Haemophagocytic lymphohistiocytosis after heart transplantation: a case report

Christian Danielsson, Kristjan Karason, and Göran Dellgren

Background
Haemophagocytic lymphohistiocytosis (HLH) is an uncommon but serious systemic inflammatory response with high mortality rates. It can be triggered by malignancy or infectious agents, often in the context of immunosuppression. Literature covering HLH in heart transplantation (HTx) is scarce.

Case summary
A 25-year-old male with a history of celiac disease underwent HTx at Sahlgrenska Hospital in 2011 due to giant cell myocarditis and was treated with tacrolimus, mycophenolate mofetil (MMF), and prednisolone. He developed several episodes of acute cellular rejections (ACR) during the first 3 post-HTx years, which subsided after addition of everolimus. In May 2017, the patient was admitted to the hospital due to fever without focal symptoms. He had an extensive inflammatory reaction, but screening for infectious agents was negative. Haemophagocytic lymphohistiocytosis was discussed early, but first dismissed since two bone marrow biopsies revealed no signs of haemophagocytosis. Increasing levels of soluble IL-2 were considered confirmative of the diagnosis. Even with intense immunosuppressant treatment, the patient deteriorated and died in progressive multiorgan failure within 2 weeks of the symptom onset.

Discussion
A 25-year-old HTx recipient with an extensive inflammatory response, fulfilled criteria for HLH, but the diagnosis was delayed due to normal bone marrow biopsies. A background with autoimmune reactivity and immunosuppressive therapy may have contributed to HLH, but the actual trigger was not identified. Haemophagocytic lymphohistiocytosis can occur in HTx recipients in the absence of malignancy, identifiable infectious triggers and signs of haemophagocytosis. Early diagnosis and intervention are likely to be of importance for a favourable outcome.

Keywords
Heart transplantation • Haemophagocytic syndrome • Haemophagocytic Lymphohistiocytosis • Case report

Learning points
- Haemophagocytic lymphohistiocytosis (HLH) is an uncommon but serious systemic inflammatory response with high mortality rates.
- Haemophagocytic lymphohistiocytosis can occur in heart transplant recipients in the absence of malignancy, identifiable infectious triggers and signs of haemophagocytosis.
- On suspicion of HLH a bone marrow biopsy should be performed according to the HLH 2004 protocol, but a negative find is not sufficient to rule out the diagnosis.

Corresponding author. Tel: +46 31 342 26 21, Email: christian.danielsson@vgregion.se

Handling Editor: Matteo Cameli

Supplementary Material Editor: Peysh A. Patel

© The Author(s) 2020. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Introduction

Haemophagocytic lymphohistiocytosis (HLH), or haemophagocytic syndrome, is an uncommon but serious systemic inflammatory response with mortality rates of around 50% when occurring in recipients of solid organ transplants. It can occur as a primary form where genetic factors contribute to a dysfunctional immune system, or as a secondary reactive variant, when infections or malignancy may act as triggers, often in the context of immunosuppression. It is characterized by a dysfunctional activation of morphologically benign histiocytes with subsequent haemophagocytosis. Clinical manifestations include high fever, pancytopenia, and hepatosplenomegaly, while common laboratory findings consist of high levels of ferritin, hypertriglyceridaemia, and increased soluble CD25 (α-chain of IL-2 receptor).

Timeline

| Year | Events |
|------|--------|
| 2011–2013 | Orthotopic heart transplantation due to giant cell myocarditis. Several episodes of treatment-requiring acute cellular rejections (ACR) leading to more potent immunosuppressive regimen. Pacemaker due to 3rd degree ativoventricular block. |
| 2017 | Beginning of May: Fever and malaise at home, initially interpreted as common cold. |
| 8–14 May | Progressing symptoms and admission to local infection clinic. Haemophagocytic lymphohistiocytosis (HLH) suspected but bone marrow biopsy is negative shifting diagnostic focus. |
| 14 May | Progressing renal and heart failure. Transported to Sahlgrenska University Hospital for myocardial biopsies. |
| 15 May | Myocardial biopsies without signs of ACR. Haemophagocytic lymphohistiocytosis once again suspected leading to a second bone marrow biopsy. |
| 16 May | Clinical deterioration, empiric HLH treatment is added. Second bone marrow biopsy negative but results from IL 2-receptor analysis considered confirmative of HLH diagnosis. |
| 17 May | Massive organ failure and intense treatment efforts. Patient dies. |

Case presentation

A 25-year-old male with a history of celiac disease underwent heart transplantation at the Sahlgrenska University Hospital in 2011 due to giant cell myocarditis. He was placed on an immunosuppressive regimen comprising of tacrolimus, MMF, and prednisolone. Rejection surveillance with endomyocardial biopsies was performed according to a protocol during the first year and, thereafter, only on indication. During the first 3 post-transplant years the patient developed several treatment-requiring episodes of acute cellular rejections, but this subsided when the immunosuppressive maintenance protocol was intensified with everolimus. In 2013, a routine electrocardiogram revealed ativoventricular (AV) block III and the patient received a pacemaker. Over the following years, there were no further significant complications and graft function remained essentially intact.

In the beginning of May 2017, the patient developed a fever without any focal symptoms. After a week at home without improvement, he was admitted to the local infection clinic and underwent extensive screening for potential infectious causes. Laboratory tests showed an extensive inflammatory reaction, but screening for a wide array of viral causes with real-time PCR, as well as bacterial cultures, were negative. Electrocardiogram from May 2017 revealed a biological sinus tachycardia with a rate of 108 and supraventricular extrasystoles. Further, a QRS morphology consistent with right bundle branch block (RBBB) and left anterior fascicular block (LAFB), and high QRS amplitudes in the limb leads indicating left ventricular hypertrophy. Initial chest X-rays were unremarkable, and an abdominal ultrasound showed no signs of organomegaly. Serum concentrations of immunosuppressive drugs were adequate. In the absence of an apparent infectious cause, intravenous hydrocortisone was added to the treatment to counteract the inflammation.

Due to the presence of pancytopenia [Hb 97 g/L (134–170), WBC $2.1 \times 10^9/L$ $^{3,7}$ platelet count 139 $\times 10^9/L$ (145–348)], elevated ferritin levels [1378 µg/L (30–400)], hypertriglyceridaemia [4.1 mmol/L (0.45–2.6)] and decreased fibrinogen [1.37 g/L (1.8–3.8)], also HLH was considered a differential diagnosis at this early stage. However, since a bone marrow biopsy showed no obvious signs of haemophagocytosis the investigative focus shifted towards other possible explanations. Empiric treatment with wide spectrum antibiotics (cefotaxime) was initiated. Despite the current treatment, the patient’s condition continued to deteriorate. Due to worsening heart and renal function the patient was transferred to the local cardiology clinic, and owing to a growing suspicion of an acute allograft rejection, he was transported to the Sahlgrenska University Hospital for further evaluation and treatment.

At the Sahlgrenska hospital, echocardiography showed impaired systolic graft function (ejection fraction = 35%) but myocardial biopsies showed no signs of rejection. Persisting pancytopenia and further elevation of ferritin and triglycerides once again highlighted HLH. A second bone marrow sample still revealed no signs of haemophagocytosis, but the levels of soluble IL-2 where clearly elevated [6000 U/mL (45–1100)], which was considered confirmative of HLH. Due to respiratory deterioration the patient was transferred to the cardiothoracic intensive care unit and received mechanical ventilation. He was treated with intravenous betamethasone and human immunoglobulin (KIOVIG). Herpes simplex (HSV) 1 virus was detected with PCR analyses of serum (log 2.48) and treatment with acyclovir was added. At this stage, the patient exhibited severe deterioration with the development of pulmonary oedema and circulatory shock. He...
was placed in veno-venous extracorporeal membrane oxygenation (ECMO), but a progressive multiorgan failure could not be reversed and the patient died 2 weeks after the initial onset of symptoms.

Discussion

We describe a case of HLH in a heart transplant recipient with a fatal outcome. Haemophagocytic lymphohistiocytosis is a rare disorder and only a handful of case studies in heart transplanted patients have been reported previously.1,4–6,8 In our case, a timely diagnosis was challenging and response to treatment was poor. We therefore believe that our experience can add to the existing base of knowledge.

The first diagnostic guidelines for HLH where published in 1991 and have since then developed into the HLH-2004 protocol (Table 1), which today is the most widely used diagnostic guideline in clinical practice for adults.7 On suspicion, the diagnostic importance of finding haemophagocytosis in bone marrow samples has been emphasized, also in heart transplant recipients.1 Even though our patient at an early stage fulfilled five of eight criteria, sufficient for identifying HLH, the diagnosis was delayed due to negative bone marrow biopsies shifting the focus to other serious conditions more frequently occurring in this patient population. The presence of haemophagocytosis in bone marrow has actually been shown to have a limited predictive value for the HLH diagnosis,9 but may still be of importance to rule out other causes of cytopenias.10 Burns et al.4 describes similar problems with identifying the underlying cause behind the HLH in their case, although it is described as almost certainly infection associated. Reactive HLH is most often associated with virus infections, where the strongest aetiological connection has been drawn to herpes viruses, especially Epstein-Barr virus (EBV).4 Previous cases of HLH in heart transplanted patients reaffirm this.5,8 However, in our case the only viral analysis with positive outcome was a HSV-1 PCR, but since the log was only 2.18, we find it unlikely to be the trigger.

The rarity of HLH, the lack of specific laboratory or clinical tests and the variability in clinical manifestation often contribute to a diagnostic delay. Most cases of HLH do however warrant an early and aggressive treatment for favourable outcomes. Upon high clinical suspicion of HLH, treatment should therefore begin early, even though diagnostic tests are not finished. The main principle of HLH treatment is to suppress life-threatening inflammation, and the current recommendation for induction therapy comprises betamethasone and etoposide. It is also essential to try to identify and treat any underlying triggering condition. Prophylactic treatment for opportunistic infections, immunoglobulin supplementation, and careful monitoring for improvement or deterioration are needed. If the patient recovers after an 8-week induction period, the HLH treatment can

Table 1 Diagnostic criteria for reactive haemophagocytic lymphohistiocytosis according to the HLH 2004 protocol

- Fever
- Splenomegaly
- Cytopenia affecting ≥ 2 lineages of peripheral blood cells:
  - Anaemia (haemoglobin < 90 g/L)
  - Thrombocytopenia (<100 × 10⁹/L)
  - Neutropenia (<1.0 × 10⁹/L)
- Hypertriglyceridaemia (<3.0 mmol/L, fasting value) and/or hypofibrinogenaemia (1.5 g/L)
- Hyperferritinaemia (>500 mg/L)
- Low or absent natural killer cell activity
- Elevated soluble IL-2 receptor levels (>2400 U/mL)
- Haemophagocytosis in bone marrow, spleen or lymph nodes

At least five out of the eight criteria must be fulfilled for the diagnosis. No evidence of malignancy must be present. The table also shows which diagnostic criteria the patient in this case report fulfilled (italics).

Figure 1 (A) Haematoxylin and eosin stain, scale bar 50 μm. Ordinary bone marrow with normal distribution of haematopoietic cells. No sign of malignancy. (B) CD68 stain, scale bar 100 μm. Bone marrow with normal number of histiocytes/macrophages.
be weaned off. In case of no improvement, treatment continues as a bridge to allogeneic haematopoietic stem cell transplantation.11

In summary, even though the patient in an early stage fulfilled necessary criteria to identify HLH, a definitive diagnosis was delayed due to the absence of haemophagocytosis in a bone marrow biopsy (Figure 1). Moreover, neither biopsies nor other investigations could provide an answer to the underlying cause, leaving us unaware of what essentially triggered the HLH. Thus, it is important to be aware that HLH may occur in the absence of malignancy, an apparent infectious trigger or signs of haemophagocytosis in a bone marrow biopsy. When the diagnosis was set, the patient was in such a deteriorated state that we were not sure if he could survive the addition of etoposide to his treatment. Perhaps a definitive diagnosis could have been achieved earlier if diagnostics according to the HLH-2004 protocol had been adhered more thoroughly as soon as HLH was suspected. Even so, the severity and quick progress of the HLH in our patient leaves us with the question if treatment would have been effective even if initiated at an earlier stage.

Funding
Swedish Heart and Lung Foundation (20160671); and ALF/LUA research grant (ALFGBG-21431) from the Sahlgrenska Academy and University Hospital.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: G.D. has a research grant from Astellas regarding an immunosuppressive study in lung transplantation (ScanCLAD study), and a research grant from Abbott regarding an LVAD destination study (SweVAD study), but none applicable to this study. There are no financial conflicts of interest disclosures from any of the authors.

References
1. Masri K, Mahon N, Rosario A, Mirza I, Keys TF, Ratliff NB, Starling RC. Reactive hemophagocytic syndrome associated with disseminated histoplasmosis in a heart transplant recipient. J Heart Lung Transplant 2003;22:487–491.
2. Janka G, Zur Stadt U. Familial and acquired hemophagocytic lymphohistiocytosis. Hematol Am Soc Hematol Educ Program 2005;2005:62–68.
3. Filippovich AH. Hemophagocytic lymphohistiocytosis (HLH) and related disorders. Hematol Am Soc Hematol Educ Program 2009;2009:127–131.
4. Burns BF, Walley VM, Davies RA, Auclair F, Bormans J. Hemophagocytic syndrome complicating cardiac transplantation. Cardiovasc Pathol 1998;7:47–50.
5. Reuland AK, Engelhardt M, Meyer PT, Stroh AL, Lubbert M, Finke J, Schmitt-Graff A, Zirlik A, Wasch R. Aggressive plasmablastic lymphoproliferation complicated by hemophagocytic syndrome 12 years after heart transplant. Leuk Lymphoma 2012;53:1845–1848.
6. Thomas G, Hraiech S, Dzierz S, Weiller PJ, Ene N, Serratrice J, Secq V, Ambrosi P, Drancourt M, Roch A, Papazian L. Disseminated Mycobacterium lentiflavum responsible for hemophagocytic lymphohistiocytosis in a man with a history of heart transplantation. J Clin Microbiol 2014;52:3121–3123.
7. Henter JI, Horne A, Aricó M, Egeler RM, Filippovich AH, Imashuku S, Ladasch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–131.
8. Pucci A, Grasso M, Arbustini E. Myocardial involvement due to a disseminated human cytomegalovirus infection in a heart transplant recipient. A case report. G Ital Cardiol 1989;19:330–333.
9. Ho C, Yao X, Tian L, Li FY, Podoltsev N, Xu ML. Marrow assessment for hemophagocytic lymphohistiocytosis demonstrates poor correlation with disease probability. Am J Clin Pathol 2014;141:62–71.
10. Lehnerb K, Nichols KE, Henter JI, Girschikofsky M, Greenwood T, Jordan M, Kumar A, Minkov M, Rosée Weitzman LP; Study Group on Hemophagocytic Lymphohistiocytosis Subtypes of the Histiocyte Society. Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. Haematologica 2015;100:997–1004.
11. Jordan MB, Allen CE, Weitzman S, Filippovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. Blood 2011;118:4041–4052.