Systematic *Yersinia enterocolitica* in an iron overloaded and immunocompromised thalassemic patient

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**Summary**

We report the case of a 43-year-old woman who presented with lower abdominal pain, maculopapular rash, arthritis of the left knee and left ankle joints, with a history of thalassemia and heavy iron overload. She was also on haemodialysis therapy three times a week for end stage renal therapy. *Yersinia* *enterocolitica* and *Yersinia pseudotuberculosis* cause yersiniosis, a diarrhoeal illness. Members of the genus *Yersinia* are gram-negative cocacobilli; they are facultative anaerobes in the family Enterobacteriaceae. Serological examinations revealed positive IgA and IgG antibodies against *Yersinia enterocolitica* outer membrane proteins (Yops) for YopD(4a) and Yop M(2a) and IgG for LorV (V antigen). Enteritis an reactive arthritis presented as the primary manifestation of *Y. enterocolitica* infection. Important risk factors include iron overload, cirrhosis, and immune suppression. The patient was successfully treated with oral ciprofloxacin.

**Introduction**

*Yersinia enterocolitica* belongs to the genus *Yersinia*, and to the family Enterobacteriaceae. The genus *Yersinia* includes 11 species, 3 of which are important human pathogens: *Yersinia pestis*, *Yersinia enterocolitica*, and *Yersinia pseudotuberculosis*. Clinical presentation includes enteritis and enterocolitis, and extraintestinal manifestations such as lymphadenitis, reactive arthritis, erythema nodosum, uveitis and septicaemia. Enteric yersiniosis is a foodborne disease which is transmitted through the faecal-oral route. The species *Y. enterocolitica* is subdivided into 6 biotypes. Biotype 1A is non-pathogenic while the 5 other biotypes (1B, 2-5) cause human and/or animal infections. The biotype the most frequently responsible for human infections worldwide is biotype 4, which is almost systematically associated with serotype O:3 (4/O:3), followed by bioserotype 2/O:9. Although *Y. enterocolitica* represents the third cause of bacterial diarrhoea in Europe, after campylobacteriosis and salmonellosis reports of human yersiniosis are scarce in West Africa. Overall, *Y. enterocolitica* infection occurs more frequently in Europe than in North America. Conditions associated with iron-overload such as chronic liver disease, hemochromatosis, and thalassemias have been associated with an increased risk of invasive yersiniosis. Yersiniosis is also a complication of iron overload syndromes treated with desferrioxamine.

**Case Report**

A 43-year-old female with transfusion depended thalassemia major and chronic heart and liver iron overload LIC (liver iron concentration): 17.1 mg Fe/g dry tissue treated with daily s.c deferoxamine presented to outpatient clinic with a maculopapular rash over the back and the trunk. She also complained of a two-day history of lower abdominal pain, nausea, vomiting, and mild non-bloody watery diarrhoea without mucus. Her most recent blood transfusion was five days prior to the onset of symptoms. In recent past medical history she was on the 19th week of treatment with Ledipasvir-Sofosbuvir for chronic HCV infection (in a 24 weeks protocol) due to progressed cirrhosis with a liver ultrasound showing a nodular liver with splenomegaly and a transient elastography of 33.3 kPa. At the end of 4th and 12th week of treatment HCV type 1 RNA was undetectable.

On her past medical history she began receiving haemodialysis therapy three times a week at the age of 32 years for end stage renal failure related to HCV-cryoglobulinemic glomerulonephritis.

**Laboratory investigations**

Blood examination revealed: leukocytopenia WBC 3.10×10^9/L (neutrophils 70.0%, lymphocytes 20.3%, monocytes 4.7%, eosinophils 1.8%, basophils 0.6%), thrombocytopenia platelet count 91×10^3/µL and worsening of anaemia Hb 4.9 mmol/L (with a baseline of 5.4 mmol/L for the patient), peripheral blood smear showed hypochromic and small hyperchromic cells.
an unidentified microorganism resembling Bacterium lignieri and Pasteurella pseudotuberculosis, and pathogenic for man. Y. pseudotuberculosis is a rare cause of respiratory tract infections. In patients with homozygous beta-thalassemia (2,7,8) are at increased risk for serious Yersinia enterocolitica infections. Data have suggested that Yersinia may be a ferrophilic bacterium that requires a higher level of readily available iron for the initiation of growth than do other pathogens. Yersinia does not elaborate a siderophore but can use those from other bacteria. In the gastrointestinal tract there is an abundance of siderophore compounds from other organisms, creating an environment favourable for yersinial growth. In rare cases, Y. enterocolitica septicaemia has been observed following transfusion with packed red cells(2,7,8). Yersinia organisms are ferrophilic and capable of multiplying slowly in stored units of red cells at cold temperatures before they are transfused. In one prospective study conducted in 1998 to 2000, the incidence of transfusion associated Yersinia sepsis was 1 in 23.7 million red cell transfusions.

The relation between virulent YE infection, iron, and deferoxamine is peculiar and has been clarified recently. YE lacks a natural high-affinity iron chelator and therefore cannot absorb iron directly, it is dependent on bacterial siderophores in the gut, for

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**Table 1. Serum antibodies of Yersinia.**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical diagnosis</th>
<th>Without clinical manifestations</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>10 days with ciprofloxacin</td>
<td>1 month</td>
</tr>
<tr>
<td></td>
<td>IgA</td>
<td>IgG</td>
</tr>
<tr>
<td>YopM(2a)</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>YopH(2b)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>LorV</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>YopN(4b)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>YopP(30)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>YopE(5)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
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which it does have high-affinity receptors. Transfusion may increase tissue iron available for invasive YE, and the presence of deferoxamine, a siderophore obtained from Streptomyces pilosus, further enhances the virulence of YE by providing additional siderophores in large quantities for which abundant iron is already available. The combination of an iatrogenic siderophore and abundant iron markedly enhances the virulence of YE.

Deferoxamine has long been administered parenterally as an iron chelating agent to patients with iron overload, however, it adds to the risk of infection by Y. enterocolitica. Our patient was iron overloaded on deferoxamine therapy (7,8) at the time of the acute infection. Treatment for HCV and haemodialysis rendered our patient further immunologically vulnerable.

The organism, often cultured in blood, can also be recovered from stool, appendix, mesenteric lymph nodes, and distal ileum. Infections of extraintestinal sites include lymphadenitis, arthritis, osteomyelitis, pneumonia, endocarditis, meningitis, and dermatitis.

The most common post-infectious sequelae are erythema nodosum and reactive arthritis; these are particularly common in Northern Europe and, for the latter, among those with the HLA-B27 tissue type.

Yersinia is a gram-negative bacillus in the Enterobacteriaceae family (6,10). Yersinia can appear small and coccobacillar in Gram-stained smears. It exhibits bipolar staining described as a safety pin shape on Giemsa staining. Yersinia grow on blood, chocolate, and MacConkey agar, but may be overgrown by other organisms due to slow growth. Yersinia can form pinpoint colonies on both blood agar and MacConkey agar in 24 hours, particularly Y. pseudotuberculosis. Yersinia are catalase positive, oxidase-negative and ferment glucose. Y. enterocolitica appears as small, lactose-negative colonies on MacConkey in 48 hours. Serologic tests can be used to support a diagnosis of yersiniosis. They are serogrouped using antisera produced against cell surface lipopolysaccharide antigens, known classically as the O antigens. For Y. enterocolitica, biogroup and serotype are correlated. The most common are serotype O:9 biotype 2, serotype O:3 biotype 4 and serotype O:8 biotype 1B. Simple agglutination assays have been developed for diagnosis of yersiniosis. In addition, enzyme linked immunosorbent assays (ELISA) and immunoblotting can be used to detect IgG, IgA, and IgM class antibodies. A positive IgM assay supports the diagnosis of acute yersiniosis, as does a fourfold rise in antibody titers between acute and convalescent titers drawn several weeks apart.

Antibody levels begin to rise within the first week of illness, peak the second week and then return to normal within 3-6 months. In our case positive antibodies followed acute infection and persisted for many months. Antibodies develop against the Yersinia outer membrane proteins (Yops). It has been reported that the assays used to detect antibodies against Yops are more sensitive and specific than stool culture and other serologic diagnostic methods. In our case serologic findings were interpreted positive with post-infectious sequelae oscillating antibody titers upon the activity of their illness.

Lately a multiplex PCR assay with dual priming oligonucleotide system (DPO system-based mPCR) was developed for the simultaneous detection of Yersinia enterocolitica.

The mortality rate associated to Y. enterocolitica infection can reach as high as 50% in immunocompromised individuals. Antimicrobial treatment (1) varies among serogroups, and the microorganism is usually susceptible in vitro to cotrimoxazole, aminoglycosides, tetracycline, and fluoroquinolones, but is resistant to penicillin, ampicillin and first-generation cephalosporins due to the presence of two chromosomal genes encoding beta-lactamase, blaA and blaB, which confer a broad-spectrum or first-generation cephalosporins resistance, respectively.

Recommendations arising from this case report indicate that diarrhoea, even in the absence of fever and abdominal findings, in a patient with iron overload should alert the clinician to the possibility of yersiniosis. For patients with β-thalassemia, especially if symptoms occur shortly following a blood transfusion, clinical suspicion should be heightened.

References

5. Neubauer H, Sprague LD, Scholz H, Hensel A. [Diagnosis of Yersinia enterocolitica infection. For patients with ß-thalassemia, especially if symptoms occur following a blood transfusion, clinical suspicion should be heightened.]

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