LETTERS

Tenosynovitis with acute onset: unexpected giant cell tumour of the tendon sheath

E Kruithof, D Baeten, P Dierckxsens, E M Veys, F De Keyser

The “case study in diagnostic imaging”, reported by Peh et al illustrates nicely a giant cell tumour of the tendon sheath as a slowly progressing, mildly tender mass of the wrist.1 Here we report another case of giant cell tumour of the tendon sheath, which had an unusual disease onset.

A 33 year old man presented with acute swelling and severe pain of the palmar side of the right hand. He had symptoms of carpal tunnel syndrome, and upon clinical examination swelling of the flexor tendon sheaths of the wrist as well as the fourth and fifth fingers was seen. There was no history of trauma or exposure to tuberculosis.

His erythrocyte sedimentation rate and C reactive protein were within the normal range; rheumatoid factor was absent. Mantoux testing and a chest x ray examination were negative. A radiograph of the right hand was normal. Because of deteriorating pain and swelling, a surgical exploration with tenosynovectomy was performed. Macroscopically this showed an exuberant brownish synovial proliferation with numerous villonodular projections, which was not encapsulated. There was no evidence for recent haemorrhage. Histological examination showed proliferation of the synovial lining, subintimal infiltration with mononuclear polyhedral cells—often with a histiocytic aspect, scattered multinucleated giant cells (fig 1A), and haemosiderin laden and lipid laden macrophages (fig 1B). Although the infiltrate was markedly dense, regional variations in cellularity were seen. Compact areas alternated with more non-cohesive zones with cleft-like spaces appearing as artificial tears. This histological pattern is characteristic for a diffuse giant cell tumour of the tendon sheath, which is histologically very similar to pigmented villonodular synovitis.2

Differential diagnosis of tenosynovitis of the hand with occurrence of multinucleated giant cells is a feature of rheumatic diseases such as rheumatoid arthritis, tubercular and non-tubercular mycobacterial infections, and foreign body granulomas.3–5 In this patient neither his history or additional examinations suggested these diseases, although acute onset and severe pain are not commonly reported in giant cell tumour of the tendon sheath.

REFERENCES

Figure 1 Tenosynovial biopsy on light microscopy. (A) Multinucleated giant cells in a background of mononuclear cells with abundant extracellular haemosiderin deposition (paraffin embedded section, haematoxylin and eosin stain, magnification ×640). (B) Haemosiderin laden macrophages and lipid laden macrophages (foamy cells) (paraffin embedded section, haematoxylin and eosin stain, magnification ×640).
Skin manifestations are some of the most common clinical symptoms and signs seen in patients with systemic lupus erythematosus (SLE). However, necrotising subcutaneous infection, in particular necrotising fasciitis, is rarely encountered. It is a rapidly progressive and destructive infection of the subcutaneous tissue, associated with mortality and long term morbidity of the affected patients.1 We describe a patient with SLE and liver cirrhosis complicated by severe necrotising fasciitis who had been receiving corticosteroid treatment for 20 years. Necrotic skin tissue cultures grew both *Staphylococcus aureus* and *Serratia marcescens*. Despite aggressive treatment, including administration of antibiotics, emergency debridement, and total plasma exchange for severe liver damage, she died of disseminated intravascular coagulation and multiple organ failure owing to serious bacterial infection after two months in hospital. This case suggests that severe necrotising fasciitis may occur in SLE without lupus flare up during long term treatment with low dose corticosteroids.

CASE REPORT

A 58 year old Japanese woman, who had been receiving oral prednisolone treatment for SLE for 20 years, was admitted to our hospital because of a swollen and erythematous left leg. She had taken 5 mg prednisolone daily for more than 10 years and no other immunosuppressive agents. She had had liver cirrhosis due to hepatitis C virus infection five years earlier. In December 1999 she had small wound in her left ankle. There was widespread violaceous discoloration of the skin and scattered bullae over the left knee and thigh with oedema extending from the ankle to mid-calf (fig 1A). On admission, she was in septic shock and had multiple organ failure, including hepatic and renal dysfunction. Her vital signs on arrival were blood pressure 82/62 mmHg, body temperature 38.0°C, pulse rate 80 beats/min, and respiratory rate 18/min. She had jaundice without ascites. She was alert and answered questions properly. Laboratory investigations showed a white blood cell count of 21.6×10^9/l with 54% segmented and 29% bands, a haemoglobin level of 131 g/l, a platelet count of 133×10^9/l, C reactive protein (CRP) 130 mg/l, blood urea nitrogen 17.9 mmol/l of urea, creatinine 216 µmol/l, aspartate aminotransferase 135 IU/l, alanine aminotransferase 90 IU/l, and total bilirubin 136 µmol/l. Blood glucose was 5.8 mmol/l, and glycolhaemoglobin was 0.052. Immunoserological analysis showed C3 0.4 g/l, C4 0.3 g/l, CH50 18.4 U/ml, and anti-double stranded DNA antibody 5 U/ml. Blood culture was negative for bacteria or fungi. Antibodies to hepatitis C virus and its RNA were both positive. There was no cryoglobulinaemia.

Emergency debridement of the anterior, posterior, and lateral compartments of the left leg was performed. Methicillin sensitive *Staphylococcus aureus* and *Serratia marcescens* were recovered from necrotic tissue culture. Fosfomycin 4 g/day and sulfamicillin tosilate 1.125 mg/day were substituted for the initial broad spectrum antibiotics. A skin biopsy specimen including subcutaneous tissue showed extensive infiltration of inflammatory cells along the superficial fascia, a characteristic of necrotising fasciitis (fig 1B). Over the ensuing days her vital signs and renal function improved once. The CRP levels decreased to 30–50 mg/l but her liver dysfunction worsened and total plasma exchange was started on the 16th hospital day. She died of disseminated intravascular coagulation and multiple organ failure including hepatic failure eight weeks after the admission to hospital. There was no lupus flare up during the treatment of necrotising fasciitis.

DISCUSSION

Infection is a major cause of death in patients with SLE.2 Active SLE itself contains many forms of immunological dysfunction, which may account for the increased susceptibility to infection. The abnormalities include acquired and inherited complement deficiencies, immunoglobulin deficiency, defects in chemotaxis, phagocytic activity, and delayed hypersensitivity. Even in clinical remission, an increased tendency to develop infections has been reported among patients with SLE.3 The decreased complement level in our patient might have been caused by consumption due to severe infection because there were no clinical symptoms of lupus flare up before and after admission to hospital.

Treatment with corticosteroids and other immunosuppressive agents may further have affected the increased susceptibility to infection. Corticosteroids decrease inflammatory response, effector cell response in cell mediated immunity, and immunoglobulin synthesis.4 Necrotising fasciitis is uncommon but might occur in SLE during immunosuppression due to high dose corticosteroid treatment.5 In this condition *Serratia marcescens* might be a potential pathogen causing necrotising fasciitis in susceptible hosts.6 In our patient, prolonged steroid administration might have increased the risk of infection and caused the fragility of skin tissue, which in turn allowed easy access of bacteria into the circulation. Liver cirrhosis may be associated with necrotising fasciitis caused by an infection of enteric bacterium such as *Escherichia coli*.7

**Figure 1** (A) Preoperative appearance of the swollen and erythematous left leg with purpura, skin ulcer, and bullae formation. (B) Light micrograph of skin biopsy specimens including superficial fascia. The arrow indicates thrombosis of subdermal blood vessels. Arrowheads denote epidermal detachment. Blister show massive inflammatory cell infiltration in subcutaneous tissue and superficial fascia. (Haematoxylin and eosin, original magnification ×200.)

**References**


chemotherapy. On day 5 after G-CSF administration, fever and doses of paclitaxel and nedaplatine as for the first cycle, and assessment of drug toxicity. He was treated with the same patient’s informed consent to keep his serum at –80°C for (fig 1).

giant cell reaction, but no crystals or rheumatoid nodules inflammatory infiltration accompanied by foreign body-type findings of formalin fixed synovial tissue showed severe and left hand joints were chosen for the biopsy. Microscopic arthroscopy in the most symptomatic joint. The left elbow determine the cause of the polyarthralgia we carried out locyte colony stimulating factor (G-CSF; lenograstim). To starting chemotherapy, arthralgia and myalgia accompanied by rising fever suddenly occurred on the fifth consecutive day of subcutaneous administration of 100 µg/day of granu-locyte colony stimulating factor; IL, interleukin.

We report the case of a 69 year old man with non-small lung cancer, who developed arthralgia and myalgia twice during chemotherapy using 210 mg/day of paclitaxel and 110 mg/day of nedaplatine for every four week cycle. After starting chemotherapy, arthralgia and myalgia accompanied by rising fever suddenly occurred on the fifth consecutive day of subcutaneous administration of 100 µg/day of granulocyte colony stimulating factor (G-CSF; lenograstim). To determine the cause of the polyarthralgia we carried out arthroscopy in the most symptomatic joint. The left elbow and left hand joints were chosen for the biopsy. Microscopic findings of formalin fixed synovial tissue showed severe inflammatory infiltration accompanied by foreign body-type giant cell reaction, but no crystals or rheumatoid nodules (fig 1).

During the second cycle of chemotherapy we obtained the patient’s informed consent to keep his serum at –80°C for assessment of drug toxicity. He was treated with the same doses of paclitaxel and nedaplatine as for the first cycle, and G-CSF was also given from day 10 after the start of chemotherapy. On day 5 after G-CSF administration, fever and grade 2 myalgia in the legs suddenly developed. During the attack, granulocytosis (neutrophil cell count 10.4×10¹¹/l) and a raised level of C reactive protein (80 mg/l) were seen. Before the two cycles of systemic chemotherapy, gallium scintigraphy and magnetic resonance imaging showed thoracic spinal metastasis. However, thyroid function, parathyroid function, renal function, uric acid serum levels, and electrolytes in the peripheral blood were within normal limits. Rheumatoid factor or autoimmune antibodies in the serum were negative. Neutrophil cell count, C reactive protein and histamine levels, and G-CSF and interleukin 8 (IL8) concentrations in the peripheral blood were examined on days 0, 8, and 16 (during the attack) (table 1).

**Table 1 Laboratory findings**

<table>
<thead>
<tr>
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<th>Day 0</th>
<th>Day 8</th>
<th>Day 16</th>
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<tr>
<td>WBC (×10⁹/l)</td>
<td>5.3</td>
<td>1.2</td>
<td>10.4</td>
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<tr>
<td>CRP (mg/l)</td>
<td>2.0</td>
<td>12.6</td>
<td>80.0</td>
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<tr>
<td>Histamine (pg/ml)</td>
<td>550</td>
<td>960</td>
<td>350</td>
</tr>
<tr>
<td>G-CSF (pg/ml)</td>
<td>16.8</td>
<td>31.5</td>
<td>36.6</td>
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<tr>
<td>IL8 (pg/ml)</td>
<td>&lt;10.0</td>
<td>&lt;10.0</td>
<td>25.4</td>
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Day 0, before infusions of paclitaxel and nedaplatine; day 8, before subcutaneous G-CSF administration; day 16, during the attack.

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**Figure 1** Microscopic findings of synovial tissue in the left elbow joint. The synovial membrane is hypertrophied and fine microvilli can be seen. Amorphous eosinophilic material deposition accompanied by foreign body-type giant cell reaction (arrows) was seen. Haematoxylin and eosin staining, ×100. Bar represents 100 µm.

**DISCUSSION**

Arthralgia and myalgia are well known side effects of long term infusion of paclitaxel, usually lasting for 2–6 days. On the...
other hand, G-CSF induced bone and generalised muscle pain are considered to be rare side effects during the neutrophil recovery phase. Histamine has been suggested to be one of the chemical mediators which cause oedema in bone; the resultant increase in pressure leads to pain. Gudi et al reported that histamine induced arthritis during chemotherapy combined with G-CSF administration. It has also been reported that paclitaxel-induced arthralgia or myalgia is augmented by G-CSF. Recently, pseudogout during systemic high dose chemotherapy with G-CSF administration or reactivation of rheumatoid arthritis in Felty’s syndrome treated with G-CSF have been reported.

For this report we assessed the relationship between clinical course and laboratory findings. Polyarthralgia and myalgia with rising fever developed on the fifth consecutive day of subcutaneous administration of G-CSF. Peak concentrations of histamine in the serum showed on day 8, but the serum IL8 concentration was higher during the attack. G-CSF mediated acute synovitis accompanied by foreign body-type giant cell reaction was suggested to be a cause of the rising fever and raised levels of serum IL8.

On the basis of these findings, G-CSF mediated non-rheumatic synovitis with foreign body-type giant cell reaction is suspected to possess a new responsiveness to G-CSF during chemotherapy. Close observation of a greater numbers of cases will be necessary to determine which insidious joint diseases may be caused by G-CSF.

ACKNOWLEDGEMENT

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Severe skin reaction after leflunomide and etanercept in a patient with rheumatoid arthritis

F Soliotis, M Glover, A S M Jawad

CASE HISTORY

A 32 year old Pakistani woman developed a symmetrical polyarthritis, with a high erythrocyte sedimentation rate, in 1991. Within a few months, erosions developed and her rheumatoid factor became positive. The antinuclear antibodies were negative. Between 1991 and 1999 she was treated with sulfa-salazine, sodium aurothiomalate, azathioprine, methotrexate, d-penicillamine, and hydroxychloroquine sequentially, but each drug had to be stopped either because of intolerance or leucopenia.

Her disease remained active and deformities developed. Her condition was maintained with 7.5 mg oral prednisolone and non-steroidal anti-inflammatory drugs. In April 2000 leflunomide was added. Three daily doses of 100 mg leflunomide were followed by 20 mg a day maintenance dose. Ten days later, she developed a vesicular rash over the trunk and the proximal parts of the arms and legs (fig 1). Leflunomide was discontinued and cholestyramine was introduced for wash out. A skin biopsy showed focal epidermal necrosis with parakeratosis and lichenoid changes. Direct immunofluorescence was negative. The antinuclear and anti-dsDNA antibodies remained negative, but the anti-Ro antibodies were positive. No other features suggested a diagnosis of lupus. The dose of prednisolone was raised to 20 mg a day and topical corticosteroids were used. The skin lesions healed within a month with residual pigmentation and the prednisolone dose was reduced to 7.5 mg a day. Six months later there was a minor flare up of the rash. A skin biopsy showed resolving lichenoid changes.

Her arthritis remained active, and in February 2001 etanercept was introduced in a dose of 25 mg subcutaneously twice a week. Treatment continued with 7.5 mg prednisolone. A vesicular erythematous rash started after the second injection of etanercept, which worsened and spread to affect the trunk and the arms and legs after the fourth injection (fig 2). The rash was much more aggressive than the previous one. Etanercept was discontinued; the prednisolone dose was raised to 30 mg a day. A skin biopsy again showed areas of central necrosis surrounded by a rim of perivascular inflammation and there was also an inflammatory infiltrate at the dermoepidermal junction with necrosis of the basal keratinocytes. Again the anti-Ro antibodies became positive and in a higher titre. The lesions took several months to settle leaving pigmented scars.

DISCUSSION

Leflunomide, an inhibitor of pyrimidine synthesis, has recently been introduced in the treatment of patients with
rheumatoid arthritis (RA). Skin side effects include dry skin, alopecia, eczema, rash, pruritus, and, rarely, Steven-Johnson syndrome and toxic epidermal necrolysis.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein that is used for the treatment of active RA if there is inadequate response to disease modifying antirheumatic drugs (DMARDs). A variety of skin rashes have been reported in controlled trials of etanercept in the treatment of RA. Most have been mild and only one reported case had a grade 3 rash (generalised symptomatic maculopapular or vesicular) (Wyeth Laboratories, unpublished data). The rash usually appears two to three weeks after the start of treatment.

Recently, three cases of acute discoid lupus and two cases of subacute cutaneous lupus erythematosus (SCLE) have been reported during treatment of patients with RA with etanercept. One of the two patients reported with SCLE developed anti-Ro antibodies. About 15% of patients treated with etanercept develop anti-dsDNA antibodies and 11% develop antinuclear antibodies.

Although our patient had positive anti-Ro antibodies, the blistering rash clinically and histologically was not in keeping with SCLE or other forms of lupus.

The initial leflunomide-induced rash (toxic epidermal necrosis) seen in our patient has been described previously. The rash that developed after etanercept was a more severe form of a similar drug induced reaction. Clinically and histologically the etanercept-induced rash was in keeping with erythema multiforme. It took several months of treatment with moderate doses of prednisolone for the rash to settle. Erythema multiforme has been associated with drugs such as sulphonamides, antimalarial drugs, penicillin, and salicylates, infections, lymphomas, and systemic lupus erythematosus. Our patient did not have any features to suggest any concurrent infections, lymphoma, or lupus.

Our patient developed toxic epidermal necrosis after leflunomide and erythema multiforme after etanercept. Both skin reactions, which are often drug related, share a similar pathogenesis, which is also suggested by the appearance of anti-Ro antibodies. Our case highlights that serious skin reaction to more than one DMARD including etanercept can occur in susceptible patients. What factor or immune phenotype determines this outcome is not clear. However, it poses a serious problem in the management of certain patients with RA.

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Clinical, radiographic, and thermographic assessment of osteoarthritis in the knee joints

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It has been reported that thermography enables the evaluation of non-steroidal anti-inflammatory drugs for the treatment of rheumatic synovitis. However, few reports mentioned the relation between skin temperature and symptoms, physical signs, and radiographic features in patients with osteoarthritis (OA). In this study we evaluated the correlation between radiographic and clinical findings and skin temperature measured by thermography for the assessment of OA in the knee joints in the Comprehensive Health Examination Programme at Y-town, Japan in 1999.

PATIENTS AND METHODS

The assessments were performed on 974 knees of 169 men and 318 women who had a mean (SD) age of 57.6 (4.3). The following physical examinations of the knees were carried out: local tenderness, joint swelling, local heat, McMurray test, Lachmann test, instability of collateral ligaments, patellofemoral joint (PFJ) grinding test, range of joint motion, and thigh girth. Walking and stair climbing ability were graded using the Hospital for Special Surgery (HSS) knee rating scores and Lysholm knee scoring scale. Present or past pain continuing for more than one month was recorded.

The distance between the medial and lateral tibiofemoral joints (MTFJ and LTFJ) was measured on the anteroposterior radiographs. Radiographic scoring of osteophytes (0, none; 1, doubtful; 2, minimal; 3, moderate) at four sites (medial and lateral condyle of both tibia and femur) was recorded.

The thermographic index (TI) and heat distribution index (HDI) were obtained by thermographic apparatus (TH5108ME, NEC Medical Systems, Japan). The TI has been defined as the average surface temperature of local skin area and HDI as ±1SD from the mean surface temperature. The whole anterior knee of 10 cm² was assessed for HDI. Three different areas of 3×3 cm were studied for TI: Tm, TI of MTFJ; Tl, TI of LTFJ; and Tp, TI of 10 cm above the patella. Tm was considered as the control value. To minimise the effect of the variation of individual skin temperature, normalised Tm and Tl (ΔTm and ΔTl) were calculated by subtracting Tp from Tm and Tl (ΔTm=Tm−Tp, ΔTl=Tl−Tp). High ΔTm means high skin temperature on MTFJ and high ΔTl means high skin temperature on LTFJ. Residents with severe knee deformity, rheumatoid arthritis, vascular disease, positive sign of PFJ grinding test were excluded, because we focused on the OA change of the MTFJ and LTFJ in this study.

Statistical analyses were carried out by unpaired Student’s t test, Pearson’s correlation coefficient test, and Kruskal-Wallis test. A p value of <0.05 was considered significant.

RESULTS

The thermographic and radiographic findings showed that narrowing of the MTFJ space was significantly associated with a rise in skin surface temperature (p<0.01) (table 1). ΔTm correlated significantly with the size of osteophytes at all sites measured, and ΔTl correlated at two of four sites (fig 1). These

| Table 1 Correlation between radiographic, clinical assessments, and normalised TI (ΔTm, ΔTl) |
|---------------------------------|---------------------------------|
|                                | Normalised Tm (Mean value (SD)) | Correlation coefficient | p Value | Normalised Tl (Mean value (SD)) | Correlation coefficient | p Value |
| Distance of MTFJ               | 0.548                           | <0.001**                   | NS      | 0.232                           | NS                      | NS      |
| Distance of LTFJ               | 0.106                           | NS                         | NS      | 0.247                           | NS                      | NS      |
| Present pain                   | <0.001**                        | 0.001**                    | NS      | <0.001**                        | 0.001**                | NS      |
| Tenderness                     | <0.001**                        | 0.001**                    | NS      | <0.001**                        | 0.001**                | NS      |
| Joint swelling                 | 0.006**                         | NS                         | NS      | 0.019**                         | 0.011**                | NS      |
| Local heat                     | 0.001**                         | 0.001**                    | NS      | 0.001**                         | 0.001**                | NS      |
| McMaster’s test                | 0.001**                         | 0.001**                    | NS      | 0.001**                         | 0.001**                | NS      |
| Lachmann’s test                | 0.002**                         | NS                         | NS      | 0.002**                         | NS                      | NS      |
| Instability of collateral ligaments | 0.001**               | NS                         | NS      | 0.001**                         | 0.001**                | NS      |
| Walking ability                |                                  |                            |         |                                  |                        |         |
| Walking and standing unlimited | 0.62 (0.82)                     | <0.001**                   | 1.98 (6.31) | 0.017*                          |                        |         |
| 5–10 Blocks, standing >50 min  | 0.31 (0.71)                     | 1.02 (0.82)                | 0.66 (1.08) | 0.71 (0.84)                    |                       |         |
| 1–5 Blocks, standing 15–50 min | 0.19 (0.74)                     | 0.85 (0.81)                | 0.48 (1.08) | 0.66 (0.80)                    |                       |         |
| Walking <1 block               | 0.16 (0.72)                     | 0.93 (0.86)                | 0.45 (0.87) | 0.65 (0.929)                   |                       |         |
| Stair climbing ability         | 1.3 (0.42)                      | 0.65 (0.929)               | 1.52 (5.79) | 0.005**                        |                       |         |
| No problem                     | 0.66 (0.80)                     | <0.001**                   | 1.52 (5.79) | 0.005**                        |                       |         |
| Slightly impaired              | 0.45 (0.87)                     | 1.38 (0.8)                 | 0.16 (0.72) | 0.65 (0.929)                   |                       |         |
| One step at a time             | 1.3 (0.42)                      | 0.65 (0.929)               | 1.52 (5.79) | 0.005**                        |                       |         |
| Impossible                     | 0.65 (0.929)                    | 0.65 (0.929)               | 1.52 (5.79) | 0.005**                        |                       |         |
| Knee operation experience      |                                  |                            |         |                                  |                        |         |
| Flexion                        | −0.654                          | <0.001**                   | −0.666  | 0.004**                         |                       |         |
| Extension                      | −0.435                          | <0.001**                   | −0.486  | 0.008**                         |                       |         |
| Thigh girth                    | −0.479                          | 0.015*                     | −0.472  | 0.027*                          |                       |         |

Student’s t test, Kruskal-Wallis test, Pearson’s correlation coefficient test. *p<0.05, **p<0.01.
data indicate that residents with larger osteophytes in the
MTFJ have higher skin surface temperature. We could not find
any correlation between HDI and the radiographic findings.

The correlation between skin temperature and clinical
symptoms showed that the residents with present or past pain
have significantly higher $\Delta T_m$ or $\Delta T_l$ ($p<0.01$). We also found
that many clinical findings correlated with the increase of skin
temperature indicated by normalised TI ($\Delta T_m$ and $\Delta T_l$), as
shown in table 1. HDI on the knee only correlated with joint
swelling and tenderness ($p<0.01$).

DISCUSSION
In this study we used HDI and normalised TI to indicate the
skin surface temperature. The normalised TI correlated more
significantly with the clinical and radiographic parameters
than the HDI. Therefore, it was suggested that the normalised
TI is more useful for evaluation of the disease activity than the
HDI. Further study is needed to confirm the accuracy and
sensitivity of normalised TI for the screening of OA.

In the clinical situation raised skin temperature is
sometimes seen as local heat in patients with OA in the knee
joints. However, as far as we know no published report has
assessed the relation between skin temperature and clinical or
radiographic findings in OA knees. In this study, thermogra-
phy provided objective data of skin temperature that was
compared with other physical parameters, showing a correla-
tion between skin temperature and clinical, and radiological
evidence of OA in the knee joints. Synovial inflammation and
subchondral change have been reported to affect the OA
cascade.8–11 Dieppe et al used scintigraphy to show that
subchondral bone metabolism is related to the progression
and symptoms of OA in the knees.8 It is suggested that the
skin temperature evaluated by thermography may be due to
the increased synovitis or subchondral bone activity, or both,
in the OA knee joint.
CD5+ B cells and uveitis

J Jiménez-Alonso, M Omar, M A López-Nevot, F Pérez-Álvarez, M Toribio, C Hidalgo, J M Sabio

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Absence of human parvovirus B19 DNA in myoepithelial sialadenitis of primary Sjögren’s syndrome

V De Re, S De Vita, V Battistella, A Marzotto, M Libra, G Ferraccioli, M Boiocchi

Sjögren’s syndrome (SS) is an autoimmune disease that mainly affects exocrine glands and presents as persistent dryness of the mouth and eyes owing to functional impairment of the salivary and lacrimal glands. The histological hallmark is local infiltration of lymphocytes, which play a major role in tissue damage. Although B cells represent a minority of the lymphoid infiltrates in SS tissue, they may undergo polyclonal activation and oligoclaron/monoclonal expansion, which may, in turn, predispose them to a still unidentified B cell neoplastic transformation. The process of B cell activation and expansion is presumably a consequence of a chronic, although at present unidentified, antigenic stimulus that activates specific subsets of B lymphocytes. This process resembles a germinol centre reaction, in which B cells that express the antigen receptor with the highest affinity for the stimulatory antigen are selected, giving rise to the oligoclaron/monoclonal population seen in the advanced phases of the disease.

We recently analysed seven monoclonal lymphoproliferations from six patients with primary SS according to the European Criteria of 1993; (one patient with SS showed a monoclonal B cell population in two subsequent parotid specimens). DNA was extracted from frozen parotid biopsy specimens, and a B cell monoclonal expansion was verified by the VDJ protocol of amplification. The immunoglobulin antigen receptor (IgR) variable region genes and third complementarity determining region segments (CDR3), which mainly contribute to the antigenic specificity of the IgR, were sequenced.

Comparison of the deduced amino acid sequences of the CDR3 region with antibodies of known specificity reported in a database, showed in six cases a high similarity between VH and CDR3 and rheumatoid factor (RF) antibodies, presumably a database, showed in six cases a high similarity between VH and CDR3 and rheumatoid factor (RF) antibodies, presumably present in 30–60% of the population positive to B19 antibodies, which infects not only erythrocytes and erythroblasts but also megakaryocytes, endothelial and epithelial cells and is possibly involved in several autoimmune diseases, we searched for B19 genomes in tissues affected by the SS associated lymphoproliferative processes. This was in agreement with the proposed models for the pathogenesis of MALT lymphoma.

A polymerase chain reaction (PCR) amplification using the Ampliquality B19 kit (Ab ANALITICA srl, Padova, Italy) was performed, in accordance with the manufacturer’s instructions, to search for the presence of B19 DNA in parotid specimens affected by SS. The PCR products were analysed on 2% agarose gel stained with ethidium bromide. Positive cases must show a fragment of 218 bp, which derives from amplification of the 1390 to 1608 region of the viral genome.

The region encoding for the β-globin gene was also amplified by PCR to confirm the quality of DNA (data not shown). Despite the high sensitivity of the PCR approach, B19 DNA was not detected in patient 5, who showed a high homology of

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Sjögren’s syndrome (SS) is an autoimmune disease that mainly affects exocrine glands and presents as persistent dryness of the mouth and eyes owing to functional impairment of the salivary and lachrymal glands. The histological hallmark is local infiltration of lymphocytes, which play a major role in tissue damage. Although B cells represent a minority of the lymphoid infiltrates in SS tissue, they may undergo polyclonal activation and oligoclaron/monoclonal expansion, which may, in turn, predispose them to a still unidentified B cell neoplastic transformation. The process of B cell activation and expansion is presumably a consequence of a chronic, although at present unidentified, antigenic stimulus that activates specific subsets of B lymphocytes. This process resembles a germinal centre reaction, in which B cells that express the antigen receptor with the highest affinity for the stimulatory antigen are selected, giving rise to the oligoclaron/monoclonal population seen in the advanced phases of the disease.

We recently analysed seven monoclonal lymphoproliferations from six patients with primary SS according to the European Criteria of 1993; (one patient with SS showed a different monoclonal B cell population in two subsequent parotid specimens). DNA was extracted from frozen parotid biopsy specimens, and a B cell monoclonal expansion was verified by the VDJ protocol of amplification. The immunoglobulin antigen receptor (IgR) variable region genes and third complementarity determining region segments (CDR3), which mainly contribute to the antigenic specificity of the IgR, were sequenced.

Comparison of the deduced amino acid sequences of the CDR3 region with antibodies of known specificity reported in a database, showed in six cases a high similarity between VH and CDR3 and rheumatoid factor (RF) antibodies, presumably autoantibodies produced against an infectious agent(s), and in one case an antibody putatively reactive with parvovirus B19 (table 1). This suggests that RF producing cells have a role in SS pathogenetic events, as recently confirmed by Martin et al.

Because human parvovirus B19 is a common DNA virus, present in 30–60% of the population positive to B19 antibodies, which infects not only erythrocytes and erythroblasts but also megakaryocytes, endothelial and epithelial cells and is possibly involved in several autoimmune diseases, we searched for B19 genomes in tissues affected by the SS associated lymphoproliferative processes. This was in agreement with the proposed models for the pathogenesis of MALT lymphoma.

A polymerase chain reaction (PCR) amplification using the Ampliquality B19 kit (Ab ANALITICA srl, Padova, Italy) was performed, in accordance with the manufacturer’s instructions, to search for the presence of B19 DNA directly in the parotid specimens affected by SS. The PCR products were analysed on 2% agarose gel stained with ethidium bromide. Positive cases must show a fragment of 218 bp, which derives from amplification of the 1390 to 1608 region of the viral genome.

The region encoding for the β-globin gene was also amplified by PCR to confirm the quality of DNA (data not shown). Despite the high sensitivity of the PCR approach, B19 DNA was not detected in patient 5, who showed a high homology of
corresponds to a negative control deprived of DNA.

The authors thank Dr P Tonel for help with the letter. Supported in part by the Italian Association for Cancer Research.

**Table 1** Deduced amino acid sequences of VH-CDR3 and VK-CDR3 and high similarity with protein sequence with known antigenic specificity

<table>
<thead>
<tr>
<th>Cases</th>
<th>Most similar VH or VK germline segments</th>
<th>VH-CDR3 or VK-CDR3 deduced amino acid sequences</th>
<th>Protein sequence with known specificity producing a high significant similarity</th>
<th>E Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>VH</td>
<td>V4.59; D2.15; J2</td>
<td>DRYCSGGSCFDWYFD</td>
<td>(U85234) rheumatoid factor</td>
<td>6e08</td>
</tr>
<tr>
<td>1</td>
<td>V3.7; D3.22; J3</td>
<td>GDYDSSDYYIDAFDI</td>
<td>(U03400) rheumatoid factor</td>
<td>0.48</td>
</tr>
<tr>
<td>2</td>
<td>V4.59; D2.15; J2</td>
<td>DRYCSGGSCFDWYFD</td>
<td>(U85234) rheumatoid factor</td>
<td>8e08</td>
</tr>
<tr>
<td>3</td>
<td>V3.11; D3.22; J3</td>
<td>GDYDSSDSDFHVYII</td>
<td>(U85242) rheumatoid factor</td>
<td>0.002</td>
</tr>
<tr>
<td>4</td>
<td>V3.7; D1.20; J1</td>
<td>DLRPRFSAFDAFI</td>
<td>(AF092498) antibody against parovirus B19</td>
<td>0.025</td>
</tr>
<tr>
<td>5</td>
<td>V6.1; D7.27; J6</td>
<td>APSWATNYYYGMDV</td>
<td>(AAB58433) rheumatoid factor</td>
<td>6e04</td>
</tr>
<tr>
<td>6</td>
<td>V1.69; D5.18; J4</td>
<td>EGHKDTMVPFDY</td>
<td>(l19288) rheumatoid factor</td>
<td>3e06</td>
</tr>
<tr>
<td>7</td>
<td>V3.20; J1</td>
<td>QQYGSSPPRTF</td>
<td>(225028) rheumatoid factor</td>
<td>0.074</td>
</tr>
<tr>
<td>1</td>
<td>V3.20; J3</td>
<td>QQYGTSPFT</td>
<td>(40727) rheumatoid factor</td>
<td>0.073</td>
</tr>
<tr>
<td>2</td>
<td>V3.20; J1</td>
<td>QQYGSSPRT</td>
<td>(225028) rheumatoid factor</td>
<td>0.073</td>
</tr>
<tr>
<td>3</td>
<td>V3.15; J1</td>
<td>QHYNNWPPWVT</td>
<td>(L48242) rheumatoid factor</td>
<td>0.025</td>
</tr>
<tr>
<td>4</td>
<td>V3.15; J1</td>
<td>QHYNNWPPWVT</td>
<td>(48242) rheumatoid factor</td>
<td>0.025</td>
</tr>
<tr>
<td>5</td>
<td>V3.20; J1</td>
<td>QQYGSSPPY5</td>
<td>(227950) rheumatoid factor</td>
<td>3.3</td>
</tr>
<tr>
<td>6</td>
<td>V3.20; J1</td>
<td>QQYGNSPLT</td>
<td>(l19293) rheumatoid factor</td>
<td>0.16</td>
</tr>
</tbody>
</table>

*Smallest sum probability according to BLAST similarity search programme. The E value is inversely correlated with statistical significance.

The search in the database was performed adding 3 AA in position 5′ and 7 AA in position 3′ to the CDR3 sequence for the VH gene and 1 AA in position 5′ and 4 AA in position 3′ for the VK gene; †the GenBank accession number of the protein sequence is reported in brackets.

**REFERENCES**


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Spectrum of psoriatic spondyloarthropathy in a cohort of 100 Spanish patients

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In their initial work, Moll and Wright recognised five patterns of psoriatic arthritis (PsA)—namely, distal joint disease, oligoarthritis, polyarthritis, arthritis mutilans, and spondylitis. Although psoriatic spondyloarthropathy was recognised as a specific pattern of PsA, it has become clear that the presence of isolated spondyloarthropathy (SpA) in PsA is unusual, and in most cases, it occurs with peripheral arthritis. We undertook the present work to analyse the clinical features of our patients with psoriatic SpA and to compare the different subgroups included within the psoriatic SpA spectrum.

One hundred patients with psoriatic SpA, defined in accordance with the European Spondyloarthropathy Study Group (ESSG) criteria, were consecutively recruited and their clinical records were analysed in this retrospective cross sectional study. All patients were evaluated according to a standard protocol, and their functional ability was assessed using the Health Assessment Questionnaire-Specific for SpA (HAQ-S). We included patients with isolated axial involvement, as well as those with axial plus peripheral disease. The study group was divided according to the articular patterns seen during the past five years of follow up. The presence of mutilans forms and distal interphalangeal (DIP) disease was also recorded.

We performed HLA-B27 typing by serological methods and HLA-Cw typing by molecular biology techniques (SSOP-PCR) in our 100 patients and in 177 blood donors of the same racial origin. Sacroiliac radiographic changes were graded as follows: 0, normal; 1, possible; 2, minimal; 3, moderate; and 4, ankylosis. All symptomatic joints were radiographed. At least two senior rheumatologists read all x ray films, and there was a complete agreement, except for three cases, where consensus was achieved.

Categorical data were analysed by Pearson’s χ² analysis and Fisher’s exact test, whereas continuous data were compared by analysis of variance. Relative risk (RR) was calculated by Woolf’s method.

According to the clinical patterns seen during the past five years of follow up, 23 patients developed isolated axial disease only (M:F ratio 3.6:1), 36 showed a mixed pattern of axial disease and polyarthritis (M:F ratio 1:1), and 41 had oligoaxial disease (M:F ratio 1.7:1).

Thirty four patients carried the HLA-B27 antigen compared with a normal distribution of this allele of 7% in the control group (RR 7, p<0.0004), whereas HLA-Cw*0602 was seen in 58 of the 100 patients compared with a frequency in the control group of 18% (RR 6.2, p<0.0001). This last allele was equally distributed among the three articular categories.

Table 1 Comparison of psoriatic spondyloarthropathy subgroups. Continuous data are expressed as mean (standard deviation)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pure axial pattern (n=23)</th>
<th>Polyaxial pattern (n=36)</th>
<th>Oligoaxial pattern (n=41)</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43 (11)</td>
<td>54 (12)</td>
<td>46 (15)</td>
<td>0.039</td>
</tr>
<tr>
<td>Psoriasis duration (years)</td>
<td>16 (9)</td>
<td>19 (8)</td>
<td>17 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Arthritis duration (years)</td>
<td>10 (6)</td>
<td>13 (7)</td>
<td>10 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Psoriasis onset age (years)</td>
<td>27 (10)</td>
<td>35 (13)</td>
<td>29 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Arthritis onset age (years)</td>
<td>33 (8)</td>
<td>40 (12)</td>
<td>37 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Psoriasis-arthritis latency (years)</td>
<td>8 (4)</td>
<td>8 (7)</td>
<td>14 (10)</td>
<td>0.07</td>
</tr>
<tr>
<td>Family history (%)</td>
<td>17</td>
<td>19</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td>IBP (%)</td>
<td>83</td>
<td>36</td>
<td>37</td>
<td>0.009</td>
</tr>
<tr>
<td>Neck pain (%)</td>
<td>22</td>
<td>25</td>
<td>27</td>
<td>NS</td>
</tr>
<tr>
<td>Radiological neck involvement (%)</td>
<td>35</td>
<td>56</td>
<td>39</td>
<td>NS</td>
</tr>
<tr>
<td>Marginal syndesmophytes (%)</td>
<td>26</td>
<td>19</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>Para-marginal syndesmophytes (%)</td>
<td>13</td>
<td>28</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>Bilateral SI (%)</td>
<td>56</td>
<td>31</td>
<td>37</td>
<td>NS</td>
</tr>
<tr>
<td>Unilateral SI (%)</td>
<td>44</td>
<td>44</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>Onychopathy (%)</td>
<td>30</td>
<td>75</td>
<td>51</td>
<td>0.015</td>
</tr>
<tr>
<td>ESR (mm/1st h)</td>
<td>27 (20)</td>
<td>47 (26)</td>
<td>20 (21)</td>
<td>0.0001</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>1.60 (2.50)</td>
<td>190 (160)</td>
<td>100 (130)</td>
<td>NS</td>
</tr>
<tr>
<td>C3 (g/l)</td>
<td>1.3 (0.3)</td>
<td>1.2 (0.3)</td>
<td>1.2 (0.3)</td>
<td>0.037</td>
</tr>
<tr>
<td>C4 (g/l)</td>
<td>0.3 (0.1)</td>
<td>0.2 (0.1)</td>
<td>0.3 (0.1)</td>
<td>0.045</td>
</tr>
<tr>
<td>IgG (g/l)</td>
<td>13.70 (2.60)</td>
<td>16.05 (5.00)</td>
<td>12.17 (2.80)</td>
<td>0.029</td>
</tr>
<tr>
<td>IgM (g/l)</td>
<td>1.93 (1.02)</td>
<td>1.71 (0.73)</td>
<td>1.55 (0.89)</td>
<td>NS</td>
</tr>
<tr>
<td>IgA (g/l)</td>
<td>3.12 (1.42)</td>
<td>2.85 (1.29)</td>
<td>2.86 (1.86)</td>
<td>NS</td>
</tr>
<tr>
<td>Erosive disease (%)</td>
<td>4*</td>
<td>75</td>
<td>37</td>
<td>0.0001</td>
</tr>
<tr>
<td>DIP disease (%)</td>
<td>17</td>
<td>64</td>
<td>51</td>
<td>0.015</td>
</tr>
<tr>
<td>HAQ-S (mean)</td>
<td>1.4 (0.4)</td>
<td>1.8 (0.4)</td>
<td>1.3 (0.3)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

IBP, inflammatory back pain; SI, sacroiliitis; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; DIP, distal interphalangeal joint; HAQ-S, Health Assessment Questionnaire-Specific for spondylarthropathy.

*Erosive coxofemoral joint disease.
Table 1 compares the articular categories found in this study. A satisfactory definition is still lacking for PsA, in particular for psoriatic SpA, and therefore we reported only those cases fulfilling the criteria given by the ESSG, in order to standardise our observations and to enable comparisons with other past or future reports. After a minimum of five years of observation, we have found that three clear patterns of psoriatic SpA are easy to document—namely, isolated axial disease, polyaxial disease, and oligoaxial pattern. Moreover, DIP disease and mutilans forms did not remain as independent patterns over time.

Patients with isolated axial disease were more often men, and had more clinical (inflammatory back pain), radiological (bilateral sacroilitis and marginal syndesmophytes), immunogenetic (HLA-B27), and extra-articular (uveitis) features which strongly correlate this group with idiopathic ankylosing spondylitis. We found that the spondylitic process was similar between groups, though patients with polyaxial disease had more neck radiological damage than the other patients, probably because this group had more peripheral erosions and a longer duration of arthritis (table 1). Involvement of the neck was associated with arthritis duration (p=0.043) and peripheral erosions (p=0.037), confirming previous reports.

Unquestionably, more than 50% of patients with PsA have DIP joint disease, but the presence of isolated DIP disease is still controversial, as is its role as a prognostic marker. Our observations suggest that DIP disease is a typical feature of PsA rather than an additional articular category, and that it is mostly associated with peripheral forms of the disease; indeed, the highest percentages of onychopathy and DIP disease were seen among patients with the polyaxial pattern, whereas the lowest percentages were found in the group with isolated axial disease (table 1). This latter observation is at odds with the supposed association between DIP disease and sacroilitis or the reported association between HLA-B27 and DIP disease. We have obtained data which point not only to a different genetic basis in psoriatic SpA models but also to different pathogenic mechanisms. As a whole, in our study HLA-B27 was a stronger risk factor for isolated and oligoaxial variants of psoriatic SpA than for the polyaxial one. In this last group we found higher rates of complement consumption, more peripheral erosions, poorer functional performance, and higher immunoglobulin (IgG) values, supporting the view that immunocomplexes may be an important mechanism of tissue injury in psoriatic polyarthritides. On the other hand, the ileocolonoscopic studies of Schatteinan et al found gut lesions resembling those of inflammatory bowel disease in patients with psoriatic oligoarthritis and spondylitis but not in patients with psoriatic polyarthritides.

In summary, some HLA, clinical and pathogenic data support the subdivision of psoriatic SpA as proposed in the present report.

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Severe skin reaction after leflunomide and etanercept in a patient with rheumatoid arthritis

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