In summary, we have reported a decidedly unusual case that we were unable to classify as a rare isolated case or an underdiagnosed disease.

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Ledicia Álvarez Paredes[a,*], Luis Buzón Martín[b], María Ortega Lafont[a], Miguel Ángel Morán Rodríguez[b]

[a] *Servicio de Microbiología, Hospital Universitario de Burgos, Burgos, Spain*
[b] *Unidad de Enfermedades Infecciosas, Servicio de Medicina Interna, Hospital Universitario de Burgos, Burgos, Spain*

* Corresponding author.
E-mail address: lalvarezpa@saludcastillayleon.es
(L. Álvarez Paredes).

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Haemophagocytic lymphohistiocytosis secondary to Epstein-Barr virus infection with fatal outcome☆

Linfohistiocitosis hemofagocítica secundaria a infección por virus de Epstein-Barr de evolución fatal

Most primary infections with Epstein-Barr virus (EBV) are subclinical and go unnoticed. Infectious mononucleosis is the best-known acute clinical manifestation of EBV. It usually resolves normally, but may follow a complicated course, which rarely includes lymphoproliferative syndromes such as haemophagocytic lymphohistiocytosis (HLH), a very serious condition.[1]

We present a case of HLH secondary to EBV with a fatal outcome.

A 26-year-old man with no prior history of note came to the emergency department due to signs and symptoms of abdominal pain, vomiting, diarrhoea and a fever of up to 40 °C. Splenomegaly and inguinal lymphadenopathy were palpated on examination. Laboratory testing revealed: total bilirubin 5.5 mg/dl, GPT/GOT/GGT 469/382/460 IU/l, alkaline phosphatase 319 IU/l, LDH 450 IU/l, ferritin 2632 ng/ml, CRP 10.42 mg/dl, leukocytes $2250 \times 10^3/\mu l$ (neutrophils $1360 \times 10^3/\mu l$ and lymphocytes $0.73 \times 10^3/\mu l$), haematocrit 35.9% and platelets $100{,}000 \times 10^3/\mu l$.

He was admitted to internal medicine, where his clinical course was unfavourable, as his fever persisted, his liver panel gradually worsened (with a pattern of cytolysis and cholestasis) and he experienced moderate pancytopenia with a high percentage of immature forms in peripheral blood. An abdominal CT scan detected hepatosplenomegaly with retroperitoneal, iliac and inguinal lymphadenopathy, suggesting that a myeloproliferative syndrome could be ruled out.

He received broad-spectrum antibiotic treatment with meropenem and vancomycin. Endocarditis was ruled out by ultrasound.

Serologies: HIV, CMV and HCV negative; Paul Bunnell positive, with EBV Ag early IgG positive, EBV capsid IgG and IgM positive, EBV EBNA IgG negative and EBV EBNA IgM positive, which confirmed acute infection with EBV.

Biopsy of crural lymphadenopathy: reactive lymphoid proliferation with morphologic and immunophenotypic characteristics consistent with infectious mononucleosis with no clonality demonstrated by immunohistochemistry.

He was admitted to the ICU after 12 days due to respiratory failure. He developed multi-organ failure (respiratory, haemodynamic, renal and hepatic) and required vasoactive support, mechanical ventilation and renal replacement therapy. He underwent a PET/CT scan (inconclusive), a bone marrow study (global hypercellularity, slight increases in plasma and eosinophils and prominent haemophagocytosis) and an immunophenotype study by means of flow cytometry of bone marrow and peripheral blood (B population very limited with no monoclonality data; no disease population detected).

High EBV viral load (PCR) in peripheral blood (4.34×10^5), on telescoping catheter (3.29×10^3) and in bronchial aspirate (6.29×10^6). Serology for Leishmania negative. Also ruled out in bone marrow.

Laboratory monitoring showed persistent very high ferritin (peak: 19,097 ng/ml); an abnormal liver panel; and severe hypertriglyceridaemia (680 mg/dl), hypofibrinogenaemia (87 mg/dl), thrombocytopenia (up to $16{,}000 \times 10^3\ \mu l$) and neutropenia ($N < 100 \times 10^3\ \mu l$). These findings, along with a sustained high fever, were consistent with HLH.

Treatment was started with aciclovir, dexamethasone 20 mg/24 h, rituximab 750 mg, etoposide 150 mg (dose adjusted to kidney and liver failure) and prophylaxis for infection with *Pneumocystis jirovecii* (co-trimoxazole) as well as antifungal prophylaxis (posaconazole).

Bone marrow aspiration was repeated after 12 days and revealed a phenomenon of haemophagocytosis.

Soluble CD25 was not determined (this is correlated with HLH activity).[2]

The patient died after a 15-day stay in the ICU in a situation of refractory multi-organ failure, severe pancytopenia with high needs for transfusion of blood products and upper gastrointestinal bleeding due to stress-induced gastropathy, which was associated with cerebral oedema with transtentorial herniation secondary to hyperammonaemia of multifactorial origin.

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HLH is an aggressive, potentially fatal syndrome secondary to abnormalities in immune activation characterised in terms of pathology by generalised histiocytic proliferation and haemophagocytosis. Its pathophysiological mechanisms are not well known; however, excessive inflammation and destruction of tissues appears to be related to deficient activation of natural killer cells and T lymphocytes which do not manage to eliminate activated macrophages, leading to their accumulation and a secondary increase in cytokines.[3]

Its origin may be primary (genetic mutation) or secondary. Both origins are often associated with viral infections[4]; EBV is among the viruses most often involved.

It mainly occurs in children. It is characterised by fever, generalised lymphadenopathy, hepatosplenomegaly, hepatitis, pancytopenia and coagulopathy. A third of patients have neurological symptoms, 16% have kidney dysfunction and 42% require ventilatory support.

Our patient had the diagnostic criteria for HLH established in the HLH-2004 protocol,[5] with a sustained fever >38 °C, hepatosplenomegaly, hyperferritinaemia, hypertriglyceridaemia, abnormal liver function, coagulopathy and hypofibrinogenaemia. No genetic study was performed.

A bone marrow study along with clinical and laboratory findings confirmed his diagnosis. Due to the syndrome's high mortality, it is not always necessary to meet these criteria to start treatment.

HLH-2004 recommends initial treatment with dexamethasone and etoposide for 4 weeks when the syndrome is caused by EBV. Etoposide, in addition to inducing apoptosis and limiting the release of inflammatory cytokines, inhibits synthesis of EBV nuclear antigens and transformation of infected cells. Treatment with rituximab would also be advised since the virus replicates predominantly in B cells.[6,7]

Starting treatment early is essential for survival. Even if treated is started early, the syndrome has a high rate of mortality. Those with neurological signs and symptoms and sustained high levels of ferritin have a worse prognosis.

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Beatriz Nieto Martino, Ángela Alonso-Ovies*, Raquel del Olmo Monge

Servicio de Medicina Intensiva, Hospital Universitario de Fuenlabrada, Fuenlabrada, Madrid, Spain

* Corresponding author.
E-mail address: a.alonso@salud.madrid.org (Á. Alonso-Ovies).

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