Successful treatment of severe rheumatoid vasculitis by infliximab

L Unger, M Kayser, H G Nüsslein


Rheumatoid vasculitis (RV) is a severe complication of rheumatoid arthritis (RA), which like a primary necrotising vasculitis can affect any organ but characteristically presents with painful cutaneous ulcers and systemic inflammation.1,2 Usually patients with refractory RA are affected who, therefore, had already undergone extensive immunosuppressive treatment. The prognosis is poor and most patients die from infectious complications, cardiac failure, or cerebral insult.3–6 Cyclophosphamide (CYC) is the preferred treatment but is often not well tolerated and does not contain the synovitis.3 We report the cases of three patients with RV who could not sufficiently be treated by CYC and steroids but responded very well to infliximab infusion therapy.

CASE REPORTS

Case 1

A 48 year old male patient with longlasting RA was admitted because of general malaise, dyspnoea, oedema, pleural and pericardial effusions, increased creatinine and liver enzymes, leucocytopenia, thrombocytopenia, decreased C4 and CH50, and increased levels of circulating immune complexes. The diagnosis of RV was established. The patient’s condition did not sufficiently improve after treatment with steroid pulses, high dose CYC, or even plasmapheresis. He developed a life threatening heart failure caused by a “swinging heart” due to the pericardial effusion, which required immediate and repeated drainage (fig 1). As a last resort we decided to start infliximab treatment at 3 mg/kg. After the first infusion his condition improved rapidly and the pericardial effusion, in particular, disappeared within two weeks. All laboratory findings returned to normal. He continues to receive infliximab every eight weeks and is in good clinical condition. Even the activity of his RA, previously not sufficiently controlled by methotrexate alone, has decreased significantly.

Case 2

A 60 year old woman with a history of aggressive seropositive RA for 36 years suddenly developed painful ulcers on her left leg. The diagnosis of RV was established by biopsy from the ulcer rim. CYC bolus therapy was started and steroids also had to be increased. She responded partially to CYC, but the ulcers did not heal completely. Because of infections and leucopenia the dose and interval of the infusions often had to be adjusted. After 17 boli within 22 months the CYC therapy was stopped because of severe leucopenia. The lesions worsened after an ineffective trial of cyclosporin A (fig 2A). Infliximab was given at 3 mg /kg in weeks 0, 2, and 6 and thereafter every eight weeks. After the first infusion his condition improved rapidly and the pericardial effusion, in particular, disappeared within two weeks. All laboratory findings returned to normal. He continues to receive infliximab every eight weeks and is in good clinical condition. Even the activity of his RA, previously not sufficiently controlled by methotrexate alone, has decreased significantly.
Low dose methotrexate osteopathy in a patient with polyarticular juvenile idiopathic arthritis

M Rudler, J Pouchot, F Paycha, S Gentelle, A Grasland, P Vinceneux

Low dose methotrexate (MTX) is widely used in the treatment of rheumatoid arthritis (RA) and various rheumatic disorders, including juvenile idiopathic arthritis (JIA). MTX is a folate antagonist, and its main adverse effects, which include haematological and hepatic toxicities, are well known. Used in high dosages in paediatric oncology, MTX has been associated with an osteopathy which is characterised by bone pain, osteoporosis, and insufficiency fractures of the legs. The occurrence of MTX osteopathy in patients treated with low dose MTX has been reported but is still debated.

CASE REPORT
A 36 year old woman presented with severe polyarthralgias lasting for the past two months. She had a 27 year history of polyarticular type JIA, and had received prednisone up to 10 mg/day for the past 25 years. She had no history of osteoporotic or insufficiency fractures. Physical examination showed multiple synovitis of hands, wrists, knees, and ankles. Laboratory investigations showed a slight increase of C reactive protein of 7.5 mg (weight 56 kg, height 156 cm, albumin 42 g/l, serum creatinine 60 µmol/l).

In the absence of significant improvement, two months later, the weekly dose of MTX was increased to 10 mg. One month later, while she had a persistent active polyarthritis, and after having received a cumulative dose of 97.5 mg of MTX, she complained of sudden and spontaneous onset of right groin pain that was relieved by rest. Standard radiographs showed a fracture of both inferior and superior right pubic ramus. Serum calcium and 25-hydroxycholecalciferol levels were normal. Pain resolved with rest in a few weeks. Treatment with MTX was maintained.

Two months later, the patient presented with bilateral leg pain increased by weight bearing and relieved by rest. At that time, the received cumulative dose of MTX was 137.5 mg. Standard radiographs were normal but bone scanning with technetium-99m disclosed multiple areas of increased uptake (superior and inferior right pubic ramus, pubic symphysis, left hip, bilateral femoral condyles, right calcaneum) characteristic of multiple new insufficiency fractures (fig 1). MTX osteopathy was suspected and the treatment was discontinued.

DISCUSSION
MTX osteopathy was initially reported in children with acute leukaemia treated with a high dose of MTX. Patients present with severe leg pain, osteopenia, and insufficiency fractures. Several reports have also suggested that the occurrence of spontaneous insufficiency fractures is more common than expected in patients with inflammatory rheumatism treated with low dose MTX. The effect of MTX on bone mineral density has been rarely studied. In patients with RA, low dose MTX treatment was not associated with increased bone loss in the lumbar spine or the femoral neck at three years. However, among the patients who were also receiving prednisone (≥5 mg/day), MTX use was associated with greater bone loss.

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in the lumbar spine, suggesting that the addition of MTX to prednisone may cause more bone loss than would be expected from corticosteroid treatment alone. Recently, Uehara et al have shown in vitro that MTX impairs bone formation by inhibiting the differentiation of osteoblast precursors.

More on anticardiolipin and anti-β₂ glycoprotein I in systemic sclerosis

C M Antonioli, E Danieli, P Airò, R Cattaneo, A Tincani

Patients with systemic sclerosis (SSc) may have arterial and venous thrombosis and, according to the limited and controversial data available, may have an increased incidence of pregnancy losses. These observations preceded the definition of antiphospholipid syndrome (APS) as the association of thrombosis and pregnancy loss with anti-phospholipid antibodies (aPL), and did not focus on patients with SSc. However, the association of thrombosis and aPL detected as lupus anticoagulant (LAC) and/or anticardiolipin antibodies (aCL), although rare, was described in SSc, supporting the possible existence of a “secondary” APS in SSc.

In view of the fact that most aCL are directed to β₂ glycoprotein I (αβ₂GPI), the possibility that patients with APS may be negative for aCL, but positive for αβ₂GPI, and considering the scarcity of data examining this issue in SSc, we read with great interest the recent study by Schoenroth et al, who examined the frequency of αβ₂GPI in SSc. The authors found IgM αβ₂GPI in 2/26 (8%) patients and IgG in none. This finding did not seem to be related to any clinical or laboratory features. In another report, 80 patients with SSc were studied using an enzyme linked immunosorbent assay (ELISA) detecting the complex cardiolipin/β₂GPI. A similar prevalence of aCL/β₂GPI (10% IgG and 6% IgM), was found and a significant correlation between the presence of aCL/β₂GPI IgG and isolated pulmonary hypertension.

In patients with inflammatory arthritis receiving corticosteroids, MTX treatment should be considered as an additional risk factor for stress fractures. As far as we know this is the first reported case of MTX osteopathy in a patient with JIA. Rheumatologists should be aware of this complication as it may be easily confused with synovitis. Involvement of the leg articular or periarticular area should raise diagnostic clinical awareness. A bone scan is particularly useful for the diagnosis.

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with pulmonary hypertension. Anti-
was significantly associated with a history of thrombosis and
(p=0.02). According to the Sapporo criteria
and pulmonary hypertension were significantly related
\chi^2\text{es}: one was aCL
had a significant history of pregnancy loss without thrombo-
conditions, none of these conditions was found in this patient.
Although these events can be related to other thrombophilic
specific, but allowed the identification of a woman with deep
thromboses: two were aCL+
patients had “primary” (that is, not secondary to lung fibrosis)
whereas the other one was aCL+ and LAC+, but a
defined as having “aCL
β−2GPI+,
β−2GPI+, but two were aCL+
β−2GPI+,
β−2GPI+; aCL and anamnestic thrombosis were signifi-
cantly related (p<0.01; \chi^2\text{ with Yates’s correction). Two patients had “primary” (that is, not secondary to lung fibrosis)
(p=0.02). According to the Sapporo criteria\textsuperscript{6} three patients had a significant history of pregnancy loss without thrombo-
se: one was aCL− aβ−2GPI+, but two were aCL− aβ−2GPI−.
In our experience, the presence of aCL in patients with SSc was significantly associated with a history of thrombosis and with pulmonary hypertension. Anti-β−2GPI seemed to be less specific, but allowed the identification of a woman with deep vein thrombosis, two miscarriages, and livedo reticularis. Although these events can be related to other thrombophilic conditions, none of these conditions was found in this patient. The association with aβ−2GPI suggests that she might be defined as having “aCL− aβ−2GPI + APS” or “equivocal APS”.\textsuperscript{5

In conclusion, in patients with SSc and APS related
symptoms, the evaluation of aβ−2GPI can help to define the
clinical picture and the specific treatment required.

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\end{itemize}

Table 1 Clinical and laboratory features of 18 patients with SSc aCL+ and/or aβ−2GPI+

<table>
<thead>
<tr>
<th>Sex, age, subset of SSc</th>
<th>aβ−2GPI*</th>
<th>aCL*</th>
<th>IgG (OD)</th>
<th>IgM (OD)</th>
<th>IgG (GPL)</th>
<th>IgM (MPL)</th>
<th>Pregnancy loss</th>
<th>Other clinical and laboratory features</th>
<th>Antithrombotic treatment</th>
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<tr>
<td>F, 37, I</td>
<td>1.68</td>
<td>0.36</td>
<td>67</td>
<td>35</td>
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<td>No</td>
<td>No</td>
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<td>Aspirin</td>
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<tr>
<td>F, 55, d</td>
<td>0.38</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>F, 57, I</td>
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<td>DVT</td>
<td>Neg</td>
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<td>No</td>
<td>No</td>
<td>Livedo reticularis, LAC−</td>
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<td>Neg</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>PBC, LAC−</td>
<td>Aspirin</td>
</tr>
<tr>
<td>F, 54, I</td>
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<td>Neg</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Overlap PM/SLE, LAC−</td>
<td>Aspirin</td>
</tr>
<tr>
<td>F, 64, I</td>
<td>0.58</td>
<td>Neg</td>
<td>Neg</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>LAC−</td>
<td>Aspirin</td>
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<tr>
<td>M, 65, I</td>
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<td>Subclavian artery</td>
<td>15</td>
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<td>No</td>
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</tr>
<tr>
<td>F, 60, I</td>
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<td>Neg</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>Aspirin</td>
</tr>
<tr>
<td>F, 65, I</td>
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<td>Neg</td>
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<td>No</td>
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<td>Aspirin</td>
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<tr>
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<td>Neg</td>
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<tr>
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</tr>
</tbody>
</table>

*Normal values: aβ−2GPI IgG <0.13, IgM <0.28; aCL IgG <10, IgM <10. SLE, systemic lupus erythematosus; LAC, lupus anticoagulant; DVT, deep vein thrombosis; PBC, primary biliary cirrhosis; PM, polymyositis.

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