Case Report

Haemophilia-associated *Yersinia pseudotuberculosis* serotype O:1 septicaemia: the role of iron

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Septicaemia and septic arthritis due to *Yersinia pseudotuberculosis* are rare diseases with high mortality rates. Reactive arthritis caused by *Yersinia* infection is a well-known complication but septic arthritis is found at a much lower frequency. It has already been established that there is a relationship between yersiniosis and iron but there are currently no data about yersiniosis and haematological disorders such as haemophilia. We report a case of septic arthritis due to *Y. pseudotuberculosis* as an early manifestation of *Yersinia* septicaemia in a patient with severe haemophilia A. The patient had no history of immunosuppression and presented with a repeat case of haemarthrosis with a fever of unknown origin. Furthermore, he suffered from acute-on-chronic renal failure and non-ST segment elevation myocardial infarction. Arthrocentesis and blood culture tested positive for *Y. pseudotuberculosis*. Iron deposits at localized sites in the synovium in patients with haemophilia have been described, and as *Yersinia* infections are common in patients with secondary iron overload, we felt that a review of the literature was in order. Severe *Yersinia* infection is often associated with iron overload, a condition that might occur as a side effect in the treatment of haemophilia. Iron overload, which plays an important role in the pathogenesis of haemophilic arthropathy, may have increased the virulence of *Y. pseudotuberculosis* in the present case.

Case report

A 73-year-old man suffering from repeat cases of haemarthrosis due to severe haemophilia A presented with haemarthrosis of the left knee and a fever (38.3 °C) of unknown origin. Prior to admission, only factor VIII concentrate was used to treat the haemophilia; the patient had not received any blood transfusions. The medical history revealed reduced global cardiac function (ejection fraction 25%), moderate aortic valve stenosis, moderate mitral and tricuspid insufficiency, chronic hepatitis C, chronic renal failure and peripheral artery occlusive disease on both sides with post-thrombotic syndrome. Laboratory findings revealed an increased blood leucocyte count of 14 800 cells ml⁻¹, a C-reactive protein level of 204.4 mg l⁻¹ and a procalcitonin level of 14.38 ng l⁻¹. A chest X-ray revealed right-sided pleural effusion but no pulmonary infiltrates. Empirical intravenous piperacillin–tazobactam plus clarithromycin therapy was started on admission. Due to acute-on-chronic renal failure and non-ST segment elevation myocardial infarction (NSTEMI) (hs-troponin T 2613 pg l⁻¹), haemodialysis and loading with acetylsalicylic acid (500 mg) was started. Furthermore, an arthrocentesis was performed. Abdominal ultrasound showed hepatosplenomegaly, cholecystolithiasis (one concrement) and renal cysts but no other pathology. *Yersinia pseudotuberculosis* was isolated from synovial fluid and blood culture and identified with 99% confidence by using the VITEK 2 System (bioMérieux). For confirmation, 16S rRNA gene sequence analysis was also performed using an 807 nt fragment (GATC), resulting in 100% sequence similarity to *Y. pseudotuberculosis*. No other pathogen was identified by culture, molecular methods or serological diagnostic procedures. The isolate was susceptible to extended-spectrum antimicrobial agents including ampicillin, amoxicillin–clavulanic acid, piperacillin–tazobactam, ce- furoxime, cefotaxime, ceftriaxone, cefazidime, imipenem, meropenem, ertapenem, ciprofloxacin, moxifloxacin, gentamicin, tobramycin, tigecycline and trimethoprim–sulfamethoxazole but showed intermediate susceptibility to

Abbreviation: NSTEMI, non-ST segment elevation myocardial infarction.

One supplementary figure is available with the online version of this paper.
tetracycline. Blood cultures, performed on admission, 17 h prior to arthrocentesis, yielded the same pathogen.

Serotyping of the isolate yielded the serotype O:1. The presence of high pathogenicity island genes was determined by using PCR. The *irp2* gene was detected by PCR, which encodes the iron-repressible high molecular mass protein HMWP2 that is presumably involved in the production of yersiniabactin (Lucier et al., 1996; Schubert et al., 1998). The primers used for the PCR were as follows: 5'-AGAGAAC-GCAAGTTATCCATAATCG-3' (forward) and 5'-ATTGGATCCTAATCTGCTCAAAACCGGTCGTCTG-3' (reverse).

Despite adequate antibiotic therapy, the condition of the patient deteriorated over the days following admission and catecholamine therapy had to be increased as the patient became septic. The patient died a few days later in septic cardiogenic shock. No post-mortem examination was performed.

**Discussion**

*Y. pseudotuberculosis* is found worldwide, isolates of which can be divided into 21 different serological groups based on variations in the O-antigen of the lipopolysaccharide (Wren, 2003). Due to its similarity to *Yersinia enterocolitica*, and on the basis of several outbreaks in Scandinavia and Japan, it has been established that transmission is caused by ingestion of contaminated food or water (Jalava et al., 2004; Nuorti et al., 2004; Vincent et al., 2008). Person-to-person transmission, for example within a family, is also conceivable. Contact with domestic animals does not play an important role, since the reservoir includes mammals (especially rodents and their predators) and birds (Fukushima et al., 2001; Niskanen et al., 2003). *Y. pseudotuberculosis* is a rarely found pathogen that usually causes acute gastroenteritis, mesenteric lymphadenitis and diarrhoea, also mimicking acute or subacute appendicitis in humans. Infections in animals occur more frequently than in humans.

The present case, in a patient with haemophilia A who presented with repetitive haemarthrosis and fever, illustrates the high mortality rate of *Y. pseudotuberculosis* infection. As it has been established that there is an association between yersiniosis and iron (Chiu et al., 1986; Lucier et al., 1996), we reviewed the literature for the role of iron in *Yersinia* infection. Interestingly, an association between haemophilia and *Yersinia* septicaemia has, to our knowledge, not yet been identified.

16S rRNA gene sequence analysis demonstrates the close phylogenetic relationship between *Y. pseudotuberculosis* and *Yersinia pestis* (Supplementary Fig. S1, available in JMM Online). Both pathogens are comparable with regard to their virulence, which was established following intravenous injection in mice (Une & Brubaker, 1984). In the current case, the patient was treated with pipericillin–tazobactam plus clarithromycin, but in a murine animal model, β-lactam antibiotic therapy for *Y. pseudotuberculosis* infection was inferior to other agents such as quinolones (Lemaitre et al., 1991). Nevertheless, the comorbidities NSTEMI and acute-on-chronic renal failure should also be taken into account.

The development of septicaemia may be due to bacterial translocation from the digestive tract, but, in this case, the true mode of infection remains unclear. Usually, domestic animals that eat rodents are considered to be possible transmitters of the micro-organism to humans. The patient was immobile, had no direct contact with wild animals and did not live in a rural environment. He lived with cats and dogs but they were tested by a veterinarian and found to be negative for *Yersinia*. Furthermore, the patient had not received any blood transfusions, which is relevant as the transfusion of *Y. enterocolitica*-contaminated blood has been reported previously (Leclercq et al., 2005). Theoretically, the route of infection could have been via initial synovial infection or via the arthrocentesis itself but haematogenous dissemination into the knee seems more plausible, since blood cultures taken before arthrocentesis were positive for the same isolate and contamination with *Yersinia* is very uncommon.

Reactive arthritis and acute interstitial nephritis are well-known complications following *Yersinia* infection and are more common among patients with histocompatibility antigen HLA-B27. Septic arthritis following *Yersinia* infection has also been reported, but at a much lower frequency. Joint infections are more frequently dominated by *Y. enterocolitica* rather than *Y. pseudotuberculosis* (Chol et al., 2008; Cormier et al., 2007) and only a few cases of *Y. pseudotuberculosis* septicaemia have been reported (Deacon et al., 2003; Ljungberg et al., 1995, 1996; Mashiba et al., 2008; Paglia et al., 2005; Rathmell et al., 1999; van Zonneveld et al., 2002). Debilitating diseases such as hepatic cirrhosis, HIV-related immunodeficiency, malignancy, diabetes, anaplastic anaemia and thalassaemia may cause a patient to have a predisposition to *Yersinia* septicaemia (Ljungberg et al., 1995; Mashiba et al., 2008).

Interestingly, the septicaemic form of *Yersinia* infection is more common in patients who have a secondary iron overload and has a high mortality rate of about 75% (Chiu et al., 1986). Treatment of iron-overloaded patients with desferrioxamine has been associated with *Yersinia* septicaemia because this iron chelator enhances the growth of the organism and appears to inhibit polymorphonuclear leukocyte defence against the infection (Cantinieux et al., 1988). Iron overload often occurs as a side effect during treatment of haemophilia. Iron appears to play a central role in the development of haemophilic arthropathy (Raffini & Manno, 2007). In patients with haemophilia, iron deposits can be found at localized sites in the synovium showing diffuse lymphocyte infiltration and neovascularization in the deep subsynovial layers (Roosendaal et al., 1998). In the present case, iron levels were not measured in the patient; nevertheless, we cannot exclude the possibility that there were elevated iron levels.
or localized iron overload in the factor VIII concentrate that was administered prior to admission. Deposits of iron localized to the joints may explain how septic Yersinia arthritis can occur before manifestation of severe septicemia as the virulence of these pathogens is associated with siderophore production and iron metabolism (Heesemann et al., 1993).

In conclusion, we report the case of a patient with severe haemophilia A who presented with Y. pseudotuberculosis infection, causing septic arthritis in the context of septicemia. In our opinion, the importance of the association of yersiniosis with haematological disorders has not been fully recognized until now. The present case emphasizes the need to consider such a pathogen as a possible cause of septicemia, especially in the absence of other causative pathogens.

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References


