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Hemophagocytic lymphohistiocytosis in a patient with myelomatous activity after autologous bone marrow transplant.

Motolinia-Muñoz Y[1,2], Gastélum-Cano JM[1,2], Tenorio-Páez C[1,2], Ruiz-Argüelles GJ[1,3]

Abstract

Hemophagocytic lymphohistiocytosis is a difficult diagnostic and infrequent hyperinflammatory syndrome. Patients with malignant hematological diseases are especially prone to develop it. Multiple myeloma (MM) is reported among diseases that present association with secondary HLH (sHLH). However, this association is poorly studied. Here we describe the case of a 68-year-old male patient, Mexican mestizo, who was diagnosed with MM in 2008 and attended to the Center for Hematology and Internal Medicine for evaluation. The patient reported weight loss of 9 kg, fatigue and weakness. Laboratory studies showed serum protein electrophoresis (sPEP) without monoclonal band pattern; urine immunofixation electrophoresis test (uIFE) positive for gamma heavy chain and kappa light chain; serum immunofixation electrophoresis test (sIFE) negative. Bone marrow biopsy and aspiration showed a normocellular bone marrow with 1.2% of plasmatic cells. Bone marrow immunophenotyping by flow cytometry found no neoplasic cells. The X-ray scanning showed a radiolucid area in cranium, probably corresponding to osteolytic lesions; spine with crushed lumbar discs and ilium osteolysis. In May 18th of 2016 new findings in laboratories studies including sIFE positive for IgG-Lambda and sPEP with monoclonal band pattern in gamma fraction were reported. An outpatient autologous peripheral blood stem cell transplantation (APBSCT) was performed in February 11th of 2017. On Day + 4 he was admitted at intensive care unit for transplant subsequent events. A new bone marrow biopsy and aspiration was carried out and showed 32.3% of plasmatic cells. Histiocytes with Hemophagocytic phenomenon were observed. To the knowledge of the authors, this case is de sixth associated to myelomatous activity and the third after APBSCT.

KEYWORDS: hemophagocytic lymphohistiocytosis; hemophagocytic syndrome; multiple myeloma; malignancy; bone marrow transplant

[1] Laboratorios Clínicos de Puebla, Puebla, México.
[2] Universidad Popular Autónoma del Estado de Puebla, Puebla, México.
[3] Centro de Hematología y Medicina Interna, Puebla, México.

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Correspondence
Dr. Guillermo J Ruiz Argüelles
gruiz1@hsctmexico.com

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Linfohistiocitosis hemofagocítica en un paciente con actividad mielomatosa posterior a un trasplante de médula ósea autólogo

Motolinia-Muñoz Y[1,2], Gastélum-Cano JM[1,2], Tenorio-Páez C[1,2], Ruiz-Argüelles GJ[1,3]

Resumen

La linfohistiocitosis hemofagocítica es un síndrome hiperinflamatorio raro y de difícil diagnóstico. Los pacientes con enfermedades hematológicas son propensos a padecerla. El mieloma múltiple está entre las enfermedades que se asocian con linfohistiocitosis hemofagocítica adquirida. No obstante, esta asociación está escasamente estudiada. Se describe el caso de un paciente de 68 años de edad, mestizo mexicano, a quien se le diagnosticó mieloma múltiple en 2008 y acudió al Centro de Hematología y Medicina Interna de Puebla, México. El paciente refirió pérdida de peso de 9 kg en 2 meses, fatiga y debilidad. Los estudios de laboratorio revelaron: electroforesis de proteínas séricas sin banda monoclonal; inmunofijación en orina positiva para cadenas pesadas gamma y ligeras kappa; inmunofijación en suero negativa. El mielograma mostró médula ósea normocelular con 1.2% de plasmocitos. No se detectaron células neoplásicas en el inmunofenotipo en médula ósea por citometría de flujo. Se realizó serie ósea con imágenes de cráneo en las que se observaron zonas radiolúcidas, probablemente correspondientes a lesiones osteolíticas. En la columna se observó aplastamiento de cuerpos vertebrales lumbares, con zonas de osteólisis en iliaco derecho e izquierdo. En mayo de 2016 los estudios de laboratorio mostraron en la inmunofijación en suero una banda monoclonal IgG-lambda y la electroforesis de proteínas séricas mostró una banda monoclonal incluida en fracción gamma. Se realizó de manera extrahospitalaria un trasplante autólogo de células progenitoras hematopoyéticas de sangre periférica (TACPHSP) en febrero de 2017. En el D + 4 se ingresó a terapia intensiva por eventos derivados del trasplante. Un nuevo aspirado de médula ósea reveló 32.2% de plasmocitos y se observaron células con fenómeno de hemofagocitosis. Para nuestro conocimiento, este caso de linfohistiocitosis hemofagocítica asociado con actividad mielomatosa sumaría el sexto en la bibliografía y el tercero reportado posterior a un TACPHSP.

PALABRAS CLAVE: linfohistiocitosis hemofagocítica, síndrome hemofagocítico, mieloma múltiple, malignidad, trasplante de médula ósea.

[1] Laboratorios Clínicos de Puebla, Puebla, México.
[2] Universidad Popular Autónoma del Estado de Puebla, Puebla, México.
[3] Centro de Hematología y Medicina Interna, Puebla, México.

Correspondencia
Dr. Guillermo J Ruiz Argüelles
gruiz1@hsctmexico.com

INTRODUCTION

The term hemophagocytosis refers to activated histiocytes phagocytizing erythrocytes, leukocytes, platelets and precursors cells.[1] Hemophagocytic syndrome, better denominated as hemophagocytic lymphohistiocytosis is a difficult diagnostic and infrequent hyperinflammatory syndrome[2] because of its non-specific symptoms and lack of gold standard for detection.[3,4] It was first described in 1939 for Scott and Robb-Smith,[1,2] characterized by fever, pancytopenia, splenomegaly and hemophagocytosis in hematopoietic organs[1,5] as a consequence of uncontrolled activation of histiocytes and lymphocytes, and a storm of cytokines.[6]

Hemophagocytic lymphohistiocytosis (HLH) is traditionally divided in: *1)* Primary HLH (genetic), which typically appears in children with genetic mutations affecting T and NK cells granule-dependent cytotoxic function, and *2)* Secondary HLH (acquired) frequently manifesting in older ages, with infectious or non-infectious triggers.[4,6]

There is not genetic abnormality or immunodeficient syndrome associated with sHLH and can occurs in any age.[4] Nevertheless, viral triggers are the most frequent, with herpes viruses (62% of all virus), particularly Epstein-Barr virus (43% of herpes viruses) being the most common.[4,7] In the other hand, underlying conditions are malignant hematological diseases,[4] mainly lymphoma (34.7%).[2] In these cases, HLH can appear with clinic profile of emerging malignant disease or evolving during the treatment of the disease. Concomitant infections are commonly present and can mask the root malignancy.[8]

Multiple myeloma has been included among malignant diseases associated with sHLH[4,8] and there are few cases reported.[9-13] Nonetheless, such relation has been poor studied. The present case report describes a patient with multiple myeloma who received an outpatient APBSCT and was admitted to intensive care unit because subsequent events, getting the finding of histiocytes infiltration in bone marrow showing hemophagocytic phenomenon.

CASE REPORT

A 68 years old male patient, Mexican mestizo who was diagnosed with multiple myeloma in 2008 and attended to the Center for Hematology and Internal Medicine for evaluation. The patient reported weight loss of 9 kg, fatigue and weakness. Laboratory studies showed serum protein electrophoresis (sPEP) without monoclonal band pattern; urine immunofixation electrophoresis test (uIFE) positive for gamma heavy chain and kappa light chain; serum immunofixation electrophoresis (sIFE) test negative. In the complete blood cell count RBC 5.02 x 10^{12}/L, Hb 15.0 g/dL, Hct 47.2%, MCV 94 fL, RDW 16.9%, WBC 8.1 x 10^{9}/L, lymph 56%. Serum β-2 microglobulin 2.304 mg/L; LD 275 IU/L; creatinine 0.63 mg/dL; Ca 4.6 mEq/L, P 2.3 mEq/L; bone marrow biopsy and aspiration showed a normocellular bone marrow with 1.2% of plasmatic cells. Bone marrow immunophenotyping by flow cytometry found no neoplasic cells. The X-ray scanning showed a radiolucid area in cranium, probably corresponding to osteolytic lesions; spine with crushed lumbar discs and ilium osteolysis. Along 3 years the patient was treated with diverse schemes that included thalidomide, lenalidomide, bortezomib and aspirin as prophylaxis.

On May 18th of 2016, a positive result for monoclonal band pattern of gamma globulin in sPEP and presence of monoclonal band IgG-Lambda in sIFE were reported. Weekly I.V. bortezomib 175 mg and thalidomide 100 mg were administrated. In spite of that, monoclonal band pattern persisted and patient required APBSCT. Conditioning regimen was set with

trimethoprim-sulfamethoxazole (TMP/SMX) 800 mg/160 mg, itraconazole 100 mg and filgrastim 300 mg. High-dose therapy with melphalan 200 mg/m^2 was applied and APBSCT was performed on February 11th of 2017; the graft consisted in approximately 1 x 10^6 CD34$^+$ cells/kg collected after three apheresis. On D + 2 ondansetron 8 mg, TMP/SMX 800 mg/160 mg and itraconazole 100 mg were restarted. On Day + 4 he was admitted at intensive care unit (ICU). At the time of admission, patient was sleepy, with dry oral mucous membrane, referring gastrointestinal bleeding; vital signs reported: blood pressure 134/84 mmHg, cardiac frequency 108 bpm, respiratory rate 20 breaths per minute, temperature 37°C, oxygen saturation 96%; Hb 15.3 g/dL, WBC 0.3 x 10^9/L with 47% neutrophils. At the beginning, patient was treated with TMP/SMX, fluconazole 100 mg/IV/12h and filgrastim 300 µg/12h/SC. After 72 hours patient showed hemodynamic instability and diarrheic stools with mucus, reason for why non-invasive mechanic ventilation was started and vasoconstrictor amines were administered, as well as sedation without hemodynamic improve dependent on norepinephrine dose. Hypoventilation in both of lung bases was detected predominantly in the right one, keeping in a non-febrile condition. An intentioned search for pathogens was performed, looking for *Clostridium difficile* A-B toxin, adenovirus, cytomegalovirus and coccidia, with negative results, procalcitonin was > 10 µg/L; vancomycin was added to original therapeutic scheme. On day 8 after admission, patient registered lactate of 3.1 mmol/L, hydroelectrolytic imbalance, metabolic acidosis, hypertriglyceridemia, Hb 12.1 g/dL, HCT 36%, PLT 8.0 x 10^9/L without active bleeding. On 10th day, new laboratory analysis showed CB: 5.9 mg/dL, TBIL: 8.46 mg/dL, AST: 80 UI/L, ALT: 64.5 UI/L, GGT: 309 UI/L, ALP: 88 UI/L, and worsening thrombocytopenia with 3.0 x 10^9/L, continuing without active bleeding and hydroelectrolytic imbalance. Due to the hepatic failure, hepatotoxic drugs were suspended; new intentioned search for pathogens looking for Hepatitis A, B and C was done. On 11th day post-admission in ICU, weaning of mechanical ventilation protocol was initiated, patient was detected polypneic with increase of respiratory work, blood pressure of 160/80mmHg, non-febrile, with Arterial PO_2 of 74.9%, reason for reinitialize sedation. CT scan of thorax was performed: 90% of pneumothorax in right lung and pleural effusion. Platelet apheresis was indicated and a pleural catheter was installed, obtaining 220mL of turbid liquid and keeping stable (greatest volume reported of serohematic liquid was 180 mL at fourth day after installation). On 15th day after admission, patient reported an improving on hemodynamic stability, without vasopressor amines, functional catheter, hydroelectrolytic imbalance, cholesterol 111 mg/dL, triglycerides 262 mg/dL, decreased peristalsis, with correcting on liver function tests: TBIL: 2.54 mg/dL BC: 1.19 mg/dL, AST: 33.9 UI/L, ALT: 51.7 UI/L, GGT: 262 UI/L, ALP: 88.3 UI/L, reduction of blood urea nitrogen, non-febrile and presenting oral and digestive tube bleeding with a decreasing on Hb (11.1 g/dL) and platelets (5 x 10^9/L). Transfusion therapy was indicated and restarting of vasopressor support was evaluated. In day 17 of intrahospitalary admission, a new bone marrow biopsy and aspiration was carried out and showed 32.3% of plasmocytes; a cell population of 20% with immunophenotypic characteristics of plasmatic cells was reported by flow cytometry. Histiocytes with hemophagocytic phenomenon were observed in bone marrow staining (**Figure 1**), but none in bone marrow biopsy. Nonetheless, the latter supported myelomatous activity (**Figure 2**). Therapeutic scheme with ganciclovir 350 mg/IV/h, dexamethasone 40 mg/IV (single dose) and retiring of pleural catheter was indicated, showing later tachypnea and requiring platelet transfusion. On 23th day after admission to ICU, patient showed cholestatic pattern in liver function tests BC: 4.07 mg/dL, BU: 2.48 mg/dL, AST: 55 IU/L, ALT: 49 IU/L, neutropenia, PLT:

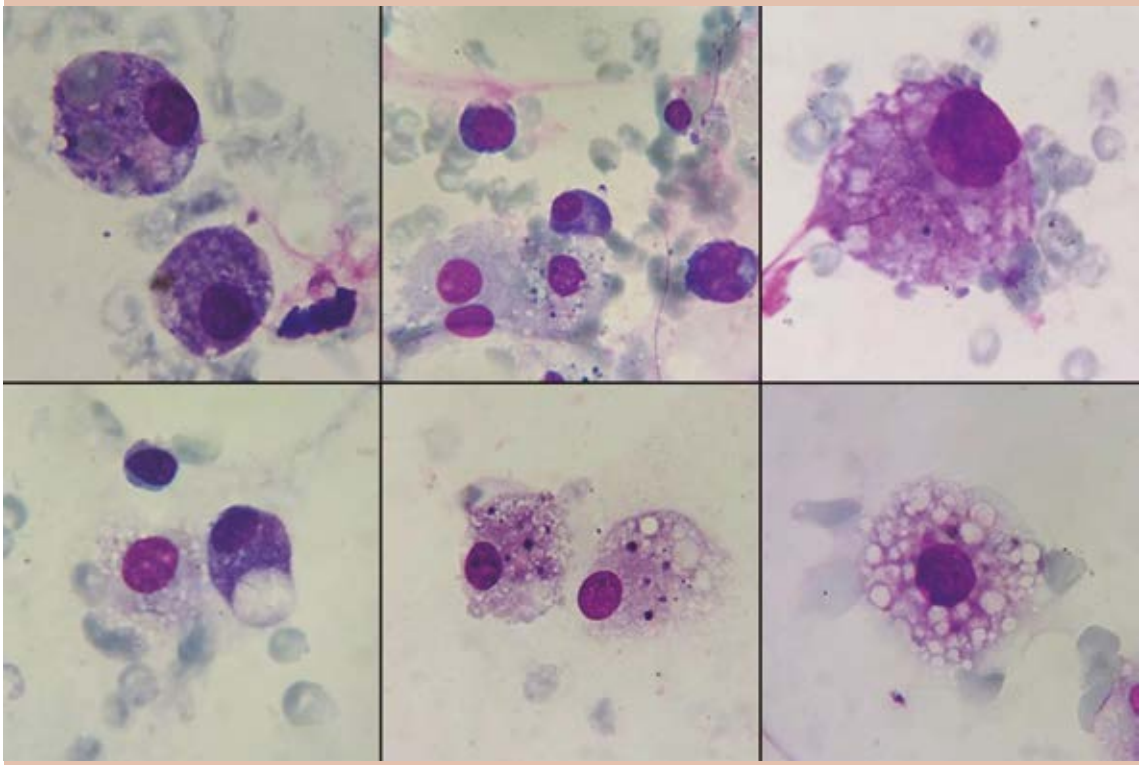

Figure 1. Typical images of bone marrow smear of the patient in which is easy to appreciate many histiocytes phagocytizing mainly red blood cells, in some of them is notable the presence of plasmatic cells that reveals myelomatous activity.

3 x 10^9/L; keeping going scheme with TMP/SMX, meropenem and ganciclovir; morphine was added. Patient finally died in March 10th of 2017 on D + 28 after APBSCT.

DISCUSSION

In accordance with Histiocyte Society 2004 Guidelines[14] as in other similar cases published in the literature,[9-13] patient showed pancytopenia as main pathologic sign; besides others like fever, hypertriglyceridemia, hepatic failure and hemophagocytosis syndrome finding in bone marrow. In spite of hard suggestive evidence for the pathology, the Histiocyte Society 2004 Guidelines establish that five of eight criteria must be fulfilled to diagnose HLH. Nonetheless, more suggestive clinical and laboratory signs just as hypofibrinogenemia or hyperferritinemia couldn't be find because they were not realized, nor necessary for diagnostic.

HLH by itself is a rare entity with an estimated annual incidence of 1:800,000 persons and 1-10:1,000,000 of children in Italy, Sweden and USA.[2] The HLH-MM association is even scarcer, to such a point that few reviews consider it.[4] In fact, to the knowledge of authors there are just five descripted cases on literature

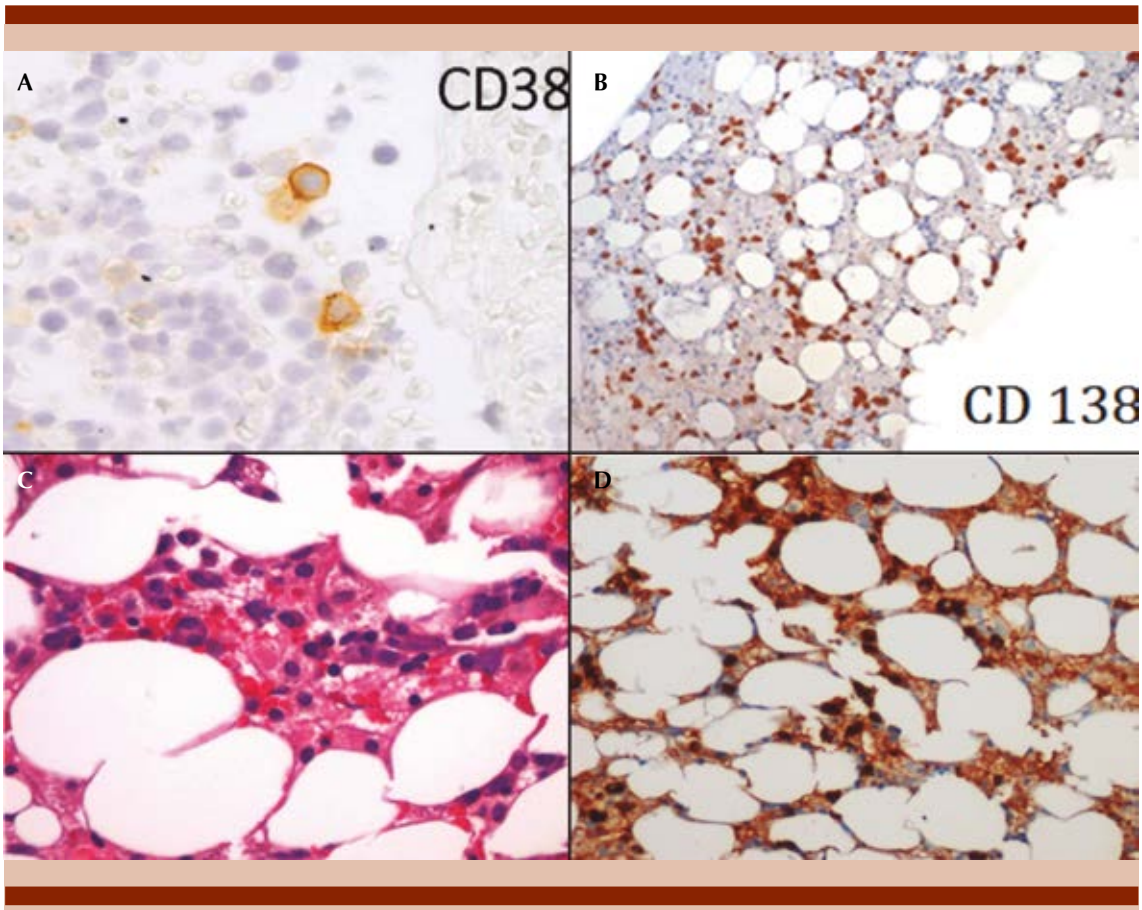

Figure 2. Images of patient's second bone marrow biopsy and aspiration that evidence the expression of CD38 (weak) and CD138 (strong) that together are usually used to investigate plasmatic cells for diagnostic of multiple myeloma (**A** and **B**, respectively). Additionally, it is possible to appreciate some plasmatic cells presence in hematoxylin-eosin stain (**C**). Furthermore, it is possible to appreciate a strong positive in lambda chains (**D**).

and two of them after APBSCT. This limited incidence additional to non-specific symptoms and the lack of a gold standard for diagnostic can be contributing to sub-diagnose HLH in patient with multiple myeloma or other neoplasia. Despite new added methods for diagnostic as quantification of soluble CD25 and activity of NK-Cells, this association apparent to be neglected. It's important to highlight this possibility because, according as physicians get it in mind more is the probability to find it, and consequently more people can be opportune diagnosed.

Among the possible triggers of HLH in multiple myeloma patients, the increase of myelomatous activity[10-12] and subsequent events accompanying APBSCT such as increased peripheral blood cytokines and immunes reconstitution,[12,13] have been considered. Moreover, to establish this relation it is necessary to replicate this model in controlled experiments. In the other hand, although the absence of pathogens has been reported by the majority of existent cases[10-13] including the present case, it is not possible to discard at all an infectious trigger, because of technical limitations of tests and the quantity

of possible suspected non-studied pathogens. However, a good approach can be the response of each patient to the treatment. Most of them have a corticosteroid compound as a therapeutic resource to brake the cytokines storm, but some have been combined with direct attack to the malignancy with chemotherapy as VAD (vincristine-adriamycin-dexamethasone)[10] or etoposide[11] which have had successful outcomes. High dose of Intravenous Immunoglobulin combined with dexamethasone have had good results.[13] In the present case, patient was treated with ganciclovir, dexamethasone, romiplostim and eltrombopag, without success.

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