Annals of the Rheumatic Diseases, 1988; **47**, 1004–1007

Immunoglobulin A in the skin of patients with ankylosing spondylitis

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SUMMARY Cutaneous immunofluorescence studies were carried out in 21 patients with ankylosing spondylitis (AS) and the results compared with those for 18 healthy subjects. The most prominent finding was the presence of IgA in dermal vessels of patients with AS (71% compared with 17% of the control group). IgG and IgM cutaneous deposits were also observed in patients with AS, but these results did not differ from those of the control group. A renal biopsy was performed in three of the patients presenting with unexplained microscopic haematuria. One of them had an IgA nephropathy, but no correlation was found between kidney and skin deposits of IgA. These findings suggest that IgA cutaneous deposits in AS are not a marker of IgA nephropathy but stress the role of immunoglobulin A in the pathogenesis of this disease.

Key words: IgA nephropathy, cutaneous immunofluorescence studies.

The discovery in 1973 by Brewerton *et al*[1] and Schlosstein *et al*[2] of the association between ankylosing spondylitis (AS) and the major histocompatibility complex, via HLA-B27, raised the possibility that immunological disturbances may be present in this disease. Several authors have investigated the humoral immune response in AS and shown that IgA is the immunoglobulin most frequently raised in the serum of these patients.[3] The meaning of this finding and its role in the pathogenesis of AS remains unclear.

Recently, a possible relation between AS and IgA nephropathy has been suggested. IgA nephropathy is characterised by immunoglobulin A deposits in the mesangial glomeruli. In 50–75% of these patients IgA is also found in the walls of superficial vessels in apparently healthy skin.[4]

This study was designed to investigate the prevalence of immunoglobulin cutaneous deposits in AS, and its possible relation with IgA nephropathy.

Patients and methods

Twenty one patients (19 male, two female) with definite AS (New York criteria) were studied. Patients with psoriasis, inflammatory bowel disease, or Reiter's syndrome were excluded. The mean (SD) age was 43 (13) and mean (SD) disease duration 16 (9) years. All were HLA-B27 positive. None of the patients had a history of dermatitis or alcoholic liver disease. Each patient was evaluated for clinical activity according to criteria described by Cowling *et al*.[5] Special attention was paid to the occurrence of haematuria or proteinuria, and if an unexplained urine analysis abnormality was found a percutaneous renal biopsy was performed. IgG, IgA, and IgM serum concentrations were measured by radial immunodiffusion, and C reactive protein (CRP) concentrations by immunonephelometry.

Punch biopsy specimens of non-sun-exposed skin of the arm were taken in all patients. The presence of deposits of IgG, IgA, IgM, and C3 was studied by direct immunofluorescence using standard methods.[6] All samples were snap frozen and stored at −70°C until cut in a cryostat and stained with rabbit antihuman IgA, IgM in a dilution of 1:10 and antihuman IgG in a dilution of 1:18. Reagents were obtained from Hoesch-Behring. Special attention was paid to the amount and pattern of immunoglobulin deposition in the dermal vessels and dermoepidermal junction.

As a control group the non-sun-exposed normal

Accepted for publication 25 April 1988.
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Fig. 1 *IgA deposits in dermal vessels: granular pattern.*

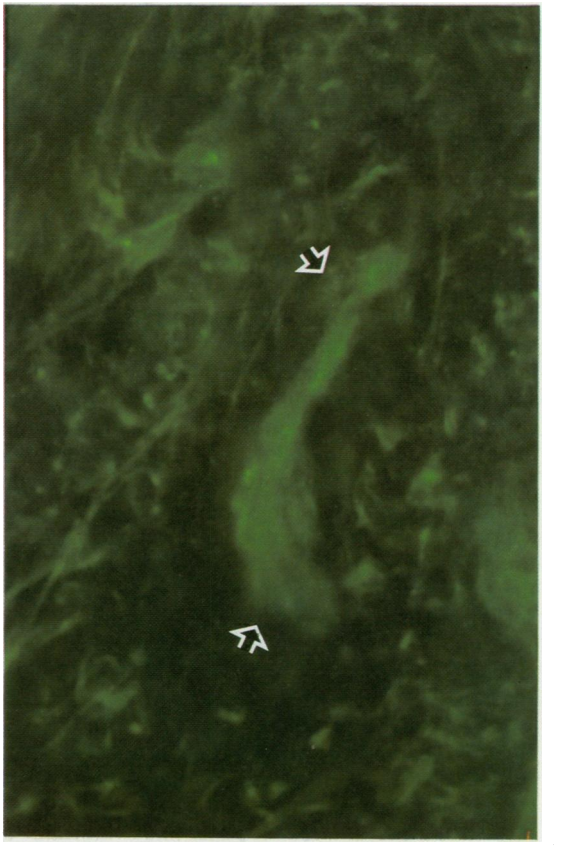

Fig. 2 *IgA deposits in dermal vessels: linear pattern.*

skin of 18 healthy subjects (16 male, two female) was studied by the same procedure. Mean (SD) age of the control group was 43 (12) years. None of the controls had alcoholic liver disease, dermatitis, nephropathy, or rheumatic complaints. The skin biopsy specimens were examined in a 'blinded' fashion by two independent observers.

Results were analysed with the χ^2 test (with Yates's correction when necessary) and Mann-Whitney U test for mean comparisons.

Results

Eighteen of 21 patients (86%) were found to have immunoglobulin deposits in the skin. IgA was detected in dermal vessels in 15 patients with AS (71%), five with a granular pattern (24%) and 10 with a linear pattern (48%) (Figs 1 and 2). Only three of the control group (17%) showed minimal linear deposits of IgA. This difference is highly significant (p=0·0006). Deposits of IgG were present in five patients (24%), IgM in three patients (14%), and C3 in nine patients (43%) (Table 1). None of the patients or controls had immunoglobulin deposition in the dermoepidermal junction.

Three of 21 patients had asymptomatic, unexplained microscopic haematuria, and a renal biopsy was performed. One of these had IgA nephropathy, but no IgA deposits in the dermis were observed.

Table 1 *Cutaneous immunofluorescence findings*

Cutaneous deposits	*AS (n=21) No (%)*	*Controls (n=18) No (%)*	*Statistical significance (χ^2)*
IgA	15 (71)	3 (17)	p=0·0006
Granular pattern	5 (24)	0 (0)	—
Linear pattern	10 (48) (3 with minimal deposits)	3 (17) (all minimal deposits)	—
IgG	5 (24) (all linear pattern)	0 (0)	p=0·08* (NS)
IgM	3 (14)	4 (22)	NS
C3	9 (43)	6 (33)	NS

*With Yates's correction.
NS=not significant.

The remaining two had granular IgA deposits in the skin but not in the kidney.

The presence of IgA with granular or linear pattern in the cutaneous specimens could not be correlated with disease duration, history of iritis or peripheral arthritis, clinical activity, IgA, IgM, IgG, and CRP plasma concentrations (data not shown).

Discussion

We are not aware of previous skin immunofluorescence studies in AS. Deposits of IgA and IgG in the skin of patients with AS using the peroxidase-antiperoxidase stain were described recently,[7] however. In rheumatoid arthritis (RA) several studies of cutaneous immunofluorescence have been carried out.[8–10] The main finding was the presence of IgM in dermal blood vessels, whereas IgA was rarely found. This discordance in cutaneous immunofluorescence findings between AS and RA supports a different immunological abnormality in the two diseases. The reason for the presence of these immune deposits in AS is unknown. Raised serum concentrations of IgA are frequently seen in AS, and in some patients this is well correlated with clinical disease activity and acute phase reactants.[5 11 12]

As tissue and serum proteins are normally in a state of dynamic interchange it is not surprising that serum factors are present in the extravascular compartments. Thus the homogeneous (linear) deposits of IgA in vessel walls may indicate an enhanced passage of proteins through the vascular endothelium. The granular deposits of immunoglobulin could be related to their high molecular weight polymeric nature, or to the presence of immune complexes, as they seem to occur in mesangial glomeruli in primary IgA nephropathy.[13]

Furthermore, an association between IgA nephropathy and AS has been reported, and the coexistence of these two diseases is probably not coincidental.[14] The prevalence of IgA nephropathy in patients with AS is unknown. Isolated microscopic haematuria without proteinuria or renal impairment is not uncommon in the early years of IgA nephropathy.[15] Interestingly, an increased incidence of recurrent haematuria in patients with AS has been described, suggesting a possible relation with IgA nephropathy.[16] Recently, Shu *et al* reported five cases of glomerulonephritis among 116 patients with AS, three of them being IgA nephropathy.[17] Significantly, the three patients with both diseases presented with isolated microscopic haematuria as the sole sign of their nephropathy. In view of these findings the true incidence of mesangial IgA nephropathy in AS may be greater than has been recognised.

As cutaneous deposits of IgA have been found in 50–75% of patients with IgA glomerulonephritis[4] the question arises whether these deposits are a marker of the presence of IgA in renal glomeruli. Preliminary data do not support this hypothesis. Although renal biopsy was performed in only three patients with AS, there is no evidence of a relation between IgA cutaneous deposits and IgA nephropathy in these patients. Further studies will be necessary to confirm these results.

The high prevalence of IgA cutaneous deposits in our patients highlights the role of this immunoglobulin in AS. Immunoglobulin A is known to be the most important immunoglobulin produced by the immune-secretor system. Thus our results further support the concept that antigenic mucosal stimulation could be important in the pathogenesis of this disease.

We would like to thank Miss Maria Sala Ticó for her skilful technical assistance. This study was supported by a grant from the Hospital Clinic of Barcelona.

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