Hemochromatosis and yersiniosis

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ABSTRACT: Two patients with documented hemochromatosis and systemic infection with *Yersinia enterocolitica* are described. The first patient presented with *Y enterocolitica* septicemia and an infected hip prosthesis which led to the diagnosis of hemochromatosis. The second patient was previously treated for *Y enterocolitica* with antibiotics but did not recover fully until aggressive phlebotomy therapy was started. The simultaneous occurrence of these two uncommon diseases is related to the ability of the yersinia organism to thrive in the presence of large amounts of iron. The association between iron overload and susceptibility to yersinia infection is reviewed within the context of these two cases. *Can J Gastroenterol* 1990;4(4):160-162

Key Words: Hemochromatosis, Iron, *Yersinia*

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RESUME: Le cas de deux patients présentant une hémochromatose et une infection systémique à *Yersinia enterocolitica* établies est décrit. Le premier souffrait d'une septicémie à *Y enterocolitica* et d'une prothèse de la hanche infectée qui a conduit au diagnostic d'hémochromatose. Le second avait déjà été soumis à une antibiothérapie pour une infection à *Y enterocolitica* mais ne s'était pas entièrement remis avant d'avoir subi une phlébotomie agressive. La survenue simultanée de ces deux maladies rares est liée à la capacité que l'organisme yersinia possède de se multiplier en présence de grandes quantités de fer. Le rapport entre une surcharge martiale et une infection à yersinia est examinée dans le contexte de ces deux cas.

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YERSINIA ENTEROCOLITICA IS AN enteric pathogen with a wide spectrum of manifestations. Because of a peculiarity in the internal iron metabolism of the organism, it cannot acquire iron readily, which is an essential growth factor for all bacteria. In the presence of an excess amount of iron, eg, in hemochromatosis, a favourable milieu is created which greatly increases the virulence of the yersinia organism. The following report describes two patients with familial hemochromatosis in which yersinia infection occurred and eventually led to the diagnosis in one patient.

CASE HISTORIES

Case 1: A 69-year-old retired farmer was admitted with a presenting complaint of diarrhea, fever, chills and myalgias. He had a past history of a right hip replacement one year prior to admission and no history of liver disease or diabetes. Blood cultures were drawn as an outpatient and grew *Y enterocolitica* and the patient was admitted to hospital. At the time of admission vital signs were normal. Hepatomegaly was

TABLE 1
Iron and yersinia infections

Hemochromatosis (1-8)
Hemosiderosis (8-13)
Oral iron therapy (21)
Parenteral iron therapy (19,20)
Oral iron overdose (22,23)
Thalassemia (14-18)
Sideroblastic anemia (15)
Hemodialysis (19)
Deferoxamine therapy (14-16,24)

detected as well as marked pain and limited range of motion of the right hip prosthesis. The patient was treated with intravenous imipenem. The hip joint was surgically explored and a purulent exudate found in the joint space which also grew *Y enterocolitica*. Laboratory investigations showed a hemoglobin of 13.4 g/dL, alanine aminotransferase 114 iu/L, aspartate aminotransferase 70 iu/L, ferritin 3060 µg/L, and transferrin saturation 78%. A computed tomography scan of the abdomen showed increased density of the liver suggestive of iron overload, and a percutaneous liver biopsy confirmed a diagnosis of hemochromatosis with micronodular cirrhosis. Family investigations led to a similar diagnosis of hemochromatosis and cirrhosis in his 69-year-old brother. Weekly phlebotomy therapy was started and he had an uneventful recovery from his septicemia after two weeks of intravenous imipenem and three weeks of oral ciprofloxacin as an outpatient.

Case 2: A 60-year-old male presented to this institution on referral from a peripheral hospital with fever and chills and a blood culture positive for *Y enterocolitica*. Two months previously he had experienced a diarrheal illness followed by more general systemic symptoms of fever, chills, lethargy and anorexia. Blood cultures at that time were also positive for *Y enterocolitica*. He was treated in the referring centre with a course of intravenous gentamycin and his symptoms abated. Previous examination had revealed hepatomegaly and an elevation in liver enzymes and serum ferritin, and investigations led to a liver biopsy demonstrating hemochromatosis with micronodular cirrhosis. Family studies revealed several siblings with hemochromatosis. Pertinent past

medical history included a 25 year history of osteoarthritis, primarily affecting the hands and knees, and recently diagnosed type II diabetes mellitus, well controlled on diet alone. Physical examination showed the patient to be febrile with a temperature of 37.5°C, and hepatosplenomegaly was detected. Laboratory investigation revealed slight elevations in alanine aminotransferase and aspartate aminotransferase, 69 and 37 iu/L, respectively, and an elevated serum ferritin of 3444 µg/L.

Therapeutic phlebotomies were initiated on admission and three were performed over the patient's one week hospital stay. His fever subsided over the first three days with no antibiotic therapy.

The patient was discharged and continued to undergo phlebotomy twice weekly over the next eight months; he had no further recurrence of his diarrheal or febrile illnesses.

DISCUSSION

Yersinia infection manifesting as septicemia and peritonitis has previously been described in eight patients with hemochromatosis (1-8), and in a wide variety of other clinical settings associated with iron overload (Table 1). Several patients with hemosiderosis (9-11) including Bantu hemosiderosis (12,13) have been described with hepatic abscesses and septicemia. Multiple hepatic abscesses are perhaps the most common presentation of yersinia in the setting of iron overload (9).

Iron-loading anemias such as thalassemia and sideroblastic anemia have also been described with yersinia infections (14-18). An increased incidence of yersinia has been described in hemodialysis patients (19), which are often iron overloaded because of parenteral iron therapy. Parenteral iron therapy in newborns (20) has also been associated with yersinia infections. Multiple hepatic abscesses which grew *Y enterocolitica* have been described in a patient who had been on long term oral iron therapy (21). Infants who had accidentally ingested large doses of oral iron have also developed severe yersinia infections (22,23). The use of the chelating agent deferoxamine to remove

excess iron has also resulted in yersinia infections in patients and in experimental animal studies (16,24).

The association between iron overloaded states and infections with yersinia is likely related to the mechanism of iron accumulation and metabolism by the yersinia organism. Bacterial organisms normally obtain iron by the release of chelator substances called siderophores, which bind and solubilize iron before they re-enter the bacteria by receptor-mediated endocytosis (25,26). *Y enterocolitica* is unique because it lacks siderophores yet has receptors for them (25,27,28). The most virulent strains of yersinia may have the ability to synthesize high molecular weight proteins which allow them to catch the iron bound to other iron-containing molecules such as transferrin, ferritin and lactoferrin (29). The chelating agent deferoxamine is a siderophore produced by *Streptomyces pilosus* and can be used by yersinia for the acquisition of iron (16,24). It removes excess iron from tissues and provides *Y enterocolitica* with iron in a soluble and easily assimilable form.

Experimental animal studies have shown that deferoxamine greatly enhanced the susceptibility of iron loaded mice to *Y enterocolitica* and reduced the LD₅₀ by over a millionfold (16).

In the first case, and in another case of hemochromatosis (1), the yersinia septicemia was the presenting symptom which led to the diagnosis of hemochromatosis. In the second case, phlebotomy therapy resulted in resolution of the infection without antibiotic therapy. Since yersinia infection is relatively uncommon (30), patients with systemic yersinia infections should undergo further investigation for conditions associated with pathological iron overload, and phlebotomy therapy should be instituted along with appropriate antimicrobial therapy.

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