Rare disease

Overwhelming primary Epstein–Barr virus infection requiring corticosteroid treatment

Marije Gordinou de Gouberville,^{1,2} Martien Janssen,¹ Anita Schrande-van der Meer,¹ Matthijs Eefting,³ Nathalie Delfos,¹ Cees van Nieuwkoop⁴

¹Department of Internal medicine, Rijnland Hospital, Leiderdorp, Netherlands;

²Surgical Department, Ligula Hospital, Mtwara, Tanzania;

³Department of Haematology, Leiden University Medical Centre, Leiden, Netherlands;

⁴Department of Internal medicine, Hagaziekenhuis, Den Haag, Netherlands

Correspondence to Miss Marije Gordinou de Gouberville, mc.gordinou@gmail.com

Summary

A 20-year-old woman presented with a 2-week history of fever and malaise. Physical examination was unremarkable. Viral infection was suspected and Epstein–Barr virus serology confirmed acute infectious mononucleosis. During admission, she gradually developed pancytopenia and liver enzyme abnormalities. The patient clinically deteriorated with persisting fever, orthostatic hypotension and hepatosplenomegaly. Bone marrow examination showed haemophagocytic lymphohistiocytosis (HLH). Treatment with high-dose corticosteroids was started and patient recovered quickly. Ferritin decreased immediately, fever resolved within 3 days, viral clearance was reached within 3 weeks. Steroid therapy was gradually tapered off in three months. The Histiocyte Society recommends immunochemotherapy with steroids, etoposide and cyclosporine. Potential side effects of etoposide are severe bone marrow depression and leukaemia. Our patient survived on corticosteroids alone. Early recognition of HLH and prompt treatment are of utmost importance for survival. Treatment with steroids alone can be life-saving.

BACKGROUND

Epstein–Barr virus (EBV) infection can lead to a potentially lethal syndrome called haemophagocytic lymphohistiocytosis (HLH). HLH is characterised by uncontrolled lymphocyte proliferation and macrophage activation. Cytokine storm leads to a fulminant clinical course.^{1,2} HLH comprises a familial form and a secondary form, triggered by infection, auto-immune disease or malignancy. EBV is the most frequent cause of secondary HLH (EBV-HLH) and most prevalent among Asian people.³ In HLH, phagocytosis of all cell lines occurs, which can be demonstrated by bone marrow or lymph node examination.⁴ Activated macrophages secrete ferritin, which can be used as a diagnostic tool and a follow-up measure. Diagnostic criteria for HLH are described by the international Histiocyte Society.⁵ If left untreated, the prognosis of EBV-HLH is ultimately fatal, but even with treatment mortality is 25%.

In this case-report, we present an atypical presentation of primary EBV infection in a young woman. During admission, a natural development of EBV-HLH was revealed. For adults with EBV-HLH, evidence-based treatment guidelines are lacking but according to the Histiocyte Society the mainstay of treatment should be a combination chemotherapy (corticosteroids, etoposide and cyclosporine). Here we present a case in which a natural course of developing fulminant EBV-HLH was observed which was treated and cured with corticosteroids alone.

CASE PRESENTATION

In 2009, a previously healthy, 20-year-old Dutch woman was admitted because of hypotension and somnolence. For

2 weeks, she suffered from fever, malaise, weight loss and postural dizziness with syncope. Travel history revealed a city-trip to Hongkong 2 months earlier, no other visit to the tropics. Her partner reported two episodes of febrile illness, in the previous 2 months. New Influenza A (H1N1) was epidemic at the moment of presentation.

On admission, our patient appeared ill, with fever (40°C) and drowsiness. Blood pressure was 108/62 mm Hg, and 70/50 mm Hg in upright position. Besides a single slightly enlarged cervical lymph node and periorbital oedema, physical examination was unremarkable. There were no signs of pharyngitis.

INVESTIGATIONS

Laboratory tests at presentation showed a slightly elevated C-reactive protein 28 mg/l (ref <8), aspartate aminotransferase 41 U/l (ref <30), alanine aminotransferase 13 U/l (ref <34) and normal leucocyte count with atypical lymphocytes. Adrenal insufficiency was ruled out by adrenocorticotrophic hormone stimulation test. Chest radiography was normal and urine and blood cultures were sterile. A viral infection was suspected and confirmed by EBV serology consistent with acute infectious mononucleosis. Serology for HIV, cytomegalovirus, hepatitis B and C virus was negative, and a blood smear ruled out malaria. PCR for H1N1 virus was negative. Fever persisted, and progressive liver enzyme abnormalities (ASAT 2582 U/l; ALAT 672 U/l), pancytopenia (Hb 5.7 mmol/l; leucocytes $3.9 \times 10^9/L$; thrombocytes $59 \times 10^9/L$) and disseminated intravascular coagulation (DIC) (activated partial thromboplastin time 53.4 s; prothrombin time 17.6 s; D-dimer >5000

Figure 1 Bone marrow aspiration smear showing haemophagocytosis of neutrophils, erythrocytes, platelets and erythroblasts by a histiocyte. Haemophagocytic lymphohistiocytosis is a potentially lethal complication of Epstein–Barr virus infection (May–Grunwald–Giemsa stained, magnification x400).

ng/l; fibrinogen 0.7 g/l) developed. Intravascular haemolysis was excluded. DIC was complicated by large haematoma after venous punctures. Serum ferritin, measured on the tenth day after admission, was 1452 µg/l (ref <150); within 2 days it increased to over 195.000 µg/l. Chest and abdominal imaging revealed hepatosplenomegaly but no signs of lymphoma. EBV-HLH was confirmed by bone marrow examination on the tenth day of admission (figure 1).

DIFFERENTIAL DIAGNOSIS

Haemophagocytic lymphohistiocytosis

- Familial
- Secondary after infection, auto-immune disease, malignancy.

TREATMENT

Treatment with high-dose corticosteroids (1 mg/kg) was started on the twelfth day of admission, supplemented with fresh frozen plasma to correct coagulopathy. Steroid therapy was gradually tapered off within 3 months.

OUTCOME AND FOLLOW-UP

The patient recovered quickly with resolution of fever within 3 days. Laboratory values gradually normalised (figure 2). Viral clearance occurred within 3 weeks. Complementary genetic research, as her mother had an Indonesian background, ruled out the known genetic predispositions for HLH (mutations in perforin 1, UNC-13D or syntaxin 11). During further 12 months of follow-up, she remained well without any signs of recurrence.

DISCUSSION

Infectious mononucleosis is generally a self-limiting disease and only a minority of patients with signs of severe illness or complications are being hospitalised. However, in rare cases EBV infection can lead to EBV-HLH. The diagnosis of HLH can be delayed when physicians focus on other feverish diseases like sepsis or when epidemiological factors,

Figure 2 Haemophagocytic lymphohistiocytosis following Epstein–Barr virus infection is characterised by fever, pancytopenia and elevated ferritin. On day 12 of admission, corticosteroid treatment was started and patient recovered.

like H1N1, influence the differential diagnosis and investigation. In this case, EBV-HLH was considered because of clinical signs of severe inflammation with prolonged fever, lymphadenopathy, hyperferritinemia, progressive liver enzyme abnormalities and the gradual development of pancytopenia. It was confirmed by serology and bone marrow examination. The latter is confirmative in about 58% of cases with haemophagocytosis.⁴

HLH can be either hereditary or secondary due to autoimmune diseases, haematologic malignancies or infections. In case of EBV infection, HLH is associated with underlying disorders like familial haemophagocytic lymphohistiocytosis and X linked lymphoproliferative syndrome. In the latter, affected boys develop proliferation of B- and T lymphocytes in response to EBV infection, with severe hepatitis and haemophagocytosis as result.

According to the Histiocyte Society, the mainstay of treatment of HLH is high-dose corticosteroids, accompanied by etoposide and cyclosporine-based regimens.⁵

⁶ However, these recommendations are predominantly based on studies in children. Large studies in adults are lacking. Therefore treatment decisions of HLH in adults are supported by case-reports. Etoposide might cause severe bone marrow suppression, limiting its use.⁷

Besides that, etoposide is associated with myelodysplastic syndrome and acute myeloid leukaemia.^{8,9} A limited number of cases with different, less toxic treatment regimens with different outcomes are described, among which some cases survived on corticosteroids alone,^{2,6,10} which is supported by our case-report, and a single case which resolved spontaneously.¹¹ Finally, allogeneic stem cell transplantation is treatment of choice in familial HLH, and it can be used as salvage therapy in refractory cases of secondary HLH.⁵

Many factors can cause diagnostic delay and physicians may hesitate to use immunochemotherapy when not all diagnostic criteria are met, which frequently occurs in the early phase of HLH. Our case clearly demonstrates that prompt recognition of HLH, followed by early treatment with corticosteroids alone can be life-saving. We decided to treat with corticosteroids alone to avoid potential adverse effects of etoposide and cyclosporine on top of the severe illness with signs of systemic inflammatory response, DIC, cytopenias and hyperferritinemia. This treatment decision turned out to be highly effective. As such, this argues for a strategy towards the start of high-dose corticosteroids in all patients with EBV-HLH and reserve intensive chemotherapy for those cases who fail to show an immediate respond to corticosteroids alone or those with a genetic predisposition. However, our case also illustrates that timing may be difficult as infectious mononucleosis can progress gradually to EBV-HLH. We suggest using a low threshold for corticosteroid treatment in such patients. So far, there are no reports of worsening infectious mononucleosis by treatment with corticosteroids, but lessons from transplantation immunology and EBV infection are of concern. Therefore, the exact role of corticosteroids in acute overwhelming forms of EBV infection, whether this meets the criteria for EBV-HLH or not should be elucidated in further studies. Furthermore, the threshold for testing genetic susceptibility should be low, as in X linked HLH additional treatment is highly recommended.⁵

Learning points

- ▶ EBV-HLH needs to be considered in overwhelming infectious mononucleosis with prolonged fever, splenomegaly and cytopenias.
- ▶ When EBV-related infectious mononucleosis in adults requires hospitalisation, the threshold for treatment with high dose corticosteroids should be low to prevent further complications and death.
- ▶ Early initiation of corticosteroids without the use of additional immunochemotherapy can be life-saving in severe EBV-HLH.

Competing interests None.

Patient consent Not obtained.

REFERENCES

1. Su IJ, Chen RL, Lin DT, *et al.* Epstein-Barr virus (EBV) infects T lymphocytes in childhood EBV-associated hemophagocytic syndrome in Taiwan. *Am J Pathol* 1994;**144**:1219–25.
2. Kasahara Y, Yachie A. Cell type specific infection of Epstein-Barr virus (EBV) in EBV-associated hemophagocytic lymphohistiocytosis and chronic active EBV infection. *Crit Rev Oncol Hematol* 2002;**44**:283–94.
3. Janka G, Imashuku S, Elinder G, *et al.* Infection- and malignancy-associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. *Hematol Oncol Clin North Am* 1998;**12**:435–44.
4. Gupta A, Tyrrell P, Valani R, *et al.* The role of the initial bone marrow aspirate in the diagnosis of hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2008;**51**:402–4.
5. Henter JI, Horne A, Aricó M, *et al.* HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007;**48**:124–31.
6. Imashuku S, Kuriyama K, Teramura T, *et al.* Requirement for etoposide in the treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. *J Clin Oncol* 2001;**19**:2665–73.
7. Lee JS, Kang JH, Lee GK, *et al.* Successful treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis with HLH-94 protocol. *J Korean Med Sci* 2005;**20**:209–14.
8. Pui CH, Ribeiro RC, Hancock ML, *et al.* Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. *N Engl J Med* 1991;**325**:1682–7.
9. Imashuku S, Teramura T, Tauchi H, *et al.* Longitudinal follow-up of patients with Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. *Haematologica* 2004;**89**:183–8.
10. Imashuku S. Treatment of Epstein-Barr virus-related hemophagocytic lymphohistiocytosis (EBV-HLH); update 2010. *J Pediatr Hematol Oncol* 2011;**33**:35–9.
11. Belyea B, Hinson A, Moran C, *et al.* Spontaneous resolution of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2010;**55**:754–6.

This pdf has been created automatically from the final edited text and images.

Copyright 2011 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.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Gordinou de Gouberville M, Janssen M, Schrander-van der Meer A, Eefting M, Delfos N, van Nieuwkoop C. Overwhelming primary Epstein-Barr virus infection requiring corticosteroid treatment. *BMJ Case Reports* 2011;**10**:1136/bcr.08.2011.4643, date of publication

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