LESSON OF THE MONTH

Chronic fatigue, arthralgia, and malaise

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Case report

A 25 year old female veterinary nurse presented with a six year history of general malaise and severe fatigue. Associated with this she described frequent (monthly) episodes of polyarthralgia affecting all joints but with a predilection for the small joints of the hands and the wrists. When present this was accompanied by mild morning stiffness. In addition she experienced colicky abdominal pain, sometimes with diarrhoea, occasionally with blood mixed with her faeces. Other complaints consisted of low back pain, sore gritty eyes, and an inability to perform any physical exercise at the time of these symptoms. Her symptoms had been remarkably consistent, with no recent change to their pattern.

Six years ago she had been on a working holiday at a veterinary practice situated in New York state, USA. After eating a dish made with "blue fish" she had immediately developed severe nausea, vomiting, and malaise. Although all her acute symptoms resolved, her other symptoms started on return to the United Kingdom. She was investigated twice, at different hospitals, before being referred to this department. It had been found that her symptoms were helped by treatment with 30 mg prednisolone daily for the severe episodes and a maintenance dose of 5 mg daily. Severe episodes were occurring three to four times a year. Non-steroidal anti-inflammatory drugs, sulphasalazine, and other treatments of inflammatory bowel disease had not helped her symptoms. On all occasions the examination and investigations had been reported as normal including markers of inflammation, connective tissue disease, and radiological and histological gastrointestinal studies. No blood had been seen in her faeces. No diagnosis was made other than a seronegative arthralgia.

She had managed to continue her job throughout this period but was becoming increasingly unable to perform other physical activities and rested completely at weekends. She was well supported by her partner and family and had no features or history to suggest a depressive illness. She had no other relevant medical history and there were no familial illnesses. Foreign travel before the illness had only been to the United States. Subsequently she had been to Ireland, where she had also worked, and on holiday to India.

On examination she was a thin but fit 25 year old with no features of connective tissue disease, fibromyalgia, or Sjögren's syndrome.

There was no joint deformity, swelling, or restriction of movement, and no lymphadenopathy or splenomegaly. Investigations showed normal haematology except for a persistently raised international normalised ratio (INR) at 1.2-1.4, normal range <1.14 (lupus anticoagulant was not detected), normal biochemistry including creatinine kinase, cortisol, negative porphyria screen, and serum angiotensin converting enzyme. She had negative stool cultures (these had been negative consistently as had sigmoidoscopy, endoscopy, and associated biopsies six months previously) and a negative glycocholate breath test. Serology to borrelia, brucella, and toxoplasmosis was negative as was serology to herpes viruses, hepatitis B, enteroviruses, and parvovirus. Her HLA tissue type was A2,B7,B50(21),DR15(2),DR4 (not normally associated with autoimmune disease). Her chest radiograph was normal. A full autoantibody screen, including extractable nuclear antigens, was negative. An ophthalmological review showed no evidence of an abnormality. *Yersinia* serology was requested and was negative to *Y enterocolitica* and *Y pseudotuberculosis* I, II, III, and V. Serology to *Y pseudotuberculosis* type IV was positive for IgM at a titre of 1:320. There had been no history of recent typhoid vaccination.

Treatment was commenced with high dose tetracyclines for one month. After three months the serology had reverted to normal, as had her abnormal INR. Over this period the patient required no steroid medication, worked full time, and became able to exercise without restriction. She experienced occasional mild arthralgia, which resolved spontaneously.

Discussion

Yersinia pseudotuberculosis is usually found in rodents or birds with spread to other debilitated animals through contamination of their food by faeces. Infection of humans is thought to occur by ingestion of contaminated food or from handling infected animals. Diagnosis is made by serological means as only during the acute episode is isolation possible.^{1,2} In humans, like the more common *Y enterocolitica*, it causes an enterocolitis with fever, diarrhoea, and inflammation of the mesenteric lymph nodes³⁻⁵ and sometimes a pseudoappendicitis,⁶ presumably accounting for the abnormal INR. It has also been documented as producing an acute arthritis⁷⁻⁹ which is of the classic sacroiliac pattern in those

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Accepted for publication
6 February 1996

who are HLA-B27 positive.^{9 10} In most of these cases it has been described as producing a clearly defined, acute inflammatory arthritis, sacroilitis, or tenosynovitis around the time of the initial infection. It can persist, particularly in those who are HLA-B27 positive.

We are not aware of any studies on the long term follow up of patients with *Y pseudotuberculosis*. However, in subjects with *Y enterocolitica* there are data on the long term sequelae of infection. In one study 31 patients were followed up because they developed acute arthritis immediately after infection with *Y enterocolitica*.¹¹ After five years, 10 out of 31 patients still had arthralgia, six were asymptomatic, and the remaining 15 had ongoing arthropathy and arthritis. Of those with arthralgia five out of 10 had not had antibiotic treatment when compared with one of the six patients who had no symptoms. The HLA status of those who had an active arthritis is not recorded.

Our case highlights several important aspects. It shows the importance of an occupational history. There would have been a strong possibility that the infection was acquired at work. In such patients with a history of arthralgia, abdominal pain, and diarrhoea *Yersinia* infections should be considered to the same extent as brucellosis; particularly as it is well documented that acute *Y pseudotuberculosis* infection can be asymptomatic.¹² Presumably what happened in New York was an episode of gastroenteritis and the "blue fish" was a red herring. What is interesting is that subsequently there were no features to suggest an acute inflammation, a fact that made diagnosis more difficult. Although it is not widely described, in common with the *Y enterocolitica* study, *Y pseudotuberculosis* can give persistent infection manifesting as joint pains and arthralgia.¹¹ If such infections are not sought they will remain undiagnosed.

The serology is the most important diagnostic tool as cultures can be negative even during acute infection.¹² Although typhoid vaccination and salmonella may cross react with the serology for *Y pseudotuberculosis* IV, in this case there was no history of recent typhoid vaccination. Salmonella would have been isolated from the intensive microbiology that was performed and the loss of IgM seropositivity on specific treatment all strongly suggests a diagnosis of *Yersinia*. The clinical features of this illness, the resolution of these on treatment, and the loss of IgM seropositivity

all suggest that this case represented persistent rather than an acute infection, although we cannot entirely exclude the second possibility.

This case highlights the importance of a thorough occupational history and the fact that *Y pseudotuberculosis* can cause a chronic low grade infection but with severe consequences. The response to treatment we obtained suggests that its diagnosis was worthwhile. It is therefore important that *Yersinia* infection is screened for in the investigation of unexplained persisting arthralgia and arthritis. This, and other treatable infection, may be responsible for a proportion of those cases of seronegative arthritis.

The lesson

- Careful consideration of occupation may be important
- A long history and previous investigation does not always indicate an untreatable condition
- A number of infections can cause persistent arthralgia – namely, *Yersinia*, borrelia, parvovirus, brucella, campylobacter, shigella, chlamydia, hepatitis B and C, persistent Epstein-Barr virus, and cytomegalovirus.

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