LETTERS

Necrotising myositis in Behçet’s disease: characteristic features on magnetic resonance imaging and a review of the literature

H Sarui, T Maruyama, I Ito, N Yamakita, N Takeda, M Nose, K Yasuda


Musitis is rarely associated with Behçet’s disease. We report such a case with characteristic magnetic resonance imaging (MRI) findings, and review the literature.

CASE REPORT

A 29 year old man was first admitted to Matsunami General Hospital because of high fever and muscle pain of both lower legs, finally resulting in him being unable to walk. Painful multiple subcutaneous nodules of both lower legs and the left arm were seen. There was no history of trauma. Total leucocytes, erythrocyte sedimentation rate, and C reactive protein were raised. The serum creatine kinase value was normal. An MRI study of the lower legs (fig 1) showed a focal mass-like lesion, about 3 cm in diameter, in the left gastrocnemius muscle with a decreased intensity on a T1 weighted image compared with that for normal muscle. Gadolinium enhanced T1 weighted images showed a well defined rim of contrast enhancement and a hypointense central area. An axial T2 weighted image showed bright signal intensity in and around the focal mass-like lesion. The same MRI findings were seen in the other nodules of the lower legs. Computed tomography (CT) did not disclose the focal mass-like lesion. Antibiotics were not effective. The symptoms and multiple nodules resolved spontaneously about one month after admission, and the patient was discharged.

One month after discharge, he was admitted to our hospital because of a relapse, with similar symptoms. Painful multiple subcutaneous nodules of both lower legs, in different areas from those of his previous admission, were found. MRI findings of the mass lesions were similar to those of the previous admission.

On admission the patient had polyarthritis and skin lesions. Recurrent aphthous ulcerations had been noted over the previous two years. Pathergy testing was positive. A skin biopsy was performed and showed thrombophlebitis. HLA-B51 was positive. From these results, Behçet’s disease was diagnosed. A biopsy of a nodule from the left gastrocnemius muscle was carried out. Examination of the muscle biopsy specimen obtained from the nodular lesion showed an inflammatory granulation predominantly with an infiltration of neutrophils and macrophages, associated with focal central necrosis of the muscle and perivascularitis in the surrounding muscular tissue. A culture of the tissue specimen was negative for bacteria.

These findings were consistent with necrotising myositis. The symptoms and multiple nodules of the legs resolved spontaneously. After discharge, colchicine was given, and no painful multiple subcutaneous nodules have reappeared.

DISCUSSION

We reviewed nine cases of Behçet’s disease with myositis reported in English1–9 and the present case (table 1). Three were generalised and seven were localised myositis. Painful multiple nodules were not described in the cases. All of the localised cases involved the legs. In our case the histological findings were similar to most of the other reported localised cases; it seems possible that vasculitis as a component of Behçet’s disease may participate in the pathogenesis of myositis.

MRI has proved to be better than CT scans for the detection of soft tissue diseases—notably, muscle disorders, but was not described in the cases reviewed above. In diabetic muscle infarction and pyomyositis, a gadolinium infusion showed a slightly enhanced rim and a dark central area in T1 weighted images. Our case suggests that radiological differentiation among these lesions is difficult. A prompt biopsy and a cell culture should be carried out.

Colchicine may be useful for treating genital ulcers, erythema nodosum, and arthritis of Behçet’s disease, especially in women.10 In the cases reviewed here, only one patient...
received colchicine during the acute phase of myositis, with no striking effect on the myositis. In our case, necrotising myositis did not recur after the administration of colchicine. The usefulness of colchicine for prevention of myositis in Behçet’s disease needs to be further studied.

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REFERENCES
Systemic lupus erythematosus with haemophagocytosis and severe liver disorder

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We report the case of a 30 year old woman who was diagnosed with systemic lupus erythematosus (SLE) and had received prednisolone and cyclosporin A (CsA). In November 1999 a haematological examination showed a slight increase in transaminases. With no improvement in transaminase values, CsA was discontinued, and prednisolone was continued at 20 mg/day. Because of general malaise, she was admitted in January 2000.

CASE REPORT

A haematological examination showed a marked decrease in white blood cells (WBC) to $1.4 \times 10^9/l$, with a slight anaemia, but platelets were within the normal range. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were considerably increased to 617 U/l (normal 13–33) and 350 U/l (normal 6–27), respectively. Ferritin was also increased to 2306 ng/ml (normal 5–178). C reactive protein (CRP) was increased to 7.9 mg/l (normal 0–4). Anti-double stranded DNA antibodies were increased to 297.8 IU/ml (normal 0–11.9). CH50 17 U/ml (normal 30–50) showed severe hypocomplementaemia. Soluble interleukin 2 receptor (sIL2R) was high at 807 U/ml (normal 145–519). Serum studies for hepatitis B virus, hepatitis C virus, herpes simplex virus, and Epstein-Barr virus were negative. Direct immunoperoxidase staining using a monoclonal antibody (HRP-C7) measurement, a marker of cytomegalovirus (CMV) antigenaemia, was 1/34 000. This level is associated with asymptomatic CMV antigenaemia. The CRP declined and CMV became negative, with no rises before activation of SLE. However, owing to the negative results of serum studies for several viruses, SLE itself was thought to be the cause of haemophagocytosis.

Possible causes of haemophagocytosis include viral infections in this patient, as well as SLE itself, because the disease was active. However, owing to the negative results of serum studies for several viruses, SLE itself was thought to be the cause of haemophagocytosis.

DISCUSSION

Psoriasis of active SLE. Both immune complex and hypocomplementaemia and also activated T cells played an important part in the mechanism of haemophagocytosis in our patient. CsA, which inhibits helper T cells, was effective, suggesting that cytokines also were important in the mechanism of haemophagocytosis.

In SLE, greatly increased transaminases are uncommon. In our patient, according to the definition and diagnostic criteria for CMV infection-induced hepatitis and cholangitis, CMV hepatitis was unlikely. Infections due to viruses other than CMV were also unlikely because no inclusion body was found. In addition, an examination of her liver did not point to a hepatic disorder induced by a thrombotic event. Steatosis found in SLE is generally accepted as a condition associated with drugs such as corticosteroids. However, hepatic disorder in our patient occurred as part of active SLE, and activated T lymphocytes and hypercytokinaemia played important roles as in the mechanism of haemophagocytosis, because sIL2R was high and improved as the clinical symptoms and liver transaminases improved with combined treatment with corticosteroids and CsA.
In systemic sclerosis (SSc), which affects the microcirculation and leads to fibrosis of skin and internal organs, the oesophagus and the colon are involved. In SSc, a few ultrastructural examinations of the oesophageal and rectal wall have been made, but no study has been carried out on the stomach. This prompted us to examine the gastric wall of a patient with SSc by transmission electron microscopy (TEM) in order to investigate the components of the muscle coat.

CASE REPORT
In 1997 a 52 year old woman, with limited SSc (lSSc) since 1979, came to our attention. She had Raynaud’s phenomenon, sclerodactyly, antinuclear antibodies, and Sjögren’s syndrome, but no lung, heart, and kidney disease. From the onset of her SSc, the patient had severe involvement of the distal oesophagus, which was confirmed by oesophagogastroscopy. In May 1998 the gastro-oesophageal symptoms worsened despite treatment (ranitidine and, later, omeprazole and cisapride) and the patient underwent a Nissen-Rossetti laparoscopic fundoplication. Eight months later, as she became progressively unable to eat, she underwent a total gastrectomy with a Roux-en-Y oesophagojejunal anastomosis, indicating an ineffective filament contraction.

Samples of gastric anterior wall near the greater curvature, from the fundus, corpus, and antrum, were obtained, processed routinely for electron microscopy and, then, ultrathin sections were observed by TEM. The small number of fibroblasts found in the gastric muscle layers suggests that elastin and collagen fibres may be produced by smcs themselves, and not by fibroblasts, as shown in SSc skin. Indeed, considerable amounts of elastin were often found in invaginations of smc cell membrane. The fibrosis enveloping smcs might account for impaired cellular contraction and its propagation from cell to cell.

Several smcs were either contracted, with thickened dense bands (fig 1B), or stretched, with long and thin dense bands along the cell membrane (fig 1A), indicating a different stage of smc contraction in the SSc stomach. These observations disagreed with the ultrastructural findings in SSc oesophagus, where only thickened dense bands were seen, while long and thin dense bands were noticed in patients with diffuse oesophageal spasm.

In smcs, cytoplasmic vacuolisation and swollen mitochondria (fig 1A) were often found. Moreover, myofilaments and thickened dense bodies were severely disarrayed (fig 1B), indicating an ineffective filament contraction.

In myenteric plexus, large sized neurones showed well preserved Golgi apparatus, rough endoplasmic reticulum, some lipofuscin bodies, and diffuse slight cytoplasmic vacuolisation. Nerve bundles containing many axons were close to vessels and smcs.

The axoplasm of nerve fibres was pale, oedematous, and scarce in neurotubules and neurofilaments, with occasional swollen mitochondria and lipofuscin bodies (figs 1C and E) as reported in nerve amyelinc bundles of SSc rectum wall.

In SSc stomach, as seen in SSc oesophageal muscle coat, nerve endings close to smcs and vessels showed conserved morphology with intact synaptic vesicles containing electron dense granules (fig 1D). Often, abundant elastic and collagen fibres enveloped nerve endings, separating them from smcs (fig 1D). This finding, together with the alterations in the axoplasmic cytoskeletal elements, may account for the impairment of cellular contraction and its propagation from cell to cell.

Ultrastructural study of the muscle coat of the gastric wall in a case of systemic sclerosis

L Ibba-Manneschi, A Del Rosso, S Pacini, A Tani, P Bechi, M Matsucci Cerinic

in axonal transport and in electric transmembrane transmission, respectively. These observations substantiate the alterations in nervous transmission that might be responsible for GI dismotility in advanced SSc.

Small vessels of the gastric muscle wall were lined by preserved endothelial cells, and the basement membrane was sometimes thickened or laminated, or both (fig 1E). In SSc skin and rectum wall microvessels, on the contrary, swollen endothelial cells occluding the lumen, and thickened and laminated perivascular basal lamina, were seen. Therefore, further studies on the GI tract of patients in the early phase of SSc are warranted in order to understand and clarify the primary target of the disease and its progression.

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Relapse of rheumatoid arthritis after substitution of oral for parenteral administration of methotrexate

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We read with interest the letters: “Is parenteral methotrexate worth trying?” by Osman and Mulherin and “Intramuscular methotrexate in inflammatory rheumatic disease” by Burbage, Gupta, and Lim. We would like to present our findings, which indicate that parenteral methotrexate (MTX) may be more efficient than oral MTX at the same dose and in the same patients with inflammatory joint disease.

During the second half of 2000 we were faced with an unexpected shortage of parenteral MTX (ABIC, Israel) which lasted for more than five months, and patients were switched to oral MTX (Lederle, Germany). This gave us the opportunity to evaluate the difference in efficacy of parenteral versus oral administration of low dose MTX.

CASE REPORTS
Eight patients (seven female) with a mean age of 55 (38–70) years, who fulfilled the following criteria, were analysed retrospectively: (a) all had inflammatory joint diseases (four seropositive rheumatoid arthritis (RA), two seronegative RA (revised American Rheumatism Association criteria for RA), and two RA-like psoriatic arthropathy); (b) all were receiving parenteral MTX and were in complete clinical remission (fulfilling at least five of six criteria for complete clinical remission in RA); (c) all had an exacerbation of their disease when switched from parenteral to oral MTX at the same weekly dose and without any interval between the two treatments.

Ninety seven patients with inflammatory joint diseases were treated with parenteral MTX. Eighty one of them were faced with the drug supply shortage. Four patients remained in clinical remission for five months without MTX treatment. Eighteen who were not advised to switch immediately had an exacerbation of their disease within three weeks. The other 59 patients were switched to oral MTX without any treatment interval. Ten of the 59 patients received an oral dose more than 2.5–5 mg higher than the parenteral dose; no exacerbation occurred. Forty nine patients were switched to the same oral dose, 2.5–5 mg higher than the parenteral dose; no exacerbation occurred. Forty nine patients were switched to the same oral dose, 2.5–5 mg higher than the parenteral dose; no exacerbation occurred.

The following variables were investigated: duration of the disease and of the remission period, x ray imaging (joint erosions), concurrent treatment, MTX weekly dose, EULAR disease activity score (DAS28 with three variables) at the time of relapse and two months after renewing the parenteral MTX treatment, compared with remission period.

Table 1 summarises the patients’ details. These patients did not differ from the patients who did not have an exacerbation after switching. All eight patients were in stable remission which had lasted for three years on average. Relapse occurred quite rapidly: 3–10 (mean 6) weeks after switching. The mean (SD) DAS28 activity index rose from 1.8 (0.4) to 4.9 (0.4).Within two months after reinstition of the previous parenteral MTX marked improvement was noted from DAS28 activity index rose from 1.8 (0.4) to 4.9 (0.4).

DISCUSSION
After oral administration MTX is rapidly but incompletely absorbed. Its bioavailability is about 70% at low doses (<10 mg/m²), approximately 15–20% lower than that of intramuscular (IM) or intravenous (IV) MTX. In addition, there is a marked interindividual and a moderate intraindividual variability in the extent of absorption of oral MTX. Oral administration in doses above 25 mg/day is associated with lower bioavailability due to the saturation of the absorption mechanism. Thus in high doses the parenteral administration is mandatory. IM MTX showed higher bioavailability than oral MTX either as tablets or as solution. However, other studies have shown a similar MTX concentration after oral, IM, or IV administration.

To compare the relative bioavailability of oral versus intramuscular administration in patients with RA, the pharmacokinetics of MTX at both the usual starting dose of 7.5 mg and at established higher maintenance doses was examined in 21 patients. Pharmacokinetics measurements were repeated six and 18 months after baseline while patients were receiving maintenance doses of MTX (17.0 (3.8) mg). The relative bioavailability of the maintenance dose was reduced by 13.5% as compared with the initial dose of 7.5 mg. The area under the curve of the serum concentration versus time curve

REFERENCES
was significantly lower for oral than for IM administration at usual maintenance doses, but similar at an MTX dose of 7.5 mg a week. The authors concluded that clinicians using MTX should not assume constant and complete bioavailability across the dose range. The findings explained the benefit which follows the switching from oral to parenteral administration in patients receiving maintenance doses of MTX as well as the failure of the inverse switching reported here. It should be mentioned that all our patients were treated with MTX in doses higher than 7.5 mg/week and from the study of Hamilton and Kremer it seems that it is only safe to switch from IM to oral administration at a dose of 7.5 mg/week. Two other recent studies also supported a switch to parenteral MTX in patients previously intolerant of, or who have failed to respond to, oral MTX.

Various drugs currently used in RA may interact with MTX. It is known that corticosteroids do not interfere with the pharmacokinetics of MTX, whereas chloroquine may reduce gastrointestinal absorption of the drug. This might be relevant to two of our patients (Nos 5 and 6, table 1).

In conclusion, polyarthritis may be exacerbated owing to switching from parenteral to oral MTX using the same dosage. Reinstitution of IM MTX usually suppresses the disease activity.

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**Table 1**

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>Period of remission (years)</th>
<th>MTX dose per week during substitution PO for IM (mg)</th>
<th>Concurrent treatment</th>
<th>Activity index (DAS28) during remission/relapse (weeks)</th>
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<tr>
<td>1</td>
<td>RA sero(+ve)</td>
<td>63</td>
<td>10/3</td>
<td>1.25</td>
<td>Pred 5 mg/d</td>
<td>1.7/4.7</td>
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<tr>
<td>2</td>
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<td>47</td>
<td>12/2</td>
<td>1.25</td>
<td>Pred 5 mg/d</td>
<td>1.7/4.7</td>
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<tr>
<td>3</td>
<td>RA sero(+ve)</td>
<td>47</td>
<td>8/4</td>
<td>1.25</td>
<td>Pred 5 mg/d</td>
<td>1.7/4.7</td>
</tr>
<tr>
<td>4</td>
<td>RA sero(+ve)</td>
<td>38</td>
<td>1/0.5</td>
<td>1.25</td>
<td>Pred 5 mg/d</td>
<td>1.7/4.7</td>
</tr>
<tr>
<td>5</td>
<td>RA sero(+ve)</td>
<td>70</td>
<td>15/4</td>
<td>1.25</td>
<td>Pred 5 mg/d</td>
<td>1.7/4.7</td>
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<tr>
<td>6</td>
<td>RA sero(+ve)</td>
<td>87</td>
<td>12/5</td>
<td>1.25</td>
<td>Pred 5 mg/d</td>
<td>1.7/4.7</td>
</tr>
<tr>
<td>7</td>
<td>RA sero(+ve)</td>
<td>53</td>
<td>3/2</td>
<td>1.25</td>
<td>Pred 5 mg/d</td>
<td>1.7/4.7</td>
</tr>
<tr>
<td>8</td>
<td>RA sero(+ve)</td>
<td>55</td>
<td>7/6</td>
<td>1.25</td>
<td>Pred 5 mg/d</td>
<td>1.7/4.7</td>
</tr>
<tr>
<td>9</td>
<td>RA sero(+ve)</td>
<td>55</td>
<td>8/5</td>
<td>1.25</td>
<td>Pred 5 mg/d</td>
<td>1.7/4.7</td>
</tr>
<tr>
<td>10</td>
<td>PsA</td>
<td>55</td>
<td>15/4</td>
<td>1.25</td>
<td>Pred 5 mg/d</td>
<td>1.7/4.7</td>
</tr>
<tr>
<td>11</td>
<td>PsA</td>
<td>55</td>
<td>18/4</td>
<td>1.25</td>
<td>Pred 5 mg/d</td>
<td>1.7/4.7</td>
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</table>

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**REFERENCES**

Spontaneous spondylodiscitis caused by *Klebsiella oxytoca*

J M Sabio, M López-Gómez, J Jiménez-Alonso

**CASE REPORT**

A 51 year old man with an antecedent of intravenous heroin addiction and two months’ history of progressive thoracolumbar pain without fever was referred for investigation. Physical examination showed mild tenderness to palpation over D12-L1 and a painful paravertebral musculature contraction that limited movements of the back. Motor examination and deep tendon reflexes were normal. Several skin ulcers and venepuncture lesions in arms, hands, and legs were seen. The remainder of the examination was otherwise unremarkable.

Laboratory findings showed an erythrocyte sedimentation rate of 62 mm/1st h; C reactive protein 83 mg/l, fibrinogen 7.6 g/l, and a white blood cell count of 11.6×10^9/l with 78% polymorphonuclear cells. A chest radiograph and the remainder of the routine blood and urine determinations were normal. A Mantoux intradermor reaction test (2 UI PPD-RT23) was positive (15 mm in diameter). Serological tests for *Brucella* and HIV were negative. Likewise, a skin ulcer specimen was examined and polymicrobial flora were isolated. A roentgenographic study of the lumbar spine showed degenerative changes and osteoporotic vertebral fractures in D12 and L1, and narrowing of the disc space at D12-L1. Magnetic resonance imaging (MRI) confirmed narrowing of the disc space at D12-L1, with end plate destruction of D12 and L1 (fig 1). Finally, a fine needle biopsy of the disc guided by computed tomography was performed and the specimen culture was positive for *K. oxytoca*. In accordance with the antibiogram results, the patient received intramuscular ceftriaxone (2 g/day for six weeks). Two months later the patient had completely recovered and MRI showed significant improvement of the vertebral lesion.

**DISCUSSION**

*Klebsiella* species are an important cause of nosocomial and community acquired infection. Most of the *Klebsiella* strains implicated in invasive infections are *K. pneumoniae* and <13% of episodes of bacteraemia by *Klebsiella* were due to *K. oxytoca*.** This micro-organism has been associated with urinary, respiratory, biliary tract, skin, and intravascular device infections.** Although unusual, some cases of spondylodiscitis caused by *K pneumoniae* have been reported.** However, as far as we know this is the first reported case of SIS due to *K oxytoca*.

The clinical presentation of this patient was similar to that reported in other cases of SIS, irrespective of the causative organism.** Schoferman et al pointed out that the infectious agents which play a part in SIS may be of relatively low virulence, causing an insidious onset and a subacute clinical course. This is in contrast with primary vertebral osteomyelitis, in which patients present a more acute course with obvious infection. In our case, blood cultures were negative. Honan et al found that 10/16 patients with spontaneous discitis also had negative blood cultures,** underlining this possibly low virulence, although it might also be explained by the fact that discitis is delayed with respect to the bacteraemia.

Likewise, it is remarkable that in the series of Lin et al, pyogenic metastatic foci were not found in any of the 43 patients with *K oxytoca* bacteraemia.** These issues suggest that *K oxytoca* may also have only a small ability to cause septic emboli and perhaps for this reason septic complications due to *K oxytoca* (such as SIS) are unusual.

Lin et al found that the most common underlying diseases associated with *K oxytoca* bacteraemia were hepatobiliary diseases, neoplastic diseases, and diabetes mellitus.** Other predisposing factors were prior antimicrobial treatment, urinary catheterisation or manipulation, corticosteroid treatment, recent surgery, and respiratory assistance. In our patient, none of these situations were present. He had only an active intravenous heroin addiction, and was negative for HIV infection when the spondylodiscitis developed. Many authors have concluded that immunological dysfunction has a relatively minor role in the pathogenesis of infection in injection drug users, compared with the repeated parenteral introduction of non-sterile material.** Nevertheless, some immunological disorders have been reported, such as a depression of

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**Figure 1** MRI showing the narrowing of the disc space at D12-L1, with end plate destruction of D12 and L1.
the blastogenic response of peripheral blood mononuclear cells to pokeweed mitogen and a depression of phagocytosis, superoxide production, and bactericidal activity of polymorphonuclear cells from intravenous heroin users.19 In these patients, osteomyelitis infection is usually due to \( S. aureus \) and \( P. aeruginosa \), and the skin and the oral cavity are the most common point of entry. \( K. oxytoca \) is an unusual microorganism present in the skin, dregs being its principal source. Contamination by objects used for intravenous heroin introduction may be a possible cause of the \( K. oxytoca \) infection in this case. Likewise, skin ulcers are extremely common in intravenous drug users. Although \( S. aureus \) and \( \beta \)-haemolytic streptococci remain the most common isolates, other Gram negative bacilli such as \( K. oxytoca \) have an important role. Our patient had skin ulcers and these may be other possible points of entry for \( K. oxytoca \), but in our case this microorganism could not be isolated.

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REFERENCES
imaging and ultrasound have shown that the lesion always present in dactylitis is flexor tendon tenosynovitis and that arthritis of the adjacent joints may be absent. In addition, our studies on dactylitis have demonstrated that physical examination has a high specificity and sensitivity in diagnosing dactylitis and that, therefore, imaging techniques are not essential in routine practice.

uSpA include forms of SpA that fail to meet criteria for the definite forms. Recent epidemiological studies using the Amor and/or the ESSG criteria for all forms of SpA have shown that uSpA is more common or as common as ankylosing spondylitis. The clinical spectrum of uSpA is wide, resulting from the various combinations of clinical and radiological manifestations. These include peripheral arthritis, peripheral enthesitis, dactylitis, inflammatory spinal pain, buttok pain, sacroiliitis, chest wall pain, acute anterior uveitis, aortic insufficiency together with conduction disturbances, each of which may also occur in isolation. In 1977 De Ceular et al described the cases of young and middle aged B27 subjects with isolated dactylitis. In 1988 Siegel and Baum reported the same situation in B27 positive children.

In the past few years attention has been drawn to late onset uSpA. In 1995 we reported on 23 patients with uSpA who had the first symptom after the age of 45 years. Of these, 12 had three or more manifestations of SpA, seven showed two manifestations, and four only one. Of these four, two had peripheral enthesitis and two acute anterior uveitis. The present report expands the clinical spectrum of late onset SpA with the inclusion of isolated dactylitis.

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** Poor predictive value of antinucleosome and antineutrophil cytoplasmic antibodies in a 270 inception cohort of patients with early naked arthritis of less than one year’s duration**

J-M Berthelot, A Saraux, M Audrain, P Le Goff, M Hamidou, J-Y Muller, P Youinou

In most studies examining the outcome of early arthritis, lupus and vasculitides are rare events, occurring in only 1–3% of cases. However, they should be diagnosed as quickly as possible. Thus, it might be worth testing patients with early arthritis for the presence of anticytoplasmic neutrophil antibodies (ANCA). Indeed, a strong positivity for ANCA might suggest that vasculitides, including Wegener’s disease and microscopic polyangiitis, were probably present before the onset of the clinical features typical of these disorders. Similarly, and in addition to looking for antinuclear antibodies (and/or anti-dsDNA antibodies), it has been claimed that testing for antinucleosome antibodies might be a valuable additional test for the early detection of lupus; this last subset of autoantibodies has shown good sensitivity (56%) and excellent specificity (97%) for longlasting systemic lupus erythematosus (SLE). However, these assumptions have not yet been supported by data from an inception cohort of patients with early unclassified arthritis tested by routine methods.

We tested for ANCA by indirect immunofluorescence (IIF) (1:20 dilution) and for antineutrophil-IgG by a commercial enzyme linked immunosorbent assay (ELISA) kit (BMD DNA-NUC-LISA) in the baseline sera of 270 patients with early onset arthritis without clinical signs suggestive of visceral disease. We then followed up these patients for a mean (SD) of 28.5 (12.1) months.

For the ANCA testing, although 23/270 (9%) baseline sera were positive, neither of the two patients later diagnosed as having vasculitides were positive by IIF-ANCA. Moreover, for both patients, even testing for anti-proteinase 3 (anti-PR3) and anti-myeloperoxidase (anti-MPO) by ELISA was negative at baseline.
For antinucleosome testing, at the 10 IU threshold suggested by the manufacturer, 109/270 (40%) sera were positive, including 51/114 (45%) rheumatoid arthritis (RA) and 20/34 (59%) spondyloarthropathy (SpA). However at the 20 IU threshold only 4% were still positive, including 2/33 (6%) unclassified arthritis, 5/105 (5%) RA, 2/52 (4%) SpA, 1/5 (20%) sicca syndrome, and only 1/5 (20%) patients later diagnosed as having SLE. Moreover for this single patient, the diagnosis was already firmly established, especially as the antinuclear antibody titre was 1/1000 and anti-dsDNA were positive. Hence the positive predictive value for SLE of antinucleosome testing was 1/11, and the sensitivity 1/5.

These low sensitivities do not support the working hypothesis that systematic screening for IIF-ANCA and antinucleosome antibodies is useful for the diagnosis of vasculitides in early arthritis and of SLE in patients with “naked” arthritis. Such results were somewhat expected, given that systemic vasculitis or SLE with arthritis as precursor are quite uncommon events. However, they confirm that determination of ANCA and antinucleosome antibodies should not be carried out in the absence of clinical extra-articular manifestations, especially as low ANCA titres have already been demonstrated in a large percentage of more benign conditions like early RA and early SpA.** We would therefore quite agree with the conclusion of Merkel et al, that instead of systematic screening for ANCA by IIF, only those patients with features atypical for RA, SpA, or undifferentiated arthritis should be tested for ANCA, using an ELISA for anti-PR3 and anti-MPO together with IIF-ANCA.*

Likewise in our cohort, antinucleosome antibodies were positive at low values at baseline in several conditions other than SLE and in only 1/5 patients with SLE. There are few reports on antinucleosome antibodies and SLE, and thus definite conclusions cannot be reached about the overall additional value of this test to support the diagnosis of SLE.** However, our results strongly suggest that systematic testing for antinucleosome antibodies should not be a substitute for a careful search for all visceral signs suggestive of lupus in a patient presenting with seemingly “naked” arthritis.

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Cogan's syndrome with antineutrophil cytoplasmic autoantibody

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Cogan’s syndrome is a rare disease characterised by non-syphilitic interstitial keratitis with vestibuloaditory dysfunction, including loss of hearing, tinnitus, and vertigo. We report here a case of Cogan’s syndrome positive for antineutrophil cytoplasmic antibody (ANCA). This case is interesting in consideration of the pathogenesis of this syndrome.

CASE REPORT
In May 1999 a 61 year old man was admitted to our hospital with fever and myalgia localised to the lower part of both legs. He had a history of lung tuberculosis at 22 years old, chronic sinusitis at 30, and bilateral otitis media at 53. On admission, laboratory tests showed a white blood cell count of 11.2 x 10^9/l and a CRP level of 63 mg/l. Serum levels of creatine kinase, alanine aminotransferase, and aspartate aminotransferase were normal, and a urinary examination were normal. A serological test was positive for perinuclear ANCA (pANCA) and myeloperoxidase ANCA (MPO-ANCA; 105 EU/ml (normal <10 EU/ml)), but negative for syphils and cytoplasmic ANCA (cANCA). Electromyographic findings were normal. Although the pathological change of vasculitis was not detected in the biopsied muscle, the presence of microscopic polyangiitis was...
highly suspected based on the high titre of MPO-ANCA. Prednisolone (30 mg/day) was given at once, and after one month the levels of C reactive protein (CRP) and MPO-ANCA decreased to 5 mg/l and 12 EU/ml, respectively, with clinical improvement.

While receiving continuous prednisolone treatment, in August 2000, the patient suddenly developed severe frontotemporal headache and vertigo. The CRP level increased to 43 mg/l. Two weeks later, complete hearing loss of his left ear developed. Immediate administration of betamethasone (10 mg/day) for three days did not improve his hearing.

In January 2001 myalgia and weight loss developed and continued, and the levels of CRP and MPO-ANCA were raised at 68 mg/l and 46 EU/ml, respectively. In February 2001 redness of both eyes due to keratouveitis suddenly occurred, which improved after treatment with corticosteroid eye drops. Cyclophosphamide (50 mg/day) was also given together with betamethasone (1.5 mg/day), and complete clinical and serological remission was obtained (CRP 5 mg/l, MPO-ANCA 10 EU/ml). A diagnosis of Cogan’s syndrome was made based upon the clinical constellation of keratouveitis, sensorineural hearing loss, and suspected systemic vasculitis.

DISCUSSION

Previously, Cheson et al reviewed 53 cases of Cogan’s syndrome; 10/18 vessel or muscle biopsy specimens showed inflammatory vascular changes, of which four were considered to be diagnostic of polyarteritis in large and medium sized arteries. ANCA is widely used as a useful diagnostic marker for small vessel vasculitis, including Wegener’s granulomatosis, microscopic polyangiitis, pauci-immune necrotising crescentic glomerulonephritis, and Churg-Strauss syndrome, although this test is occasionally positive in various other conditions. Recently, it has been reported that the combination of immunoassays for anti-MPO and indirect immunofluorescence for pANCA is highly specific for the diagnosis of systemic vasculitis. Until now, five cases of Cogan’s syndrome associated with ANCA have been reported, including ours, and two of them also showed ANCA related glomerulonephritis. In our case, pANCA and MPO-ANCA were positive, and audiovestibular abnormalities and keratouveitis were present, but other manifestations of systemic vasculitis were not noted. We speculate, therefore, that all sizes of arteries may be affected in Cogan’s syndrome.

The cause of Cogan’s syndrome is still unknown. Interestingly, upper respiratory tract infections have been reported to precede the onset of Cogan’s syndrome in 40% of cases, suggesting that one of the triggering factors may be upper respiratory infection. Our patient also had a history of upper respiratory infection. The research group in the National Institute of Health found that patients with Cogan’s syndrome had sig-

supported by seroepidemiological studies. It is suggested that the bacteria adhere to endothelial cells, because Chlamydia pneumoniae is detected in atherosclerotic plaques by both polymerase chain reaction and culture. In our case, the IgG titre to Chlamydia pneumoniae was negative, but the IgA titre was positive (2.23, cut off point 0.9). We suggest that the IgG titre might have been negative in our case because the titre was measured several months after treatment with corticosteroid and cyclophosphamide.

This case suggests a possibility that antinuclear antibodies are related to the pathogenesis of Cogan’s syndrome, although further studies are required to confirm this hypothesis.

REFERENCES

CASE REPORT

A 51 year old factory worker presented with a two year history of pain and swelling of the right index and middle finger metacarpophalangeal (MCP) joints. He had no significant past medical history and there was no family history of arthritis. Examination showed bony deformity and diminished range of movement at the right index and middle MCP joints. The left hand and other joints were normal. There were no abnormalities on examination of his cardiovascular system or abdomen.

His job in a car assembly factory for the previous 10 years had involved lifting mesh car components from a container using only his right hand, and he estimated that he would carry out this manoeuvre about 4000 times in a day.

Radiographs of his right hand showed joint space narrowing and osteophytes at the right second and third MCPs (fig 1A). The left hand was radiologically normal (fig 1B).

His rheumatoid factor, blood count, and erythrocyte sedimentation rate were negative/normal. Serum alkaline phosphatase was 150 U/l (normal 30–130). Fasting glucose was 5.8 mmol/l. Serum ferritin was 1184 ng/ml (normal 20–350) with a serum iron of 42 µmol/l (normal 14–31) and transferrin saturation 80% (normal 20–30). Genetic studies showed him to be homozygous for the Cys282 Tyr mutation, the genotype found in over 90% of patients with haemochromatosis in the UK. He was diagnosed with haemochromatosis and treated by venesection.

His family members have been screened for the condition. One son aged 29 years has been found to have a transferrin saturation of 60%. Ferritin level is normal. Genetic testing has been carried out and shown him to be a compound heterozygote with Cys282 Tyr and His 63 Asp mutations, a genotype associated with haemochromatosis in 20% of cases. He is at present being kept under surveillance.

DISCUSSION

There have been reported cases of undiagnosed haemochromatosis presenting as exercise related joint pains in recreational runners with underlying haemochromatosis arthropathy. However, this patient’s unilateral arthritis suggests that minor trauma may interact with genetic haemochromatosis to determine the distribution of joint damage. This is consistent with the observation of Lee et al, who described unilateral arthropathy on the normal side of a patient with haemochromatosis and a hemiparesis.

Whether the course of arthritis is altered by venesection is unclear. However, it is important to make an early diagnosis of haemochromatosis in a patient presenting with arthropathy because venesection may prevent internal organ damage.

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