic lymphohistiocytosis. *Ann Hematol* 2017;96:1667–72.
- 11 Zuazu JP, Duran JW, Julia AF. Hemophagocytosis in acute brucellosis. *N Engl J Med* 1979;301:1185.
- 12 Karaman K, Akbayram S, Bayhan GI, *et al*. Hematologic findings in children with brucellosis: experiences of 622 patients in eastern Turkey. *J Pediatr Hematol Oncol* 2016;38:463–6.
- 13 Kokkini G, Giotaki HG, Moutsopoulos HM. Transient hemophagocytosis in *Brucella melitensis* infection. *Arch Pathol Lab Med* 1984;108:213–6.
- 14 Verde F, Johnson PT. One not to miss: ovarian vein thrombosis causing pulmonary embolism with literature review. *J Radiol Case Rep* 2012;6:23.
- 15 Zaidan R, Al Tahan AR. Cerebral venous thrombosis: a new manifestation of neurobrucellosis. *Clin Infect Dis* 1999;28:399–405.
- 16 Rüggeger K, Tarr P, Karatolios K, *et al*. Brucellosis and thrombosis of the inferior vena cava. *Vasa* 2017;46:60–3.
- 17 Tolaj I, Mehmeti M, Ramadani H, *et al*. Brucellosis associated with deep vein thrombosis. *Infect Dis Rep* 2014;6.
- 18 Heller T, Bédard S, Wallrauch C, *et al*. Patterns of hepatosplenic brucella abscesses on cross-sectional imaging: a review of clinical and imaging features. *Am J Trop Med Hyg* 2015;93:761–6.

Copyright 2018 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