Prevalence of hypothyroidism among Arabs with rheumatoid arthritis

Sir, Reports in the literature on the association between rheumatoid arthritis (RA) and autoimmune thyroid disease are conflicting [1–3]. As part of our ongoing molecular and metabolic studies on patients with RA, we investigated thyroid function in Arabs with RA attending two rheumatology clinics in Kuwait in order to find out whether there was an increased prevalence of hypothyroidism.

Forty-eight consecutive Arabs with RA seen between January and December 1997 at the rheumatology clinic of the Amiri Teaching Hospital and an urban private clinic in Kuwait were recruited into the study. All patients fulfilled the American College of Rheumatology criteria for the diagnosis of RA [4] and were receiving at least one disease-modifying anti-rheumatic drug, such as hydroxychloroquine, sulphasalazine, methotrexate and azathioprine, at the time of the study.

The control group consisted of 90 subjects with similar demographic features and from the same sources, but with non-inflammatory rheumatic diseases. Informed consent was obtained from all patients and controls.

All subjects were screened for thyroid disease by the estimation of serum-sensitive thyroid-stimulating hormone (TSH) concentrations using Immulite (Diagnostic Product Corporation, Los Angeles, CA 90045, USA) TSH kits. Subjects with serum TSH values of >3.80 mU/l (normal range 0.23–3.80) had further evaluation which included detailed history and physical examination, and collection of blood samples for serum free thyroxine (FT4), anti-thyroglobulin and anti-thyroid microsomal autoantibodies. Subjects with confirmed thyroid disease also underwent a thyroid scan using technetium 99m-pertechnetate (Tc-99m O4−).

Anti-thyroglobulin and anti-thyroid microsomal antibodies were detected by indirect haemagglutination (IHA) test using Thymune-T (turkey erythrocytes sensitized with purified human thyroglobulin) and Thymune-M (turkey erythrocytes sensitized with purified human microsomal antigens) kits obtained from Wellcome Diagnostics, UK.

In the RA group, there were 43 women and five men, and their ages ranged from 27 to 67 yr (mean ± s.d. = 47 ± 11 yr). In the control group, there were 80 women and 10 men, and their ages ranged from 25 to 70 yr (mean ± s.d. = 49 ± 12 yr).

Seven patients in the RA group (15%), as compared to none in the control group (0%), had elevated serum TSH levels. The seven patients with elevated serum TSH were women and their ages ranged from 31 to 66 yr (mean ± s.d. = 48 ± 13 yr). Six of the seven had subclinical hypothyroidism (normal serum FT4) and the remaining patient had clinical hypothyroidism (FT4 = 7.36 pmol/l, normal range 9.23–23.80) with symptoms of generalized weakness and fatigability. Anti-thyroglobulin antibodies were found in three patients with titres ranging from 1:10 to 1:1280, and anti-thyroid microsomal antibodies were detected in the sera of all the seven patients with elevated TSH (Table 1).

Of the seven RA patients with hypothyroidism, five were available for thyroid scan. Although three of the five had mild goitre on physical examination of the neck, all of them showed diffuse goitre with prolonged acquisition of technetium 99m-pertechnetate on thyroid scan.

Our results showed a higher prevalence of hypothyroidism among Arabs with RA than in the normal population. Subclinical hypothyroidism was the most frequent thyroid disease associated with RA. This is in agreement with the reports of Caron et al. [5]. The use of a sensitive TSH assay seems to increase the detection of subclinical hypothyroidism. Staub et al. [6] reported evidence for ‘end-organ’ metabolic abnormalities progressing on a continuum from an abnormal TSH test to overt clinical hypothyroidism. The increased serum TSH seen in some of our patients with RA in the absence of abnormal serum FT4 concentrations may support this hypothesis.

In the literature, the incidence of autoimmune thyroiditis in patients with RA is variable. Becker et al. [7]

Table 1. Demographic, clinical and biochemical features of rheumatoid arthritis patients with hypothyroidism

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (yr)</th>
<th>RA duration (yr)</th>
<th>Erosions</th>
<th>Extra-articular manifestations</th>
<th>RF titre</th>
<th>ATGA titre</th>
<th>ATMA titre</th>
<th>TSH mU/l</th>
<th>FT4 pmol/l</th>
<th>Thyroid scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>4</td>
<td>+</td>
<td>−</td>
<td>0</td>
<td>0</td>
<td>1:100</td>
<td>4.32</td>
<td>15.52</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>18</td>
<td>+</td>
<td>−</td>
<td>1:40</td>
<td>1:1280</td>
<td>1:400</td>
<td>5.14</td>
<td>9.73</td>
<td>Goitre</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>3</td>
<td>−</td>
<td>+</td>
<td>1:40</td>
<td>1:5120</td>
<td>1:6400</td>
<td>9.57</td>
<td>10.82</td>
<td>Goitre</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>4</td>
<td>−</td>
<td>−</td>
<td>1:40</td>
<td>0</td>
<td>1:100</td>
<td>4.30</td>
<td>13.90</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>18</td>
<td>+</td>
<td>−</td>
<td>1:320</td>
<td>1:10</td>
<td>1:6400</td>
<td>36.90</td>
<td>7.36</td>
<td>Goitre</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>5</td>
<td>−</td>
<td>−</td>
<td>1:160</td>
<td>0</td>
<td>1:100</td>
<td>11.19</td>
<td>11.64</td>
<td>Goitre</td>
</tr>
<tr>
<td>7</td>
<td>44</td>
<td>5</td>
<td>−</td>
<td>−</td>
<td>1:320</td>
<td>0</td>
<td>1:100</td>
<td>5.62</td>
<td>17.04</td>
<td>Goitre</td>
</tr>
</tbody>
</table>

* = Present; − = absent; RF = rheumatoid factor; ATGA = anti-thyroglobulin antibody; ATMA = anti-thyroid microsomal antibody; TSH = thyroid stimulating hormone; FT4 = free thyroxine; ND = not done.
reported 10% of histological Hashimoto’s thyroiditis in a post-mortem study of 51 patients with RA. In contrast, Youinou et al. [8] showed no difference between patients with RA and normal control subjects. The difference in these results could be explained either by the criteria used for the diagnosis of RA or by the assays used to determine anti-thyroid antibodies. Each patient with hypothyroidism in our study had at least one anti-thyroid autoantibody present in the serum. This suggests that the cause of hypothyroidism in RA patients in this study is likely to be autoimmune thyroiditis.

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Etoposide in Wegener’s granulomatosis

Srn, Wegener’s granulomatosis (WG) is a life-threatening disease characterized by necrotizing granulomatous inflammation of the upper and lower airways, systemic vasculitis and necrotizing glomerulonephritis. Prior to steroid treatment, mean survival was 5 months [1]. Corticosteroids alone improved the average survival from 5 to 12.5 months. Combined cyclophosphamide and corticosteroid therapy has resulted in only 15% of patients dying from their disease or treatment complications over a mean follow-up of 8 yr in the NIH series [2]. Remission was obtained in 75% of cases, but on extended follow-up 50% of patients experience one or more relapses. Short- and long-term toxicities are increas-ingly recognized, including serious infections and cyclophosphamide-induced cystitis and bladder cancer [3].

Etoposide is a semisynthetic epipodophyllotoxin derivative that is effective in a wide variety of human malignancies, including neoplastic disorders of the monocyte/macrophage lineage and lymphoproliferative diseases. Etoposide has also been used in non-malignant diseases, such as idiopathic hypereosinophilic syndrome, Langherans cell histiocytosis or viral-associated haemophagocytic syndrome. Alternative treatment with oral etoposide has been advocated in cyclophosphamide-resistant WG in single case reports [4, 5].

We report on four patients who suffered from biopsy-proven, c-ANCA-positive WG. Etoposide treatment aimed at: (a) induction of remission in a severe cyclophosphamide- and steroid-resistant flare (patient 1); (b) achieving complete remission in smouldering WG, with orbital pseudotumour (patient 2) or pauci-symptomatic persistent alveolar haemorrhage (patient 3); (c) replacement of methotrexate treatment after a serious Pneumocystis pneumonia (patient 4). All patients had been previously treated with monthly i.v. cyclophosphamide pulses (see Table 1). Etoposide was administered orally on a sequential basis (100 mg/day for 1 week every month) in association with standard steroid treatment.

In patient 1, severe generalized WG flare included pulmonary nodules, pannusitis, haematuria, central nervous system vasculitis, mononeuritis multiplex and myocardial infarction. Disease was resistant to i.v. then oral cyclophosphamide administered for 3 months associated with steroids and plasma exchanges. Induction treatment with etoposide was efficient after 2 weeks. Since there was no ‘wash-out’ period, a late response to or cumulative effects of cyclophosphamide treatment cannot be entirely excluded. Complete remission was obtained with normalization of C-reactive protein serum levels. The prednisone daily dosage could be reduced from 70 to 10 mg over 6 months. After 15 months of etoposide treatment, WG relapsed with lung involvement.

In patient 2, generalized WG was controlled with long-term monthly i.v. cyclophosphamide (cumulative dose of 51 g), except for smouldering orbital pseudotumour. Cyclophosphamide was stopped and methotrexate was prescribed. Methotrexate was stopped after 7 months because of stomatitis. Maintenance treatment with etoposide was started. Although orbital inflammation did not disappear, exophthalmia diminished over 8 months and the prednisone daily dosage could be lowered to 4 mg. After 15 months, the size of the orbital pseudotumour increased. Etoposide was then switched for oral cyclophosphamide and the orbital pseudotumour stabilized but did not recede. Because of mild aregenerative anaemia, a bone marrow biopsy was performed which showed dysmyelopoiesis, attributed to cumulative use of cytotoxic drugs.

In patient 3, generalized WG was controlled with long-term monthly i.v. cyclophosphamide (cumulative dose of 26 g). After 2 yr from disease onset, although clinical respiratory status and haemoglobin levels
Table 1. Data on WG patients 1–4

<table>
<thead>
<tr>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td>Sex</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Age at WG onset (yr)</td>
<td>49</td>
<td>53</td>
<td>39</td>
<td>51</td>
</tr>
<tr>
<td>Previous treatment</td>
<td>i.v.-cyp, o-cyp, pe</td>
<td>i.v.-cyp, mtx</td>
<td>i.v.-cyp, mtx, co</td>
<td>i.v.-cyp, mtx</td>
</tr>
<tr>
<td>Previous duration of WG (months)</td>
<td>24</td>
<td>204</td>
<td>108</td>
<td>60</td>
</tr>
<tr>
<td>Duration of etoposide treatment (months)</td>
<td>15</td>
<td>15</td>
<td>26</td>
<td>38</td>
</tr>
<tr>
<td>Concomitant therapy</td>
<td>prd</td>
<td>prd</td>
<td>prd</td>
<td>prd, co</td>
</tr>
</tbody>
</table>

co, co-trimoxazole; cyp, cyclophosphamide (intravenous, i.v.; oral, o); mtx, methotrexate; pe, plasma exchanges; prd, prednisone.

remained normal, bronchoalveolar lavage (BAL) cytology repeatedly showed definite alveolar haemorrhage. Methotrexate was started and rapidly stopped because of hepatitis. Because of several bouts of moderate sinusitis and bronchitis, along with alveolar haemorrhage, etoposide was initiated. The respiratory tract and general status stabilized, but asymptomatic alveolar haemorrhage was persistently demonstrated by BAL cytology. C-Reactive protein was normal. The prednisone daily dosage could be reduced from 30 to 10 mg over a 5 month period. Etoposide was stopped after 26 months because of smouldering WG relapse heralded by pulmonary nodules.

In patient 4, complete remission of generalized WG was obtained with long-term monthly i.v. cyclophosphamide (cumulative dose of 22 g) followed by weekly methotrexate. Persistent pulmonary nodules were considered sequelae. The course was abruptly complicated by adult respiratory distress syndrome caused by Pneumocystis infection. Methotrexate was stopped and switched for etoposide maintenance treatment. The prednisone daily dosage could be reduced to 11 mg. After 38 months, etoposide was stopped because pan-sinusitis with high C-reactive protein levels recurred. Pulmonary nodules had enlarged slightly.

Conventional views regarding the treatment of WG have recently been challenged by different observations. First, a distinction has been made between treatments aimed at the induction of remission and treatments directed at the maintenance of remission, i.e. preventing the relapse of the disease [6]. Second, improvement in treatment results over the years has been related not only to treatment efficacy, but also to recognition of more limited forms of disease. Third, specific organ involvement, such as subglottic stenosis or orbital pseudotumour, may have a smouldering course, often independent of WG activity in other organs and especially resistant to medical treatment. Fourth, oral cyclophosphamide urothelial toxicity is substantial, with an estimated incidence of bladder cancer after the first month of etoposide cessation was active WG relapse, which occurred in all cases after a mean of 23.5 ± 11 months. The cause of etoposide cessation was active WG relapse, which occurred in all cases after a mean of 23.5 ± 11 months. We conclude that etoposide has no clear-cut effect for the induction or maintenance of complete remission in WG. Moreover, etoposide treatment has a major drawback which has recently been put forward: two children who were treated at a low cumulative dose, mostly in oral form for one of them, developed secondary acute myelogenous leukaemia with 11q23 chromosome abnormalities [10]. Since ‘safe’ levels of etoposide exposure are unknown, we suggest that its use should be limited to life-threatening, cyclophosphamide-resistant active WG when there is no alternative treatment.

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3. Talar-Williams C, Hijazi YM, Walther McM, Lineham WM,
Allergic pancytopenia to trimethoprim-sulphamethoxazole for *Pneumocystis carinii* pneumonia following methotrexate treatment for rheumatoid arthritis

Sr,

Methotrexate (MTX) is now the most common treatment for rheumatoid arthritis (RA). The safety profile and tolerability of low-dose MTX appear to be very favourable [1]. However, in MTX-treated RA patients, cases of *Pneumocystis carinii* pneumonia (PCP) have been described, for which trimethoprim-sulphamethoxazole (TS) represents the treatment of choice. Nevertheless, the association of MTX with TS is strictly contraindicated because the two molecules are supposed to use similar folate-dependent pathways, leading to a toxic effect [2]. In an MTX-treated RA patient with PCP, we show that the severe pancytopenia related to TS may be induced through an allergic mechanism.

A 63-yr-old man, with seronegative RA for 30 yr, has been treated with MTX 10 mg/week i.m. for 3.5 yr, and prednisone 4 mg/day for 6 yr. He developed progressive dysphagia, fever and dyspnoea with pneumonia. PaO2 was 6.3 kPa, PaCO2 3.8 kPa and the pH 7.50. Bronchoalveolar lavage revealed *P. carinii* infection. RA was inactive. Gastroscopy was normal. Haemoglobin was 74 g/l with MCV 93 fl, platelets 309 000/mm³, WBC 8370/mm³ with 7530/mm³ neutrophils and 460/mm³ lymphocytes. Levels of blood CD4- and CD8-positive cells were 274/mm³ (normal 500–1700) and 156/mm³ (normal 250–1200), respectively. He was negative for HIV. MTX was stopped. TS and methylprednisolone i.v. were given. Eleven days later, a pancytopenia occurred with WBC 920/mm³ and 640/mm³ neutrophils, haemoglobin 85 g/l with a MCV 85 fl and platelets 38 000/mm³. TS was stopped and switched to atovaquone and aerosols of pentamidine isothionate. Moreover, severe mouth and oesophageal mycosis was treated with a drinkable suspension of amphotericin B and fluconazole i.v., and mouth herpes with acyclovir i.v. This treatment was started after the beginning of the pancycopenia. After a month, bronchoalveolar lavage was sterile, WBC was 18 830/mm³ with 15 720/mm³ neutrophils, haemoglobin 112 g/l with MCV 106 fl and platelets 312 000/mm³. CD4 and CD8 counts were 1153/mm³ and 696/mm³, respectively. A long-term prophylaxis of PCP was discussed. Sensitivity to TS was studied *in vitro* using measurements of leukotriene C4 release by interleukin-3-stimulated whole blood basophils in response to trimethoprim-sulphamethoxazole (TS), benzoate and sulphites.

### Table 1. Measurements of leukotriene C4 release by IL-3-stimulated whole blood basophils in response to trimethoprim-sulphamethoxazole (TS), benzoate and sulphites

<table>
<thead>
<tr>
<th>Allergen (µg/ml)</th>
<th>TS</th>
<th>Benzoate</th>
<th>Sulphites</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>100</td>
<td>130</td>
<td>50</td>
</tr>
<tr>
<td>20</td>
<td>120</td>
<td>150</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>110</td>
<td>90</td>
</tr>
</tbody>
</table>

*Whole-blood leucocytes were pre-activated with IL-3 before incubation with allergen. Levels of leukotriene C4 were measured by radioimmunoassay. A specific induction of 100 pg/ml of leukotriene C4 with the allergen was considered positive.*

Letters to the Editor

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An unusual case of pigmented villonodular synovitis of the spine: benign aggressive and/or malignant?

Sir, Ruling out a giant cell tumour of bone (GCT) and assessing the real nature, benign or malignant, of the lesions in some exceptional clinically aggressive cases of pigmented villonodular synovitis (PVNS) may be difficult. We aim to discuss these aspects in a patient with spinal PVNS.

A 60-yr-old man presented in February 1992 with a 2 week history of low back and left thigh pain. Examination showed left L4 root involvement. X-rays revealed disappearance of the left L2 and L3 pedicles. Computed tomography (CT) and magnetic resonance imaging (MRI) scans disclosed a soft-tissue mass which invaded the spinal muscles between the L1 and L5 vertebrae, the L2 and L3 bodies and pedicles, and compressed the thecal sac in the spinal canal behind the L2 and L3 vertebrae. Signal intensity was decreased on T1 sequence, heterogeneous on T2 sequence and enhanced with gadolinium. Microscopic examination of a surgical biopsy disclosed a dense proliferation of histiocytes, with an occasional nodular distribution. Included within this cell proliferation were scattered some multinucleated giant cells, groups of foamy fat-laden macrophages, and numerous cellular and extracellular haemosiderin pigments as revealed by Perls staining. There was no evidence of malignancy. The immunohistochemical results were as follows: cytokeratin, EMA, desmin and muscle-specific actin negative; vimentin, LN5, α-1 antichymotrypsin and lysozyme positive. Surgical resection was incomplete due to the thecal sac adherence and the muscle infiltration. Pathological and immunohistochemical studies showed the same proliferation, which, in some places, had a fringed appearance and surrounded a tenosynovial-type tissue. The diagnosis of histologically benign PVNS was made. After surgery, the patient underwent radiotherapy (45 Gy from L1 to L5). The only remaining symptom was moderate low back pain.

The lumbar and thigh pain recurred in April 1993. The MRI scan showed that the initially solely lumbar soft tissue mass now invaded the paravertebral spaces between T9 and S1 vertebrae and that there was destruction of the T10, T11 and T12 bodies and pedicles (Fig. 1). Microscopic examination of a paravertebral dorsal muscle surgical biopsy showed the same typical microscopic and immunohistochemical features of benign PVNS.

Signs of a T10-level spinal cord compression appeared in July 1993, and surgical decompression and biopsies of the dorsal spinal canal mass were performed. Pathological study revealed a dense proliferation of star-shaped cells with hyperchromatic nuclei, which were scattered in a loosely woven myxoid connective tissue. More peripheral were mononuclear cells with an eosinophilic cytoplasm and sometimes hyperchromatic, sometimes pale, nuclei which occasionally displayed vacuoles or nucleoli. Some were voluminous, with an irregular nucleus, a high nucleocytoplasmic ratio and atypical mitotic features. Neither giant nor histiocytic cells were observed. The immunohistochemical profile was similar to that reported in the previously biopsied specimens. Palliative chemotherapy (epirubicin,
lesional tissues were removed. Every examined slice was typical of PVNS. Unfortunately, dorsal spinal canal lesions were not studied.

Our patient initially presented with a voluminous benign lumbar giant cell lesion. GCT and PVNS were considered. Clinical and morphological data are not distinctive [1, 2]. Giant cell lesions may also be difficult to separate by histological means [3–5], synovial villi are inconstantly identified in spinal PVNS [1] and immunohistochemical markers are no more specific for PVNS than GCT [3]. In our patient, histiocytic proliferation and haemosiderin granules were more prominent, and giant and foam cells more scarce than usually observed in GCT, and features of synovial-type tissue were observed. We then concluded that the patient had PVNS.

Twenty months after the initial surgical resection, signs of a T10-level spinal cord compression appeared. Malignancy was suspected on the basis of changes in the cytological appearance and the clinical behaviour. Indeed, a very few reports relate malignant tumours of the tendon sheath or the synovium with co-existing PVNS or previous PVNS with malignant transformation [6]. An increase in cell polymorphism and in the number of mitoses, and a decrease in the number of multinucleated giant cells, both of which we observed, seem to be the most pertinent changes as regards malignancy [7, 8]. Some of these malignant PVNS appeared after previous radiotherapy, which could not be implicated in our patient. These cases fit with one or other of the two criteria of Enzinger and Weiss [9], who defined malignant PVNS as lesions in which PVNS co-exists with frankly malignant areas or, alternatively, malignant recurrence of an initially benign PVNS. However, strictly speaking, the dorsal spinal canal lesions of our patient do not correspond to the description of Enzinger and Weiss: typical aspects of PVNS were neither present nor previously documented. Bertoni et al. [6] have recently expanded the criteria of Enzinger and Weiss to five extensive, recurrent and/or metastasizing extraspinal cases lacking previous PVNS, which they considered as primary malignant PVNS or ‘sarcoma’ of the synovium. Several histological features were comparable to those observed in our patient. As compared to benign PVNS, the mononuclear cells were larger, had a deep eosinophilic cytoplasm, and large and hyperchromatic nuclei, with occasional prominent nucleoli; benign giant cells and xanthomatous cells were less evident and might even be absent; when performed, the immunohistochemical evaluation gave the same results as those reported in PVNS. However, as illustrated by our observation and previously highlighted [6], malignant and locally aggressive diffuse forms may be histologically difficult to distinguish. As for us, we considered that the pathological data and the aggressive clinical course, despite previous surgery and radiotherapy, were sufficient to initiate chemotherapy.

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High serum level of macrophage-colony stimulating factor (M-CSF) in adult-onset Still’s disease

Sir, Adult-onset Still’s disease (AOSD) is a systemic inflammatory disorder of unknown aetiology and pathogenesis. It is characterized by quotidian fever, evanescent rash, arthralgia, arthritis, polyserositis, hepatosplenomegaly, leucocytosis, and conspicuously high CRP levels and erythrocyte sedimentation rate, although rheumatoid factor and antinuclear antibodies are formally considered. Clinical and morphological data are not inconstantly identified in spinal PVNS [1] and immunohistochemical markers are no more specific for PVNS than GCT [3]. In our patient, histiocytic proliferation and haemosiderin granules were more prominent, and giant and foam cells more scarce than usually observed in GCT, and features of synovial-type tissue were observed. We then concluded that the patient had PVNS.

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implicated in regulating the production and function of cells of the monocyte/macrophage lineage [3].

Serum samples were obtained from five patients (age 39.80 ± 12.79 yr, one male and four females) with disease activity in the severely active stage. The sampling in four of the cases took place at time of onset before treatment (disease duration 3–6 weeks from onset to sampling), while one case was sampled at the time of recurrence before re-treatment (disease duration 3 yr; treatment: 40 mg of prednisolone tapering down to drug free for 2 yr). Each patient was diagnosed as having AOSD and satisfied the criteria described [2], and their serum M-CSF concentrations were measured by ELISA. Their mean values (mean ± s.d.: 4.386 ± 1.273 ng/ml) were significantly greater than those in patients with rheumatoid arthritis in the active stage (age 54.44 ± 15.38 yr, one male and eight females; disease duration 3–8 yr; drug treatment: prednisolone and/or mizoribine) (mean ± s.d.: 1.791 ± 0.783 ng/ml, n = 9) or the values (mean ± s.d.: 1.271 ± 0.364 ng/ml) of healthy volunteers (age 48.80 ± 18.68 yr, n = 10, two males and eight females) (Fig. 1). M-CSF may be one of the candidate factors that activates the reticuloendothelial system in AOSD patients. As previously reported, AOSD patients in clinically active stages show high serum levels of IL-6, TNF-α and interferon gamma (IFN-γ). IL-6 and TNF-α are mainly produced by activated macrophages, and IFN-γ is produced by activated T cells and NK cells, and acts as a macrophage-activating factor. As a result, we tentatively propose that M-CSF is a cytokine acting upstream of macrophage differentiation and the activation pathway in

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Microscopic polyangiitis associated with antiphospholipid syndrome

Sir. The association between antiphospholipid syndrome (APS) and vasculitis continues to evoke great interest [1, 2]. Most of the available literature pertains to classical polyarteritis nodosa and APS [2–4]. We report here a patient with microscopic polyangiitis associated with APS.

A 27-yr-old male presented with digital gangrene involving the little fingers of both hands of 3 months duration. He was found to have hypertension 15 days prior to admission and was on antihypertensives (nifedipine and atenolol) and aspirin 75 mg daily. The patient also complained of myalgias and arthralgias. There was no history of fever, photosensitive skin rash, oral ulcers or alopecia. The past medical history was remarkable for one episode of venous thrombosis involving the left lower limb 4 yr ago. Venography performed then at another institution had revealed subtotal obliteration of the left common iliac and left external iliac veins, for which the patient had received heparin. He had remained asymptomatic until 3 months ago when he developed insidious-onset digital gangrene. The patient was a non-smoker. Examination revealed a well-built male with blood pressure of 134/100 mmHg in the right upper limb. Physical examination was negative for anaemia, cyanosis, clubbing, jaundice or oedema of the feet. All peripheral pulses were normally palpable. The tips of both little fingers revealed gangrene. No lymphadenopathy or organomegaly was apparent. Cardiorespiratory examination was unremarkable. Neurological examination revealed intact sensations and no motor weakness was apparent. Deep tendon reflexes were elicited normally. However, the left plantar response was equivocal.

Fig. 1. High level of serum M-CSF in adult-onset Still’s disease. Serum samples were obtained from patients with adult-onset Still’s disease (AOSD), rheumatoid arthritis (RA) and healthy volunteers (Normal). Concentrations of M-CSF were measured by ELISA at Otsuka Assay Research Laboratory (Tokushima, Japan).


albumin 2.4 g) with 5–6 red cells and 7–8 white cells/high-power field. Fasting blood sugar, blood urea nitrogen, serum creatinine and aminotransferases were within normal limits. The C3 component of complement was normal. Antinuclear antibodies were negative, while antineutrophil cytoplasmic antibodies (pANCA) were positive by indirect immunofluorescence. Antiendothelial cell antibodies (IgG) were positive in moderately high titres (80 GPL U/ml, normal range: <10 U). Lupus anticoagulant was negative. Hepatitis B and C serologies were negative. Ultrasonography of the abdomen and echocardiography were normal. Kidney biopsy revealed pauci-immune focal proliferative glomerulonephritis. Fundoscopic examination was within normal limits. MRI of the brain revealed multiple small cortical infarcts in the frontoparietal areas.

A diagnosis of microscopic polyangiitis with APS was made and the patient treated with methylprednisolone pulses, i.v. pulse cyclophosphamide, oral prednisolone, low-dose aspirin and oral anticoagulants. At 6 months of follow-up, the patient is doing well with trace proteinuria and inactive urinary sediment. The hypertension is controlled with medication.

Our patient had pauci-immune focal proliferative glomerulonephritis with pANCA and negative hepatitis serologies. He would be classified as microscopic polyangiitis according to the Chapel Hill Consensus conference [5]. A positive history of venous thrombosis with digital gangrene, cortical infarcts and moderately high titres of antiendothelial antibodies would qualify him as APS. Lupus anticoagulant was not present in our patient. Nearly 30% of the patients with APS may have one antibody without the other. The vasculopathy of APS is thought to be thrombotic in origin [1]. However, vasculitis may co-exist in patients with APS. Although classical polyarteritis nodosa has been reported earlier in association with APS, our patient, to the best of our knowledge, represents the first case of microscopic polyangiitis in association with APS. The clinical recognition of vasculitis in APS is vital for instituting appropriate therapy.

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Giant cell arteritis in a patient with limited cutaneous systemic sclerosis

Sir, We report a patient with limited cutaneous systemic sclerosis (SSc) who unusually developed digital gangrene as a result not of microvascular occlusion, but of giant cell arteritis. She presented in September 1992 when aged 64 yr with a 2 week history of painful discoloured second and third toes of her right foot. SSc had been diagnosed 15 yr previously on the basis of sclerodactyly, calcinosis, telangiectasiae and Raynaud’s phenomenon. She was Scl-70 antibody positive. She had suffered recurrent ulceration of digits, and had already undergone amputations of the right ring finger, left index finger and tip of the left second toe. On examination, pulses in the foot were not palpable and there was dry gangrene of the right second and third toes.

On admission, full blood count, serum biochemistry and urinalysis were all normal. The ESR was 14 mm/h. She was IgG ANA positive (1/100) and ds DNA antibodies were negative. Anticentromere antibodies, ANCA and antiproteinase 3 antibodies were not detected, and serum complement levels (C3/C4) and immunoglobulins were normal. Cryoglobulins were not detected. The hepatitis B and C serologies were negative. She was Scl-70 antibody positive. She had suffered recurrent ulceration of digits, and had already undergone amputations of the right ring finger, left index finger and tip of the left second toe. On examination, pulses in the foot were not palpable and there was dry gangrene of the right second and third toes.

Despite treatment with i.v. prostacyclin, the digital circulation did not improve, and a below-knee amputation of the right leg was performed on 31 December 1992. Histology of the amputated specimen showed some of the larger arteries to be obliterated by a vasculitis, the grossest of which is demonstrated in Fig. 1. In some arteries, the inflammation consisted of a mixture of mononuclear cells that reacted for CD68 (monocyte macrophage marker) in the inner portion of the media, whereas in others the inflammation was granulomatous with a mixture of giant cells, lymphocytes and macrophages centred on the elastic laminae. The patient was commenced on prednisolone 30 mg daily. Wound healing was poor with breakdown of the skin over the lateral side of the stump, and complicated by cellulitis. The dose of prednisolone was gradually reduced to 10 mg daily over the subsequent 6 months. Over that period, she remained well. However, in June 1993, she was admitted to hospital because of infected ulcerations on the left foot, resistant to antibiotic treatment. The white blood count was 13.7 x 10^9/l, haemoglobin 14.0 g/dl, platelet count 371 x 10^9/l and the ESR 75 mm/h. The dose of prednisolone was increased to 30 mg daily as it was thought that these ulcers might be vasculitic. However, the ulcers did not heal and another below-knee amputation was performed in July 1993. No histology is available from the second specimen.
She remained well for some months, and was last reviewed in clinic in March 1995. She died in another hospital.

In patients with SSc presenting with digital ischaemia, the cause is usually non-inflammatory microvascular occlusion. The case reported was therefore unusual, firstly, because the vascular pathology was inflammatory and, secondly, because large vessels were involved, although recently an increased prevalence of macrovascular disease in patients with SSc has been reported [1]. There is only one previous report in the literature of giant cell arteritis (temporal arteritis) occurring in association with SSc [2].

Vasculitis has rarely been reported as a complication of SSc. Thomas and Winkelmann [3] called attention to lower limb cutaneous ulceration in patients with SSc as a clue to an underlying vasculitic process. Oddis et al. [4] reported seven cases of vasculitis in patients who were known to have SSc, but also had features of Sjögren’s syndrome, six of them were anti-Ro antibody positive. Our patient did not have features of Sjögren’s syndrome. We have previously reported that a proportion of patients with severe digital ischaemia have histological vasculitis, but the histological picture was quite different from that in the patient reported here [5]. Therefore, a proportion of patients with SSc do demonstrate inflammatory changes in their blood vessel walls and if this is the case then this may influence management because corticosteroids and/or immunosuppressant treatment may be indicated. However, in our patient, giant cell arteritis was a surprise finding on histology which could not have been predicted prior to amputation: there was no clinical evidence of systemic inflammation and the ESR was normal prior to the first amputation. Although giant cell arteritis typically affects head and neck vessels, a small but significant proportion of patients have involvement of the large arteries of the extremities [6].

In summary, our case report demonstrates that severe digital ischaemia in a patient with SSc may not simply reflect non-inflammatory small-vessel disease. Other causes should be considered, in order to avoid missing potentially medically or surgically treatable lesions.

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Silastic prostheses—a forgotten cause of lymphadenopathy in rheumatoid arthritis

Sir, We describe the case of a 63-yr-old woman, with a 20 yr history of rheumatoid arthritis, who presented with an inflamed puckered lesion in the left axilla. Twenty years earlier, she had had a right-sided simple mastectomy for ductal carcinoma in situ (DCIS), with...
subsequent breast reconstruction with silicone prosthesis using deep tissue expansion.

Her rheumatoid disease had been controlled for many years with myocrisin injections and subsequently with the addition of methotrexate. Over the years, progressive deformity necessitated silastic joint replacement of two MCP joints. Fourteen years earlier, the left index MCP joint was replaced, and just prior to presentation with the lesion, her left middle MCP joint was replaced and the original silastic joint was found to have fractured, but was otherwise stable.

The lesion in the left axilla was biopsied and this showed a 6-mm-diameter moderately differentiated infiltrating mammary carcinoma of no special histological type (Bloom’s grade 2). Small foci of DCIS were present within the tumour, suggesting that this was a new primary developing in the axillary tail of the breast. Axillary lymph nodes were palpable and the following month she underwent an axillary clearance. Pathological examination revealed 14 lymph nodes up to 15 mm diameter. These exhibited a granulomatous reaction to particulate material (Figs 1 and 2), indicating a silastic lymphadenopathy.

There is a great discrepancy in the occurrence of silastic lymphadenopathy reported. Swanson observed it in 0.01% of his patients [1], whereas in a review of the literature in 1995 regarding long-term complications of silastic joint implants, silastic lymphadenopathy was reported in 0.08% of implants [2]. However, in a study of 23 patients investigated prospectively, 13% had silastic lymphadenopathy [3]. Despite this variation, silastic lymphadenopathy remains a rare clinical occurrence and the relationship between joint replacement and the discovery of lymph involvement is easily obscured by the long time interval [4] (in this case, probably 14 yr).

Despite this woman’s history of breast cancer, silastic reactive changes were found to be present in the lymph nodes, not malignant changes as suspected clinically. Alternatively, these silastic reactive lymph node changes could have been thought to be due to the breast prosthesis, but the histology showed changes compatible with the silastic joint implant. Therefore, silastic adenopathy should always be considered in the differential diagnosis of any rheumatoid patient with lymph node enlargement who has previously received a silastic arthroplasty.

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Increased antibody responses to Klebsiella serotypes K26, K36 and K50 in patients with ankylosing spondylitis

Sir, We have read with great interest the paper by Tiwana et al. [1] on the antibody responses to Klebsiella serotypes in sera from patients with ankylosing spondylitis (AS) vs controls.

The authors used the Klebsiella serotypes K26, K36...
and K50, which were previously shown by our group to predominate in serum of HLA-B27-positive AS patients [2–4]. The investigators also tested for antibodies to serotypes K2, K3, K17 and K21. Elevated IgG levels to K17, K36 and K50, and of IgA to K2, K3, K21, K26, K36 and K50, were detected in AS patients. The authors conclude from this that not only K26, K36 and K50, but also other serotypes are involved in the immune response in AS patients. We disagree with this conclusion. In our view, their interpretation of the results is dubious both because of the methodology used and the lack of certain essential data.

Because the capsular polysaccharides are structurally similar, different K antigens could cross-react in serum. To distinguish between specific and non-specific cross-reactions, each serum reacting positively to several serotypes should be further titrated since the titre of the cross-reaction is lower than the specific homologous reaction [5, 6]. The authors tested sera at a dilution of 1:200. As far as is evident from the text, they performed no further titration of their positive sera. Therefore, the specificity of the positive reactions to serotypes K2, K3, K17 and K21 is uncertain.

In our recent serological studies on antibody responses to the entire 77 Klebsiella serotypes in AS, we initially screened the sera for antibodies at a working dilution of 1:1000. Multiple reacting sera were further diluted up to 1:5000 to exclude non-specific cross-reactions. The titration resulted in the exclusion of non-specific cross-reactions and in significantly higher antibody titres to the serotypes K26, K36 and K50, but not to the other 74 serotypes in patients with HLA-B27-positive AS or acute anterior uveitis [2–4].

Because the study of Tiwana et al. lacks titration of positive sera, we suggest taking with care, at this stage, the conclusion that Klebsiella serotypes other than K26, K36 and K50 are involved in the immune response in AS patients.

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Acroparaesthesia—a typical finding in vitamin D deficiency

Sir. Paraesthesiae of the finger tips, toes and the circumoral region are classical findings in the hyperventilation syndrome [1] and hypocalcaemia [2]. Gloth et al. [3] have recently suggested that vitamin D deficiency can cause a hyperaesthetic pain syndrome, but when classical paraesthesia with pins, needles or burning sensation of the fingers and toes is present in vitamin D deficiency, it is traditionally believed to be caused by hypocalcaemia.

We studied 44 Arab women with vitamin D deficiency. The mean serum level of 25-OH-vitamin D in the group was 6.7 ± 0.6 nmol/l (mean ± s.e.m.); secondary hyperparathyroidism was seen in 55% [14.9 ± 1.8 pmol/l (normal range: 1.3–7.6)]; subnormal serum levels of 1:200. As far as is evident from the text, they performed parathyroidism was seen in 55% [14.9 ± 1.8 pmol/l (normal range: 1.3–7.6)]; subnormal serum levels of calcium were seen in only 6%. Twenty-six participants (59%) complained of classical paraesthesiae in the hands and feet. There seemed to be no difference in clinical presentation between hypocalcaemic and normocalcaemic individuals. The participants underwent high-dose vitamin D treatment; s-25-OH-vitamin D increased significantly (34.4 ± 2.0 nmol/l; P < 10<−17>), while parathyroid hormone (PTH) was normalized (6.7 ± 0.7 pmol/l; P < 10<−6>). In the post-treatment group, paraesthesiae were present in only five participants (P < 10<−5>) and only two participants reported no improvement of the symptoms.

Our finding of paraesthesia in vitamin D deficiency despite normocalcaemia suggests that acroparaesthesia is an important early clinical sign of vitamin D deficiency. Further, our results suggest that the symptom may efficiently be cured by vitamin D treatment.

In vitamin D deficiency, decreased intestinal absorption of calcium is seen. Normal serum calcium levels are maintained by secondary hyperparathyroidism, resulting in augmentation of the calcium liberation from bone. However, both vitamin D and PTH are known to be important factors in calcium transport over the cell membrane. Therefore, it seems reasonable to suggest that disturbances in intracellular calcium in the peripheral nerve endings could cause paraesthesiae.

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