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Scientific letters

Spontaneous bacterial peritonitis due to *Helicobacter pylori* in a cirrhotic patient with human immunodeficiency virus and hepatitis C virus coinfection☆

Peritonitis bacteriana espontánea por Helicobacter pylori *en paciente cirrótico coinfectado por virus de la inmunodeficiencia humana y virus de la hepatitis C*

We present the case of a 46-year-old man with a history of parenteral drug use as well as co-infection with hepatitis C virus [HCV] (genotype 1b) and human immunodeficiency virus [HIV] (stage A3) who was admitted due to abdominal pain and ascites. One year earlier, the patient had suffered from an initial episode of ascitic oedematous decompensation with spontaneous bacterial peritonitis, for which he was taking norfloxacin as secondary prophylaxis. At the time of admission, the patient was not on antiretroviral treatment and had a CD4 count of 199 cells/μl, an HIV RNA viral load of 21,000 copies/ml and an HCV RNA viral load of 1,070,000 IU/ml. Liver elastography one month prior to admission had shown 35 kPa and found fibrosis stage 4 and Child–Pugh class B (bilirubin 0.5 mg/dl, INR 1.7, ALT 147 IU/l, creatinine 0.72 mg/dl, haemoglobin 10.5 g/dl, platelets 57,000 and leukocytes 3100/mm^3). One year earlier, he had suffered from an initial episode of ascitic oedematous decompensation with spontaneous bacterial peritonitis, for which he was taking norfloxacin as secondary prophylaxis. A paracentesis on admission showed an inflammatory fluid (laboratory values: leukocytes 800, mononuclear cells 93%, glucose 103 mg/dl and proteins 1.1 g/dl). Treatment was started with ceftriaxone and albumin. After 84 h of incubation of the ascitic fluid in blood culture bottles (BacT/ALERT® FAN, BioMérieux, Marcy l'Étoile, France), curved Gram-negative bacilli with a tendency to cluster were seen to grow. After 4 days of subculture, small; transparent; catalase-, oxidase- and urease-positive colonies grew in pure culture on chocolate agar plates. Analysis using MALDI-TOF® (bioMérieux) yielded no conclusive profiles for identification of this strain. The microorganism was definitively identified using sequencing of the 16S rRNA gene by PCR. This yielded a concordance of 99.9% with sequences of *Helicobacter pylori* (*H. pylori*) (GenBank number 382S94E7014). A day earlier, the patient had requested voluntary discharge. Antimicrobial sensitivity was determined using Etest® (bioMérieux), according to EUCAST criteria, and showed sensitivity to tetracycline, clarithromycin and amoxicillin and resistance to metronidazole and levofloxacin. A genotypic study showed 2 critical mutations in the *gyrA* gene (C261 A/C and A272 A/G) as well as the absence of the *cagA* virulence factor and the s2m2 variant allele of the *vacA* gene.

When the microbiological results were known, the patient was contacted. As he refused to be readmitted, he was prescribed outpatient treatment with amoxicillin, clarithromycin and omeprazole for 14 days.

One month later, the patient was readmitted with abdominal pain, ascites and ascitic fluid with a predominance of mononuclear cells. Both bacterial culture and detection of the microorganism through PCR of the 16S rRNA gene were negative. The patient was empirically treated with ceftriaxone, and his condition resolved. As the patient had mononuclear chronic peritonitis, magnetic resonance imaging and exploratory laparoscopy were performed. Neither yielded conclusive findings on a peritoneal level. Mycobacterial cultures of ascitic fluids from both stays were negative. During his first stay, he underwent endoscopy to screen for oesophageal varices. This showed portal hypertensive gastropathy and grade I varices. As this test was performed before the microorganism was known to grow in ascitic fluid, no biopsies or other tests intended to detect *H. pylori* were done.

To date, very few cases have been documented in humans in whom *H. pylori* was isolated from ordinarily sterile samples,[1–3] including series of spontaneous bacterial peritonitis with negative culture and analysis using PCR and sequencing of the 16S rRNA gene.[4] While most cases of spontaneous bacterial peritonitis are due to bacterial translocation and haematogenous seeding, we could not explain how the microorganism reached the ascitic fluid in this case as no blood was drawn for culture on admission. However, it is well known that other species of *Helicobacter* spp. (*H. fennelliae* and *H. cinaedi)* cause bacteraemia in cirrhotic and immunosuppressed patients and grow in ordinary liquid media.[5] In our case, mass spectrometry (MALDI-TOF®) did not prove a useful tool for identifying *H. pylori*.[6] It is interesting to note that study of the vacA and cagA virulence factors (linked to colonisation of the stomach mucosa) of our strain showed a profile that differed significantly from the profile of strains that usually colonise the stomach and duodenum.[7] We do not know whether these differences, along with others, would be those responsible for a hypothetical invasive profile in this case. In addition, it was interesting to see how using norfloxacin selected a resistant strain in this patient, sample contamination being an implausible explanation for our case. Although there is not much information on the sensitivity of *H. pylori* to third-generation cephalosporins, the evidence published supports the hypothesis that they would have been effective in this case, given the patient's good clinical course.[8]

This strange case raised a number of questions that we were unable to answer. Should *H. pylori* be included among the causes of mononuclear chronic peritonitis in cirrhotic patients? Could *H. pylori* be analogous to *Neisseria gonorrhoeae* in that it has strains with an "invasive profile" capable of causing remote disease? Can *H. pylori* cause bacteraemia like other species from the genus *Helicobacter* spp.?

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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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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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