LETTERS

Weight loss with purpura and pain at the distal femora
K F Haegele, N J Buechner, C A Stueckle, L C Rump, S M Weiner

Paraneoplastic syndromes may occur as the first clinical symptom at an early stage of malignant diseases in about 7–10% of cases.1 As presented here, intensive investigations may be necessary to uncover an early curable tumour.

CASE REPORT
A 72 year old man presented with multiple purpuric and necrotising skin eruptions (sized 2–20 mm) covering mainly the extremities and, to a lesser extent, the trunk. He had noticed a weight loss of 12 kg in the past 2 months. There was a history of smoking with chronic obstructive pulmonary disease and partial colectomy because of a benign adenoma. Laboratory investigations showed a normal erythrocyte sedimentation rate (9 mm/1st h), but C reactive protein was raised (43 mg/l). Serological markers, such as antinuclear antibodies, antineutrophil cytoplasmic antibodies, cryoglobulins, and hepatitis B and hepatitis C were excluded. A diagnostic procedure was performed to exclude a neoplasm, but, chest radiography, abdominal ultrasonography, gastroscopy, and colonoscopy were normal. Prednisone was

Figure 1  (A) Musculoskeletal ultrasound demonstrated an echogenic irregular focus above the surface of the distal femoral bone with distal acoustic shadowing (longitudinal scan). (B) Plain radiography of the right femur disclosed smooth, lamellated periosteal new bone formation, consistent with hypertrophic osteoarthropathy. (C) A bone scan showed irregular increased uptake involving the distal femur bilaterally. (D) Computed tomography of the chest showed a small mass at the right lung.
complete remission of bone pain and vasculitis without evaluation 6 months after excision of the tumour showed a thoracic surgeon and the tumour was excised. Re-
puncture showed a highly differentiated adenocarcinoma of the lung. No metastasis was seen. The patient was referred to the lung was performed. A suspect lesion of 1.9 cm in diameter in the right lung was seen (fig 1D). A transthoracic standard chest radiographs a computed tomographic scan of the lung shows no pathological findings. Tomography of the lung should be performed in the presence of unexplained vasculitis or periostitis, or both, even if standard chest radiography of the lung shows no pathological findings.

Even though there was no sign of a tumour on the chest radiographs a computed tomographic scan of the lung was performed. A suspect lesion of 1.9 cm in diameter in the right lung was seen (fig 1D). A transthoracic puncture showed a highly differentiated adenocarcinoma of the lung. No metastasis was seen. The patient was referred to a thoracic surgeon and the tumour was excised. Re-
evaluation 6 months after excision of the tumour showed complete remission of bone pain and vasculitis without immunosuppressive treatment.

**DISCUSSION**

Our patient presented with two paraneoplastic syndromes: hypertrophic osteoarthropathy and cutaneous vasculitis.

Hypertrophic osteoarthropathy is most commonly seen in Pierre-Marie-Bamberger’s syndrome. This syndrome is characterised by the concurrence of clubbed fingers, arthralgia, and painful periostitis of the extremities, and occurs in pulmonary, cardiac, hepatic, or intestinal diseases.1 Rarely, periostitis may be the only manifestation of Pierre-Marie-Bamberger’s syndrome as in our patient. The periostitis is the result of subperiosteal bone formation, occurring mainly on the distal diaphysis of the long bones. Effusions into the large joints with little inflammatory cell exudation are a frequent finding. The diagnosis of periostitis is usually made by radiography and by bone scan. As we showed, musculo-
skeletal ultrasound may also visualise periostitis, but it is needed especially to look for periostial lesions far from the adjacent joints. Table 1 presents other conditions associated with periostitis.

Non-small lung cell cancer is the most common malignancy associated with both Pierre-Marie-Bamberger’s syndrome and cutaneous vasculitis.2,3 However, hypertrophic osteoarthropathy is more common (4.9% in one study) than paraneoplastic vasculitis in patients with lung cancer.4–7 Differential diagnosis includes polyarteritis nodosa and systemic lupus erythematosus; both have been associated with periostial reactions and vasculitis in anecdotal reports.8–10 However, as demonstrated by our case, computed tomography of the lung should be performed in the presence of unexplained vasculitis or periostitis, or both, even if

<table>
<thead>
<tr>
<th>Diseases associated with periostitis</th>
<th>Predominant location of periostitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophic osteoarthropathy</td>
<td>Distal diaphysis of long bones and metacarpal joints</td>
</tr>
<tr>
<td>Psoriatic onycho-pachydermoperiostitis</td>
<td>Terminal phalanx</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Phalanges of fingers and toes</td>
</tr>
<tr>
<td>Reiter’s syndrome</td>
<td>Phalanges of fingers and toes</td>
</tr>
<tr>
<td>Athletic overuse (running, jumping)</td>
<td>Upper and lower extremities</td>
</tr>
<tr>
<td>Osseous fasciitis</td>
<td>Variable</td>
</tr>
<tr>
<td>Periostitis ossificans</td>
<td>Variable</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Lower extremities</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Variable</td>
</tr>
<tr>
<td>Facial infections</td>
<td>Mandibule, orbita</td>
</tr>
<tr>
<td>Florid reactive periostitis</td>
<td>Phalanges of hands and feet</td>
</tr>
<tr>
<td>Osteoblastoma</td>
<td>Variable</td>
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<tr>
<td>Bizarre parosteal</td>
<td>Bones of the hands and feet</td>
</tr>
<tr>
<td>osteochondromatous proliferation</td>
<td>(Nora’s tumour)</td>
</tr>
<tr>
<td>Chondroosarcoma</td>
<td>Variable</td>
</tr>
<tr>
<td>Treatment with interleukin 11</td>
<td>Cleavage, long bones</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Variable</td>
</tr>
<tr>
<td>Chronic leg ulcers</td>
<td>Tibia</td>
</tr>
<tr>
<td>SAPHO syndrome</td>
<td>Variable</td>
</tr>
</tbody>
</table>

**Table 1** Differential diagnosis of periostitis

**REFERENCES**


Authors’ affiliations
K F Haegaele, N J Buechner, L C Rump, S M Weiner, Medizinische Klinik I, Marienhospital, Klinikum der Ruhr-Universität Bochum, Herne, Germany
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Long term infliximab treatment for severe psoriatic arthritis: evidence of sustained clinical and radiographic response

F Rinaldi, G Provenzano, A Termini, M Spinello, F La Seta


Psoriatic arthritis (PsA) affects about 30% of patients with psoriasis and is a chronic inflammatory rheumatic disease, with the development of erosive and deforming arthritis in about 40% of patients.1 Tumour necrosis factor α (TNFα) has an established role in the pathogenesis of PsA, and the TNFα receptor blocker etanercept has been approved for its treatment.2

There are also encouraging data about the efficacy of infliximab,3–5 but its long term efficacy and safety in PsA have been questioned.6

METHODS AND RESULTS

We evaluated in an open label, 2 year study the safety and efficacy of infliximab in association with methotrexate for patients with severe PsA. This study was an extension protocol of an initial 6 month study.7

Four men and eight women with PsA and active disease despite treatment with methotrexate + steroid + non-steroidal anti-inflammatory drugs had been enrolled and treated with five infusions of infliximab (Remicade, Centocor) at a dose of 5 mg/kg at weeks 0, 2, 6, 14, and 22. Thereafter the patients continued treatment with 5 mg/kg every 6 or 8 weeks for up to 2 years.

The patients had a mean (SD) age of 48.4 (13.6) years and a mean duration of articular symptoms of 8.6 (5.6) years. Eleven of the 12 patients had a polyarticular pattern of disease with predominantly peripheral arthritis. Two patients had been withdrawn from the study before the fifth infusion owing to the occurrence of severe diseases and another patient had to stop infliximab after the seventh infusion owing to a lymphadenitis due to cytomegalovirus. Nine patients continued infliximab treatment for up to 2 years.

The following outcome measures were evaluated: patient evaluation of global health status (100 mm visual analogue scale (VAS)); patient global assessment of disease activity (100 mm VAS); patient assessment of pain (100 mm VAS); Health Assessment Questionnaire (HAQ) scores; physician global assessment of disease activity (100 mm VAS); swollen joint count; tender joint count; erythrocyte sedimentation rate (ESR); C reactive protein level (CRP); Psoriasis Area and Severity Index (PASI).

The American College of Rheumatology (ACR) improvement criteria for rheumatoid arthritis with 20%, 50%, and 70% improvement were also assessed.

Radiographs of the hands and wrists were obtained at baseline and at 2 years for the patients with peripheral polyarthritis completing 2 years of infliximab treatment and were scored according to the modified Sharp’s method.8 At week 26 a significant decrease (p<0.05, by t test for paired data) had been seen for all variables, with the exception of ESR. At 1 and 2 years a significant decrease was maintained for all the outcome measures, with the persisting exception of ESR (table 1). Seven patients had received infliximab every 8 weeks, two of them every 6 weeks owing to a partial loss of efficacy.

At 1 year, 8/9 (89%) patients met the ACR20 and 6/9 (67%) patients the ACR70. At 2 years 9/9 (100%) patients met the ACR20 and 5/9 (56%) patients the ACR70.

Eight of nine patients completing 2 years of infliximab treatment had a predominantly peripheral polyarthritis. In these eight patients we did not observe a significant increase of radiographic Sharp’s score from baseline (table 2). In 5/8 (63%) patients we did not see any increase in Sharp’s score at the end of 2 years of infliximab treatment.

DISCUSSION

Our data suggest that long term treatment with infliximab may be highly effective for patients with severe PsA. These results are in partial contrast with those from another observational study,7 but similar to other recent observations.9 TNFα neutralising agents are being used by an increasing number of patients with PsA and the Italian Society of Rheumatology has recently published specific guidelines for their appropriate use.10

PsA is a heterogeneous disease and we need larger studies and more data to better select patients with PsA who may benefit from anti-TNFα treatment.

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**Table 1** Outcome measures at baseline, week 26, years 1 and 2. Values are given as mean (SD)

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Baseline (12 patients)</th>
<th>Week 26 (10 patients)</th>
<th>Year 1 (9 patients)</th>
<th>Year 2 (9 patients)</th>
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</thead>
<tbody>
<tr>
<td>Patient health status</td>
<td>28.3 (22.1)</td>
<td>63.0 (23.6)*</td>
<td>77.2 (10.9)*</td>
<td>77.8 (13.9)*</td>
</tr>
<tr>
<td>Patient pain</td>
<td>84.2 (17.3)</td>
<td>33.0 (27.1)*</td>
<td>33.3 (29.6)</td>
<td>27.6 (20.6)*</td>
</tr>
<tr>
<td>Patient disease activity</td>
<td>82.5 (18.6)</td>
<td>28.0 (16.2)*</td>
<td>27.8 (27.7)*</td>
<td>25.5 (16.7)*</td>
</tr>
<tr>
<td>HAQ score</td>
<td>2.0 (0.6)</td>
<td>0.9 (1.1)*</td>
<td>0.6 (0.0)*</td>
<td>0.6 (0.6)*</td>
</tr>
<tr>
<td>Physician disease activity</td>
<td>74.2 (14.4)</td>
<td>27.0 (17.0)*</td>
<td>22.2 (19.9)</td>
<td>23.3 (15.5)*</td>
</tr>
<tr>
<td>Tender joint count</td>
<td>31.7 (22.9)</td>
<td>9.6 (12.7)*</td>
<td>10.1 (12.0)*</td>
<td>3.7 (4.4)*</td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>9.9 (6.6)</td>
<td>2.3 (4.6)*</td>
<td>1.9 (4.3)*</td>
<td>0.5 (1.1)*</td>
</tr>
<tr>
<td>ESR (mm/1st h)</td>
<td>21.6 (15.5)</td>
<td>20.2 (20.4)</td>
<td>14.3 (10.8)</td>
<td>21.1 (16.9)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>0.9 (0.9)</td>
<td>0.2 (0.4)*</td>
<td>0.2 (0.5)*</td>
<td>0.3 (0.5)*</td>
</tr>
</tbody>
</table>

*p<0.05 as compared with baseline (determined by t test for paired data)
Topical tacrolimus treatment in a patient with dermatomyositis

C E Lampropoulos, D P D’ Cruz


Dermatomyositis is an idiopathic inflammatory process manifested by proximal muscle weakness and cutaneous lesions such as Gottron’s sign, heliotrope rash, erythematous photosensitive rash, or periungual erythema. Other unusual cutaneous manifestations are ichthyosis, panniculitis, erythroderma, lichen planus, vesicle and bullae emissions of the lamps. In 2002, MTX was discontinued as it was no response and HCQ was discontinued. The extensive cutaneous lesions were temporarily relieved with oral prednisolone. The photosensitive rash worsened after exposure to fluorescent lamps, and monochromator light testing showed a marked papular reaction and sensitivity to the emissions of the lamps. In 2002, MTX was discontinued as it had had no efficacy on the skin lesions.

One year later she had a severe flare of her skin disease over the face, arms, and upper chest without any proximal weakness. Tacrolimus ointment 0.1% was suggested as an alternative treatment and with her informed consent she started applying it twice a day over the affected areas. Four weeks later there was a good response of the skin rashes, except for the proximal myopathy. Tacrolimus ointment was restarted and the lesions improved. To date, her cutaneous lesions remain in remission with continuous use of the ointment.

DISCUSSION

Tacrolimus—isolated in 1984 from the fungus Streptomyces tsukubaensis—is a macrolide immunomodulator FK506, which acts on T lymphocytes and inhibits interleukin 2 transcription as well as other cytokines. Since 1989 it has been widely used in preventing graft rejection after transplantation (liver, kidneys, lungs). In 2000 tacrolimus ointment was approved for the treatment of atopic dermatitis. Efficacy is similar or even better than corticosteroids (especially in children or for facial lesions, where only weak steroids can be used), without
the adverse effects of skin atrophy (no impairment of collagen synthesis) and serious systemic absorption. Common side effects are burning sensations, itching, or erythema, which usually decline as treatment is continued owing to improvement of the skin’s condition. Tacrolimus also seems to be effective in resistant cutaneous lesions of other diseases such as psoriasis, localised scleroderma, chronic actinic dermatitis, pyoderma gangrenosum, Behçet’s disease, lichen planus, rheumatoid ulcers, and steroid rosacea.

To date, there are a few case reports and a pilot study suggesting good therapeutic efficacy of tacrolimus ointment in connective tissue diseases like dermatomyositis. Our patient’s cutaneous lesions, which had been refractory to any previous treatment, seemed to respond well. These results suggest that tacrolimus ointment could be considered as an alternative treatment for resistant cutaneous lesions in dermatomyositis.

References

Currently, little information is available about the interaction between anti-tumour necrosis factor (TNF) treatment and surgery.1

In an attempt to evaluate the relative safety of anti-TNF and its impact on the course of disease in patients with rheumatoid arthritis (RA) undergoing surgery, we included in a retrospective study all such patients followed up in a regional network. The network allows close follow up as the patients regularly renew their prescription at the hospital. Surgical outcomes focused on infection and other complications together with the postoperative impact on RA disease activity. A flare of RA was defined as an increase in the joint count and global assessment of >20%. Fifty surgical procedures were recorded in 30 patients with RA (25 women), with a mean age of 54.6 years, a mean disease duration of 12.3 years, and a mean of 3.7 previous disease modifying antirheumatic drugs. In 38 cases, anti-TNF was associated with a disease modifying antirheumatic drug (methotrexate 33 cases) and with general steroid treatment in 41/50 patients receiving a mean of 8.2 mg/day of prednisone. The TNF blocker at the time of surgery was infliximab (n = 26), etanercept (n = 13), adalimumab (n = 11), with a mean exposure to an anti-TNF agent of 12.1 months (range 1–42). Discontinuation of the anti-TNF agent occurred before surgery in 18/50 patients, and for the rest, surgery was performed between two anti-TNF injections.

Table 1 summarises the type of surgery; the mean follow up after surgery was 14 months (range 1–42). No major complications, especially infections, occurred in either group whether the anti-TNF agent was discontinued or not. Three cases (6%) of minor postoperative side effects were recorded (delay of wound healing of 1–2 weeks). Six cases (12%) of moderate short lasting RA flares were reported occurring with each TNF blocker, in orthopaedic surgery, and significantly associated with anti-TNF interruption before surgery (5 interruptions/6 cases of flare versus 13 interruptions/44 surgical procedures without flare; Fisher’s exact p value = 0.02).

In this group of patients with classic RA receiving an anti-TNF agent, the main result was the absence of a major complication after surgery, particularly pyogenic infection.2,1 Methotrexate does not seem to have deleterious impact upon surgical outcome in RA.4

In Crohn’s disease, Marchal et al found no significant differences in postoperative early minor or major complications or in duration of hospitalisation between infliximab exposed and infliximab naïve patients.5 In RA, Bibbo and Goldberg found similar rates of complications in both groups (16 patients receiving an anti-TNF agent compared with 15 matched anti-TNF naïve patients) in foot and ankle surgery.6

In our study the overall rate of complication is lower than reported in large studies of anti-TNFα treatment, irrespective of surgery. For example the percentage of patients developing severe infection is 2% in the ATTRACT study7 (infliximab in RA), 4% in the ACCENT study in Crohn’s disease,8 and up to 18% in some RA cohort studies.9 The retrospective design, the size of our population, the absence of comorbidities and of a control group may represent bias in the present study. Recently, Giles et al reported an increased risk of infection (odds ratio = 5.3) during orthopaedic surgery for patients receiving an anti-TNF agent.10

Our observational study did not find an increased frequency of adverse events related to uninterrupted use of anti-TNF treatment in patients with RA undergoing surgery.

Table 1

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>No of patients</th>
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<tr>
<td>Orthopaedic</td>
<td>39</td>
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<tr>
<td>Foot and ankle</td>
<td>13</td>
</tr>
<tr>
<td>Hand and wrist</td>
<td>11</td>
</tr>
<tr>
<td>Total joint replacement</td>
<td>12</td>
</tr>
<tr>
<td>Hip</td>
<td>4</td>
</tr>
<tr>
<td>Shoulder</td>
<td>3</td>
</tr>
<tr>
<td>Knee</td>
<td>2</td>
</tr>
<tr>
<td>Elbow</td>
<td>1</td>
</tr>
<tr>
<td>Finger</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>3</td>
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<tr>
<td>Non-orthopaedic</td>
<td>11</td>
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<tr>
<td>Head and neck</td>
<td>5</td>
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<tr>
<td>Abdomen</td>
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REFERENCES


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Increase in methotrexate dose in patients with rheumatoid arthritis who have an inadequate response to infliximab

P Ornetti, E Solau, P Gaudin, J Sibilia, J-M Berthelot, X Puechal, C Tavernier, J F Maillefert, on behalf of the “Club Rhumatismes et Inflammation”, from the French Society of Rheumatology

The strategy needed for patients with inadequate response to treatment with infliximab and methotrexate (MTX) is not well defined. It has been suggested that an increase in the infliximab dosage, a shortening of the intervals between infusions, or a switch to another anti-tumour necrosis factor α agent might provide clinical benefit. Another less expensive strategy might be to increase the MTX weekly dose in patients not co-treated with MTX at the maximal dose. This study aimed at evaluating the efficacy of increasing the MTX dose in patients with rheumatoid arthritis (RA) with active disease despite treatment with infliximab and MTX.

METHODS AND RESULTS

Data were obtained from six rheumatology departments that measure the 28 joint count Disease Activity Score (DAS28) before each infliximab infusion. All patients with RA with active disease despite infliximab treatment, because two main hypotheses can be put forward for explanation: (a) the increase in the MTX dose induces a clinical response in a relevant number of patients; (b) the observed response is due to a regression to the mean effect; adjustment in the MTX dose is likely to be proposed when disease activity increases, so the observed improvement in disease activity might have occurred without a change in the MTX dose. Such a hypothesis was recently proposed to explain the improvement observed after infliximab dose escalation.

Table 1 Disease activity before, and at the first (8 weeks) and second (16 weeks) infliximab infusion after MTX dose adjustment

<table>
<thead>
<tr>
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<th>Before adjustment</th>
<th>First infliximab infusion</th>
<th>After adjustment</th>
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</thead>
<tbody>
<tr>
<td>MTX dose (mg/weekly)</td>
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<tr>
<td>DAS28</td>
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<td></td>
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<tr>
<td>Tender joint count</td>
<td></td>
<td></td>
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<tr>
<td>Swollen joint count</td>
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<tr>
<td>ESR (mm/1st h)</td>
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<td>Patient global assessment</td>
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</table>

Results are shown as mean (SD).

**p<0.05; ***p<0.01.

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The T348M mutated form of cryopyrin is associated with defective lipopolysaccharide-induced interleukin 10 production in CINCA syndrome


The term autoinflammatory disease has been proposed to describe a group of disorders characterised by attacks of seemingly unprovoked inflammation without increased levels of autoantibodies or increased numbers of autoreactive T cells. Such inflammatory conditions are often associated with mutations of genes of the pyrin superfamily. For instance, mutations in cryopyrin (CIAS1, NALP3, PYPAF1) have been found in about 50% of patients with CINCA syndrome. These patients are characterised by neonatal onset of cutaneous symptoms, chronic meningitis, and joint manifestations with recurrent fever and inflammation. Despite the description of several mutations within the cryopyrin gene, it remains unclear how the resulting amino acid changes modify the function of this protein and why inflammation develops under these conditions. A recent study demonstrated increased spontaneous interleukin (IL) 1 production by macrophages expressing the R260W mutated form of cryopyrin.

METHODS AND RESULTS
We identified a patient with CINCA syndrome who had a T348M mutation of the cryopyrin gene using genomic DNA extracted from whole blood, as described previously. Because cryopyrin is largely expressed in monocytes and neutrophils, we performed functional in vitro tests using blood leucocytes of this patient (table 1) at three time points: A. medium inflammatory activity (9.59×10⁸ blood neutrophils/l); B. high inflammatory activity (14.950×10⁹/l); and C. low

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41 years</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td>Fever</td>
<td>Periodic</td>
</tr>
<tr>
<td>Rash</td>
<td>Maculopapular</td>
</tr>
<tr>
<td>Arthralgia and arthritis</td>
<td>Transient</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Swelling</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Transient</td>
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<tr>
<td>Pericardial effusion</td>
<td>Transient</td>
</tr>
<tr>
<td>Suffering from abdominal pain and persistent haemorrhagic diarrhoea with increasing age</td>
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</tr>
<tr>
<td>Anemia</td>
<td>Persistent</td>
</tr>
<tr>
<td>No increased levels of autoimmune antibodies</td>
<td></td>
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<tr>
<td>No increased levels of haemorrhagic diarrhoea with increasing age</td>
<td></td>
</tr>
<tr>
<td>Skin histology: cellular infiltrate mainly containing neutrophils</td>
<td></td>
</tr>
<tr>
<td>Cranial MRI: internal hydrocephalus and empty sella</td>
<td></td>
</tr>
<tr>
<td>Lumbar puncture: sterile chronic meningitis</td>
<td></td>
</tr>
<tr>
<td>No growth or mental retardation</td>
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<tr>
<td>Cranial MRI: internal hydrocephalus and empty sella</td>
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<td>Lumbar puncture: sterile chronic meningitis</td>
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<td>No growth or mental retardation</td>
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We then excluded an intrinsic defect of spontaneous neutrophil point C (300 mg infliximab).

Figure 1 T348M cryopyrin-expressing PBMCs generated IL1 but not IL10 upon LPS stimulation. The same cells, however, produced IL10 after PHA stimulation (for culture conditions, see text). The lack of IL10 production after LPS stimulation did not appear to be dependent on the inflammatory condition of the patient (time points A, B, and C, see text). T348M cryopyrin-expressing PBMCs, but not normal PBMCs, generate large amounts of IL1 upon PHA stimulation. The horizontal dashed lines represent the mean cytokine levels generated by normal PBMCs after stimulation with LPS and PHA (n = 4; means (SEM) were as follows: LPS-induced IL1: 666 (142) pg/ml; PHA-induced IL10: 621 (157) pg/ml; LPS-induced IL1: 2108 (521) pg/ml; PHA-induced IL10: 40 (29) pg/ml).

DISCUSSION

As far as we know, this is the first study providing direct evidence that microbial antigens may trigger an abnormal inflammatory response in an autoinflammatory disease. In contrast, a primary defect of apoptosis, which has been suggested in earlier studies, was, at least in T348M cryopyrin-expressing neutrophils, not seen. Additional investigations should be performed to examine the functional consequences of other known mutations in the genes of the pyrin superfamily. Moreover, further work is required to define the exact hierarchy of signalling events after LPS stimulation to define the place of cryopyrin in this pathway, including its distal molecular targets.

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REFERENCES


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Churg-Strauss vasculitis syndrome and leukotriene receptor antagonists

J Ng, R Savage, F McQueen


A 28 year old Middle Eastern woman presented to hospital with shortness of breath and new onset numbness of her foot. Five years previously, in Iraq, she had been diagnosed with severe brittle asthma and sinusitis. After 2 years of management with oral (up to 15 mg prednisone) and inhaled steroid, zafirlukast, a leukotriene receptor antagonist (LRA) was added to her treatment regimen. Despite this, her asthma remained poorly controlled and zafirlukast was stopped after 12 months. Subsequent clinical improvement allowed the prednisone dose to be tapered and then stabilised at 7.5 mg/day. By the time she migrated to New Zealand she had been receiving that dose for 1 year.

At presentation to Auckland City Hospital she was clinically in left ventricular failure with a raised jugular venous pressure. Neurological examination disclosed features of a common peroneal nerve palsy, presumed to be a manifestation of mononeuritis multiplex. Investigations showed a leucocytosis with extreme eosinophilia (white cell count $28.3 \times 10^9/l$, eosinophils $13.3 \times 10^9/l$) and erythrocyte sedimentation rate of 40 mm/1st h. Renal function and liver function were normal. Troponin T was raised at 0.64 µg/l (normal $<0.03$ µg/l), indicating myocardial injury. She was antineutrophil cytoplasmic antibody and antinuclear antibody negative. There was moderate left ventricular impairment on echocardiogram, with an ejection fraction of 45% and a small pericardial effusion. Chest radiography showed cardiomegaly and a fine nodular pattern at the lung bases, which resolved after starting treatment. Attempts to confirm vasculitis on sural nerve and muscle biopsies were unsuccessful.

This patient fulfilled American College of Rheumatology criteria for a diagnosis of Churg-Strauss syndrome (CSS). As there was evidence of cardiac injury, she scored 1 on the five factors score. 2

She was treated with prednisone initially at 1 mg/kg (later tapered to 15 mg/day) and given monthly pulse cyclophosphamide at 0.5 mg/m², to continue for 12 months according to the protocol proposed by Guillevin and Pagnoux. 3 She has responded well symptomatically with normalisation of the eosinophil count and erythrocyte sedimentation rate. On echocardiography, the ejection fraction remains unchanged but the pericardial effusion has resolved.

DISCUSSION

Our patient’s experience raises several interesting points. To our knowledge, this is the first case reported in Australasia of CSS occurring in a patient who had received LRA treatment. A possible causal association between the use of zafirlukast and CSS was first suggested in 1998. 4 The New Zealand Intensive Medicines Monitoring Programme has prospectively monitored adverse events in 1535 patients who received prescriptions for montelukast from 1999 to the present. 5 Forty three adverse events were considered associated with montelukast, but these did not include CSS or related features. The annual incidence of CSS in patients with asthma has been estimated at 64.4 per million patients. 6 Thus, any link between montelukast and CSS may not have been detected owing to the small size of the cohort as LRA have not been widely used in New Zealand.

In most reports of CSS occurring in patients receiving LRA, extrapulmonary vasculitic features have developed after steroid reduction. 7 8 It has been proposed that this may be because vasculitis has been “unmasked” by reduction of previously suppressive doses of steroid. 9 This would not apply in our patient as she developed features of CSS after receiving a stable dose of 7.5 mg of prednisone for 12 months.

Other explanations for the association between treatment with an LRA and CSS in this patient include the possibility that zafirlukast has an immunomodulatory role in promoting the development of vasculitis directly (albeit some time later), as has been suggested by Guilpain et al. 9 Alternatively, the association may have been purely coincidental, and the fact that zafirlukast was stopped 18 months before presentation with CSS makes it harder to implicate the drug in disease pathogenesis in this case.

REFERENCES

A major subset of patients with ankylosing spondylitis followed up in tertiary clinical care require anti-tumour necrosis factor α biological treatments according to the current guidelines

M Temel, P Atagündüz, H Direskeneli


therapeutic options for severe ankylosing spondylitis (AS) have been limited to non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and to some traditional disease modifying drugs (DMARDs) such as sulfasalazine and methotrexate. In view of open label and controlled trials of treatment with a monoclonal chimeric tumour necrosis factor (TNF) α antibody (infliximab), and with recombinant human TNF receptor (etanercept), the need for more effective second line treatments in AS seems to be met.1–4

In this study we aimed at determining the proportion of patients with active AS, despite treatment with NSAIDs and second line treatments (sulfasalazine, methotrexate), using current guidelines for anti-TNF treatment in a tertiary clinical care.

METHODS AND RESULTS

Study patients were selected according to the Modified New York criteria. ASAS and SPARTAN guidelines for biological treatments of AS were used.3 4 Ninety three patients with AS (M/F = 46/47, mean (SD) age 39.5 (11.5) years, mean (SD) disease duration 13.7 (10.5) years) were screened. The University of Marmara Institutional review board approved the study and informed consent was given by the study patients.

Eighty patients (86%) were receiving NSAIDs: 67/93 (72%) sulfasalazine and 32/93 (34%) methotrexate. Disease duration, age, disease activity defined by the Bath AS Disease Activity Index (BASDAI), and drugs used did not differ significantly between male and female patients. Of the 93 patients, 32 (34%; M/F = 17/15) and 37 patients (40%; M/F = 18/19) were defined as having active AS according to SPARTAN and ASAS guidelines, respectively.

Although high mean C reactive protein (CRP) values are considered critical in defining active AS, the higher mean CRP values detected in the male patients (male v female mean CRP, 259 v 69 mg/l, p = 0.054) did not correlate with the ratio of men and women considered to have active AS (ASAS = 18M/19F, SPARTAN = 17M/15F). Higher CRP values in this group correlated negatively with the use of sulfasalazine (r = −0.764, p = 0.05).

DISCUSSION

Our study showed that a significant number of patients had active AS (34–40%) in our patient tertiary care clinic. A recent study reflects the same need for effective treatment in AS, though that study had a higher proportion of patients with active AS (65%).3 In that study, NSAIDs were used as the first line treatment option and use of sulfasalazine and methotrexate was limited. We used combined methotrexate with sulfasalazine for persistent peripheral arthritis, which might have had modifying effects on disease activity in our study group, despite a lack of evidence that conventional DMARDs alter the course of established axial disease, and might explain the differences between the two studies.

According to current diagnostic criteria, patients with AS must have x ray changes for the diagnosis, which take months to years to establish. Two separate studies from Europe emphasise that a substantial period of active disease was already present before the diagnosis.4 5 As we now know, treatment with biological agents improves the signs and symptoms of axial disease in AS where traditional DMARDs fail.1 4 Starting DMARDs at an earlier stage of AS after the diagnosis might provide a chance to assess the effect of conventional treatment in patients with shorter disease duration and enable use of anti-TNF treatment for patients with refractory disease before the radiographic signs of established disease occur.

In a similar study of rheumatoid arthritis6 the eligibility of patients receiving routine care to receive treatment with TNFα agents, according to the inclusion criteria of the studies for biological agents, was also low (prevalence of 8%). However, current criteria for defining patients with active AS eligible for anti-TNF treatment, and patient selection criteria of major clinical trials with biological agents, do parallel each other, suggesting that current guidelines for selecting patients with active AS are suitable for routine clinical care.

In conclusion, a significant subset of the patients with AS followed up in our tertiary care clinic require more effective treatment according to current guidelines despite intensive conventional second line treatment.

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REFERENCES


Colchicine responsive periodic fever syndrome associated with pyrin I591T


FAmiliar Mediterranean fever (FMF) is a recessively inherited disorder characterised by recurrent attacks of fever and serositis that usually begin in childhood, last for fewer than 3 days, and which can largely be prevented by colchicine prophylaxis. Identification of the gene associated with FMF, MEFV, has facilitated genotype:phenotype studies, and we report here on a patient with a little described exon 9 mutation associated with an atypical inflammatory syndrome.

CASE REPORT
A 56 year old white French woman presented with normochromic anaemia, haemoglobin 61 g/l, and recent onset fatigue and headaches. Extensive investigations including upper and lower gastrointestinal endoscopy, autoantibody screens, bone marrow examination, and whole body computed tomography proved normal. There was no family history of note or consanguinity. Over the following 9 years her symptoms—comprising pyrexia, headache, and drenching night sweats—intensified, occurring about every fourth day and lasting for 24 hours. She required intermittent blood transfusions and her erythrocyte sedimentation rate remained markedly raised. Repeat bone marrow, echocardiogram, radiolabelled white cell scan, and computed tomographic imaging were normal. An investigation for infectious disease was non-diagnostic and a trial of prednisolone ineffective.

The possibility of atypical FMF was considered and was supported by complete resolution of symptoms after the introduction of colchicine 1 mg daily. Before treatment, her median serum amyloid A protein was 338 mg/l and C reactive protein 56 mg/l. Both markers were in the healthy range of <10 mg/l with colchicine (fig 1).

Sequencing of MEFV showed a single exon 9 mutation, encoding pyrin I591T; no mutations were found in exons 2, 3, 5, or 10. The TNFRSF1A gene, associated with TRAPS (tumour necrosis factor receptor associated periodic fever syndrome) was wild type. A reduction in colchicine to 0.5 mg/day led to recurrence of symptoms and acute phase response, which resolved when the dose was increased. She remains well and has a normal haemoglobin at 12 months’ follow up.

DISCUSSION
FMF is an inherited inflammatory disorder predominantly affecting people of the Mediterranean littoral, but which has been described in many populations. The gene associated with FMF, MEFV, was cloned in 1997 and comprises 10 exons. Forty eight mutations associated with FMF have been reported, just five of which are associated with 70–80% of cases. Although finding a mutation in each MEFV allele corroborates a diagnosis of FMF, the sensitivity and specificity of DNA analysis are hampered by reduced penetrance, and by the fact that only a single mutation can be identified in up to 20% of patients with classical FMF. This suggests that certain people may be especially susceptible to a single MEFV mutation, or that other as yet unidentified genes can contribute to the pathogenesis of the disease. The diagnosis of FMF therefore remains clinical, and the Tel Hashomer criteria are well validated for this purpose. Pyrin 1591T was first reported in 2001 with no accompanying clinical data. A Spanish kindred was subsequently described, in which three siblings were compound heterozygotes for pyrin 1591T and M694I, the latter a recognised variant causing FMF. Only one subject was symptomatic, and the contribution from I591T was therefore unclear. However, a pathogenic role for pyrin I591T in our patient is supported because she fulfilled diagnostic criteria for probable FMF, had attacks of characteristically short duration which responded to colchicine, and we only identified this mutation in one other case among our large referral practice, in a patient with classical FMF who had a second MEFV mutation, M694V. Furthermore, the absence of serositis and a late onset of symptoms have all been described in FMF.
This case illustrates the usefulness of a therapeutic trial of colchicine monitored objectively by frequent acute phase protein measurements in patients with undiagnosed periodic fever syndromes. It also raises the possibility that a low threshold for analysing the FMF gene might disclose a wider spectrum of associated disease.

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REFERENCES

Whale of a tale
B Rothschild, V Naples

Spondyloarthropathy is the term applied to a form of arthritis with sentinel alteration of the spine, in the form of syndesmophytes and zygapophysial joint erosions.1,2 Although a single zygapophysial joint can be damaged by pyogenic or rarely by a granulomatous infection, the only known cause of multiple zygapophysial joint erosions is spondyloarthropathy,1,2 as previously documented in the sauropod dinosaur Camarasaurus.3 Species susceptibility to spondyloarthropathy of the reactive arthritis variety has been clearly documented in non-human primates, identical in character, infectious agent involvement, and response to treatment to that found in humans.4

Observation of syndesmophytes and zygapophysial joint fusion in cetacea (for example, dolphins)1 stimulated a systematic survey of cetacean collections for evidence of spondyloarthropathy. That survey exposed a blue whale (Balaenoptera musculus) at the American National Museum of Natural History (Washington, DC) (USNM 124326) with erosions of zygapophysial joints of vertebrae 11–14 (fig 1). This specimen, collected in Newfoundland, Canada by F Leucas, contrasts with another sign of spondyloarthropathy,1,2,7 sacroiliac joint fusion, present in the mouse-like marsupial Antechinomys laniger (common name, kultarr) at the Center for Biodiversity, Illinois Natural History Survey (Champaign, IL) (UIMMH 39301).

The phylogenetic spectrum of spondyloarthropathy is now extended from the largest mammal (weighing up to 190 000 kg) that ever lived to one of the smallest, the latter weighing in at less than a twentieth of a kilogram. With apologies to Walt Disney, A whale of a tale and its all true.

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Pagetic hydrocephalus treated with zoledronate

A Morton

A case is described of severe untreated polyostotic Paget’s disease with severe skull involvement causing hydrocephalus, and its response to treatment with intravenous bisphosphonates is presented.

CASE REPORT

An 86 year old woman presented with a femoral neck fracture as result of a fall. Her daughter gave a 20 year history of progressive deafness and a 6 month history of confusion, ataxia, and urine incontinence in the setting of untreated Paget’s disease. Examination disclosed a profoundly deaf woman with whom communication was only possible by writing, typical bony changes of the skull and both tibiae, but no papilloedema or angioid streaks on fundoscopy. A modified mini-mental state examination was 21/30. Serum alkaline phosphatase (AP) was 1477 U/l (normal 30–120). Plain radiography showed severe pagetic changes affecting both hemipelvis, femora (including the site of fracture), tibiae, and the skull. Computed tomography scanning of the head showed moderate enlargement of both lateral ventricles and the third ventricle, with the fourth ventricle remaining decompressed, consistent with obstructive hydrocephalus (fig 1).

The patient declined orthopaedic intervention, magnetic resonance imaging of the brain, or neurosurgical consultation. In view of the neurological involvement her Paget’s disease was treated aggressively with three infusions of 90 mg pamidronate given weekly, and her serum AP fell to 650 U/l 4 weeks after presentation. When the effect of this seemed to be plateauing she was then given 4 mg of zoledronate intravenously (fig 2). Her serum AP fell further to 290 U/l over the next 2 months. Her daughter felt there was improvement in her hearing, but this was not documented objectively with audiometry. Unfortunately, the patient developed sudden respiratory problems and died 4 months after presentation.

DISCUSSION

Reports of about 20 cases of hydrocephalus complicating Paget’s disease have been published. Affected patients presented with ataxia, confusion, urine incontinence, and parkinsonian syndromes, and had relief of their neurological symptoms with ventricular shunting. The use of zoledronate in this case was prompted by the article by Chung and Keen, who reported an excellent response of polyostotic Paget’s disease to this drug after variable responses to various bisphosphonates and subsequent resistance to intravenous pamidronate. Randomised trials are underway comparing response rates between zoledronate and other bisphosphonates.

No competing interest.

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REFERENCES

Raynaud’s phenomenon (RP) with or without digital ulcer formation is a significant cause of morbidity for patients with systemic sclerosis (SSc, scleroderma). Lichtenstein reported oral sildenafil as a treatment of RP for patients with SSc, systemic lupus erythematosus, and idiopathic RP. His report included 10 patients from his community office practice given sildenafil, 50 mg once orally at bedtime.

METHODS AND RESULTS
We performed a retrospective chart review of 10 patients with SSc seen at a tertiary care referral centre who were offered sildenafil after standard treatments (calcium channel blockers, β blockers, angiotensin converting enzyme (ACE) inhibitors, aspirin, dipyridamole, pentoxifylline, and/or topical nitrates) had failed. Of the 10 patients, four had limited disease and six had diffuse disease. The mean (SD) age of the patients was 49.9 (9.9) years, and the mean (SD) duration of SSc was 9.5 (6.5) years. The mean (SD) duration of RP was 9.5 (7.5) years. Seven were female and three were male. Eight were white, one was African-American, and one was Hispanic. The starting dose of sildenafil varied among the patients, ranging from 12.5 mg/day to 100 mg/day, in single or divided doses.

Eight of the ten patients treated with sildenafil had a response within a few weeks, with significant reduction in the frequency and severity of RP. Of the eight patients who had digital ulcers refractory to conventional treatment, six experienced complete healing of the ulcers.

One patient, who had recently had a normal coronary arteriogram, did have some chest discomfort after taking the sildenafil. She had taken sildenafil for four months previously without any complaints. Nevertheless, the medicine was discontinued and her chest discomfort resolved. Otherwise, the medicine was well tolerated.

DISCUSSION
Sildenafil is a phosphodiesterase V inhibitor that allows accumulation of cyclic guanosine monophosphate (cGMP). cGMP causes a decrease in intracellular calcium, and the result is vascular smooth muscle relaxation and dilatation. Perhaps in those patients whose digital ulcers failed to heal while they were receiving sildenafil, the failures were the result of fibrosis and/or occlusion of vessels that did not allow further vasodilatation.

The dose prescribed was limited by the availability of the drug. Four patients were allowed only eight tablets a month and so were prescribed 100 mg tablets that were divided into quarters. This allowed the patients to take the medicine daily, albeit in small doses. We present this experience with patients with SSc with RP and digital ulcers in the hopes that further studies will be carried out to examine this new and potentially effective treatment. Clearly, traditional medical and surgical treatments for severe RP and digital ulceration are not adequate for all patients with SSc.

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REFERENCES
Oral sildenafil for the treatment of Raynaud's phenomenon and digital ulcers secondary to systemic sclerosis

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