

MATTERS ARISING

Associations of HLA-DRB and HLA-DRQ genes with two and five year outcomes in rheumatoid arthritis

We were interested in the results of the longitudinal study by Eberhardt and colleagues,¹ who examined the relationship between HLA-DRB and HLA-DRQ genes and outcomes in rheumatoid arthritis. Their results, showing a lack of relationship between HLA-DQ variants and articular disease severity, are in keeping with the results of our previous cross-sectional study that showed no influence of HLA-DQ variants on articular disease severity, in addition to demonstrating a definite relationship between homozygosity for HLA-DR4 and severity of articular disease.²

Eberhardt and coworkers have gone on to look for a relationship between HLA variants and risk of extra-articular disease. Again, in previous studies we have looked at this relationship,³ and showed in cross-sectional studies that different forms of extra-articular rheumatoid disease such as Felty's syndrome, major vasculitis, and various forms of lung disease have different HLA associations. We consider this is an important point to make, as such associations may be lost if different forms of extra-articular rheumatoid disease are analysed together.

The HLA associations in Felty's syndrome and in major forms of rheumatoid vasculitis have been particularly interesting, in that Felty's syndrome has shown an association with a particular HLA haplotype (B44-Bfs-C4A*3-C4B*Q0-DR4-DQB1*0301), while major rheumatoid vasculitis has shown associations with the DRB1*0401 variant of HLA-DR4 and with the C4 null allele, C4A*Q0.

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- 1 Eberhardt K, Fex E, Johnson U, Woolheim FA. Associations of HLA-DRB and -DQB genes with two and five year outcome in rheumatoid arthritis. *Ann Rheum Dis* 1996; 55: 34-9.
- 2 McMahon M J, Hillarby M C, Clarkson R, Hollis S, Grennan D M. Articular disease severity in rheumatoid subjects with and without Felty's syndrome. *Br J Rheumatol* 1993; 32: 899-902.
- 3 Hillarby M C, Grennan D M, Clarkson R. Immunogenetic heterogeneity in rheumatoid disease as characterised by different MHC associations (DQ, Dw and C4) in articular and extra-articular subsets. *Br J Rheumatol* 1990; 30: 5-9.

AUTHOR'S REPLY: We have read with interest the comments by Drs Grennan and Ollier regarding the relationship between HLA variants and extra-articular rheumatoid disease. We do agree that different forms of extra-articular features should be analysed separately. In our cohort, one patient developed major vasculitis, and three developed renal amyloidosis during the first

five years of disease. To date, we have not had a patient with Felty's syndrome. The number of patients is too small to permit any risk analysis, and in our paper we therefore reported only their HLA-DR-DQ pattern. Unfortunately, our genetic typing did not include the C4 null allele.

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LETTER TO THE EDITOR

Rheumatoid arthritis preceding the onset of polyarticular tophaceous gout

Rheumatoid arthritis (RA) and gout are relatively common diseases, but their co-existence is extremely rare. The diagnosis of RA and gout is hampered because 10% of patients with RA have hyperuricaemia¹ and 30% of patients with tophaceous gout may have low titre rheumatoid factor (RF).² It is necessary, therefore, to meet the terms of strict criteria before concluding that a patient has both diseases. The criteria include: seropositive erosive RA, or histological confirmation of rheumatoid nodule/pannus, and recurrent attacks of gout with identification of monosodium urate (MSU) crystals.

Up to December 1995, 14 cases of coexistent RA and gout as defined above were reported.³⁻¹⁶ We now report another case, review the literature, and discuss possible risk factors for the development of gout in our patient.

A 61 year old white woman with RA of more than 25 years duration presented in December 1994 with a swollen, painful thumb with a whitish, chalk-like discharge. Her past history included obesity and hypertension treated with hydrochlorothiazide. RA had been diagnosed based on the presence of polyarthritides in a rheumatoid distribution, and treated with different second line agents over time; at presentation she was receiving oral gold and prednisone 7.5 mg/day.

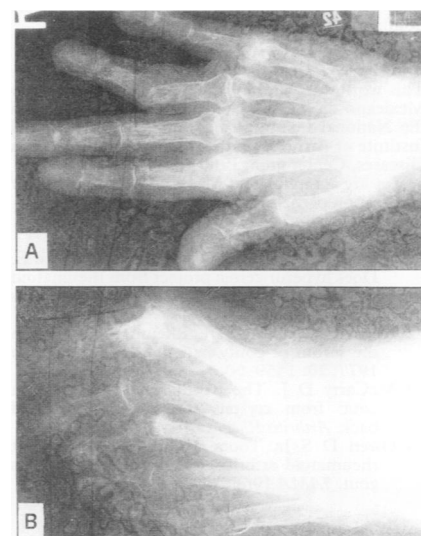
Laboratory data from 1983 revealed a serum uric acid concentration of 132 mg/l and a positive RF (titre 2560). In 1984, rheumatoid nodules over the olecranon bursae, ulnar deviation of both wrists, and swan neck deformities were observed. Fluid from both knees contained 70 000/mm³ leucocytes, with predominance of polymorphonuclear cells; MSU crystals were not found.

In November 1992, the patient had acute right ankle swelling; septic arthritis was suspected. Ankle radiographs showed changes compatible with chronic RA, and magnetic resonance showed a subtalar effusion, but an arthrocentesis was unsuccessful. Serum uric acid concentration was again increased (132 mg/l); blood cultures were negative. Her condition improved spontaneously and continued about the same until August 1994,

when she noted multiple subcutaneous nodules (2-3 mm in diameter) over the extensor surfaces of her upper and lower extremities. MSU crystals were demonstrated in the material drained from her thumb. Serum uric acid concentration was 118 mg/l and RF was negative. Radiographs of hands and feet revealed findings of RA and gout: collapse of both wrists, marked subluxations of the metacarpophalangeal joints bilaterally, large erosions of the distal phalanx of the thumb, and an erosion on the lateral aspect of the fifth right metatarsal head with calcified intraosseous tophi (figure).

The coexistence of gout and RA in our patient is unquestionable. She had evidence of seropositive destructive RA, hyperuricaemia, acute gout, and MSU crystals. Coexistent radiographic changes of RA and gout have been described previously.¹⁷ As RA is far more prevalent than gout, it would be expected that a patient with both disorders would be diagnosed first as having RA. However, in 10 of the 14 previously reported cases (among whom the ratio of men to women was 2.5:1) the first diagnosis was gout (table).

The reason for the usual mutual exclusion of RA and gout is not clear. Hyperuricaemia may have some 'protective immunosuppressive' effect.¹⁸ A blocking effect of RF on Fc receptors adsorbed on MSU crystal surfaces¹³ and a negative correlation between serum uric acid concentration and clinical activity in RA have been demonstrated.¹ As noted, hyperuricaemia occurs in about 10% of RA patients,¹⁸ and has been related to the use of aspirin and analgesics, which may affect the excretion or renal handling of uric acid. Most rheumatic diseases disproportionately affect women rather than men; however, while women are distinctly less affected by gout in premenopausal years, their frequency of gout increases afterwards.¹⁹ Predisposing factors for gout include an underlying joint disease,^{20,21} use of diuretics, and renal impairment.²² Gout in women is commonly polyarticular,²³ tophi



Radiographs of the right hand and foot. Osteoporosis, marginal erosions, subluxation of the metacarpophalangeal joints, and advanced destruction of the wrist, with sparing of metacarpal bases are characteristic of RA. Gouty tophi replace the first and second distal phalanges (A). Erosion in the lateral aspect of the 5th metatarsal head indicates RA. Tarsometatarsal joint destruction and extensive intraosseous tophi are characteristic of gout (B).