Yersinia arthritis: a clinical, immunological, and family study of 2 cases

P. J. H. S. Sheldon, N. S. Mair, and E. Fox

From the Department of Rheumatology, Leicester Royal Infirmary, the Department of Microbiology, University of Leicester, and the Public Health Laboratory, Leicester

Summary

We describe 2 patients who presented with yersinia arthritis within a period of 5 months in Leicester. Both were HLA B27 positive. Arthritis followed 2 to 3 weeks after pneumonia, abdominal pain, dysuria, and evidence of hepatic involvement in the first case, and dysuria and conjunctivitis in the second. Immunological studies showed the presence of IgM, IgG, and IgA antibodies at a significant level against Yersinia enterocolitica serotype O:3 in serum and synovial fluid, and immune complexes in the serum of the first case and synovial fluid of both. Arthopathy resolved after 16 weeks in the first case and 12 weeks in the second, the latter requiring systemic corticosteroids. Family studies revealed psoriatic spondylarthritis in the brother, and bilateral sacroiliitis in the mother of the second case. Both were HLA B27 positive. These are the fourth and fifth reported cases of yersinia arthritis in Britain. We believe the condition is probably underdiagnosed and that yersiniosis should be considered as a possibility in otherwise unexplained arthritis.

Reactive arthritis is an aseptic arthritis occurring in patients known to have had recent infection with salmonella, shigella, gonococcus, meningococcus, campylobacter, chlamydia, or yersinia. The florid form of the disease, including mucocutaneous and ocular lesions as described by Reiter, occurred in a man 1 week after an attack of diarrhoea.

Though quite commonly encountered in Scandinavia, there have been few reports of reactive arthritis or Reiter's disease associated with Yersinia enterocolitica infection in the United Kingdom. Thus between 1970 and 1976 there were only 2 reported cases of Y. enterocolitica infection and neither had arthritis. Both were probably infected while abroad. Three cases with arthritis were subsequently described.

We report 2 cases seen within a 5-month period in Leicester, together with a study of their families with particular respect to the occurrence of HLA B27, known to be involved in reactive arthritis.

Case reports

Case 1

A 33-year-old male bank clerk developed sudden left-sided chest pain extending to the left hypochondrium and made worse on breathing. There was no cough or sputum. He also had colicky lower abdominal pain but no diarrhoea. Dysuria was present and persisted intermittently for 1 week. There was no history of conjunctivitis. On examination he was apyrexial. A pleural rub was detected over the left lower zone posteriorly and there was tenderness with guarding in the left hypochondrium. Bowel sounds and rectal examination were normal. At this stage his midstream urine showed 21 x 10⁹/l white blood cells and no growth on culture. Chest x-ray showed consolidation in the posterior segment of the left lower lobe. Liver function tests showed γ-glutamyl transferase 90 IU/l (normal 0–50), alanine transaminase 112 IU/l (normal 0–35), aspartate transaminase 66 IU/l (normal 8–40), and alkaline phosphatase 351 IU/l (normal 60–260). Blood culture was sterile.

He was thought to have a chest infection and received a 10-day course of doxycycline 100 mg daily. The chest x-ray cleared over the next week, but there was persistent pain in the hips and legs. Sixteen days...
from the onset of illness there was painful swelling of the right knee and at 21 days of the right shoulder. Liver function tests were repeated and showed worsening of the previously reported changes, suggesting the presence of hepatitis, though the bilirubin level remained normal. Further investigations were as follows: haemoglobin 13.8 g/dl; white blood cell count 11.8 × 10⁹/l; plasma viscosity 2.2 cp; urea 7.1 mmol/l (43 mg/100 ml); antistreptolysin O titre 200 IU/l. Complement fixing antibodies to influenza A and B, adenovirus, Coxiella burnetii, Chlamydia psittaci, and Mycoplasma pneumoniae were negative. Tests for hepatitis B surface antigen, rheumatoid factor, and antinuclear factor were negative. Liver ⁹⁹Tc scan and electrocardiogram were normal. Knee aspirate was sterile, and pathogens were not isolated from stool cultures. Agglutinating antibodies to Y. enterocolitica serotype O:3 were present at a reciprocal titre of 640 in both serum and joint fluid (Fig. 1).

Details of immunological studies on blood and synovial fluid are shown in Tables 1 and 2.

During the next 7 weeks he developed bilateral knee effusions and pain in the dorsum of the left foot, while the pain in the right shoulder persisted. He was treated with nonsteroidal anti-inflammatory drugs (NSAID) and intra-articular steroid injections to the knees and right shoulder. At review 18 weeks after onset of illness he was well, at work for the past 2 weeks, but with slight residual shoulder pain and limitation of movement. He was off all drugs.

The patient’s family was studied and their HLA B27 status determined. (Fig. 2).

**CASE 2**

A 22-year-old bus mechanic attended the emergency department complaining of pain and swelling of the right foot of 1 week’s duration and of the left ankle for 4 days. Three weeks previously he had had painful

---

**Table 1** Immunological studies on peripheral blood and synovial fluid in 2 cases of yersinia arthritis

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood</td>
<td>Synovial fluid</td>
</tr>
<tr>
<td>Total white cell count</td>
<td>11.8 × 10⁹/l</td>
<td>—</td>
</tr>
<tr>
<td>% Neutrophils</td>
<td>—</td>
<td>18, 80†</td>
</tr>
<tr>
<td>% Lymphocytes</td>
<td>—</td>
<td>58, 20†</td>
</tr>
<tr>
<td>% T cells</td>
<td>69</td>
<td>56</td>
</tr>
<tr>
<td>% B cells</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Resting ³¹H thymidine uptake</td>
<td>924 cpm</td>
<td>—</td>
</tr>
<tr>
<td>Max. response to phytohaemagglutinin</td>
<td>12 007 cpm</td>
<td>—</td>
</tr>
<tr>
<td>Glucose concentration</td>
<td>4.0 mmol/l</td>
<td>4.1 mmol/l</td>
</tr>
<tr>
<td>C³,⁴</td>
<td>12.6 μmol/l</td>
<td>7.5 μmol/l</td>
</tr>
<tr>
<td>C⁴</td>
<td>2.6 μmol/l</td>
<td>0.96 μmol/l</td>
</tr>
<tr>
<td>Titres of immune complexes</td>
<td>1:4</td>
<td>1:8</td>
</tr>
<tr>
<td>Y. ent. O:3 maximum agglutination titres</td>
<td>1:640</td>
<td>1:640</td>
</tr>
</tbody>
</table>

*Estimated by E rosette formation. † Estimated by rosetting with antiglobulin-coated chromic chloride treated erythrocytes. ‡ Estimated by micromethod; each result represents mean of triplicate cultures. § Estimated by single radial immunodiffusion. ¶ Estimated by platelet aggregation. ‡ Samples taken 3 days apart.

² 24% Large mononuclear cells also present.

Conversion of SI to traditional units: Glucose 1 mmol/l = 18 mg/100 ml. C³ 1 μmol/l = 18.5 mg/100 ml (normal 3.9–10 μmol/l). C⁴ 1 μmol/l = 23.0 mg/100 ml (normal 0.6–2.9 μmol/l).
Yersinia arthritis: a clinical, immunological, and family study of 2 cases

Table 2  IgM, IgG, and IgA antibodies to Y. enterocolitica O:3 determined by indirect immunofluorescence in serum and joint aspirate specimens at intervals after onset of yersinia arthritis

<table>
<thead>
<tr>
<th>Case</th>
<th>Immunoglobulin class</th>
<th>Serum and joint aspirate antibody titres at</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-4 weeks</td>
<td>2 months</td>
</tr>
<tr>
<td>1</td>
<td>IgM</td>
<td>200/200*</td>
</tr>
<tr>
<td></td>
<td>IgG</td>
<td>400/800</td>
</tr>
<tr>
<td></td>
<td>IgA</td>
<td>100/100</td>
</tr>
<tr>
<td>2</td>
<td>IgM</td>
<td>1600/200</td>
</tr>
<tr>
<td></td>
<td>IgG</td>
<td>1600/800</td>
</tr>
<tr>
<td></td>
<td>IgA</td>
<td>1600/400</td>
</tr>
</tbody>
</table>

*Reciprocal titres of serum and joint aspirate, e.g. 200/200 = serum 1:200/joint aspirate 1:200. ** = No joint aspirate.

eyes and dysuria lasting 2 days. There was no history of backache, bowel disturbance, or sexual exposure. At the age of 8 years he had undergone circumcision for recurrent attacks of balanitis attributed to phimosis. At 11 years he had had acute iridocyclitis of the right eye and at 16 years the left eye had been similarly affected. One brother was said to have 'arthritis', the rest of the family being well.

Examination revealed tenderness over the dorsum of the right foot and synovial swelling and tenderness of the left ankle. Subsequently he developed effusions in both knees and a flitting arthropathy involving metacarpophalangeal and metatarsophalangeal joints. Investigations were as follows: haemoglobin 14·8 g/dl; white blood cell count 7·6 x 10⁹/l; plasma viscosity 2·02 cp; serum urate 0·256 mmol/l (4·3 mg/dl); rheumatoid factor negative; stool culture negative; radiographs of chest, spine, and pelvis normal; electrocardiogram normal. Serum and joint fluid taken 14 days after onset of arthritis showed agglutinating antibodies to Y. enterocolitica O:3 at reciprocal titres of 2560 and 1280 respectively (Fig. 1). The results of immunological studies on blood and synovial fluid are shown in Tables 1 and 2.

He was treated with NSAID for 5 weeks and tetracycline 250 mg four times daily for 10 days empirically in view of the serological evidence of acute yersinia infection. He also received corticosteroid injections into both knee joints. He was unable to return to work on account of persistently painful feet.
and was therefore started on prednisolone 15 mg daily. The joints became less painful, and the dose was reduced over a 7-week period, by which time all the drugs were discontinued, the patient being free of symptoms apart from an occasional twinge. He was able to return to work 12 weeks after the onset of illness. His family was studied and their HLA B27 status assessed (Fig. 3).

Discussion

The first case was initially very puzzling, with a combination of abdominal and chest symptoms. The diagnosis was suspected only after the appearance of arthritis. In both patients this predominantly involved the lower limbs, though the shoulder and metacarpophalangeal joints were also affected. Similar patterns of joint involvement have been recorded in other series, including migrating arthralgia.\textsuperscript{11-13} The duration of arthritis was approximately 4 months and 3 months respectively in cases 1 and 2, but it must be remembered that the second case received systemic corticosteroids 5 weeks after the onset of joint pains, enabling him to return to manual work 7 weeks later. Generally speaking case 2 had a more florid arthritis, with a failure to respond to NSAID therapy. Case 1 presented with systemic illness, the subsequent joint symptoms responding adequately to NSAID, enabling him to return to clerical work. Additionally there was biochemical evidence of hepatic involvement which improved with his arthritis. Hepatitis in \textit{Y. enterocolitica} infection has previously been described.\textsuperscript{20,21}

The titre of agglutinating antibody to \textit{Y. enterocolitica} O:3 in the serum of case 1 remained constant at 640 for at least 4 months, whereas in the synovial fluid antibody began to decline after 1 month, though it could still be detected 2 months later. In the second case serum antibody fell within 1 month, that is, before systemic corticosteroids were administered (Fig. 1). The antibody classes involved were shown by indirect immunofluorescence to include IgM, IgG, and IgA (Table 2). All 3 classes were present in both serum and synovial fluid. IgM antibodies to \textit{yersinia} were surprisingly persistent in case 1, being still detectable after 7 months, while in case 2 a striking feature was the rapid disappearance of IgA antibodies in less than 2 months. These findings differ from those of a recent study in Finland by Granfors \textit{et al.}\textsuperscript{22} who showed that in patients with severe \textit{yersinia} arthritis IgM antibodies persisted in most cases for only 1 to 3 months and always disappeared during the first 6 months after onset of infection, while IgA antibodies to \textit{yersinia} persisted for 14–16 months after onset of infection. Different methodology may account for these differences, since Granfors \textit{et al.} used the enzyme-linked immunosorbent assay technique to demonstrate the 3 immunoglobulin classes. As an explanation for the persistence of IgA antibodies the same investigators mention the possibility of antigenic stimulation from the gut and genitourinary tract (perhaps understandable in a country such as Finland, where human \textit{yersinia} infection is endemic).

The joint fluid in both cases showed a polymorphonuclear neutrophil leucocytosis, though in the first case it was of interest to note that the ratio of lymphocytes to polymorphs in synovial aspirates from the same knee 3 days apart showed a reversal at a time when immune complexes were detected (Table 1). The levels of C3 and C4, though within the normal range, were lower in synovial fluid than blood at this time, possibly as a result of classical pathway activation.

The percentage of thymic derived (T) and thymic independent (B) lymphocytes in blood and joint fluid were similar (Table 1), as was the response to phytohaemagglutinin (PHA), whereas in rheumatoid arthritis B cell percentages in synovial fluid may differ from those in blood, and the synovial fluid lymphocytes are relatively refractory to stimulation by PHA.\textsuperscript{21}

The history of ‘arthritis’ involving the brother of the second case prompted a limited study of both families, the results being shown in Figs. 2 and 3. The mother of the first case was HLA B27 positive, but neither she nor her sister (B27 negative) had clinical or radiological evidence of arthropathy. The brother of the second case was found to have psoriasis, with nail pitting and onycholysis. He also had an asymmetrical polyarthritis and bilateral radiological sacroilitis. The mother had a 2-year history of low back pain and 10 years previously had required outpatient treatment over a 1-month period for conjunctivitis. X-ray revealed bilateral sacroilitis. Both relatives were B27 positive. The father and a half-brother, both B27 negative, were clinically and radiologically normal. No other members of either family had antibodies to \textit{Y. enterocolitica} O:3.

Reactive arthritis is generally self-limited and is a benign variant within the spectrum of seronegative spondylarthropathies. At the centre of this spectrum lies ankylosing spondylitis (AS), a disorder marked by chronic progressive disability, yet the insidious nature of its onset and course make the role of an infectious agent extremely difficult to substantiate. The close association of B27 with AS and other spondylarthropathies\textsuperscript{24-26} has evoked much speculation on the mechanisms likely to be involved. Immune responses are known to be in part genetically determined in various species, including the mouse and probably man.\textsuperscript{27} In the mouse overall high
or low antibody responses have been demonstrated to a variety of antigens, and this finding has been attributed to differences in antigen handling by macrophages.\textsuperscript{20} Specific responses to some antigens have been shown to be under the control of autosomal dominant immune response (Ir) genes which are linked to the major histocompatibility system (MHS).\textsuperscript{30} The chronological sequence of events in B27-associated reactive arthritis may illustrate the interplay of infection and genetic factors, though the mechanism may not necessarily involve the (probable) linkage of the MHS to Ir genes. The 'molecular mimicry' hypothesis suggests that there is antigenic similarity between the B27-coded HLA molecule on the cell surface and determinants on certain bacteria. Consequently antibodies formed as a result of infection may cross-react with host tissues (as is thought to be the case in rheumatic fever). Alternatively the aberrant response, by its failure effectively to clear the antigen load, may result in a state of antigen excess and the formation of soluble immune complexes, which could in turn play a part in the ensuing arthritis.

Studies showing an increased incidence of faecal carriage of \textit{Klebsiella aerogenes} in patients with AS\textsuperscript{31} have been followed by evidence that antiserum raised in rabbits against certain isolates of \textit{K. aerogenes} will kill B27 positive (B27+) AS+ lymphocytes, but not B27+AS−, B27−AS+, or B27−AS− lymphocytes.\textsuperscript{22} Subsequently the same workers demonstrated that a soluble factor derived from a klebsiella K43 culture filtrate was able specifically to modify a B27-associated lymphoid cell component, rendering previously nonsusceptible B27+ lymphocytes susceptible to cytotoxicity by rabbit anti-klebsiella antiserum.\textsuperscript{23}

In an attempt to find a similar link between \textit{Y. enterocolitica} and AS other workers have raised antiserum in rabbits against 3 strains of \textit{Y. enterocolitica}, including serotype O:3. These antisera failed to exhibit cytotoxic activity against B27+AS+, B27+AS−, or B27−lymphocytes, nor was the activity of anti-B27 typing serum absorbed out by yersinia antigen preparations.\textsuperscript{24}

The true relationship between \textit{K. aerogenes}, \textit{Y. enterocolitica}, and B27 remains far from clear. Nevertheless one is tempted to postulate that in acute reactive arthritis gut infection results in a genetically determined pattern of immune response resulting in antibody synthesis and circulating immune complexes. In contradistinction faecal carriage of an organism in a genetically predisposed individual may act in 2 ways, firstly, as in the case of gut infection with the formation of immune complexes, which have been demonstrated in AS,\textsuperscript{25} and secondly through a perturbation of a cell wall component of B27-positive gut-associated lymphocytes by cytophilic bacterial cell products.\textsuperscript{26} This in turn may trigger the release of lymphokines into Batson's circulation,\textsuperscript{26} with the development of chronic inflammation and its sequelae along the appropriate channels of spread, with the clinical development of changes recognised as AS.

We thank Dr H. Thurston for permission to investigate the first case and Miss Elaine Gooch for help with the immunofluorescence tests.

References


