Spontaneous *Yersinia enterocolitica* septicemia in a patient with iron overload

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ABSTRACT: *Yersinia enterocolitica* septicemia is described in a patient with transfusional iron overload and a myelodysplastic syndrome. The organism was biotype 1 serotype 0:5,27 and carried a virulence-encoding plasmid. It was calcium-dependent, autoagglutinating and virulent to orally challenged mice, but not resistant to the bacteriocidal activity of serum. The patient had depressed neutrophil chemotaxis and bac-

tericidal activity. In this case, both host and microbial factors were present to select out this particular bacteremic disease. Patients with iron overload states should be recognized as compromised hosts and potentially susceptible to spontaneous sepsis due to *Y. enterocolitica*. **Can J Infect Dis 1990;1(2):57-60**

Key Words: Iron, Septicemia, *Yersinia*

YERSINIA ENTEROCOLITICA IS A COMMON CAUSE OF enterocolitis, but a very uncommon cause of septicemia. The pathogenesis of enteric disease is often ascribed to the carriage of a virulence plasmid (1), while the pathogenesis of bacteremic disease is more often linked to the iron overload (2-13). The virulence characteristics of most bacteremic strains are not well described. The following reports a case of sepsis in an adult immunocompromised male with combined problems of iron overload and neutrophil dysfunction, in which the bacterial strain was examined for virulence characteristics.

CASE PRESENTATION

A 55-year-old male presented with a one week history of fever, anorexia and malaise. He denied a history of diarrhea. There was a 14 year history of an evolving myelodysplastic syndrome characterized primarily by ineffective erythropoiesis with spontaneous remissions and exacerbations requiring blood transfusions totalling in excess of 500 units. He had developed transfusion hemosiderosis with hyperpigmentation, cardiomyopathy, diabetes mellitus and impaired hepatic function. He had used alcohol heavily until 12 years previously. Examination revealed him to be darkly pigmented and chronically ill with a temperature of 38.2°C, tachycardia, hepatosplenomegaly and mild epigastric tenderness. There were no significant joint findings. A heart murmur was not detected and no cutaneous lesions were seen. Fundoscopic examination was normal.

Laboratory values: Hemoglobin 118 g/L, platelet count 51×10^9 /L, leukocyte count 6.5×10^9 /L with 5.135×10^9 /L neutrophils, 0.585 band cells, 0.488

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lymphocytes, 0.260 monocytes and 0.033 reactive lymphocytes $\times 10^9/L$. Serum iron was 132 $\mu g/dL$ (normal 65 to 165); total iron binding capacity 159 (normal 245 to 420); iron saturation 83%; ferritin 2540 ng/mL (normal 10 to 320); alkaline phosphatase 145 iu/L; aspartate aminotransferase 47 iu/L; gamma-glutamyl transferase 67 iu/L; and hepatitis B surface antigen positive.

Chest roentgenogram was normal. Abdominal ultrasound confirmed hepatosplenomegaly but no intra-abdominal abscess was seen. Bone marrow biopsy demonstrated panhypoplasia and increased iron stores marked by prominent, iron-laden histiocytes. Cytogenetic studies were normal. Neutrophils were tested for chemotactic response and phagocytic and bactericidal capacity against *Staphylococcus aureus* and this strain of *Y enterocolitica* (14). Chemotaxis was not impaired; however phagocytosis and bactericidal capacity were both reduced more than 50% compared to the normal control. No differences were noted between results with *Staph aureus* and *Y enterocolitica*. Differences in either test of 20% or greater were considered significant.

Microbiologic studies: Three of six sets of blood cultures (Bactec NR6A Tryptic Soy Broth aerobic, NR7A Tryptic Soy Broth anaerobic and Dupont Isolator system) drawn in the first 12 h yielded *Y enterocolitica* sensitive to amikacin, gentamicin, netilmicin, tetracycline, trimethoprim-sulfamethoxazole, tobramycin and piperacillin, and resistant to ampicillin and cephalothin. All subsequent blood cultures were negative. No pathogens were isolated from sputum or urine. Three fecal cultures using a combination of CIN medium (Oxoid) and cold enrichment for 14 days yielded no *Y enterocolitica*. The strain of *Y enterocolitica* was identified as being biotype 1 serotype 0:5,27, and was further characterized for virulence features using methods previously described (15). The organism was found to carry a 42 megadalton plasmid, was autoagglutination positive and calcium-dependent, and absorbed Congo Red. The organism was virulent to orally challenged mice but was not resistant to the bactericidal effect of 10% pooled human serum.

CLINICAL COURSE

On admission, intravenous tobramycin 80 mg every 8 h and cefazolin 1 g every 6 h were started. On day 2, therapy was modified to tobramycin 140 mg every 8 h and piperacillin 3 g every 6 h because of failure to improve and a preliminary report of a Gram-negative organism in the blood cultures. The patient gradually improved, becoming afebrile on the sixth hospital day, and was discharged three weeks after admission. Antibiotics were con-

tinued for a total of 14 days. After six months, there was no recurrence of infection.

DISCUSSION

Y enterocolitica in humans primarily causes an acute gastroenteritis with fever, abdominal pain, nausea and diarrhea, but is also associated with mesenteric adenitis, polyarteritis nodosa and post infectious arthritis. *Y enterocolitica* infections are commonly found in Europe and less commonly in Africa, Japan, Australia and the United States. *Y enterocolitica* has been recovered from most provinces in Canada, and in one Vancouver, British Columbia hospital, yersinia organisms were isolated from the stools of up to 15.9% of patients presenting with gastrointestinal symptoms (15).

A recent review of the literature found over 100 reports of *Y enterocolitica* septicemia (2-12,16). It is a relatively rare occurrence in the absence of a focus of infection. Thirty per cent of the patients had disorders of iron metabolism including Bantu hemosiderosis, primary and secondary hemochromatosis, and thalassemia. Eighty per cent of the patients had underlying disease such as cirrhosis, diabetes mellitus, renal failure or malignancy. Over 60% had an evident focus of infection such as diarrhea, liver abscess or lung infiltrate, but no such focus was found in the present patient. Bouza (2) reported that 22% of cases occur in previously healthy individuals.

Cases have been reported of transmission of *Y enterocolitica* by transfusion of refrigerated blood (3,7,8). Although the present patient had received multiple blood transfusions, he had not received any blood products for two months prior to this admission, making transfusion an unlikely source of his infection. Studies have shown that normal human serum does not inhibit the growth of plasmid-infected *Y enterocolitica* (10,17,18) and that iron overload impairs leukocyte function with enhancement of bacterial virulence (19-23). Iron overload particularly predisposes to septicemia with *Y enterocolitica* and *Y pseudotuberculosis* since these organisms rely on exogenous iron to facilitate extraintestinal infection (24,25).

The interactions between *Y enterocolitica* and human defence mechanisms have been previously studied. Pai and DeStephano (26) observed that strains of *Y enterocolitica* that were virulent in either a rabbit or mouse model were not killed when grown at 37°C in Hanks' balanced salt solution with 0.1% gelatin and 10% normal human serum, while avirulent strains were killed. They speculated that this was similar to serum resistance seen with certain *Escherichia coli* (27) and due to an altered outer membrane protein en-

coded by the virulence plasmid. Lian and Pai (28) demonstrated that virulent strains of *Y enterocolitica* resist phagocytosis by human neutrophils. This was again due to the presence of a plasmid-mediated surface structure which could be abolished with pronase treatment (29). The strain associated with this case differed somewhat from other plasmid-carrying strains in that it was not serum-resistant. While many virulent characteristics may be related to plasmid carriage, routine testing of individual strains may not consistently demonstrate these phenomena (15). The patient had impaired phagocytic and bactericidal neutrophil function, but this was directed against both *Staph aureus* and the case strain. His neutrophils were not tested against other strains of yersinia of known plasmid carriage; thus it is not possible to say whether this strain was different in its capacity to resist neutrophil function. Testing was done after the patient had been recovered from this infection for three months; thus it was most unlikely to be due to residual effect from the yersinia. Qualitative granulocyte defects are known to occur in myelodysplasia, and probably played a role in the pathogenesis of this bacteremic episode.

This strain was characterized as biotype 1 serotype 0:5,27. Most bacteremic strains of *Y enterocolitica* that have been characterized are biotype 4 serotype 0:3 (2,9,12,13,16,30). In Vancouver, *Y enterocolitica* serotype 0:5,27 comprised less than 1% of the isolates recovered from enterically unwell patients (31). Of interest, Bottone (16) reported that five of 14 (36%) bacteremic strains of *Y enterocolitica* recovered in New York City were of this serotype, even though the predominant enteric serotype was 0:3. Similarly two of 10 (20%) bacteremic strains associated with donor blood were also defined as 0:5,27 (3). Speculatively, this

serotype may harbour an additional factor which provides some increased bacteremic potential.

Although the present patient's strain of yersinia carried the virulence plasmid, this plasmid may not be essential for bacteremia. Unfortunately, most strains associated with bacteremia have not been investigated for virulence characteristics. Foberg (30) described six strains that were autoagglutination positive, a characteristic usually linked to the virulence plasmid. Similarly, Jacobs (3) described one strain that was calcium-dependent and pyrazinamidase negative. On the other hand, Wachmuth et al (32) found the plasmid in only one of four bacteremic strains tested (serotype 0:13). This may have been an artefact because the plasmid both expresses itself and is lost at 37°C, the usual incubation temperature of blood cultures. Seto and Lau (11) reported the recovery of bacteremic strains of *Y enterocolitica* usually described as nonpathogenic (nontypable strains and strains of biotype 1 serotype 0:17). Similarly, Bottone (16) recovered two strains from blood that would usually be expected to be nonpathogenic (one strain biotype 1 serotype 0:12, and one strain nontypable). Although none of these strains was reported as being investigated for plasmid carriage, most strains of these serotypes do not carry the plasmid. In the case at hand, while both patient and microbial factors associated with yersinia infection were present, one can conclude that host factors were more important determinants than plasmid-induced microbial factors in the induction of this patient's bacteremic disease.

Patients with conditions of iron overload should be regarded as compromised hosts, not only because of the increased availability of iron for growth of *Y enterocolitica*, but also because of impaired leukocyte function.

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