European Journal of Case Reports in Internal Medicine

Haemophagocytic Lymphohistiocytosis Complicating Myelodysplasia

Geraldine Quintero-Platt[a], Carima Belleyo-Belkasem[a], Taida Martín-Santos[b], Onán Pérez-Hernández[a], Emilio González-Reimers[a]

[a] Internal Medicine Department, Canary Islands University Hospital, La Laguna University, Tenerife, Canary Islands

[b] Hematology Department, Canary Islands University Hospital, La Laguna University, Tenerife, Canary Islands

Abstract:

We describe a 62-year-old patient with a 4-year history of myelodysplasia who later developed striking features that included massive splenomegaly, rapidly evolving visual loss and a sensorimotor polyneuropathy. This led us to consider the diagnosis of haemophagocytic lymphohistiocytosis (HLH). Upon further investigation, we found that he fulfilled the necessary diagnostic criteria for HLH, including the presence of haemophagocytosis of erythroid precursors on bone marrow smear.

Keywords: Myelodysplastic syndromes, lymphohistiocytosis, hemophagocytic, polyneuropathy

Received: 17/12/2013

Accepted: 10/03/2014

Published: 28/03/2014

How to cite this article: Quintero-Platt G, Belleyo-Belkasem C, Martín-Santos T, Pérez-Hernández O, González-Reimers E Haemophagocytic Lymphohistiocytosis Complicating Myelodysplasia, *EJCRIM 2014;***1:**doi: 10.12890/2014_000016

Conflicts of Interests: The authors declare that they have no conflicts of interest in this research.

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is defined by the association of several criteria including fever, splenomegaly, bicytopenia or pancytopenia, hypofibrinogenaemia hypertriglyceridaemia and haemophagocytosis on examination of bone marrow or spleen. Additional criteria include low natural killer (NK)-cell activity, hyperferritinaemia and high soluble interleukin-2-receptor levels[1].

HLH can be fatal if allogeneic stem cell transplantation (SCT) is not performed. Mortality rates of 52% have been reported in secondary forms of HLH. Available treatment options include cytotoxic agents, corticosteroids, immunosuppressive therapy and SCT[2].

HLH may be idiopathic or it may be associated with several entities characterised by immune dysregulation. Secondary forms of HLH may occur in the context of chronic infections and malignancy. HLH has been strongly associated with myelodysplasia[3].

We report the case of a 62-year-old patient with myelodysplasia who developed unusual features and eventually fulfilled the criteria for HLH.

Case report

A 62-year-old patient had a 4-year history of refractory cytopenia with multilineal dysplasia. He also had a mild monoclonal IgG-lambda gammopathy. He was being treated with erythropoietin and G-CSF analogues. One year earlier he had developed papilloedema and impaired vision. He improved with prednisone 60 mg/day and progressive tapering but his vision deteriorated one month prior to admission and he had to be placed on the initial dose again.

He presented with a 4-day history of pain and swelling in his left leg. Deep vein thrombosis was diagnosed through ultrasonography. He was placed on anticoagulation with dalteparin and the growth factors were temporarily withheld.

A CT scan of the chest and abdomen was performed to rule out an occult neoplasm. It demonstrated a splenomegaly of 17.4 cm that had progressively increased over the last year.

Treatment with growth factors was resumed 72 h after admission and we initially obtained an adequate response. However, over the course of a month we observed progressive worsening of his pancytopenia.

A bone marrow aspirate demonstrated a hypercellular marrow with significant dyspoiesis in the erythroid and megakaryocytic series. While this smear ruled out progression to acute leukaemia, it showed haemophagocytosis of erythroid precursors *(Fig.1)*.

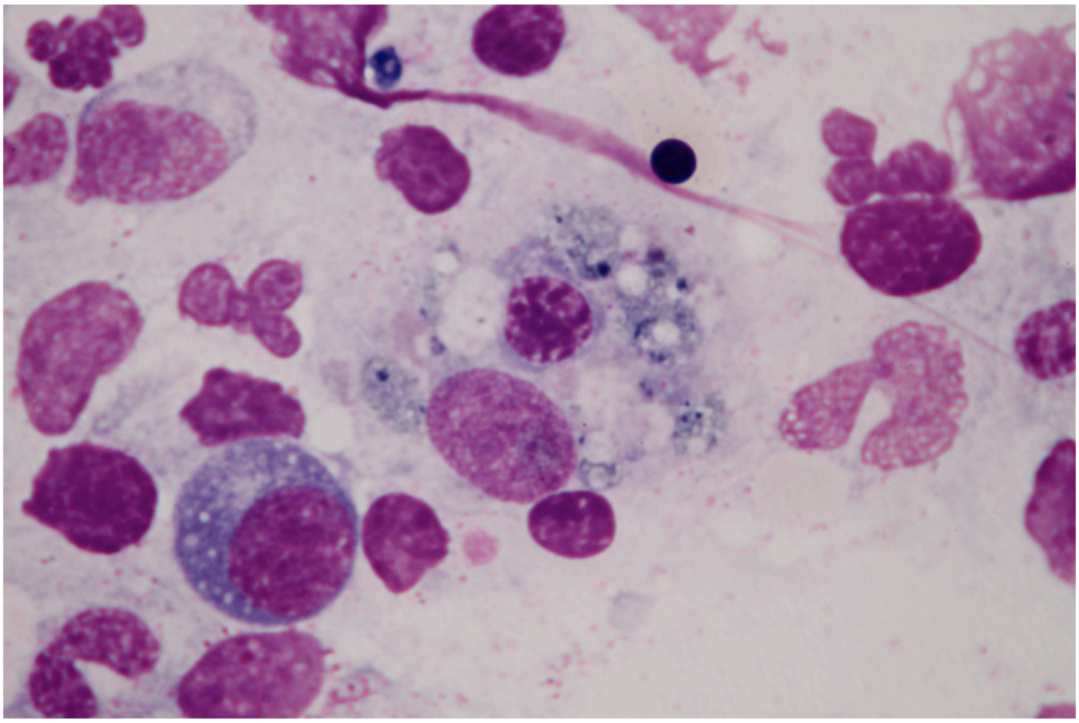

Figure 1 Bone marrow aspirate showing phagocytosis of an erythroblast by a macrophage (x100, Giemsa stain).

Doi: 10.12890/2014_000016

Due to his worsening thrombocytopenia, with a platelet count that reached 5000/mm^3, we withdrew treatment with dalteparin. Two weeks later he began to complain of pain and swelling in his left calf. Ultrasonography confirmed a new deep vein thrombosis. We resumed anticoagulation.

The patient developed recurrent respiratory infections. A chest X-ray revealed a cavitating lesion in the right lower lobe. *Pseudomonas aeruginosa* was isolated from sputum and he was placed on meropenem and tobramycin (the patient had received tobramycin for 3 days at a dosage of 200 mg/twice daily). *Aspergillus fumigatus* was later isolated from sputum. He responded well to voriconazole and caspofungin.

Throughout his hospitalisation, his visual acuity deteriorated despite treatment. Marked muscle wasting and progressive deafness also ensued. Orbital MRI ruled out leukaemic infiltration of optic nerves and nerve conduction studies revealed a sensorimotor polyneuropathy. Evoked potential testing was consistent with bilateral sensorineural hearing loss.

The patient progressively worsened and he reached a platelet count of 7000/mm^3. Anticoagulant therapy was withdrawn due to bleeding risk. The patient died two months after admission. No autopsy was performed (*Table 1*).

Variable	Reference range, adults	3rd hospital day	45th hospital day
Haemoglobin (g/dl)	13.5–17.5	9.7	8.6
Leukocytes (/mm^3)	4,500–11,100	7,800	9,000
Neutrophils (%)	50–60	83.9	96.1
Lymphocytes (%)	25–45	7.7	2.2
Monocytes (%)	3–10	8.3	1.7
Basophils (%)	0–1	0.1	0
Eosinophils (%)	1–4	0	0
Platelets (/mm^3)	150,000–400,000	62,000	14,000
Fibrinogen (mg/dl)	220–450	423	153
Triglycerides (mg/dl)	50–200	230	308
Ferritin (ng/ml)	20–300	168	348
Aspartate aminotransferase (U/l)	0–40	14	16
Alanine aminotransferase (U/l)	0–40	16	30
Alkaline phosphatase (U/l)	40–129	76	160
Gamma-glutamyl transpeptidase (U/l)	7–40	34	71

Table 1: Laboratory data

Discussion

We describe a patient with severe myelodysplasia who had several remarkable features. He had a rapidly evolving splenomegaly, progressive visual loss and a sensorimotor polyneuropathy. These unusual features prompted us to consider the diagnosis of an associated HLH. This scenario has rarely been described[3]. The diagnosis of HLH is based on several criteria [1], many of which were observed in this patient. Specifically, he had fever, pancytopenia, massive splenomegaly,

hypofibrinogenaemia and hypertriglyceridaemia. We also found haemophagocytosis of erythroid precursors on bone marrow smear. Therefore, he fulfilled the five criteria required for diagnosis. Another diagnostic criteria includes ferritin levels >500 ng/ml. However, the patient had hyperferritinaemia that did not reach this diagnostic threshold.

Splenomegaly is very uncommon in myelodysplasia, and its presence may indicate myelomonocytic leukaemia, which was ruled out by bone marrow aspirate. Splenomegaly may constitute the first sign of leukaemic transformation. It may also indicate extensive extramedullar erythropoiesis[4]. Given the rarity of splenomegaly in myelodysplasia, this clinical feature would fit better with HLH.

Polyneuropathy has been more frequently reported in HLH than in myelodysplasia[5]. The papilloedema in this patient was perhaps the first sign of optic neuritis. The progression of optic nerve involvement was halted by prednisone therapy, but later flared up when prednisone was tapered. MRI studies ruled out the presence of vascular lesions and leukaemic infiltration of optic nerve sheets.

Visual impairment has rarely been described in myelodysplasia; it may be caused by anaemic hypoxia and microvascular insufficiency. These mechanisms were probably not responsible for visual loss in this patient since the optic neuritis was initially responsive to prednisone. Despite the presence of a mild monoclonal IgG-lambda gammopathy, there were no signs of a hyperviscosity syndrome.

Another striking feature of this patient was the development of progressive deafness. A slight hearing impairment existed before admission, which worsened after being placed on tobramycin. Tobramycin was stopped after three days of treatment but hearing loss continued to progress significantly.

Cranial neuropathies have been described in HLH. A retrospective study of patients with HLH revealed that as many as 73% had evidence of central nervous system (CNS) involvement at the time of diagnosis[5].

In summary, this patient developed clinical features compatible with HLH in the last year of his life. When the diagnosis of HLH was considered, he had already developed lung aspergillosis and a severe polyneuropathy. This highlights the importance of considering the diagnosis of HLH in patients with myelodysplasia and unusual features.

Learning Points

- Haemophagocytic lymphohistiocytosis (HLH) can be a rare complication of myelodysplastic syndromes.
- HLH is ultimately fatal if timely allogeneic stem cell transplantation is not performed.
- This case highlights the importance of considering the diagnosis of HLH in patients with myelodysplasia who present with unusual features.

References

1. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis, *Pediatr Blood Cancer* 2007;**48**:124–131.
2. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis, *Blood* 2011;**118**:4041–4052.
3. Tsuji T, Yamasaki H, Arima N, Tsuda H. Hemophagocyic lymphohistiocytosis associated with myelodysplastic syndromes, *Int J Hematol* 2010;**92**:547–549.
4. Kraus MD, Bartlett NL, Fleming MD, Dorfman DM. Splenic pathology in myelodysplasia: a report of 13 cases with clinical correlation, *Am J Surg Pathol* 1998;**22**:1255–1266.
5. Haddad E, Sulis ML, Jabado N, Blanche S, Fischer A, Tardieu M. Frequency and severity of central nervous system lesions in hemophagocytic lymphohistiocytosis, *Blood* 1997;**89**:794–800.