Bacteraemia due to yersinia enterocolitica and hemochromatosis: case study

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Abstract

The authors present a case of a 66 year old male patient, admitted for fever, diaphoresis, myalgia, mental obtundation and pain in the right hypochondriac area evolving for two weeks. The imaging study of the liver shows a diffuse micronodular pattern suggestive of abcedation and Yersinia enterocolitica growth in the hemocultures. The analytic panel showed a big alteration on the iron metabolism, with the liver histopathology giving a picture of cirrhosis and stage 4 siderosis, indicating the coexistence of hemochromatosis, verified to be genetically determined by a C282Y mutation on the HFE gene. The patient was treated with a sequence of antibiotics, including a quinolone derivative, progressing with sustained but protracted clinical and radiological resolution, without reinfection or subsequent complications. A brief review is also given of the septicemia and liver abscess caused by the Yersinia enterocolitica in iron overload states.

Key words: liver abscess, hemochromatosis, Yersinia enterocolitica.

INTRODUCTION

Yersinia enterocolitica is a facultative anaerobic Gram-negative bacillus of the Enterobacteriaceae family. In the disease most usual human form it can be isolated from the feces, the mesenteric lymph nodes and in rare cases, the sputum, being isolated from the blood only in rare cases where a favorable clinical substrate can lead to septicaemic forms.[1] The clinical manifestations of infection by Yersinia enterocolitica are, in the majority of cases, gastrointestinal in nature and include enterocolitis, mesenteric adenitis and terminal ileitis. They may be complicated by post-infectious manifestations, such as reactive polyarthritis, Reiter's syndrome and erythema nodosum.[1] Disseminated forms, with septicemia and hepatic abscesses are rare,[1-3] and are associated with other underlying pathologies such as diabetes mellitus, alcoholism, malnutrition, malignant diseases, immunosuppressive therapy, liver cirrhosis, and particularly iron overloading conditions.[4,5]

The purpose of this case study is to illustrate this rare exception where sepsis caused by Yersinia enterocolitica led to the concurrent identification of Hereditary Hemochromatosis.

CLINICAL CASE

Male patient, 66 years of age, Caucasian, with no previous relevant pathological history. He visited the Emergency Service of the Hospital Sao Marcos with a high temperature ranging from 38º-39ºC, myalgia, abdominal pain, prostration and profuse sweating evolving for a fortnight. He had already visited his doctor, and had been prescribed Amoxycilin + Clavulanic Acid and Paracetamol, without showing any improvement, but rather, a deterioration in his general condition.

He had had no recent exposure to sick individuals or traveling abroad.

From his occupational history, being a farmer, it is worth noting that he had repeated contact with various kinds of animals (cows, pigs, chickens, dogs, cats).

In two of his brothers, there were reports of non-specified liver disease.

He had no history of diabetes, hepatobiliary or heart disease, changes in libido, arthralgias, skin lesions or diarrhea.

On physical examination, the patient was prostrate and somewhat confused, with pale skin, signs of peripheral vasoconstriction and jaundice of the sclerae. BP-149/85 mmHg, HR -78 bpm, and AXT-38.5ºC, with no signs of respiratory difficulty. The ganglion

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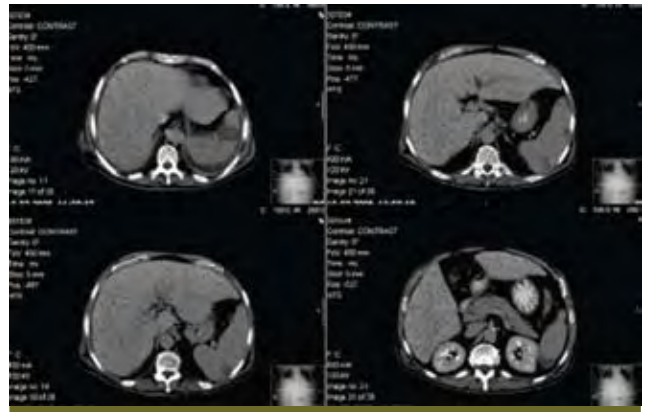
Table I

Hepatic function tests

Total bilirubin	4.10 mg/dL
Direct bilirubin	2.80 mg/dL
TGO	133 U/L
TGP	154 U/L
GGT	337 U/L
AF	166U/L
Ferritin	28680 ng/mL



Initial abdominal CT.

FIG. 1

surface chains were normal, and there was no evidence of skin lesions or osteoarticular changes. Cardiac auscultation was normal, and lung auscultation revealed decreased vesicular murmur in the lower left lung, associated with slight crepitations. The abdomen was distended and tympanitic. On palpation, the liver was nodular in texture and painful to touch, about 4 cm below the right costal margin and spleen tip.

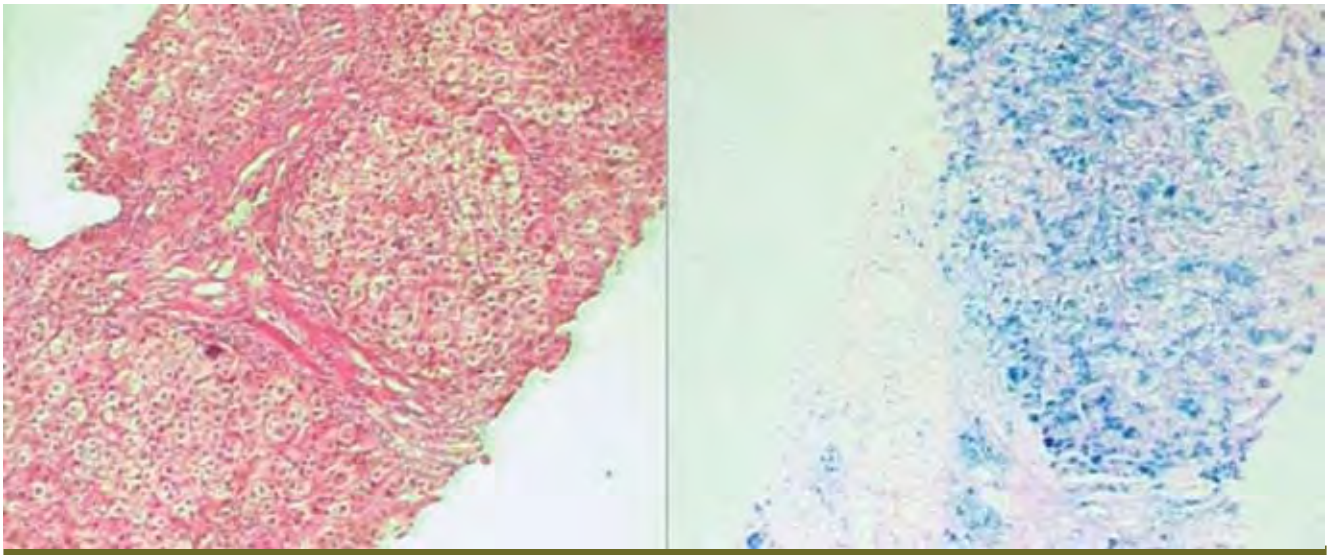
The laboratory analyses, on admittance, showed the following relevant changes: highlighted -AST-183 U/L, ALT-252 U/L, CPR-338 mg/L, total bilirubin -2.54 mg/dl, LDH-591 U/L, Na-129 mEq/L, platelets-108000/µL. Blood cultures were collected, and an abdominal ultrasound scan performed, which revealed an increase in liver dimensions, with a rugged pattern and no individualized nodules, as well as the presence of retroperitoneal adenopathies. Empiric therapy with Ceftriaxone was then initiated, reaching apyrexia on the third day.

On entry, proceeding with the research, a more extensive analytical study was requested, using infectious serology. The laboratory results (*Table I*) confirmed the changes initially identified, and the anti-infectious panel (HIV; HCV; HBV; CMV; Wright Reaction; Weil-Felix reaction; Anti-Toxoplasma; Anti-Leishmania; Anti-Parvovirus; Anti-Borrelia; Anti-Toxocara and Anti-Fasciola) was negative. For further clarification of the nature of the ultrasound findings, an abdominal CT was performed (*Fig. 1*). This examination showed marked heterogeneous hepatomegaly, with numerous micronodules scattered diffusely throughout the hepatic parenchyma, suggesting probable micro-abscesses or inflammatory/infectious granulomatous processes, and also splenomegaly with dispersed hypocaptation areas, possibly resulting from a series of strokes. In the presence of possible liver abscess formation, and while awaiting the results of the blood cultures, the decision was taken to extend the spectrum of antibiotherapy to include Tobramycin (100mg every 12 hours) and Metronidazole (1g every 8 hours), and a liver biopsy was carried out.

In additional investigation, which included study of the upper and lower digestive tract, an upper gastrointestinal endoscopy (UGIE) revealed the presence of gastric antrum erosions, with no stigmata of hemorrhage, and colonoscopy revealed diverticulosis in the left and transverse colon.

The patient's clinical condition evolved favorably, albeit slowly. The results of the blood cultures arrived, confirming growth of Yersinia enterocolitica in all the samples, which was sensitive to ciprofloxacin, cefotaxime and gentamicin, among other antibiotics. The treatment opted for was monotherapy with Ciprofloxacin.

In the liver biopsy (*Fig. 2*) the portal spaces were expanded due to fibrosis, which evolved into the form of porto-portal septa, with regenerative nodules and hemosiderin pigment deposits in the hepatocytes and Kupffer cells, and grade 4 siderosis, suggesting a condition compatible with liver cirrhosis and hemochromatosis. These elements, associated with a level of Fe-128 µg/dl, Ferritin-5440 ng/ml, and Transferrin saturation-82%, prompted a cytogenetic study with a survey of HFE gene mutations, which revealed



Hepatic histology (Hematoxylin-Eosin staining and Pearls).

FIG. 2

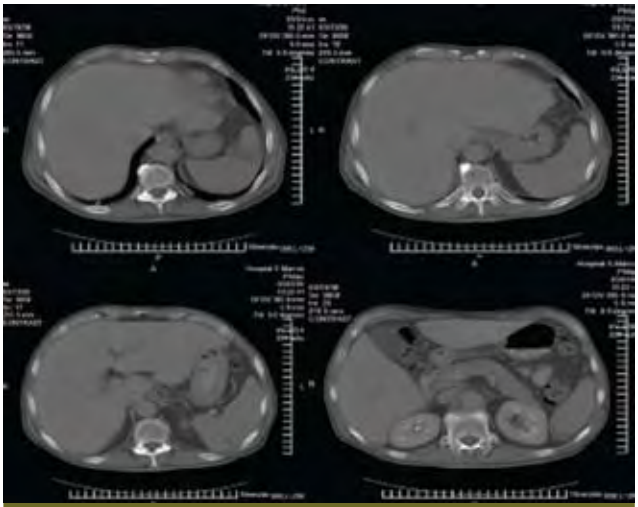
homozygosity for the C282Y mutation.

A definitive diagnosis of bacteraemia by Yersinia enterocolitica, with associated hemochromatosis and liver cirrhosis, was therefore established in the patient. On discharge, prolonged antibiotherapy with ciprofloxacin was scheduled, at first daily and then in intermittent regime, with regular phlebotomies and periodic clinical and laboratory monitoring at the clinic. The patient recovered gradually until becoming asymptomatic, with no recorded complications. Control abdominal TC *(Fig. 3)* showed a clear reduction of the number of micronodular lesions compared with the previous examination, as well as a decrease in liver size.

DISCUSSION

This case shows an exceptional situation in human pathology. Effectively, septicemia by Yersinia enterocolitica is rare[6] requiring very specific circumstances to occur, unlike the more frequent and strictly gastrointestinal manifestations. In the case discussed here, the bacteraemia alerted the authors to the need of investigating a possible associated underlying pathology, previously unknown, known to predispose the patient to this kind of complication by Yersinia. Unusually, this patient did not show at the onset the typical symptoms of gastroenteritis such as vomiting and diarrhea or pain in the right iliac fossa a characteristic of ileal involvement. In the epidemiological data assessed and in those drawn from the clinical history there was no evidence of elements leading to a suspicion of hemochromatosis. The existence of two brothers, incidentally both older than the patient in question with non-specific liver disease is not particularly useful in an environment where alcoholic liver disease is highly prevalent but is also surprising due to the advanced age and circumstances in which the diagnosis of hemochromatosis was made. This should alert to the need for their early screening through a summary study of iron kinetics, particularly when there is a family history of liver disease, heart disease or diabetes mellitus.

As we have seen, the echography showing visceromegaly and retroperitoneal adenopathy, cannot rule out sepsis, bearing in mind the patient's clinical condition and age, widening the diagnostic hypotheses to include neoplastic diseases, particularly of the lymphomatous type, without being of great value for guidance. The CT reinforces the hypothesis of an infectious process and takes into account its severity, alerting to the global involvement of the liver, and the possibility of septic splenic infarcts. Intra-abdominal septic sources were sought, particularly gastrointestinal, as the most common cause of hepato-splenic septic dissemination. This focus justified the change in strategy regarding the antibiotic coverage even with



Control abdominal CT.

FIG. 3

negative stool cultures.

The great unifying moment resulted in the identification of bacteraemia by Yersinia and from that moment onwards, the investigation became more rational and straightforward.

It can be accepted the agent sensitivity to Cefotaxime offered some protection under therapy with ceftriaxone, with the patient becoming apyretic three days later and it may even have reduced a more ominous outcome.

Based on imaging regression, it seems clear that liver micronodules were above all conditioned by the septic focus.

Septicaemic forms of infection by Yersinia enterocolitica are rare complications. The development of bacteraemia, particularly liver abscesses, is closely related to states of iron overload.[5]

In general, body iron deposits occur in the form of hemoglobin, myoglobin, and ferritin complexes. Only in situations of iron overload and high transferrin saturation, can iron bind non-specifically to other proteins making it available to be used by some microrganisms.[7] A large number of bacteria are capable of supplying their own metabolic iron needs, producing their own chelators, called siderophores. These molecules, released as low molecular weight ligands, compete for the available iron in the host. After binding to specific membrane receptors, the iron is released inside the cells.[1,4,5] In response to low iron availability in the environment, these siderophores are essential for the incorporation and use of this element by microorganisms, which depend on its viability. The Yersinia species are incapable of producing their own siderophores using those of other autochthonous species, through membrane receptors overcoming a specific limitation through a kind of parasitism.[1,5,8,9] Then Yersinia can proliferate in the intestine, where there is an abundance of foreign siderophores, however, it is unable to enter the circulatory system, except in states of overload or increased traffic of iron. Patients treated with desferrioxamine, an iron chelator that acts in the same way as a siderophore, produced by Streptomyces pilosus, or who underwent phlebotomy, mobilize endogenous iron deposits and increase its traffic in the blood stream, putting them at higher risk of sepsis by Yersinia[1,9] or relapse during treatment. This is one of the justifications for prolonged antibiotherapy. However, states of iron overload and desferrioxamine treatments are independent predisposing factors for systemic infection by Y. enterocolitica.

Cases of sepsis by Yersinia are described in association with various chronic and consumptive diseases, and also, with immunosuppressive therapies. A complication with hepatic abscesses, however, was only described in patients with iron overload states such as hemochromatosis, haemosiderosis, thalassaemia major, acute iron poisoning, chronic haemodialysis, or after long-term blood transfusion therapy.[10] This is inferred from the sample of twenty-three case studies, computed between 1949 and 2001, as reported in the literature and included in this description *(Table II)*.

Survival and prognosis of sepsis by Y. enterocolitica are excellent if diagnosed and treated early.[11] There are no firm guidelines on the ideal length of treatment, but it is certain that while excess endogenous iron is being removed there is an ever-present risk of reactivation or reinfection.

CONCLUSION

The identification of Yersinia enterocolitica in blood cultures of septic patients is a rare occurrence. Surprisingly, investigators should be alert to the coexistence of iron overloading conditions guiding their investigation in this direction. This is true even when there is no personal or family history of such complaint, no previous complaints of gastroenteritis or algic

Table II

Liver abscesses secondary to Yersinia enterocolitica in patients with underlying Hemochromatosis. Review of the literature since 1949 (from Pubmed, accessed in 03/2006).

Case	Author	Year	Gender, age	Underlying condition	Blood Liver Positive cultures		Results
1	Hassig et al.	1949	♂, 69	Cirrhosis; Hemochromatosis	?	+	Died
2	Reinicke & Korner	1977	♂, 59	Cirrhosis; Hemochromatosis	+	+	Died
3	Imhoof & Auckenthaler	1980	♂, 48	Hemochromatosis	+	+	Died
4	Van Lier et al.	1983	♂, 38	Hemochromatosis	+	+	Died
5	Kuijs & Tan	1984	♂, 42	Hemochromatosis	+	+	Survived
6	Henrion et al.	1986	♂, 74	Hemochromatosis	+	+	Survived
7	Ismail et al.	1987	♂, 65	Chronic anemia; Hemochromatosis	-	+	Survived
8	Cauchie et al.	1987	♂, 47	Cirrhosis; Hemochromatosis	+	?	Survived
9	Shibuya et al.	1988	♂, 37	Hemochromatosis; Diabetes mellitus	+	+	Died
10	Leyman et al.	1989	♂, 65	Cirrhosis; Hemochromatosis	+	+	Survived
11	Olesen et al.	1989	♂, 38	Hemochromatosis	+	-	Survived
12	Watson et al.	1989	♂, 59	Hemochromatosis; Diabetes mellitus	?	+	Survived
13	Nouel O et al.	1991	♂, 56	Hemochromatosis	+	?	Survived
14	Gayraud et al.	1993	♂, 48	Hemochromatosis; Diabetes mellitus	?	?	Survived
15	Santoro et al.	1994	♂, 52	Hemochromatosis	-	+	Survived
16	Valdillo et al.	1994	♂, 44	Hemochromatosis	-	+	Survived
17	Valdillo et al.	1994	♂, 39	Hemochromatosis	-	+	Survived
18	Valdillo et al.	1994	♂, 59	Hemochromatosis	+	+	Survived
19	Collazos et al.	1995	♂, 43	Hemochromatosis	-	+	Survived
20	Canva-Delcamre et al.	1995	♂, 68	Hemochromatosis	-	+	Survived
21	Abdelli et al.	1996	♂, 49	Hemochromatosis	?	+	Survived
22	Zapata and Garcia	1997	♂, ?	Hemochromatosis; Diabetes mellitus	+	?	Survived
23	Bergmann et al.	1998	♂, 51	Hemochromatosis	-	+	Survived
24	Hopfner et al.	2001	♂, 60	Hemochromatosis	-	+	Survived
25	Crosbie e tal.	2004	♂, 51	Hemochromatosis; Diabetes mellitus	+	?	Survived
26	Current case	2006	♂,66	Hemochromatosis	+	-	Survived

focus or characteristics of enterocolitis and the stool cultures are negative. ■

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