LETTERS

Fatal vascular occlusion in juvenile dermatomyositis

Juvenile dermatomyositis (JDMS) is a relatively rare disease characterised by vasculopathy.[1–4] Involvement of the gastrointestinal tract may occur in some subjects and is often life threatening. We describe here a case of fatal JDMS with gastrointestinal perforation. Immunohistochemical examination by antibody against factor VIII seems to be useful for evaluating the pathological basis of vasculopathy in JDMS.

A 13 year old Japanese girl was admitted in April 1994 with high fever, muscle pain, and muscle weakness. She noticed a facial rash for two months before admission. Physical examinations were; blood pressure 135/90 mm Hg, temperature 38°C, and weight 50 kg. She presented with an erythematous rash on her face, neck and arms, heliotropic eruption, Gottron's sign, and nail fold telangiectasia. Proximal muscular weakness and pain were prominent. Laboratory findings were as follows; stool occult blood negative, leucocyte count 5800/mm^3, erythrocyte count 4800 × 10^3/mm^3, thrombocyte count 109 × 10^3/mm^3, and serum C reactive protein value normal. Muscle enzyme examination showed; glutamic oxaloacetic transaminase 294 IU/l, creatinine phosphokinase 5960 IU/l, and lactate dehydrogenase 1469 IU/l. Rheumatoid factor, antinuclear antibody and other autoantibodies were all negative. Electromyogram findings showed short and small motor units. Muscle biopsy specimen showed variation in fibre size and perivascular inflammatory cell infiltration in the connective tissue. JDMS was diagnosed according to the criteria of Bohan and Peter.[2] No features of other connective tissue diseases or malignant neoplasms were present.

Intravenous prednisolone (60 mg/day) was started. However, dysphagia occurred and thrombocytopenia (41 × 10^3/mm^3) with increase in platelet associated IgG (268 ng/10^7 platelet) was apparent. Three courses of methylprednisolone pulse therapy (1000 mg/day for three days) and two courses of high dose intravenous immunoglobulin (20 g/day for five days) were prescribed followed by intravenous methotrexate (100 mg/day every two weeks). Although thrombocytopenia and the increase in serum muscle enzyme had improved, abdominal pain, haematemesis, and melaena resulting from multiple gastrointestinal ulcers were noted. Cyclophosphamide pulse therapy (750 mg/day, every two weeks) and plasma exchange were not effective and oesophageal and bowel perforation occurred. After the resection of perforated lesions, peritonitis occurred and she died of massive abdominal haemorrhage seven months after admission (fig 1).

Surgical findings showed three perforated areas (lower oesophagus, ileocaecal region, and gastric antrum). Pathological examination of these lesions showed occlusion of both arteries and veins. The internal elastic lamina of arteries were intact (fig 2A). Intimal hyperplasia was seen in some vessels and some other vessels were occluded by fibrin thrombi with proliferation of the endothelial cells, characterised by positive staining for factor VIII (fig 2B and C). Some vessels showed infiltration of lymphocytes and foamy macrophages to the adventitia and media.

In JDMS, an autoimmune connective tissue disease, the microvasculature is thought to be the fundamental site of pathology. Banker and Victor reported that the earliest pathological changes of vessels were perivascular collections of inflammatory cells, followed by intimal hyperplasia of arteries and veins.[1] Vessel lumen may be occluded by thrombi, fibrin or swollen endothelial cells.[1–4]

In our case the occluded vessels consisted of intimal hyperplasia and fibrin thrombi with proliferated cells, which were stained with anti-factorVIII antibody, an endothelial cell marker.[5] Although the level of factor VIII related antigen was not measured in this case, a high level of factor VIII related antigen in JDMS has been previously reported by some authors.[3 6–8] Our immunohistochemical findings suggest the endothelial cell dysfunction in the vasculopathy of JDMS and also suggest that anti-factor VIII antibody is useful for evaluating the pathological basis of vasculopathy in JDMS.

Thrombocytopenia seen in our case was accompanied by an increase in platelet associated IgG, and improved after treatment with prednisolone and intravenous immunoglobulin. This suggested that her thrombocytopenia resulted from autoimmune thrombocytopenia associated with dermatomyositis, which has been reported in only two adult cases.[9 10] This is the first report of autoimmune thrombocytopenia in JDMS.

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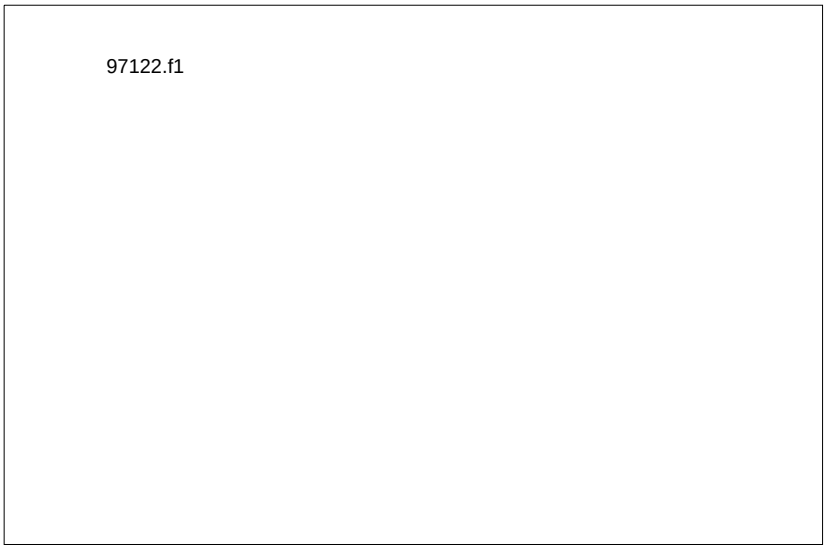

Figure 1 Clinical course. PSL=prednisolone; m-PSL=methylprednisolone; MTX= methotrexate; IVIG=intravenous immunogloburin, CY=cyclophosphamide pulse therapy; PE=plasma exchange; Plt=platelet.

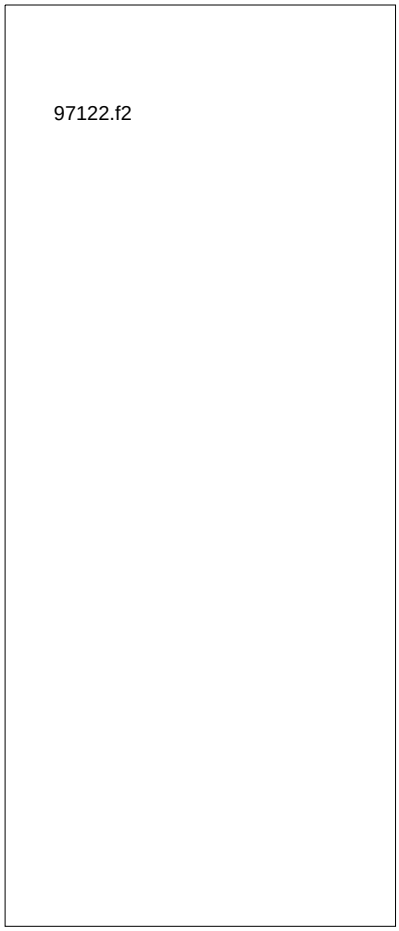

Figure 2 (A) Vascular lesion at the oesophageal perforation. Both the artery (left) and vein (right) were occluded. The internal elastic lamina of the artery was intact, elastica Van Gieson stain. (B). The serial section of figure 2A. Deep blue fibrin obliterated the lumen of the vein, PTAH stain. (C) The serial section of figure 2A and 2B. Endothelial cells were stained with anti-factorVIII antibody (F8/86, mouse IgG1, DAKO), immunohistochemical stain for factor VIII. Bar=0.5 mm.

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Polyarteritis nodosa associated with precore mutant hepatitis B virus infection

Currently there is a trend to support the use of antiviral therapy as the first line treatment of polyarteritis nodosa (PAN) associated to hepatitis B virus (HBV) infection.[1 2] A combination of a short course of corticosteroids, plasma exchange, and interferon α (INFα) has been proposed. However, we have doubts about this approach in all cases and circumstances of PAN related to HBV infection. One of these circumstances would be precore mutant HBV infection.

A 37 year old man was diagnosed with PAN. The initial clinical manifestations were mononeuritis multiplex, orchitis, mild renal failure (creatinine: 168 µmol/l, proteinuria of 0.6 g/dl), abdominal pain, and prolonged fever. Leucocytosis (30 000 WBC, 80% neutrophils), serum asparate aminotransferase: 94 U/L, serum alanine aminotransferase: 244U/l, increased erythrocyte sedimentation rate (90 mm/h) and complement consumption were also observed. Histological diagnosis was performed by testicular biopsy. Infection with HBV precore mutant was present (HBsAg +, HBeAg −, Anti HBe Ag +, Anti HBc Ab IgG/M +, HBV DNA 1180 pg/ml). Retrospective sequence analysis of the serum HBV DNA showed the presence of the precore mutant (substitution of G to A at nucleotide 1896). A therapeutic regimen of prednisone 1 mg/kg per day (twice a week) with rapid discontinuation (one week), plasma exchange, and INFα was started. Significant improvement in clinical symptoms and laboratory data, including renal function, with regression of sediment anomalities and normalisation of the creatinine occurred with this treatment. HBV DNA load (measured two weeks after INFα) and transaminases values were similar to previous range. Four weeks later, while receiving this treatment, abdominal pain, prominent leucocytosis, increased erythrocyte sedimentation rate, and decreased complement component 3 were observed again. The patient developed acute pulmonary oedema secondary to myocarditis associated with vasculitis (left ventricular ejection fraction: % EF: 38%; previous EF: 72%); electrocardiography was non-specific and serial creatine kinase measurement was in the normal range. A diagnosis of relapse of PAN with probably secondary myocarditis was made. This situation was controlled with furosemide, digoxin, and intravenous pulses of methylprednisolone 1 g/day, for three days; a pulse of cyclophosphamide 1200 mg intravenously was also administered. INFα and plasma exchange were stopped. Two weeks later the % EF was 45%, and the patient was discharged with oral prednisone and monthly cyclophosphamide pulses. Six months later the patient achieved clinical remission.

We are cautious to recommend antiviral treatment as first line treatment in polyarteritis associated with HBV. The experience with INF in the treatment of polyarteritis is still limited. To our knowledge, this is the first case report of PAN associated with a precore mutant strain of HBV incapable of synthesising HBe antigen; therefore, there is no previous experience with INF. The precore defective HBV is present in one third of patients in the Mediterranean with chronic HBV infection.[3] It has been speculated that the absence of HBe Ag in the hepatocyte membrane prevents the elimination of infected cells by immune system stimulated by INF. It is considered a viral infection with few trends to spontaneous remission and more progressive in comparison with the infection caused by the wild type virus. In general, the treatment with INF in the chronic hepatitis produced by this variate is unfavourable. The rates of relapses are very high in patients who have precore mutant compared with wild type HBV infection (40–90% compared with 13%)[4–6]; and it is recommended to include these patients in multicentric and controlled trials.[7] On the other hand, HBV mutant infection has been associated with fatal liver failure after immunosuppressive therapy.[8] Precore mutant HBV associated PAN should be considered as an individual entity whose therapeutic approach is complex and not defined at present. It is necessary to perform prospective studies to evaluate the exact role of immunosuppressive and antiviral therapy, including new antiviral agents.

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Polymyalgic presentation of Sjögren's syndrome: a report of three patients

We report on three patients who presented with polymyalgia but on subsequent clinical and laboratory assessment showed findings consistent with primary Sjögren's syndrome.

Clinical, immunological, and genetic differences exist now to classify Sjögren's syndrome (SS) more clearly into primary and secondary SS than in the past.[1 2] Primary SS patients can present with a plethora of symptoms although most patients present with sicca complaints, lethargy or arthralgia. Polymyalgia, as presenting complaints of primary SS, has not been reported previously.

Our patients presented during a two year period with proximal aching and stiffness associated with a raised erythrocyte sedimentation rate (ESR) and all three responded characteristically as in polymyalgia rheumatica (PMR) patients to oral prednisolone therapy.[3] Subsequent investigations and clinical evaluations (table 1) however raised the possibility of primary SS as the underlying condition, confirmed by the usual immunological parameters and all three patients showed some features of the sicca syndrome, although none had a history of swelling of the salivary gland.[1 2]

Follow up over at least a two year period showed that patients were relieved of their PMR symptoms but other clinical and laboratory features persisted, except for normalisation of the ESR. None, however, has yet been able to stop taking prednisolone altogether.

Table 1 Demographic and clinical details of patients

	Age	*Sex*	*Dry eyes**	*Xerostomia†*	*PMR Duration*	*ESR on presentation*	*RF*	*ANF*	*Ro*	*La*	*Protein electrophoresis*
Patient 1	54	F	+	+	2 years	65	+	+	+	+	polyclonal increase in γ globulins
Patient 2	62	F	+	−	1 year	70	+	+	+	+	polyclonal increase in γ globulins
Patient 3	52	F	−	+	6 months	58	−	+	+	+	NK

*Both subjective and objective with impaired tear production (Schirmer's test reading <5 mm in 5 minutes). †Both subjective and objective (lack of saliva pool under tongue). NK, not known.

PMR in itself is a distinct syndrome characterised by proximal aching and stiffness, associated with raised ESR and characteristically responding to adequate prednisolone therapy in a week or 10 days with a significant reduction in the ESR in that time period.[3] All three patients in this report responded in a similar manner, although they continued to have dry eyes or xerostomia, or both; Ro and La antibodies persisted. Noteworthy in this series of polymyalgia patients is the occurrence of this syndrome at a somewhat younger age than the average PMR patient.[1 4] Primary SS is a distinct entity with mainly sicca complaints but with a plethora of manifestations including arthralgia or arthritis without actual joint destruction.[1 2] We are not aware of any previous report of PMR as a presenting manifestation in this condition. PMR-like presentations have been reported in other rheumatic disorders such as rheumatoid arthritis, lupus or in association with a malignancy.[4] To our knowledge, it has not been reported either as a presenting manifestation or as a complaint in established primary SS, although inflammatory arthritis or arthralgia without joint erosions occur commonly.

It is conceivable that the diagnosis of primary SS would have been missed in these patients as their sicca complaints were not prominent, but our index of suspicion for this disorder is high as a result of our clinical and research interests. Moreover, some patients with this disorder are never diagnosed, wrongly diagnosed or diagnosed after a long delay.[1] Given our patients' circumstances and both their clinical and laboratory features we did not feel it was justifiable or even necessary to undertake an invasive test such as lip biopsy to prove that they do have primary SS.[1]

In view of our experience perhaps primary SS should be added to the list of polymyalgia-like syndromes. Longer term follow up of such patients may be of interest to further study their clinical and laboratory progression. In particular it would be important to continually evaluate these patients with regard to the sicca component of the condition. Although around 90% of patients with primary SS have dry eyes or mouth, or both, practitioners should be aware that an occasional patient may have the condition without these features as we reported in the past.[5] Whether some patients with typical PMR have subclinical or unrecognised SS is not known but we have started evaluating such patients with a view to screening for the presence of SS both on clinical and laboratory grounds.

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Duration of methotrexate treatment until partial and total remission of refractory juvenile rheumatoid arthritis

Methotrexate (MTX) was an effective treatment of resistant juvenile rheumatoid arthritis (JRA) in a double blind, placebo controlled study.[1] Its advantages over other second line agents,[2] include oral administration, once a week dose, fewer side effects than parenteral gold,[3] no known oncogenicity[4] or long term effects on fertility.[5] Therefore, paediatric rheumatologists tend to consider the use of MTX as a first choice for children with refractory JRA.[6 7]

We considered the duration of MTX therapy required for the achievement of partial and total clinical remission of JRA, and conducted a prospective open trial of all patients with JRA who were given MTX treatment at the Paediatric Rheumatology Clinic of the Rambam Medical Centre, between January 1994 and January 1997.

The patients had active JRA according to American College of Rheumatology (ACR) criteria[8] and had failed to respond to adequate courses of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids or disease modifying drugs (DMARDs). All the patients who had been previously treated with a DMARD stopped taking the drug at least three months before starting MTX; patients who had previously received MTX were excluded.

Seventeen patients were eligible for inclusion in the study; eight had a polyarticular, five systemic, and four pauciarticular disease onset.

MTX was given orally, in a total weekly dose of 0.2 mg/kg. Although additional prednisone in doses below 10 mg/day and NSAIDs were permitted, no patient received DMARDs or higher dose corticosteroids during the study period.

A partial response to MTX was defined as a 25% reduction of the active joint count or articular severity score, or both, as defined by the Pediatric Rheumatology Collaborative Study Group.[1] Remission criteria for JRA were applied as in adult rheumatoid arthritis.[9]

Seventeen patients were enrolled in the trial (nine girls and eight boys). Mean (SD) age and duration of disease activity at entry were 11.4 (5.4) and 4.5 (3.7) years, respectively. Nine patients had previously received other DMARDs.

Ten patients were taking low dose prednisone. The dose of MTX ranged from 7–15 mg/m^2/wk. Two patients required an increase of the dose to 15 mg after six months of treatment.

Fourteen of 17 patients (82%) displayed a 25% reduction in joint activity after six weeks to four months (median; nine weeks) of treatment; 10 patients (59%) went into full clinical remission after five to 26 months (median 15 months); three patients (18%) relapsed after an initial favorable response, and four (23%) did not respond to MTX.

Laboratory parameters of activity improved in 12 patients (70%).

Disease activity decreased in 15 patients (88%). The mean (SD) number of joints affected with active arthritis at the beginning of the trial was 12.2 (9.3), and decreased to 5.2 (7.1) at its completion. Duration of morning stiffness decreased by more than 50% in 10 patients (59%).

Of 10 patients who had initially been taking low dose prednisone, six (60%) were able to reduce the dose or stop taking corticosteroids altogether.

Seven (41%) patients did not respond to treatment; these were mainly children who required the higher dose of corticosteroids ($p<0.001$). Table 1 shows the clinical characteristics of responders and non-responders.

MTX is being increasingly used by paediatric rheumatologists as a first choice agent in the treatment of children with resistant JRA,[6 7] but prospective studies regarding remission of JRA with MTX are lacking. Two retrospective reports described the clinical characteristics of patients with JRA experiencing remission[10] and the frequency of relapse after discontinuation of MTX treatment.[11] The dose of MTX in those two studies was in the same range that we used in our group.

The remission rate we observed was similar to that reported in the retrospective studies, as well as the mean time to achieve clinical remission: 15 months in our study, compared with 13 months and 11 months in the Wallace[10] and Ravelli[11] studies, respectively, although some of the patients in the study conducted by Wallace received various DMARDs concomitantly with MTX.[11]

Fourteen of our patients experienced a partial remission after a median of nine weeks of treatment, but three did not sustain their remission; four others did not respond to MTX treatment at all. These patients did not differ from the responders as regards duration of disease before starting MTX, disease onset type, previous treatment with DMARDs, or severity of disease activity.

In conclusion, MTX seems to be an effective and safe drug for patients with resistant JRA. An initial favourable response can be expected in most children, and nearly two thirds of our patients experienced good clinical remission after a median treatment period of 15 months.

Table 1 Clinical characteristic of responders to MTX treatment compared with non-responders

	Responders	*Non-responders*	*p Value*
Age (y)	12.7 (5.9)	9.4 (4.1)	NS
F:M ratio	2.3:1	1:2.5	p<0.001
Disease duration (y)	4.7 (4.5)	3.4 (2.5)	NS
Polyarticular type (%)	8 (80)	5 (70)	NS
Total corticosteroid dose at entry (mg/day)	1 (1.7)	9.3 (1.2)	p<0.001
Number of active joints at entry	12.5 (9)	12.4 (10.1)	NS
Duration of morning stiffness (min)	15.5 (20.1)	34.3 (20.7)	p=0.04

Data shown as mean (SD).

In view of the limited numbers of patients who have been studied so far, further prospective controlled studies are necessary to confirm the the value of MTX in the treatment of refractory JRA.

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MATTERS ARISING

Lipid profiles in patients with rheumatoid arthritis

Munro *et al* have demonstrated a salubrious effect of hydroxychloroquine (HCQ) on lipid profiles in patients with rheumatic arthritis (RA).[1] In an accompanying editorial, Situnayake and Kitas highlight the potential importance of dyslipidaemia in RA.[2] We concur with the relevance of this problem, and would like to call attention to some additional data that supports the authors' points.

In an earlier study, we reported on the serum lipoprotein profiles of 60 men with RA.[3] According to National Cholesterol Education Program guidelines,[4] 18% of the patients had dyslipidaemia to such an extent that they would be considered at "high risk" of developing atherosclerotic cardiovascular disease (ASCVD) (that is, total cholesterol (TC) ⩾ 6.21 mmol/l or LDL-cholesterol ⩾ 4.14 mmol/l). An additional 13% had "borderline" increases in lipids (TC ⩾ 5.17 mmol/l or LDL ⩾ 3.36 mmol/l), which would be significant and merit treatment in the setting of other risk factors for ASCVD. Also, 50% of patients had depressed concentrations of HDL-cholesterol, another risk factor for ASCVD. In all, 68% of this particular group of RA patients had significant dyslipidaemia. While this was a skewed subset of RA patients (that is, older men), the results are notable.

In agreement with the findings of Munro *et al*, we demonstrated cholesterol lowering effects of HCQ in systemic lupus erythematosus (SLE) patients.[5] Although the numbers of patients in this pilot study were comparatively small, significant and dose dependent decreases in TC, TC/HDL ratio, and LDL/HDL ratio were noted in this double blind, placebo controlled study. As is the case for RA, accelerated ASCVD is an important contributor to morbidity and mortality among SLE patients.

Recently, another factor has been described that underlines the relevance of dyslipidaemia among patients with rheumatic diseases. Studies detailing the frequency of atherosclerotic complications among patients with homocystinuria have helped establish that increased concentrations of homocysteine are an important, independent risk factor for ASCVD.[6] It has been estimated that increments in total plasma homocysteine as small as 5 μmol/l confer as much additional risk for ASCVD as increases in cholesterol of 0.5 mmol/l.[7] Other than genetic background, one of the most important factors causing an increase in homocysteine is folate deficiency. This is of particular relevance to patients with rheumatic diseases, many of whom are older, and a number of whom have suboptimal dietary intake.[8] Moreover, many patients are treated with agents that directly oppose the activity of folate, particularly methotrexate.[9] Increased concentrations of homocysteine may thus represent a common risk factor for ASCVD among rheumatology patients, which at present is largely unrecognised. Because the presence of multiple ASCVD risk factors leads to a synergistic increase in disease,[10] control of dyslipidaemia may be all the more important in the care of patients with rheumatic diseases.

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Smoking, rheumatoid factors, and rheumatoid arthritis

Saag *et al*[1] reported that smokers were more often rheumatoid factor (RF) positive, had more often rheumatoid nodules and more radiographic erosions compared with non-smokers. Their report questions whether smoking stimulates RF production and thus affects the disease progression in RA. Their findings relate to previous reports that smoking increases the risk of RA,[2–8] although not all studies agree.[9] As raised RF, in particular IgA RF, is associated with poor prognosis in RA,[10] we report a positive correlation between smoking and IgA RF.

We studied 59 RA patients participating in a prospective study on RA. They comprised

Table 1 Associations between smoking and clinical and laboratory findings in patients with RA (n=59)

	Non-smokers (n=47)	*Smokers (n=12)*	*Significance*
Study cohort			
Sex (female/male)	39/8	8/4	NS
Age (y)	59 (46–69)	62 (53–67)	NS
Disease duration (y)	10 (5–16)	4 (2–15)	NS
Laboratory findings			
RF by nephelometry (IU/ml)	78 (31–161)	358 (177–555)	p=0.023
IgA RF by ELISA (AU/ml)	11 (6–31)	73 (23–165)	p=0.017
IgM RF by ELISA (AU/ml)	11 (9–41)	62 (15–135)	NS
CRP (mg/l)	8 (2–17)	11 (6–26)	NS
Clinical findings			
HAQ score*	0.8 (0.4–1.9)	0.4 (0.1–1.2)	NS
DAS score†	4.3 (3.1–5.4)	4.5 (3.8–4.8)	NS
Larsen score	39 (24–70)	45 (31–70)	NS
Rheumatoid nodules	11%	17%	NS

*HAQ: Health Assessment Questionnaire. †DAS: Disease Activity Score.

47 female patients and 12 male patients of mean age 57.0 years and mean disease duration 12 years. They were attending the rheumatology clinic at King's College Hospital, London and fulfilled the 1987 ACR criteria for RA. Forty six patients (78%) were taking one or more disease modifying drugs (DMARDs), most often methotrexate, gold or salazopyrine. RA was assessed by Disease Activity Score (DAS) using 28 tender and swollen joints, health assessment questionnaire (HAQ), Larsen score for erosions, and C reactive protein (CRP). RF was measured by nephelometry and IgA RF and IgM RF by enzyme linked immunosorbent assay (ELISA). The results are presented as medians (25th and 75th centiles). Findings were evaluated with the Mann-Whitney U test and Fisher's exact test when appropriate. The level of significance was set at 5%.

Only 12 (20%) patients were active smokers at the time of study. They had significantly higher RF levels by nephelometry (p=0.023) and higher IgA RF by ELISA (p=0.017) compared with non-smokers (table 1). IgM RF also tended to be higher among smokers (p=0.073). Of the smokers 67% had an increase in both IgA RF and IgM RF compared with only 26% of the non-smokers (p=0.014). DAS, HAQ, Larsen score, and rheumatoid nodules were similar between groups.

Our findings that smoking has a strongest association with IgA RF supports the findings of Saag *et al*.[1] They used a latex fixation test to measure RF, which will preferentially detect IgM RF and does not discriminate between RF isotypes.

Although we found no significant differences between smokers and non-smokers regarding clinical features and this contrasts with the results of Saag *et al*,[1] the prevalence of smoking in our study was low (20%) and the study cohort was also heterogenous in respect to both age and disease duration. Therefore, negative results must be treated with caution.

The association of smoking with IgA RF is interesting as IgA antibodies are important for mucosal immunity. Thus, it is tempting to speculate that smoking may activate or stimulate the mucosal immune system of the respiratory tract leading to increased production of IgA RF. A similar mechanism has previously been suggested for other diseases where mucosal immunity is important and IgA RF is occasionally raised, such as dermatitis herpetiformis and coeliac disease.[11]

We recommend that larger studies are established to evaluate the association between smoking, RF, and disease progression in RA as stopping smoking may have important advantages for RA patients.

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