CASE REPORT

Previously undiagnosed fatal familial haemophagocytic lymphohistiocytosis in a 24-year-old woman

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SUMMARY

We present a case of a 24-year-old woman with previously undiagnosed familial haemophagocytic lymphohistiocytosis (HLH). The patient presented with fevers and cough and was found to have pancytopenia. She underwent an extensive work up and initially met only 3 of 8 criteria for HLH. Owing to high clinical suspicion, soluble CD25 level was sent and HLH2004 protocol initiated. The soluble CD25 level returned elevated with other laboratory work and the patient met criteria for diagnosis of HLH. Genetic studies revealed a homozygous mutation in PRF1 with absent perforin in cytotoxic cells, consistent with familial HLH. The patient expired before intrathecal chemotherapy could be initiated. This case illustrates the potential for familial HLH to present at an older age, and highlights the importance of early recognition and initiation of treatment of HLH, as patients may not initially fulfil the diagnostic criteria for HLH, and mortality is high if left untreated.

BACKGROUND

Haemophagocytic lymphohistiocytosis (HLH) is a syndrome characterised by pathological immune activation in which most patients present acutely with multiorgan involvement. Familial HLH is caused by genetic mutations whereas acquired HLH is secondary to other conditions including malignancy, infection or rheumatological disorders. Typically, familial HLH is thought to be a disease experienced in early infancy, with survival of only a few months, if left untreated. This case illustrates the potential for familial HLH to present at an older age. It also highlights the importance of early recognition and initiation of treatment of HLH, as patients may not initially fulfil the diagnostic criteria for HLH.

CASE PRESENTATION

A 24-year-old adopted woman of Asian Indian descent with medical history significant for ulcerative colitis s/p colectomy presented as a transfer from an outside hospital, with a 1-month history of fevers, chills, night sweats, cough and pancytopenia of unclear aetiology despite extensive work up. At the outside hospital, the patient had been started on broad-spectrum antibiotics and received growth factors for her pancytopenia. A bone marrow biopsy showed hypercellular marrow consistent with growth factor treatment but no evidence of haemophagocytosis.

The medical history was notable for ulcerative colitis s/p colectomy at age 12–13 years in addition

to polycystic ovary syndrome. Home medications included metformin and an oral contraceptive. Allergies included sulfonamide antibiotics and codeine (anaphylactic reactions reported to both). The patient's family history was unknown as she was born in India and adopted at age 6 months. It had been a closed adoption so no family history was known or available. The patient was an elementary school teacher. She reported no recent travel. She had one pet dog.

Laboratories on transfer were notable for white cell count $1.7 \times 1000/\mu\text{L}$, haemoglobin 9.1 g/dL, haematocrit 29.5%, platelets $87 \times 1000/\mu\text{L}$, total bilirubin 1.97 mg/dL and direct bilirubin 1.11 mg/dL. Blood cultures had no growth. Flu A/B were negative. Ehrlichia and Babesia IgG and IgM were negative. Monospot was negative as was HIV Ab. Sputum cultures and sputum acid-fast bacilli had no growth. *Clostridium difficile* antigen was positive with negative *C. difficile* cytotoxin.

INVESTIGATIONS

The patient's initial head CT was negative, however, on day 6 of hospitalisation, the patient acutely decompensated, and she was found unresponsive and hypoxic with seizure activity. She was intubated and transferred to the intensive care unit. Her brain MRI at this time showed extensive scattered foci of T2/fluid attenuated inversion recovery hyperintensity (figure 1), consistent with acute disseminated encephalomyelitis. Her infectious disease work up was notable for low level Epstein-Barr virus viraemia and positive human metapneumovirus by nasopharyngeal swab.

Initially, she met only 3 of 8 criteria for HLH, however, due to high clinical suspicion, a soluble CD25 level was sent. Her ferritin level continued to rise, and her neurological status and cardiopulmonary status worsened. CT of the abdomen and pelvis revealed splenomegaly measuring 17–18 cm. Peripheral blood smear showed activated lymphocytes and smudge cells of uncertain significance. The soluble CD25 level returned markedly elevated at 55 000 U/mL. With the soluble interleukin 2 (IL-2) receptor elevation, the patient now met clinical criteria for HLH including cytopenias, splenomegaly, elevated ferritin and elevated triglycerides.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included infection with sepsis and multiorgan dysfunction, haematological or solid tumour malignancy, inflammatory processes

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Figure 1 Axial view of MRI of the brain with and without contrast showing extensive scattered foci of T2/fluid attenuated inversion recovery hyperintensity throughout the periventricular and subcortical white matter.

including HLH and macrophage activation syndrome (MAS). There were extensive multidisciplinary discussions held between all consulting teams (including infectious disease, haematology, neurology, pulmonary/critical care, laboratory medicine and pathology) to discuss potential diagnostic and treatment possibilities. The specificity of the IL-2 receptor marker solidified the diagnosis of HLH.

TREATMENT

The patient was initially started on intravenous immunoglobulin (IVIG) for anti-inflammatory effect due to uncertainty regarding the diagnosis and concern for precipitating worsening infection with high-dose steroids. As more laboratory work resulted, she was then started on an IL-1 receptor antagonist, given concern for HLH/MAS. Once the IL-2 receptor resulted, the patient was started on cyclosporin A, dexamethasone and etoposide per the HLH 2004 protocol. Her clinical status as well as inflammatory markers including ferritin and IL-2 levels were followed to monitor for improvement (figure 2).

OUTCOME AND FOLLOW-UP

Genetic studies for familial HLH were sent and showed a homozygous mutation in PRF1 (PRF1 PT450M) in the C2 domain associated with familial HLH. Additionally, testing revealed absent perforin expression in cytotoxic cells, and essentially absent natural killer-cell function, consistent with familial HLH.

Unfortunately, prior to the initiation of intrathecal chemotherapy per the HLH protocol, the patient developed seizures on hospital day 44. Repeat head CT showed new intracranial haemorrhage with herniation. Per family discussion, care was withdrawn and the patient passed away.

DISCUSSION

HLH is a disorder of uncontrolled immune activation that can be caused by genetic mutations (familial HLH) or acquired secondary to infection, malignancy, rheumatological or metabolic conditions. Although familial HLH typically presents at an early age, there have been increasing case reports of patients diagnosed with familial HLH at a more advanced age.¹⁻⁴ There are several gene mutations associated with familial HLH that have been identified, including PRF1, UNC13D, STX11 and

Figure 2 Line graph showing response to treatment with decreasing values for ferritin and soluble CD25 level in relation to therapies given. Treatments given indicated by arrows corresponding to date of treatment marked on graph.

STXBP2.⁵ In our patient, genetic studies revealed a homozygous mutation in PRF1, consistent with a diagnosis of familial HLH. Acquired HLH is also known as MAS when associated with a rheumatological condition (including adult onset Still's disease and systemic lupus erythematosus). In this case, we were suspecting an acquired syndrome of HLH given that the patient was not presenting in infancy, and thus were surprised to find that she did have an underlying genetic mutation consistent with familial HLH.

The diagnosis of HLH is made based on signs, symptoms and laboratory testing. The updated criteria include either (1) molecular testing consistent with HLH or (2) 5 of 8 of the

Patient's perspective

- Our 24-year-old daughter was making plans for her wedding and we were all elated. She developed cough and UTI. She saw many physicians for months and was diagnosed with bronchitis and prescribed similar medications. Her condition continued to deteriorate and she believed this was the beginning of the end of her life. Diagnosed with neutropaenia, she was admitted to a local hospital and I had her transported to a prestigious teaching hospital. A team of specialists was doing everything possible when they suspected that she had HLH. She had at this time met three of the eight criteria for this devastating fatal disease that can mimic many diseases. Unknown to the doctors was the fact that treatment should have begun immediately, instead of waiting for all eight criteria. By beginning treatment promptly the ultimate result could have meant her survival. Also, many physicians have never heard of HLH, and this delayed her admittance to the hospital.
- Our family's final wish is for *The BJM* to publish this crucial information.
- The awareness of HLH will bring forth hope in saving many lives in the future.

following criteria: fever, splenomegaly, cytopaenias affecting at least 2 lineages, hypertriglyceridaemia and/or hypofibrinogenaemia, haemophagocytosis (in bone marrow, spleen, lymph node), hyperferritinaemia, impaired NK-cell function and elevated soluble IL-2 receptor (sCD25).⁶ Presenting symptoms may be non-specific and, additionally, patients may not initially present with all of the criteria, making diagnosis challenging. However, HLH can be rapidly fatal and, thus, treatment should be initiated when there is a high index of suspicion. Treatment should include targeting the underlying disorder and controlling immune dysregulation.

In this case, the patient presented at a later age and diagnosis was delayed due to non-specific presenting symptoms. Although the diagnosis of HLH was considered soon after transfer, the patient initially did not meet criteria for the diagnosis of HLH.

Learning points

- ▶ Familial haemophagocytic lymphohistiocytosis (HLH) can present at an older age.
- ▶ Although patients may not initially fulfil the diagnostic criteria of HLH, high suspicion for HLH is necessary.
- ▶ Early initiation of treatment is warranted if there is a high clinical suspicion, especially in patients with neurological manifestations, as the disorder is often fatal without early intervention.

Treatment for HLH was initiated despite this due to high suspicion while awaiting further testing (including NK-cell function and examination of perforin expression in cytotoxic cells), which further helped to confirm the diagnosis of HLH. The results of her genetic testing (which revealed a homozygous PRF1 mutation) were unexpected given her age and lack of family history, which had been obscured by her closed adoption status. Despite the initiation of treatment per the HLH2004 protocol, the patient passed away before initiation of intrathecal chemotherapy.

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