



SCIENTIFIC LETTERS

Severe liver disease as first sign of a haemophagocytic syndrome[☆]



Afectación hepática grave como debut de un síndrome hemofagocítico

Haemophagocytic syndrome (HPS) is a severe clinical syndrome characterised by a hereditary or acquired generalised and uncontrolled hyperinflammatory reaction secondary to excessive histiocyte and lymphocyte activation, which triggers an intense cytokine response. The most common causes of HPS are infection (predominantly viral), followed by tumours (often haematological), as well as rheumatological or immune disorders.

This syndrome is clinically diagnosed by compliance with certain clinical or histopathological criteria (HLH-2004), which include haemophagocytosis in the bone marrow or other tissues including the spleen, liver, lymph nodes and cerebrospinal fluid.

It is treated with steroids, immunomodulators and etoposide together with supportive care.¹

Although it is usually mild, liver disease is commonly associated with this syndrome and may precede all other manifestations of the disease. We present the case of a patient with HPS who initially presented with severe liver disease.

The case involved a 53-year-old male farmer who used herbicides and pesticides appropriately and who had contact with voles and greyhounds.

He was admitted with a one-week history of jaundice and choluria. Initial bilirubin levels of 13.4 mg/dl were found, with GOT/GPT levels of 1434/2412 IU/l, respectively. Presenting no severe symptoms and the bloods and ultrasound scans having found no cause for concern, it was agreed to follow-up the patient's hepatitis on an outpatient basis. Eight days later, the patient was readmitted due to deteriorated biochemistry.

The differential diagnosis reasonably excluded infection (HAV, HBV, HCV, HEV, HIV, EBV, HSV1, HSV2, PVB19, CMV and TB), autoimmune disease (ANA, ANCA, MPO, AMA, AML and anti-LKM, all negative), Wilson's disease (urine copper levels normal at 24 h) and toxic and pharmacological causes. The

imaging tests revealed splenomegaly with no portal hypertension or ascitic fluid.

The lab tests found the following peak levels: bilirubin 48 mg/dl, creatinine 2 mg/dl, GOT/GPT 2310/2870 IU/l, INR 1.4 and albumin 2 g/dl. The complete blood count revealed mild thrombocytopenia (130,000 μ l) and oscillating neutropaenia (neutrophil nadir 1000 μ l).

A liver biopsy was conducted and treatment with methylprednisolone 1 mg/kg/day was started. Despite the fact that GOT, GPT and bilirubin rapidly fell to normal levels, the patient's anaemia and thrombocytopenia worsened.

Histologically, the liver biopsy found acute cholestatic hepatitis, sites of necrosis and perivenular Kupffer cells, with pigments and sites of acute cholangitis.

Given the patient's splenomegaly, reported cytopaenia, ferritin levels of 2420 ng/ml, triglycerides >420 mg/dl, acute hepatitis and kidney failure, possible HPS was suspected. Bone marrow aspiration was performed, which found a normal bone marrow cell count with prominent haemophagocytosis. HPS was finally diagnosed having ascertained compliance with five criteria (HLH-2004), and protocol HLH-94 (etoposide, dexamethasone) was implemented, together with supportive and prophylactic care (aciclovir and voriconazole). During treatment, the patient developed *Pseudomonas aeruginosa* sepsis and died a few days later from severe brain haemorrhage.

Diagnosing HPS requires a high degree of clinical suspicion. The current diagnostic criteria were drawn up in 2004 (HLH) and include: fever, splenomegaly, cytopenias, hyperferritinaemia, hypofibrinogenaemia or hypertriglyceridaemia, haemophagocytosis, elevated CD25+ levels and reduced NK cell activation. At least five of these criteria must be met to establish the diagnosis.¹

Our patient met five of these criteria, including haemophagocytosis in bone marrow. The aetiological study failed to identify the underlying cause of HPS, a finding consistent with up to one quarter of all adults with HPS reported in the literature.²

The liver is one of the most commonly affected organs in HPS, with abnormal liver function reported in up to 98% of patients, with bilirubin levels of 3–25 mg/dl and moderately increased transaminase levels.³ Cases of fulminant hepatic failure requiring liver transplant have also been reported.⁴ Our patient presented severe liver disease as the first sign of this syndrome, with bilirubin levels peaking at 48 mg/dl but with no indication of hepatic encephalopathy or fulminant hepatic failure.

Three possible theories could explain HPS-associated liver disease: (1) The underlying condition itself; (2) Hepatic infiltration by activated lymphocytes and histiocytes, and

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(3) Secondary to the cytokine storm itself (high levels of TNF-alpha and others).³ Theory number 3 is the most likely hypothesis in our patient.

Although haemophagocytosis and activated macrophage proliferation in the liver biopsy are common, in almost half of all cases only haematogenous pigments are found, as was the case in our sample. Other common findings include sinusoidal dilatation and hepatocyte necrosis. In our patient, haemophagocytosis was not detected in the liver biopsy but rather in the bone marrow aspiration.^{3,5}

The HPS mortality rate exceeds 70%, primarily due to sepsis and intracerebral haemorrhage. Apart from in cases of fulminant hepatic failure, liver disease does not usually represent the cause of death, although it does constitute a severity marker together with ferritin and thrombocytopenia.² The administration of steroids resolved our patient's hepatitis, with the gradual normalisation of bilirubin and transaminase levels as well as the gradual resolution of kidney failure, whilst maintaining high ferritin levels. Given progressive cytopenias, treatment with dexamethasone and etoposide was initiated in accordance with protocol HLH. The patient died due to sepsis and intracerebral haemorrhage.

References

1. Janka GE, Lehmborg K. Hemophagocytic syndromes. An update. *Blood Rev.* 2014;28:135–42.
2. Li J, Wang Q, Zheng W, Ma J, Zhang W, Wang W, et al. Hemophagocytic lymphohistiocytosis: clinical analysis of 103 adult patients. *Medicine (Baltimore).* 2014;93:100–5.
3. De Kerguenec C, Hillaire S, Molinié V, Gardin C, Degott C, Erlinger S, et al. Hepatic manifestations of hemophagocytic syndrome: a study of 30 cases. *Am J Gastroenterol.* 2001;96:852–7.
4. Wright G, Wilmore S, Makanyanga J, McKerrell T, Watkins J, Patch D, et al. Liver transplant for adult hemophagocytic lymphohistiocytosis: case report and literature review. *Exp Clin Transplant.* 2012;10:508–12.
5. Chen J-H, Fleming MD, Pinkus GS, Pinkus JL, Nichols KE, Mo JQ, et al. Pathology of the liver in familial hemophagocytic lymphohistiocytosis. *Am J Surg Pathol.* 2010;34:852–67.

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McKittrick-Wheelock syndrome: A rare cause of metabolic coma[☆]



Síndrome de McKittrick-Wheelock: una causa infrecuente de coma metabólico

Colorectal adenomas are benign tumours with the potential to become malignant. Their incidence ranges from 2.9% to 11.5% depending on the series.¹ Villous adenomas represent 10% of all colorectal adenomas and are normally asymptomatic, although 3% are hypersecretory.² In 1954, McKittrick and Wheelock³ were the first to report hydroelectrolyte depletion secondary to severe diarrhoea caused by this type of tumour.

We present the case of a 72-year-old female patient with a history of hypertension, type 2 diabetes mellitus and hospitalisation two years prior due to pneumonia and hyponatraemia. She attend A&E following three days of epigastric pain together with melaena in the last 24 h. The patient's relatives reported occasional vomiting and severe

diarrhoea in the previous days. Although the patient presented bradylalia and bradyphrenia, she was awake and oriented during the physical examination. She was found to be haemodynamically stable with vital signs within normal range. The abdomen was rounded but soft and depressible with signs of peritoneal irritation. There were signs of skin and mucosa dehydration. During her stay in A&E, the patient presented a reduced level of consciousness, suffered tonic-clonic seizures and went into a coma. The complete blood count conducted in A&E revealed severe hyponatraemia with sodium levels of 101 mEq/l; potassium 4.6 mEq/l; plasma hypoosmolarity without metabolic acidosis and normal kidney function.

The patient was admitted to the intensive care unit after being intubated and put on mechanical ventilation. A cranial computed tomography was performed that found no acute lesions. Volume replacement with hypertonic saline was implemented, and hyponatraemia was gradually corrected until levels of 131 mEq/l were reached. The patient regained consciousness as sodium levels were being corrected, coherently responding to verbal commands but with bradyphrenia.

Given the patient's profuse diarrhoea, a colonoscopy was performed that revealed a villous polyp (0-IIa on the Paris classification) at the hepatic flexure measuring more than 3 cm and endoscopically unresectable owing to its size, with no endoscopic signs of malignancy. The lesion showed abundant surface mucus and signs of recent bleeding (Fig. 1). The

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