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.

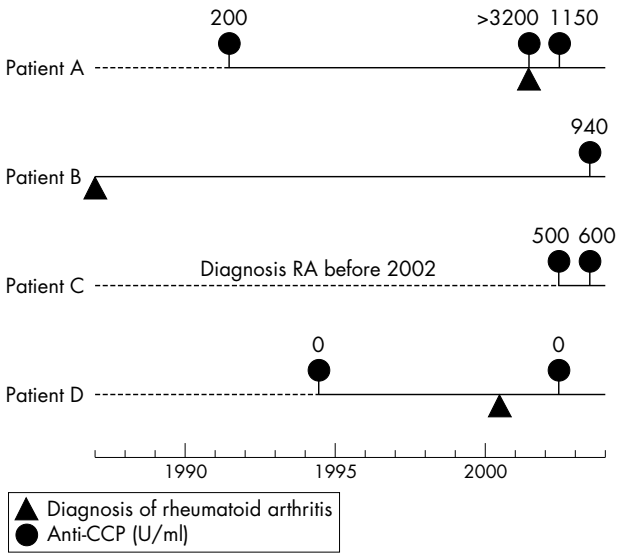

Figure 1 Timescale of the four patients with RA with the relevant anti-CCP results. Patient A (SS) 1991 RF: 50 IU/ml, 2002 RF: 200 IU/ml; patient B (SS-like) 2003 RF: 1600 IU/ml; patient C (SS-like) 2002 RF: 50 IU/ml, 2003 RF: 50 IU/ml; patient D (SS) 1994 RF: 50 IU/ml, 2002 RF: 12 IU/ml. The evaluation 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

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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.[1] 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.[2]

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^6 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.[3] It is also active in Hodgkin's disease and soft tissue sarcomas. Temozolomide is an oral prodrug of 5-(3-methyltriazen-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.[1] 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 antinuclear 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 temozolamide 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.

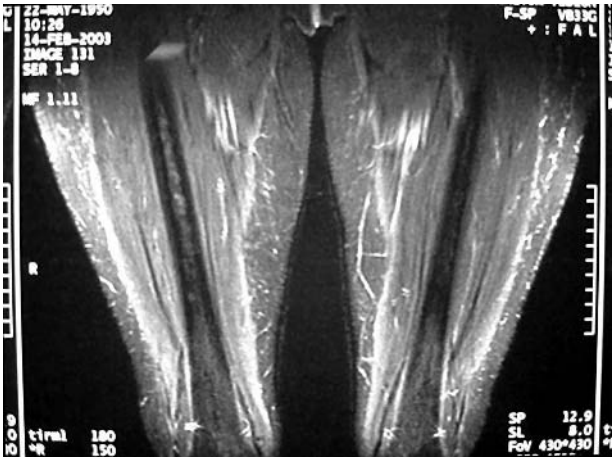

Figure 1 Magnetic resonance imaging (STIR technique) of thighs showing enhancement of the fascia.

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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Risk factors for accelerated atherosclerosis in patients with systemic lupus erythematosus

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Accelerated atherosclerosis is a recognised leading cause of morbidity and mortality in systemic lupus erythematosus (SLE),[1] 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.[2–4] 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.[5]

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,[6] 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.[4 7]

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,[2] 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*,[3] 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.[8]

DISCUSSION

Although the role of autoantibodies in atherosclerosis,[9] and particularly in accelerated atherosclerosis of SLE, is still a matter of debate,[3 10] 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,[3] opens a new promising research agenda.

Because in atherosclerosis there is evidence for an involvement of humoral immunity, an inappropriate autoimmune 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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