

# Fibroblastic rheumatism: a Scandinavian case report

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*Ann Rheum Dis* 2005;64:156–157. doi: 10.1136/ard.2003.008441

**F**ibroblastic rheumatism (FR) is a rare disorder of unknown cause first described in 1980.<sup>1</sup> We here report the first Scandinavian patient with FR.

## CASE REPORT

A 55 year old Danish woman was referred to our department in July 2000 with a 2½ year history of pain in the proximal interphalangeal (PIP) joints, knees, and ankles. The pain worsened over night and upon exercise. On examination, the right knee and the second PIP joint on the left hand were tender and swollen. The other PIP joints and both wrists were tender. On both hands there were several pink, 3–10 mm, tender and mobile skin nodules (fig 1), and a 20 mm nodule under the left foot.

All laboratory investigations were normal, including erythrocyte sedimentation rate, C reactive protein, haemoglobin, white blood cell count, platelets, and differential count. IgM rheumatoid factor, antinuclear antibodies and antineutrophil cytoplasmic antibodies were not found. An

x ray examination of the hands demonstrated osteoarthritis of the distal interphalangeal joints.

Two skin nodules were removed and examined by light microscopy (fig 2): they showed areas with densely packed uniform spindle cells surrounded by bundles of thickened collagen fibres and vascular granulation tissue. The biopsy specimens were without inflammatory cells, histiocytes, giant cells, granulomas, or foreign bodies. Special staining did not disclose any elastic fibres. Immunochemical staining of paraffin sections for myofibroblasts was positive for vimentin, but negative for desmin and  $\alpha$ -smooth muscle actin.

Treatment with celecoxib and physical therapy was started but had no effect on the symptoms.

On follow up in 2003, the patient had severe, intermittent arthralgia and she was unable to work. She had a nodular thickening of the palmar aponeurosis and a slight contracture of the fingers on both hands. x Ray findings of her hands had not changed.

## DISCUSSION

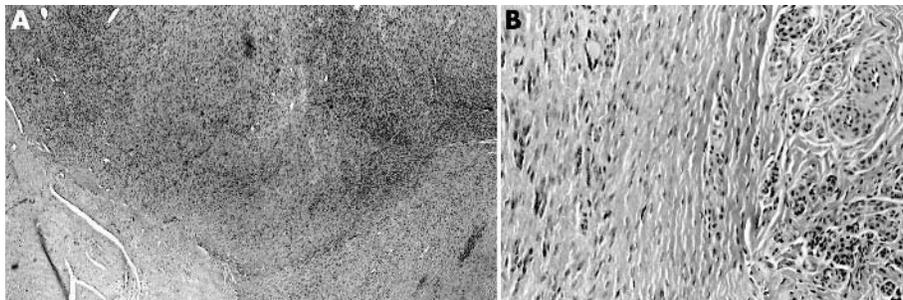
The diagnosis FR was based on the presence of skin nodules, joint symptoms, histopathological features, a poor outcome, and the absence of another diagnosis that could explain these characteristics. There was no evidence of systemic sclerosis, and the patient did not fulfil classification criteria for rheumatoid arthritis.<sup>2</sup> The hallmark of multicentric reticulohistiocytosis is giant cells of a foreign body type and histiocytes in pathological specimens.<sup>3</sup> These features were absent in both skin biopsy specimens.

With the present case included, FR has been described in a total of 18 adults and four children (table 1).<sup>4–7</sup>

The presenting symptom in FR may be joint symptoms or skin nodules, but the presence of both is pivotal for the diagnosis. A polyarthritis in small joints is often described, but a monoarthritis affecting large joints may also be seen. Subcutaneous nodules have been noticed in almost every area of the skin. They are pink or flesh coloured, 2–30 mm, and sometimes surrounded by an erythema. Some patients have a diffuse swelling of the hands, and some develop a thickening of the palmar fascia.



**Figure 1** Skin nodules adjacent to the second metacarpophalangeal, distal interphalangeal, and third PIP joints on the right hand.



**Figure 2** (A) Haematoxylin and eosin stain of a skin nodule showing a cellular area surrounded by vascular granulation tissue ( $\times 40$ ). (B) Densely packed uniform spindle cells surrounded by bundles of thickened collagen fibres ( $\times 100$ )

**Table 1** Features reported at presentation or follow up in 22 patients with fibroblastic rheumatism

	Reported cases*	Our patient	Total No of cases (%)
Female	10	+	11 (50)
<i>Musculoskeletal</i>			
Arthritis or arthralgia	20	+	21 (96)
Contracture of fingers	20	+	21 (96)
Periarticular osteopenia	10	—	10 (46)
Erosions	9	—	9 (41)
Myalgia	2	—	2 (9)
<i>Skin</i>			
Nodules	21	+	22 (100)
Thickened palmar fascia	10	+	11 (50)
<i>Skin pathology</i>			
Fibroblastic proliferation	21	+	22 (100)
Thickened collagen fibres	21	+	22 (100)
Decreased elastic fibres	10	+	11 (50)
Myofibroblasts	9	+	10 (46)
<i>Other features</i>			
Raynaud's phenomenon	8	—	8 (36)
Transient fever	8	—	8 (36)
Raised ESR	8	—	8 (36)

\*Modified from Lee *et al.*<sup>4</sup> Cases described by Chkirate and Job-Deslandre<sup>6</sup> and Colonna *et al.*<sup>7</sup> have been included.

Blood tests are not diagnostic and initial x ray examination of the affected joints is usually normal. Although being non-specific, light microscopy of nodules have shown a consistent pattern in all published cases (table 1). Occasionally, myofibroblasts<sup>8</sup> have been verified.

Nearly all patients with FR have been treated with either oral glucocorticoids, non-steroidal anti-inflammatory drugs, or disease modifying antirheumatic drugs. With different drugs, there have been reports that skin lesions are healed and the number of painful or swollen joints reduced or stabilised. However, nearly all patients, irrespective of age,

end up with contractures of the fingers and, a small number, with a destructive arthropathy. To our knowledge, complete remission has only been described in two patients treated with glucocorticoids<sup>9</sup> and low dose methotrexate.<sup>10</sup> This may indicate that, so far, only the natural history of FR has been studied.

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Accepted 9 May 2004

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## Juvenile idiopathic arthritis associated with autoimmune hepatitis type 2

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*Ann Rheum Dis* 2005;**64**:157–158. doi: 10.1136/ard.2004.021360

**J**uvenile idiopathic arthritis (JIA) is one of the most common chronic disorders in childhood and affects 1 in 1000 children.<sup>1</sup>

Recently, the International League of Associations for Rheumatology proposed consensus criteria for the classification of childhood arthritis under the term JIA.<sup>2</sup> JIA defines an arthritis developing in patients aged 16 years or younger that has no known cause.

Liver disturbance, although not characteristic of JIA, is common and it has been attributed not only to the liver disease associated with rheumatoid diseases themselves but also to many other factors, such as fatty infiltration, drug toxicity, thrombotic accidents, or autoimmune liver disease.<sup>3–4</sup>

Autoimmune hepatitis (AIH) is an unresolving inflammation of the liver of unknown cause.<sup>5</sup> AIH type 2 (AIH 2) is

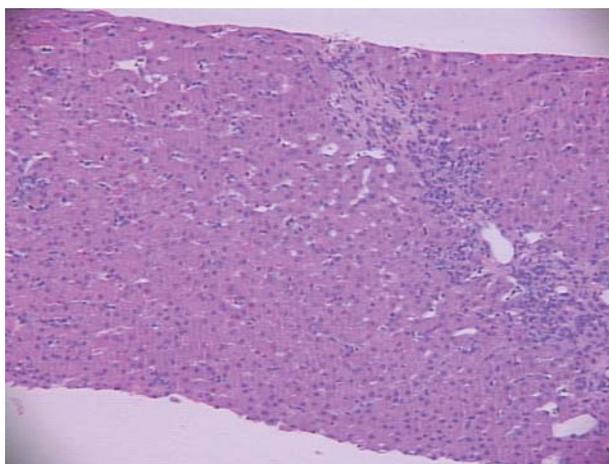
characterised by the presence of anti-liver kidney microsomal autoantibodies (LKM-1) directed against cytochrome P450IID6.<sup>6</sup> Early recognition of the disease and prompt institution of treatment are essential to avoid progression to subacute hepatic failure and the possible need for liver transplantation.

We report an unusual association—namely, a case of severe AIH type 2 in a girl with JIA.

#### CASE REPORT

An 8 year old girl was referred to our paediatric rheumatology clinic in June 2003 for assessment of possible JIA because of fever and joint disease affecting the right knee, with synovitis confirmed by ultrasound examination.

At admission she had laboratory evidence of a vigorous response in the acute phase with high erythrocyte



**Figure 1** Autoimmune hepatitis: portal and periportal lymphoplasmocytic inflammation with hepatitis at the portal-parenchymal interface (active interface hepatitis). Magnification  $\times 20$ .

sedimentation rate and C reactive protein concentration, neutrophilia, and thrombocytosis. Aminotransferases (alanine aminotransferase (ALT) 123 IU/l, aspartate aminotransferase (AST) 87 IU/l, normal value 5–40 IU/l) were increased, and hypergammaglobulinaemia (27 g/l) and increased serum IgG (18.00 g/l) were detected. The indirect immunofluorescence method showed high titres of circulating antinuclear antibodies (ANA; 1/640) and anti-liver/kidney microsomal antibodies (LKM-1; 1/160), whereas anti-smooth muscle antibodies (ASMA), and antimitochondrial antibodies (AMA) were absent. The child's HLA haplotype was A2, B8, DR3, DRw52, DQ2, and the family history was unremarkable for autoimmune diseases.

The girl was discharged after 6 days in hospital with a diagnosis of JIA, on oral non-steroidal anti-inflammatory treatment and physiotherapy (to maintain normal joint range and muscle power).

When seen again, 6 weeks later, her clinical improvement continued but aminotransferases (ALT 123 IU/l, AST 87 IU/l) were still increased, and hypergammaglobulinaemia (26 g/l) and increased serum IgG (16.90 g/l) persisted.

Hepatitis A, B, C, D, E, and G, cytomegalovirus, and Epstein-Barr virus infections were ruled out by appropriate tests, which included serum HBV-DNA and HCV-RNA. High titres of ANA (1/640) and anti-LKM-1 antibodies persisted, whereas ASMA and AMA were absent. A percutaneous liver biopsy<sup>7</sup> was performed and disclosed hepatitis with bridging necrosis and features consistent with autoimmune hepatitis (portal and periportal lymphoplasmocytic inflammation, active hepatitis at the portal-parenchymal interface, bridging, and spotty necrosis) (fig 1). The diagnosis of AIH type 2 was confirmed and characterised as "definite" by using the

scoring system of the International Autoimmune Hepatitis Group.<sup>8,9</sup> After treatment with prednisone (2 mg/kg daily) and azathioprine (2 mg/kg daily) AST and ALT concentrations returned to normal in 5 weeks and striking reduction of immunoglobulin levels and IgG (0.96 g/l) were seen.

## DISCUSSION

The diagnosis of AIH in children with JIA is of paramount importance to guiding treatment and formulating prognosis. Mild abnormalities in liver function tests are common in children with JIA; as few of them undergo liver biopsy, AIH might go undetected.

In conclusion, we believe, in according with Kojima and coworkers<sup>10</sup> that liver histology is warranted in differentiating AIH from liver disease associated with rheumatoid disease and must be performed in all children affected by rheumatoid disease associated with persistent alterations in liver function tests.

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Accepted 7 April 2004

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# Absence of fetal cell microchimerism in cutaneous lesions of lupus erythematosus

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*Ann Rheum Dis* 2005;64:159–160. doi: 10.1136/ard.2003.020297

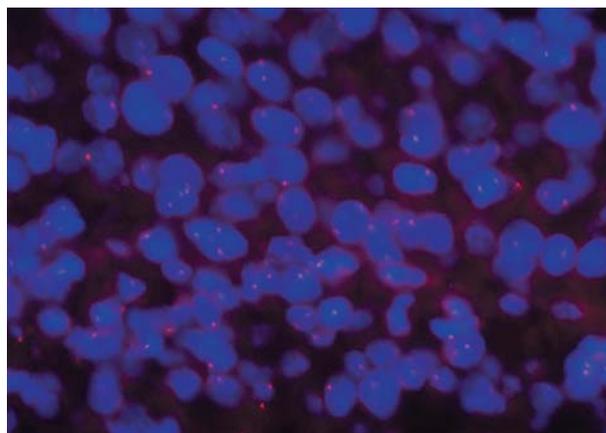
Fetal cell microchimerism develops in all human pregnancies<sup>1</sup> and has been associated with autoimmune diseases such as systemic sclerosis.<sup>2</sup> It has been suggested that these disorders may be the consequence of an immune reaction between fetal and maternal cells in women after pregnancy. More recently, results from our laboratory suggest that microchimeric cells of fetal origin may differentiate into thyrocytes<sup>3</sup> or hepatocytes<sup>4</sup> in thyroid and liver specimens from women with non-autoimmune diseases. We therefore developed an alternative hypothesis suggesting that microchimeric stem cells may have the ability to participate in the maternal response to tissue injury.<sup>5</sup>

Systemic lupus erythematosus (SLE) is an autoimmune disease that predominantly affects women and can target multiple organ systems with severe life threatening complications. In some patients, however, lupus is limited to skin involvement, with discoid or subacute cutaneous lesions, and few of these patients develop severe disease.<sup>6</sup> Mosca *et al* recently reported that the number of microchimeric cells found in patients with lupus nephritis was higher than in lupus patients without nephritis.<sup>7</sup> Their results suggest that the severity of the disease may influence the level of fetal cell microchimerism.

## METHODS AND RESULTS

To further investigate the relationship between fetal cell microchimerism and SLE, we examined biopsy specimens of affected skin from women with previous male pregnancies affected with lupus as well as other skin disorders for the presence of male microchimeric cells. Affected skin sections from six patients with lupus erythematosus (five cases of systemic and one case of cutaneous lupus) and four patients with dermatomyositis or mycosis fungoides (table 1), all with at least one male pregnancy, were analysed for the presence

of microchimeric male cells by fluorescence in situ hybridisation (FISH) using probes specific for the X and Y chromosomes. Between three and six sections were examined from each subject and the scoring was blinded according to the diagnosis or the pregnancy history of the patients. No microchimeric male cells were detected in any tissue sections from these subjects. More than 90% of the nuclei had two detectable X chromosome signals (fig 1). We also examined skin sections from six women with no history of a male pregnancy; these sections also had no detectable male cells. Both X and Y chromosome signals were detected in >90% of nuclei from male control tissue.



**Figure 1** FISH analysis of epidermal keratinocytes. Two X chromosome signals (red) are detected in almost all cells at  $\times 400$  magnification. As all chromosome signals may not be in the same plane of focus, some cells appear to have only one X chromosome. No evidence of a Y chromosome signal (green) was found in any female tissue examined.

**Table 1** Subject history and results of FISH analysis

Subject	Age	Diagnosis	Male pregnancy	Blood transfusion	Sections examined (n)	Male cells detected
1	61	SLE	Yes	Yes	5	No
2	36	CLE	Yes	No	5	No
3	42	SLE	Yes	No	3	No
4	50	SLE	Yes	No	3	No
5	41	SLE	Yes	No	5	No
6	34	SLE	Yes	Yes	5	No
7	74	DM	Yes	Yes	6	No
8	42	MF	Yes	No	4	No
9	59	MF	Yes	No	5	No
10	89	MF	Yes	No	5	No
11	35	SLE	No	No	5	No
12	49	DM	No	No	5	No
13	31	DM	No	No	5	No
14	27	MF	No	No	5	No
15	56	MF	No	No	4	No
16	26	MF	No	No	4	No

No patient had a history of a male twin or a solid organ transplant at the time of biopsy.

SLE, systemic lupus erythematosus; CLE, cutaneous lupus erythematosus; DM, dermatomyositis; MF, mycosis fungoides.

## DISCUSSION

The results presented here support the findings of other studies that have reported the lack of an association between fetal cell microchimerism and SLE.<sup>8,9</sup> Recently, we reported the case of a woman with severe SLE and demonstrated the presence of large numbers of male cells, presumably of fetal origin, in necropsy specimens from her clinically affected tissues.<sup>10</sup> This patient had a severe vasculitis and ultimately died of intestinal necrosis and perforation. In contrast, all of the patients in the present study were alive, underwent skin biopsies, and had better prognoses than the case in our previously published report.

Possibly, the cases of cutaneous and moderate systemic lupus in the current study do not cross the threshold of disease severity to recruit microchimeric cells to areas of tissue damage. Therefore, the results of the present study combined with those of our previous case report support the findings by Mosca *et al* and suggest that extensive maternal tissue damage may be required for the development of microchimerism in cases of SLE.

## ACKNOWLEDGEMENT

Dr Khosrotehrani was supported by the "Fondation René Touraine pour la recherche en dermatologie" in Paris, France.

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Accepted 10 March 2004

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# Diagnostic value of anti-cyclic citrullinated peptide antibodies to detect rheumatoid arthritis in patients with Sjögren's syndrome

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*Ann Rheum Dis* 2005;**64**:160–162. doi: 10.1136/ard.2004.021477

**S**jögren's syndrome (SS), prevalence 3–4%,<sup>1</sup> is a chronic autoimmune disorder characteristically affecting the salivary and lacrimal glands. Rheumatoid arthritis (RA), prevalence 1–4%, is a chronic inflammatory autoimmune disease.<sup>2</sup>

The diagnosis of RA relies mainly on clinical manifestations and serological markers such as rheumatoid factors (RF). The sensitivity of RF in RA is 75% and the specificity 74%.<sup>3</sup> Furthermore, RF is positive in 40–70% of patients with primary SS.<sup>4</sup> Many patients with primary SS and chronic polyarthritis consequently have RF without ever developing RA. An enzyme linked immunosorbent assay (ELISA) test has been developed that recognises a cyclic variant of a citrullinated peptide (CCP).<sup>2</sup> The sensitivity of the first generation anti-CCP test in RA ranges from 41 to 68%,<sup>5,6</sup> the sensitivity of the second generation is 82%.<sup>7</sup> The specificity, however, is 96–98%.<sup>3,5–7</sup>

We analysed data from 164 patients who were diagnosed as SS according to the revised version of the European criteria.<sup>8</sup> These criteria allow a diagnosis of SS if at least four items out of six or three objective items are present. Unfortunately, no single laboratory test is sufficiently reliable to confirm a clinical

diagnosis of SS.<sup>9</sup> Therefore, a second group was assembled with patients in whom three items were present and in whom no other disease could explain the sicca symptoms. This group is further referred to as Sjögren's-like syndrome.

The medical records from all patients were further investigated for RA, according to the 1987 revised criteria.<sup>10</sup> RF and anti-CCP antibodies were determined in the same serum samples using the ELISA anti-CCP mark 2 (second generation) kits from Immunoscan RA, Euro-Diagnostica AB (Arnhem, Netherlands) and the IgM RF ELISA test. All the data were analysed using the SPSS/PC software, version 11.0.

Table 1 shows that both groups were similar. Furthermore, it shows that anti-CCP has a high specificity (98.8%), in contrast with the low specificity of RF (60.6%).

The diagnostic value of the RF test in patients with SS is questionable because of its low specificity (60.6%) in such patients. In this study we found a specificity of 98.8% for anti-CCP in the SS population for RA. The major strength of these data is to emphasise the fact that anti-CCP is not present in patients with primary SS who do not have RA, in contrast with the high prevalence of RF in patients with primary SS.

**Table 1** Characteristics of all patients

Characteristic	All patients (n = 164) (≥3 SS items)	SS (n = 108) (≥4 SS items)	SS-like syndrome (n = 56) (3 SS items)
Age (years), mean (range)	56.3 (20.1–87.3)	57.1 (24.9–87.3)	54.6 (20.1–81.9)
Female/male ratio	9.25/1	8/1	13/1
Follow up			
Years	855.8	627.0	225.4
Median	3.65	4.30	2.75
Range	0–21.6	0–21.6	0.2–15.9
Anti-SSA/Ro, No (%)	94 (57)	77 (71)	17 (30)
Anti-SSB/La, No (%)	71 (43)	62 (57)	9 (16)
RF, No (%)	67 (41)	52 (48)	15 (27)
Anti-CCP, No (%)	5 (3)	3 (3)	2 (4)
Anti-CCP, No (%)			
Specificity (%)	98.8	98.1	100
Sensitivity (%)	75	50	100
PPV (%)	60	50	100
NPV (%)	99.4	98.1	100
RF			
Specificity (%)	60.6	52.8	75.9
Sensitivity (%)	100	100	100
PPV (%)	6.0	3.8	13.3
NPV (%)	100	100	100
McNemar's test (p value)	<0.0001	<0.0001	<0.0001
κ Value (95% CI)	0.058 (–0.013 to 0.129)	0.021 (–0.044 to 0.086)	0.184 (–0.041 to 0.410)

\*SS, Sjögren's syndrome; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

Figure 1 shows an overview of patients who have RA. Patients A and D have SS and RA, patients B and C have Sjögren's-like syndrome and RA while patients E and F do not have RA (RF was negative in both patients), but have a borderline anti-CCP. They could develop RA at a later stage. Patients A, B, and C have a positive anti-CCP.

In this study only four patients were diagnosed with RA. This limits the accuracy of the sensitivity, but is excellent for calculating the specificity. The rationale for this study is the fact that it is important to select only those patients with RA from a group in which most have a positive RF test, with the

help of a specific diagnostic test such as the anti-CCP test. When a cut off value of 100 U/ml for anti-CCP is used, the specificity of anti-CCP for RA is 100%.

We conclude that the RF test for the diagnosis of RA in patients with SS has no value because about 40% of patients with SS have positive RF tests (94% of these tests are false positive). The anti-CCP test, on the other hand, has a high specificity for RA.

## ACKNOWLEDGEMENTS

We thank Jane Meijlink for her help with the English translation.

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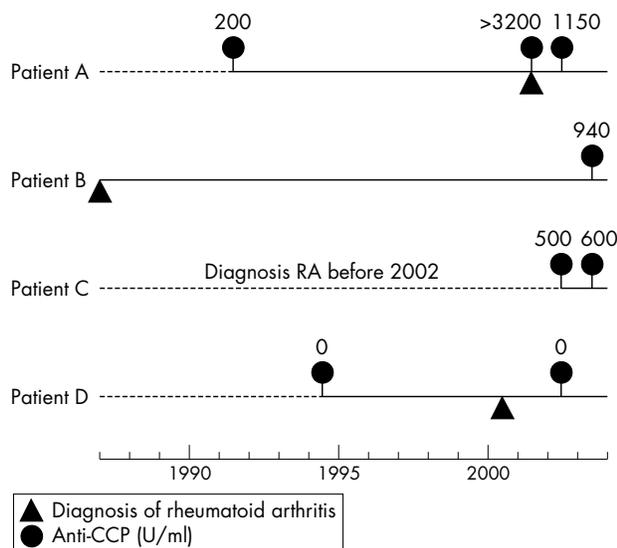
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Accepted 22 August 2004

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**Figure 1** Timescale of the four patients with RA with the relevant anti-CCP results. Patient A (SS) 1991 RF: 50 IU/ml, 2002 RF: 200 IU/ml; patient B (SS-like) 2003 RF: 1600 IU/ml; patient C (SS-like) 2002 RF: 50 IU/ml, 2003 RF: 50 IU/ml; patient D (SS) 1994 RF: 50 IU/ml, 2002 RF: 12 IU/ml. The evaluation criteria for anti-CCP are as follows: ≤25 U/ml are defined as negative, >50 U/ml are positive. Samples with >25 U/ml and <50 U/ml were considered as borderline. The evaluation criteria for RF are as following: negative (<12 IU/ml) and positive (≥12 IU/ml).

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## Chemotherapeutic induced fascial oedema

I Lim, R Kefford, N Manolios

Chemotherapeutic agents have well recognised toxicities in addition to the usual features of nausea, vomiting, and myelosuppression. Toxicity affecting the skin and subcutaneous tissue is uncommon and poorly documented. Of the chemotherapeutic drugs, bleomycin is the best known for its ability to cause skin hyperpigmentation, Raynaud's phenomenon, and thickening of subcutaneous tissues resembling scleroderma, especially affecting the fingers.<sup>1</sup> The taxanes, a class of antimicrotubule agents can cause macules, papules, plaques, and nail changes. Docetaxel, in particular, has been described as causing scleroderma-like changes.<sup>2</sup>

The triazene derived compounds, dacarbazine and temozolomide, are chemotherapeutic agents similar to the nitrosoureas, which act as alkylating agents, predominantly through the methylation of the O<sup>6</sup> position of guanine in DNA. Dacarbazine is an intravenous preparation with single agent activity against malignant melanoma with reported partial remission rates up to 20% and median response durations of 4–6 months.<sup>3</sup> It is also active in Hodgkin's disease and soft tissue sarcomas. Temozolomide is an oral prodrug of 5-(3-methyltriazene-1-yl)-imidazole-4-carboxamide, the active metabolite of dacarbazine. Its major advantage is improved penetration into spaces, such as the central nervous system.

The dose limiting toxicity of both dacarbazine and temozolomide is myelosuppression. Nausea and vomiting occurs in up to 90% of patients.<sup>1</sup> Skin toxicity is not described with either agent. In this case report, we describe the occurrence of fascial oedema and scleroderma-like skin changes with the use of these agents in the treatment of metastatic melanoma.

### CASE REPORT

A 52 year old white woman presented with a 3 week history of "heaviness" of both thighs. She had also noted increasing tightness and swelling affecting both thighs, both shoulders, and the right side of her face and neck. There was no preceding history of Raynaud's phenomenon or musculoskeletal problems.

Four months earlier, she had been diagnosed with metastatic melanoma involving the liver and lung. Palliative chemotherapy with single agent dacarbazine was started (1700 mg infusion over 5 days every 3 weeks). There was a good response and the lung and liver metastases resolved. Four cycles of the dacarbazine chemotherapy were completed before the start of her lower limb symptoms. Other medical history consisted of hyperthyroidism treated with propylthiouracil, and a previous episode of idiopathic pancreatitis.

On examination, the skin was shiny and taut over the back of both thighs, extending over both buttocks. There was similar skin tightness over both shoulders, with less involvement of the right side of her face. No pitting was

demonstrable. There were no peripheral stigmata of chronic sclerodermatous disease (telangiectasia, calcinosis, synovitis, sclerodactyly, or abnormal nailfold capillaries). The quadriceps and hamstring musculature were only mildly tender.

A full blood count and serum biochemistry, including creatine kinase, were normal. The patient was clinically and biochemically euthyroid. Erythrocyte sedimentation rate and C reactive protein were normal. She had a positive anti-nuclear antibody (speckled pattern with titre 1/160, as well as nucleolar pattern with titre 1/640). Extractable nuclear antigens, double stranded DNA, and antineutrophil cytoplasmic antibodies were not detectable. Magnetic resonance imaging (using the STIR technique) of her lower limbs disclosed marked subcutaneous oedema with involvement of the fascia (fig 1). Open muscle biopsy of the right upper lateral thigh was unhelpful, with no evidence of inflammatory infiltration. The biopsy was unfortunately too superficial, with no fascia included. No malignant cells were seen in the biopsy sample and all cultures were negative.

A diagnosis of fascial oedema was made and the only change to her management was that dacarbazine chemotherapy was stopped. Over 2 weeks, the skin tightness and softening of subcutaneous tissues visibly reduced, with associated improvement in her symptoms.

Dacarbazine was again restarted, with five further cycles given, for the liver metastases. She then developed cerebral metastases, and dacarbazine was changed to temozolomide to enhance central nervous system penetration. After the first course of temozolomide at the usual dosage of 250 mg on days 1–5, she redeveloped the skin tightness in a similar distribution. Unfortunately, the patient soon developed a dense left hemiplegia. Chemotherapy was stopped and the patient admitted to a palliative hospital.

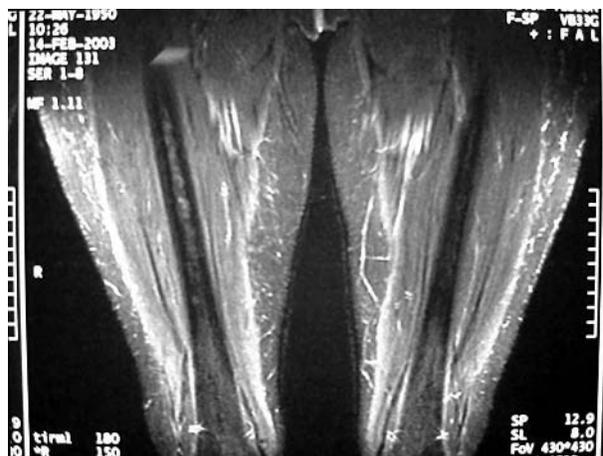


Figure 1 Magnetic resonance imaging (STIR technique) of thighs showing enhancement of the fascia.

## DISCUSSION

Fascial oedema is an uncommon condition of unknown cause that mimics scleroderma, with swelling, stiffness, reduced flexibility of limbs, and thickening of the subcutaneous tissue. Fascial oedema is not usually related to drug toxicity.

We report here the first case of diffuse fascial oedema with scleroderma-like skin changes in a female patient with metastatic melanoma being treated with dacarbazine and its analogue temozolamide. In this case a strong temporal relationship was found between the skin changes seen and drug use. Possible explanations of these skin changes include a direct drug effect; altered immune regulation secondary to drug or disease, leading to the development of autoantibodies and subsequent disease; paraneoplastic effect of melanoma; or coincidence. However, the improvement of clinical signs and symptoms followed by recurrence of these on rechallenge strongly favours a drug effect.

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Accepted 26 March 2004

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# Risk factors for accelerated atherosclerosis in patients with systemic lupus erythematosus

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*Ann Rheum Dis* 2005;**64**:163-164. doi: 10.1136/ard.2004.024299

**A**ccelerated atherosclerosis is a recognised leading cause of morbidity and mortality in systemic lupus erythematosus (SLE),<sup>1</sup> and therefore the identification of patients with SLE at risk for cardiovascular (CV) events is important. However, the mechanisms of premature atherosclerosis associated with SLE are still unknown, with lupus itself a possible candidate and the role of traditional and non-traditional risk factors still uncertain.<sup>2-4</sup> It has been recently suggested that mechanisms inherent to SLE might predispose the vascular wall to acceleration of the atherosclerotic process through traditional risk factors.<sup>5</sup>

## METHODS AND RESULTS

We performed high resolution carotid ultrasonography in 48 consecutive patients (43 women, 5 men, aged 19-77 years) fulfilling the American Rheumatism Association criteria for SLE,<sup>6</sup> without clinical evidence of overt atherosclerosis or diabetes. Plaque at carotid bifurcation was found in 6/48 (13%) and abnormal intimal medial thickness (IMT, considered "abnormal" if > 0.7 mm) in 8/48 (17%) patients.

Older age and high blood pressure were confirmed to be strongly associated with carotid lesions. Patients with plaque or abnormal IMT were significantly older (mean (SD) 69 (7) v 39 (12) years or 62 (14) v 39 (14) years,  $p < 0.0001$  and  $p = 0.0014$ , respectively) and higher blood pressure (>140/90 mm Hg or treatment with antihypertensive drugs) was also more common in plaque positive (67%) than in plaque negative (7%) patients ( $p = 0.0001$ ).

Moreover, among traditional risk factors, we found that men with SLE tended to have plaque more often (20%) than women with SLE (12%), in accord with recent observations both on patients with SLE and the general population.<sup>4,7</sup>

We did not find any relationship between carotid abnormalities, cumulative prednisone intake, or inflammation markers (erythrocyte sedimentation rate, fibrinogen, and C reactive protein). As recently pointed out,<sup>2</sup> inflammation markers, which fluctuate as a consequence of disease activity and treatment, cannot serve as suitable risk markers in SLE, even if increasing evidence indicates that atherosclerosis is an inflammatory disease.

An intriguing finding of our study was the negative association between carotid abnormalities and antinuclear antibodies (ANA). Plaque was more common in ANA negative patients (40%) than in ANA positive patients (9%) ( $p = 0.0495$ ). Our observation may be consistent with the recent study of Roman *et al*,<sup>3</sup> who found that anti-Sm and anti-RNP autoantibodies were less common in patients with plaque, and none of the six Sm positive patients of our series had plaque. Interestingly, it has been recently suggested that Sm antibodies exert a protective effect against coronary artery calcification in SLE.<sup>8</sup>

## DISCUSSION

Although the role of autoantibodies in atherosclerosis,<sup>9</sup> and particularly in accelerated atherosclerosis of SLE, is still a matter of debate,<sup>3,10</sup> the proposed existence of two clinical patterns of SLE, one at higher risk of CV events, characterised by limited autoantibody production, and the other at lower risk but with a wider autoantibody spectrum,<sup>3</sup> opens a new promising research agenda.

Because in atherosclerosis there is evidence for an involvement of humoral immunity, an inappropriate auto-immune response inherent to the process of SLE might have a role in chronic plaque development. On the other hand, aggressive immunosuppressant drugs for more severe diseases might lower or even suppress autoantibody production. Moreover, a genetic predisposition linked to autoantibody repertoires and to clinical subsets of disease cannot be ruled out.

More studies are needed to assess whether ANA testing might represent an additional tool for identifying patients with SLE at risk for CV events.

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Accepted 6 May 2004

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# Angiotensin converting enzyme (ACE) gene polymorphisms and lupus disease severity: a promising link

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*Ann Rheum Dis* 2005;**64**:164–165. doi: 10.1136/ard.2004.020834

The ACE insertion/deletion (I/D) polymorphism has been inconsistently reported to be associated with systemic lupus erythematosus (SLE).<sup>1–3</sup> We proposed the hypothesis that the genetic sequence variation of ACE may not cause SLE, but may participate in disease progression. Among the 13 polymorphisms of the ACE gene recently reported, a polymorphism in exon 17, ACE 2350 G>A, has the most significant effect on plasma ACE concentrations<sup>4</sup> and has been shown to be associated with essential hypertension.<sup>5</sup> We carried out a retrospective, case-control study of the two polymorphisms for putative associations with SLE and allied phenotypes among a homogeneous Asian population.

## METHODS AND RESULTS

We investigated a sample group of 39 patients with SLE (mean (SD) age 33 (10) years; nine men) and 79 healthy control Pakistani subjects from the Aga Khan University Hospital, Karachi, matched for age (35 (9) years) and sex (20 men). Informed consent was taken from all participants and international guidelines for sample collection were followed.<sup>6</sup> All patients fulfilled the American College of Rheumatology criteria for SLE.<sup>7</sup> We used the Systemic Lupus Activity Measure (SLAM)<sup>8</sup> score at diagnosis as an indicator of disease severity; a SLAM score  $\geq 20$  indicating severe SLE and  $\leq 10$ , mild disease. Our patients predominantly had moderate disease activity (SLAM 11–19) at diagnosis and only three patients had mild SLE.

Genotyping for ACE I/D and 2350 G>A polymorphisms was done as previously described.<sup>5, 6</sup> Table 1 shows that the

differences in the distributions of the six genotypes were not significant for either of the ACE polymorphisms, as assessed by  $\chi^2$  analyses on  $3 \times 2$  tables. The groups were in Hardy-Weinberg equilibrium for both markers as shown by the  $D_A$  statistics.<sup>9</sup> The frequency of the 2350A allele increased from 17% in mild SLE to 28% in moderate disease to 32% in severe SLE.

Haplotype analysis and linkage disequilibrium (LD) statistics obtained using Powermarker version 2.0<sup>10</sup> showed that the D and 2350A alleles were in strong linkage disequilibrium (LD) ( $D = -0.23$ ,  $D' = 0.72$ ,  $\chi^2 = 64.4$ ,  $p < 0.001$ ). The extent of LD was more in severe SLE ( $D' = -0.52$ ,  $\chi^2 = 5.04$ ,  $p = 0.025$ ) than in mild to moderate disease ( $D' = -0.26$ ,  $\chi^2 = 1.42$ ,  $p = 0.23$ ). The DA haplotype was more frequent in severe SLE than in mild to moderate disease (odds ratio = 1.43, 95% confidence interval = 0.38 to 5.35,  $\chi^2 = 0.36$ , 1 df,  $p = 0.55$ ).

## DISCUSSION

SLE is present in an aggressive form (moderate to severe disease) in the Pakistani population. Although assessing SLE severity is not simple, as various factors such as response to treatment and type of organ affected and organ damage determine the nature of the disease, we used the SLAM index at diagnosis as an indicator of disease severity. All our patients presented within 6 months of symptom onset, which made SLAM at diagnosis a comparable index of SLE severity.

The ACE gene does not appear play a part in the development of SLE as shown by the lack of association of

**Table 1** Distribution of ACE 2350 G>A and I/D genotypes and allele frequencies (standard errors) as well as  $D_A$  statistics in the patients with SLE and controls

SNP	Genotypes/alleles	Patients with SLE (n = 39)	Controls (n = 79)	Association ( $\chi^2$ (2df)/p)
ACE I/D	II/ID/DD	14/14/11	27/38/14	2.26/0.32
$D_A/\chi^2$	I/D	0.54 (0.04)/0.46 (0.04) 0.07/3.14	0.58 (0.06)/0.42 (0.06) 0.0008/<0.001	
ACE 2350 G>A	GG/GA/AA	18/20/1	38/35/6	1.41/0.49
$D_A/\chi^2$	G/A	0.72 (0.07)/0.29 (0.07) -0.059/3.06	0.70 (0.04)/0.30 (0.04) -0.014/0.354	

\*Significant ( $p < 0.05$ ).

the ACE I/D and G>A polymorphisms, which is consistent with previous findings for ACE I/D.<sup>2</sup> Though the frequency of the 2350A allele was similar in both groups, its distribution was skewed towards severe SLE (SLAM >20). The D and the 2350A alleles were in strong LD and the predominant transmission of the DA haplotype in severe SLE indicated its association with severe SLE. These results support the involvement of ACE polymorphisms with increasing disease severity of SLE.

#### ACKNOWLEDGEMENTS

We are grateful to our patients for their participation and to Drs Philippe Frossard, Ata Khan, and Adil Abbas for help with patient recruitment.

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Accepted 23 May 2004

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## Rheumatoid arthritis in Poland and Lithuania: different clinical course and HLA associations despite similar genetic background

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*Ann Rheum Dis* 2005;**64**:165–166. doi: 10.1136/ard.2003.019158

A recognised feature of rheumatoid arthritis (RA) is its clinical heterogeneity, which may be caused by HLA factors. This theory is supported by observations that relatively severe and mild RA are associated with, respectively, DRB1\*04<sup>1</sup> and DRB1\*01.<sup>2–4</sup> Further, comparisons between populations show that the disease course in the Mediterranean is milder than in northern Europe,<sup>5–8</sup> correlating with a higher frequency of DRB1\*01 and lower frequency of DRB1\*04 in the former than in the latter region.<sup>6–9</sup>

#### METHODS AND RESULTS

Poland and Lithuania are neighbouring central European countries. During clinical practice we noted that RA was less severe in Lithuanian than in Polish patients. To test this observation we prospectively analysed 24 Polish and 20 Lithuanian randomly recruited patients with recent onset RA diagnosed by modified American Rheumatism Association criteria. The patients had a similar mean (SD) age (53.6 (11.4) v 57.0 (14.2) years), mean (SD) age of RA onset (52.2 (11.2) v 55.8 (14.4) years), mean (SD) disease duration (16.9 (13.6) v 13.9 (9.8) months), rheumatoid factor (RF) seropositivity (50% v 40%), and mean (SD) Steinbrocker stage (1.5 (0.5) v 1.5 (0.5)), respectively for Polish and Lithuanian cohorts. The only significant difference was higher frequency of women with RA among the Polish group (22/24 (92%) v 10/20 (50%), p<0.01).

The first assessment of the patients was performed before the start of treatment and then after 2 months and after 1 year. The analysis at baseline indicated significantly more severe disease among Polish than Lithuanian patients (table 1). After 2 months, probably as a result of treatment which was more aggressive in the Poles, disease activity in both groups decreased and most differences present at baseline were no longer seen (table 1). The clinical and laboratory results were similar also after 1 year (table 1), but radiographic analysis performed at that time showed an increase in mean (SD) erosion score and Larsen score in Poles (respectively, 0.7 (1.3) and 4.0 (6.5)), but not in Lithuanians. The difference in Larsen score progression between the two cohorts was significant (p<0.05, t test).

Because of the relative excess of men among the Lithuanian patients we also performed analysis after adjusting for the sex of the patients. We found that all the differences seen between the cohorts at baseline on univariate analysis (table 1) were also present in the multivariate analysis controlling for sex (not shown).

The participants of the study and some additional patients (in total 49 Poles and 32 Lithuanians) were genomically typed for DRB1\*01 and DRB1\*04, and 158 Poles<sup>10</sup> and 134 Lithuanians fully typed for DRB1 (low resolution) constituted ethnically matched controls. When patients were compared with their respective controls a significant increase

**Table 1** Measures of disease severity at baseline and follow up of the patients

Characteristic	Baseline				After 2 months				After 12 months			
	Poland (n = 24)		Lithuania (n = 20)		Poland (n = 24)		Lithuania (n = 16)		Poland (n = 24)		Lithuania (n = 12)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Morning stiffness (min)	126.7	67.2 <sup>1</sup>	106.1	97.9 <sup>11</sup>	71.3	68.8	51.9	38.9	54.0	56.8	31.7	36.8
Number of tender joints	12.1	4.3 <sup>2</sup>	11.3	3.2 <sup>12</sup>	6.3	4.6	8.7	3.0	4.7	4.0	5.4	3.8
Number of swollen joints	7.8	3.3 <sup>3</sup>	4.6	2.9 <sup>13</sup>	3.8	3.5	3.0	1.5	2.9	2.7	2.5	1.8
VAS	7.2	1.7 <sup>4</sup>	5.1	2.0	3.6	2.3	4.1	1.8	3.1	2.0	3.0	1.2
Ritchie index	21.7	8.6 <sup>5</sup>	16.9	6.8 <sup>14</sup>	10.0	8.6	10.0	4.5	7.5	7.4	5.8	4.0
DAS28	5.8	0.7 <sup>6</sup>	5.0	0.4 <sup>15</sup>	4.3	1.2	4.4	0.5 <sup>18</sup>	3.6	1.2	3.8	0.7
Haemoglobin (g/l)	105	16 <sup>7</sup>	123	15	110	14	123	14 <sup>19</sup>	115	18	121	40
ESR (mm/1st h)	81.6	29.1 <sup>8</sup>	39.2	12.3 <sup>16</sup>	45.1	34.7 <sup>17</sup>	27.9	16.4	27.7	18.9	23.1	10.9
Erosion score	4.2	5.3 <sup>9</sup>	0.2	0.5	ND	ND	ND	ND	4.9	5.3 <sup>20</sup>	0.3	0.6
Larsen score	33.9	17.9 <sup>10</sup>	18.1	5.3	ND	ND	ND	ND	37.9	17.5 <sup>21</sup>	18.3	4.7

Poland v Lithuania at baseline (*t* test and Mann-Whitney U test, respectively): <sup>3</sup> $p=1.4\times 10^{-3}$ , <sup>4</sup> $p=2.6\times 10^{-3}$ , <sup>5</sup> $p=7.0\times 10^{-4}$ , <sup>6</sup> $p=2.6\times 10^{-3}$ , <sup>7</sup> $p=4.8\times 10^{-2}$ , <sup>8</sup> $p=3.0\times 10^{-2}$ , <sup>9</sup> $p=3.5\times 10^{-5}$ , <sup>10</sup> $p=1.0\times 10^{-4}$ , <sup>11</sup> $p=4.2\times 10^{-4}$ , <sup>12</sup> $p=9.3\times 10^{-4}$ , <sup>13</sup> $p=1.0\times 10^{-7}$ , <sup>14</sup> $p=3.0\times 10^{-5}$ , <sup>15</sup> $p=4.5\times 10^{-7}$ , <sup>16</sup> $p=4.0\times 10^{-5}$ , <sup>17</sup> $p=3.5\times 10^{-7}$ , <sup>18</sup> $p=4.4\times 10^{-4}$ , <sup>19</sup> $p=1.9\times 10^{-2}$ , <sup>20</sup> $p=1.9\times 10^{-3}$ .

Poland v Lithuania after 2 months (*t* test and Mann-Whitney U test, respectively): <sup>19</sup> $p=8.5\times 10^{-3}$ , <sup>21</sup> $p=1.6\times 10^{-2}$ .

Poland v Lithuania after 1 year (*t* test and Mann-Whitney U test, respectively): <sup>20</sup> $p=5.4\times 10^{-3}$ , <sup>21</sup> $p=6.2\times 10^{-4}$ , <sup>22</sup> $p=5.9\times 10^{-4}$ , <sup>23</sup> $p=1.0\times 10^{-3}$ .

Poland at baseline v after 2 months (*t* test for dependent samples and Wilcoxon matched pair test, respectively): <sup>1</sup> $p=4.9\times 10^{-4}$ , <sup>2</sup> $p=7.2\times 10^{-4}$ , <sup>3</sup> $p=2.9\times 10^{-7}$ , <sup>4</sup> $p=5.6\times 10^{-5}$ , <sup>5</sup> $p=1.0\times 10^{-5}$ , <sup>6</sup> $p=1.7\times 10^{-4}$ , <sup>7</sup> $p=1.0\times 10^{-7}$ , <sup>8</sup> $p=3.0\times 10^{-5}$ , <sup>9</sup> $p=4.5\times 10^{-7}$ , <sup>10</sup> $p=4.0\times 10^{-5}$ , <sup>11</sup> $p=3.5\times 10^{-7}$ , <sup>12</sup> $p=4.4\times 10^{-4}$ , <sup>13</sup> $p=1.9\times 10^{-2}$ , <sup>14</sup> $p=2.1\times 10^{-2}$ , <sup>15</sup> $p=2.5\times 10^{-5}$ , <sup>16</sup> $p=1.2\times 10^{-4}$ .

Lithuania at baseline v after 2 months (*t* test for dependent samples and Wilcoxon matched pair test, respectively): <sup>11</sup> $p=3.5\times 10^{-2}$ , <sup>12</sup> $p=1.1\times 10^{-2}$ , <sup>13</sup> $p=5.3\times 10^{-3}$ , <sup>14</sup> $p=7.0\times 10^{-3}$ , <sup>15</sup> $p=4.9\times 10^{-3}$ , <sup>16</sup> $p=7.6\times 10^{-3}$ , <sup>17</sup> $p=1.9\times 10^{-4}$ , <sup>18</sup> $p=7.8\times 10^{-4}$ , <sup>19</sup> $p=8.1\times 10^{-4}$ , <sup>20</sup> $p=1.6\times 10^{-3}$ , <sup>21</sup> $p=8.7\times 10^{-3}$ , <sup>22</sup> $p=1.4\times 10^{-2}$ .

Poland after 2 months v after 1 year (*t* test for dependent samples and Wilcoxon matched pair test, respectively): <sup>17</sup> $p=3.9\times 10^{-2}$ , NS.

Lithuania after 2 months v after 1 year (*t* test for dependent samples and Wilcoxon matched pair test, respectively): <sup>18</sup> $p=3.8\times 10^{-2}$ , <sup>19</sup> $p=5.0\times 10^{-2}$ , <sup>20</sup> $p=1.7\times 10^{-2}$ , <sup>21</sup> $p=1.9\times 10^{-2}$ .

of DRB1\*04 (41% v 19%, odds ratio (OR) = 2.9,  $p<0.002$ ) but not DRB1\*01 (6% v 17%, NS) was found in the Polish group, whereas among the Lithuanians there was an increase of DRB1\*01 (47% v 21%, OR = 3.3,  $p<0.003$ ) but not of DRB1\*04 (22% v 15%, NS). The increase of DRB1\*01 among the Lithuanian patients was significant also when compared with the Polish patients ( $p<0.00005$ ). No statistically significant differences in the frequencies of any of the HLA\*DRB1 alleles were found between Polish and Lithuanian controls (not shown).

## DISCUSSION

The presented data are interesting in the context of studies of RA features in southern v northern Europe.<sup>6-9</sup> Although the association of mild (among Lithuanians) and severe disease (among Poles) with, respectively, DRB1\*01 and DRB1\*04 was consistent with these reports,<sup>6-9</sup> the lack of difference in distribution of HLA-DRB1 alleles among controls from both populations does not support the hypothesis that variation in population frequency of DRB1\*01 and DRB1\*04 is a general determinant of geographical differences in RA severity.<sup>6-9</sup>

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Accepted 26 March 2004

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# Lambert-Eaton myasthenic syndrome and undifferentiated connective tissue disease in a patient carrying the 8.1 ancestral haplotype

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*Ann Rheum Dis* 2005;64:167–168. doi: 10.1136/ard.2004.021436

A 49 year old woman with polyneuropathy, glomerulonephritis, leucocytoclastic vasculitis, restrictive lung disease, scleroderma-like skin changes, and myalgia, developed progressive myopathy, autoantibodies against voltage gated calcium channels (VGCCs) and a typical electromyographic pattern in accordance with a Lambert-Eaton myasthenic syndrome (LEMS). HLA typing showed that the patient carried the 8.1 ancestral haplotype (HLA-A1, B8, DR3), associated with multiple immunological diseases.<sup>1</sup> To our knowledge, this is the first presentation of LEMS occurring in a patient with undifferentiated connective tissue disease.

## CASE REPORT

Our patient initially presented at the age of 32 (in 1987) with sicca syndrome and Raynaud's phenomenon followed by arthralgia, malaise, and paraesthesia. She subsequently developed leucocytoclastic vasculitis, restrictive lung disease, scleroderma-like skin changes, and proteinuria responsive to steroids. Rheumatoid factor was occasionally positive, while C4 was persistently low to undetectable. SSB and anti-Sm antibodies were once weakly positive (but never thereafter), while low titres of antinuclear antibodies, IgM and IgG immune complexes were increased on several visits. SSA, dsDNA, UIRNP, phospholipid, cANCA, pANCA, Jo-1, and centromere antibodies were negative on several occasions. Thus, her clinical and laboratory investigations did not allow a definite diagnosis at this point.

Starting in 1996–97, the patient noticed slowly progressive loss of strength in the lower extremities (predominantly thighs), rendering her incapable of walking long distances at times. In addition, she had a vasculitic flare, which was eventually controlled with azathioprine. The myopathy, however, persisted for the following years with tolerable symptoms. Various immunosuppressive agents (including methotrexate and ciclosporin A) required for treatment of a progressive polyneuropathy due to epineural vasculitis also did not alter the course of the myopathy. Serum creatine kinase was never raised and multiple clinical and laboratory investigations did not point towards infectious, autoimmune, metabolic, or endocrine causes. In addition, Sjögren's syndrome associated with the vasculitis was diagnosed in the same year, explaining several, but not all, of her rheumatological symptoms.

In 1999, muscle weakness progressed to the upper extremities, while loss of strength, especially in both hip flexors and extensors, increased significantly (up to paresis grade 2/5 for flexors). A muscle biopsy (*M deltoideus*) performed 1 year later excluded any inflammatory infiltrates. Steroid induced myopathy was clinically suspected. Stopping the steroid treatment, however, did not relieve the myopathic symptoms. Further, the patient developed fever of unknown origin in 2001 and received netilmicin as part of the antibiotic coverage. This antibiotic (from the class of aminoglycosides known to exacerbate LEMS<sup>2</sup>) was associated with a dramatic deterioration of her muscle weakness in the lower extremities

(especially hip flexors and extensors, but also knee flexors). Electromyographic studies finally showed a pathological increment after stimulation suggestive of LEMS. Positive autoantibodies against VGCCs confirmed the diagnosis, and daily treatment with 3,4-diaminopyridine improved all myasthenic symptoms after the first dose. Extended tumour screening remains negative to date.

In 2002 the patient surprisingly developed symmetric myalgias of the upper extremities not responsive to 3,4-diaminopyridine. These distinctive muscular symptoms evolved after a gastrointestinal infection. Creatine kinase was still in the normal range, but the erythrocyte sedimentation rate was significantly raised. A high dose of steroids promptly relieved these symptoms, suggesting another, possibly vasculitic, cause for her sequelae at this time.

Finally, recent investigations showed a typical HLA pattern associated with multiple autoimmune diseases (HLA-A1, B8, DR3; table 1)<sup>1</sup> and increased basal tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) levels (10.8 pg/ml; normal range 0.1–8.1 pg/ml). Interestingly, raised serum TNF $\alpha$  was measurable, although the patient's blood was drawn after several weeks of inactive disease defined by lack of signs, symptoms, or laboratory data suggestive of a flare. The patient's only immunosuppressive drug at this time was azathioprine and tapering doses of steroids.

## DISCUSSION

LEMS is a rare autoimmune disorder of the neuromuscular junction characterised by autoantibodies against VGCCs.<sup>2</sup> Cancer is frequently associated and usually detected within 2 years after diagnosis.<sup>3</sup> Our patient, however, is a 49 year old, female non-smoker with coexisting systemic autoimmune disease. In addition, HLA-DRB\*0301, DQB1\*0201, and HLA-B8 are strongly associated with non-neoplastic LEMS, arguing against paraneoplastic mechanisms.<sup>3 4</sup>

LEMS has been reported in association with only a few systemic autoimmune diseases.<sup>5–7</sup> Here we described a patient

**Table 1** Comparison of the ancestral haplotype AH 8.1 with our patient's HLA alleles\*

	AH 8.1	Patient
Class I	<b>HLA-A1</b> HLA-Cw7 <b>HLA-B8</b>	<b>HLA-A1</b> ; HLA-A2 ND <b>HLA-B7</b> ; <b>HLA-B8</b>
Central MHC	TNF AB*a2b3; TNF N*S C2*C Bf*s C4A*Q0; C4B*B1	ND ND ND ND
Class II	<b>HLA-DRB1*0301</b> <b>HLA-DRB3*0101</b> HLA-DQA1*0501 <b>HLA-DQB1*0201</b>	<b>HLA-DRB1*0301</b> <b>HLA-DRB3*01</b> HLA-DQB1*0502 <b>HLA-DQB1*0201</b>

\*Matching haplotypes are shown in bold; ND = not determined.

with undifferentiated connective tissue disease<sup>8</sup> and Sjögren's syndrome before the development of LEMS. The diversity of autoimmune phenomena, including the recent onset of LEMS, prompted us to investigate the patient's HLA typing. In addition to the notion that this LEMS might be non-neoplastic,<sup>3,4</sup> the distinct combination of her HLA alleles indicated the presence of an ancestral haplotype (table 1) which has been associated with various autoimmune conditions.<sup>1</sup> Although polymorphisms in HLA molecules are likely to be involved in predisposition to autoimmunity, the striking association of this haplotype might also be partly explained by linkage of disease promoting genes within the central major histocompatibility complex (MHC) region. Of note, a genetically determined high setting of TNF $\alpha$  has been associated with this haplotype.<sup>9</sup> Raised levels of TNF $\alpha$  have also been linked to LEMS.<sup>10</sup> Our patient indeed showed increased serum levels of TNF $\alpha$  despite inactive disease. Thus, this central cytokine might possibly play a part in the pathogenesis of at least some of the various autoimmune phenomena seen in our patient.

In summary, this report further strengthens the link between autoimmunity to connective tissue and the nervous system, together with a common genetic susceptibility region. It also demonstrates the difficulties of differentiating muscle weakness in patients with systemic autoimmunity.

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Accepted 16 May 2004

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## Takayasu's arteritis with aortic aneurysm associated with Sweet's syndrome in childhood

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*Ann Rheum Dis* 2005;64:168-169. doi: 10.1136/ard.2003.006353

Sweet's syndrome (SS) is an acute febrile neutrophilic dermatosis, characterised by the appearance of skin lesions and fever, seldom seen in children.<sup>1,2</sup> Three reports of SS associated with aortitis in children have been published. Takayasu's arteritis (TA), a vasculitis affecting the aorta and its branches, is quite rare in childhood. Aortic lesions are characterised by stenosis, although aneurysms may be found.<sup>3,4</sup> This paper reports the case of a child presenting those two associated diseases, evolving with aortic aneurysm and congestive heart failure (CHF).

#### CASE REPORT

A 10 month old female patient presented with fever and crusty erythematous papules, in the trunk and limbs evolving to lax dermis (fig 1). A skin biopsy showed neutrophilic infiltrate in the dermis. Seven months later, the patient presented tachycardia and arthritis in hands, wrists, and ankles.

At admission, her general status was regular, she was pale, weighed 9.9 kg (2.5-10th centile), her length was 83 cm (25-50th centile), and she had heart rate of 160 beats/min and respiratory rate of 40/min. Blood pressure was 100/40 mm Hg in the right arm, 130/70 mm Hg in the left arm, 120/68 mm Hg in the right leg, and 98/40 mm Hg in the left leg. Peripheral pulses were wide and symmetric. Cardiac examination disclosed a diastolic murmur at the left sternal

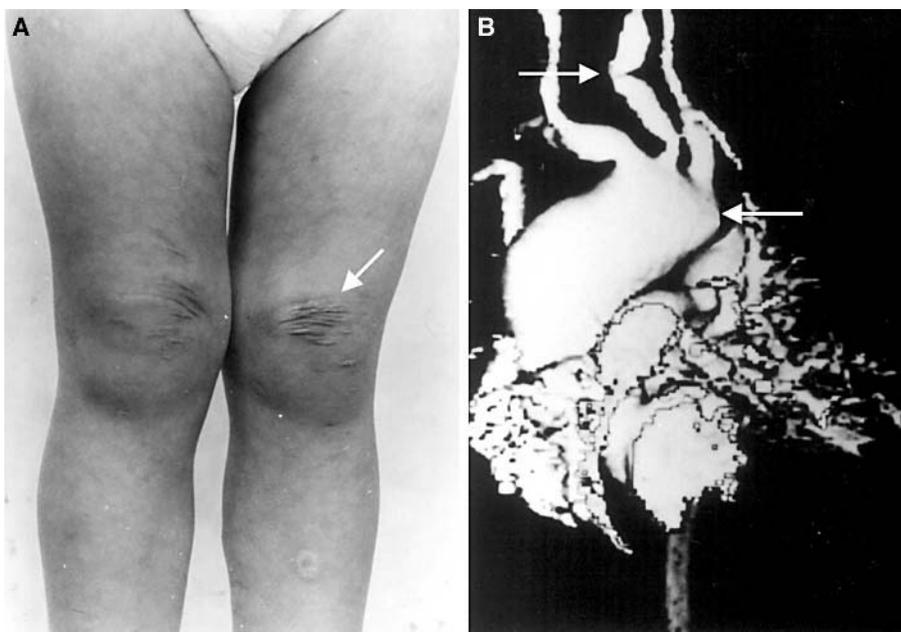
margin. Laboratory tests showed haemoglobin 91 mg/l, leucocytes  $14 \times 10^9/l$ , erythrocyte sedimentation rate 57 mm/1st h, and a negative Mantoux test. Echocardiography showed severe aortic insufficiency (AoI) and marked dilatation of the aorta. Angioresonance showed dilatation of the ascending aorta (30 mm), aortic arch (27 mm), and descending aorta (15 mm); dilatation and stenosis in the brachiocephalic branch, common carotid, and left subclavian arteries (fig 1); and the abdominal aorta and iliac caliber were decreased, with wall irregularities.

During hospitalisation, the patient presented a decrease of left upper limb pulses and ischaemia of left hand fingers. The diagnosis of TA and SS was made. Treatment was started with intravenous gammaglobulin (2 g/kg/monthly) and intravenous pulse methylprednisolone (30 mg/kg) for 3 days, monthly, followed by oral prednisone (2 mg/kg/day), progressively decreased to 10 mg/day.

Seven months later, the patient was clinically stable, the erythrocyte sedimentation rate was 24 mm/1st h, and angioresonance showed unaltered findings in the thorax, with normalisation of abdominal aorta.

#### DISCUSSION

Sweet's syndrome is an acute febrile neutrophilic dermatosis, seldom seen in infancy, characterised by fever and appearance of erythematous painful nodules, plaques, and/or



**Figure 1** (A) Lax dermis (Sweet's syndrome); (B) stenotic and aneurysmatic lesions affecting the aorta and its branches.

papules distributed over the face, trunk, and limbs. It may be associated with systemic manifestations, such as cardiovascular system abnormalities, pulmonary and renal failure. Such a syndrome has been connected with a number of rheumatic diseases, such as dermatomyositis, Sjögren's syndrome, Behçet's disease, and TA. Its cause and pathogenesis are still unknown. Autoimmune and infectious factors seem to be involved.<sup>1,2</sup>

Arthralgia and/or arthritis are seen in about 33% of adult patients. Tuerlinckx *et al* described the case of SS in a 4 month old boy, which evolved with monoarthritis of the right knee, improving after the use of systemic and intra-articular corticosteroids.<sup>5</sup> This is the second case to present such clinical manifestations in a child.

This case presented SS associated with TA with severe involvement of the aorta and its branches. Three cases reports of aortitis associated with SS in children have been published.<sup>6,7</sup> In all of them, skin lesions evolved to scars, characterising lax dermis. Vascular symptoms and signs may be insidious for long periods. Muster *et al* described the case of a 16 month old baby girl diagnosed as having SS with pulmonary involvement, who improved after receiving systemic corticotherapy. After 14 months of treatment, the patient presented ascending aorta aneurysm, AoI, and coronary stenosis, and finally died.<sup>7</sup> The anatomopathological study showed similar histological findings in skin lesions and lesions in the aorta, leading us to question whether aortitis is part of SS. Other authors believe that vascular abnormalities found in such patients fulfil the criteria of TA.

TA is a chronic inflammatory disease, affecting the aorta and its branches. In Japan, 20% of cases were found in patients aged less than 19 and just 2% in children aged less than 10 years. The American College of Rheumatology classification criteria are applicable to the paediatric group. CHF is connected with arterial hypertension, myocarditis, pericarditis, pulmonary hypertension, and AoI. Aortic insufficiency affects 7–55% of patients with TA, being more prevalent among patients with aneurysms.<sup>8–10</sup> The patient described presented CHF, probably secondary to arterial hypertension and AoI.

Another major problem presented by this patient was the presence of aneurysms in several aortic segments and branches. In childhood, vasculitis is an important cause of aneurysms, mainly Kawasaki disease and TA. Aneurysms have been reported in 2–33% of patients with TA, normally associated with stenosis. Aneurysms and AoI are considered to provide the worst prognosis for TA evolution.<sup>9,10</sup>

The reported case presents the association of two rare diseases in an infant, with manifestations seldom seen, such as lax skin, arthritis, aneurysms, and aortic insufficiency.

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Accepted 7 April 2004

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