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Anti-keratin antibodies in rheumatoid arthritis: frequency and correlation with other features of the disease

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SUMMARY

Anti-keratin antibodies (AKA) were detected in 68 out of 98 patients (69%) with classical or definite rheumatoid arthritis (RA). The intensity of the AKA reaction correlated significantly with articular index (AI), grip strength (GS), erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP) concentration, serum amyloid A (SAA) protein concentration, the level of antibodies against single stranded DNA (ssDNA) and the IgM rheumatoid factor (RF) titre. A significantly higher number of patients with nodules and Sjögren's syndrome were AKA positive compared with patients without extra-articular features (EAFs) and the AKA titre was significantly greater in the former group. The mechanisms underlying appearance of AKA are not known but may relate to an as yet unidentified structural alteration of keratin in this disease or may just reflect the rheumatoid autoimmune diathesis.

INTRODUCTION

Keratin is a major constituent of the stratum corneum of the skin and is also present in the superficial layers of the oesophageal epithelium in the rat, though not in man. During keratinization tonofibrils of the malphigian layer of the skin undergo specific changes leading to the formation of mature keratins. These highly insoluble intracellular proteins form a resistant, protective horny layer. Human keratin fraction and analogous fractions from different mammalian species behave similarly in polyacrylamide gel electrophoresis suggesting that the keratin subunit has not undergone major changes during evolution (Bauer, 1972). Their antigenicity was first reported by Pillemer, Ecker & Wells (1939). A naturally occurring antibody to animal oesophageal keratin was first reported in sera of patients with RA by Young *et al.* (1979); this was confirmed by others (Johnson *et al.*, 1981) and its presence was also noted in some patients with scleroderma, (Scott *et al.*, 1981). Interestingly, anti-keratin antibodies (AKA) have not been detected in normal sera nor in patients with a range of autoimmune and arthritic conditions.

In the present study of patients with RA we have correlated the presence of AKA and intensity of their reactions with various clinical parameters of disease activity, with the presence of EAFs, serum CRP and SAA concentrations, titre of antibodies to ssDNA and a newly described index of disease activity (IDA) derived from multivariate analysis of subjective, semi-objective and objective features (Mallya & Mace, 1981).

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PATIENTS AND METHODS

Ninety-eight patients with RA according to the American Rheumatism Association criteria (Ropes, 1959) were studied. There were 68 females and 30 males. Their ages ranged from 35–80 years (mean 60·5 years) and the duration of disease from 6 months to 38 years (mean 9·6 years). Fifty-four had definite, 43 classical and one probable RA. Thirty-eight patients had EAFs which consisted of nodules in 26, vasculitis in six, Sjögren's syndrome in 10, fibrosing alveolitis in five, Felty's syndrome in two and an isolated lung nodule in one.

The IDA was derived from a multivariate analysis which consisted of: two subjective criteria, morning stiffness (MS) and pain scale (PS); two semi-objective features, GS and AI, and two objective measures, haemoglobin (Hb) and ESR. All these variables were measured by the techniques previously described and referred to by Mallya & Mace (1981) and Mallya *et al.* (1982). Platelet count, RF, serum CRP level, SAA level and AKA were assayed precisely as described elsewhere (Roitt & Doniach, 1969; Pepys *et al.*, 1978; de Beer, Dyck & Pepys, 1982; Young *et al.*, 1979). The AKA reactions were graded visually, according to the intensity of staining, as negative (I), weak positive (II), weak–moderate positive (III), moderate positive (IV) and strong positive (V) by the same observer (BIJY) who had no access to clinical details. The anti-ssDNA was measured using a solid phase binding assay (Klotz, Minami & Teplitz, 1979).

Correlation between different variables was sought using Spearman's rank correlation coefficient and differences between groups were tested with Wilcoxon's rank sum test.

RESULTS

Sixty-eight of the 98 patients (69%) were AKA positive and 97 out of 98 (99%) were RF positive. The intensity of the AKA reaction correlated significantly with GS, AI, ESR, platelet count, serum CRP level, SAA level and anti-ssDNA titre, but not with MS, PS and Hb. (Table 1). The IDA showed a significant correlation with the AKA reaction ($P < 0{\cdot}02$), with the serum SAA level ($P < 0{\cdot}002$) and the serum CRP level ($P < 0{\cdot}001$) but not with the anti-ssDNA titre.

Table 1. Statistical significance of correlation coefficients between AKA grade and other variables in RA

	MS	*PS*	*GS*	*AI*	*anti-ssDNA*
$P <$	n.s.	n.s.	0·05	0·05	0·02
	Pl	*ESR*	*CRP*	*SAA*	*RF*
$P <$	0·007	0·002	0·001	0·002	0·001

n.s. = not significant; Pl = platelets.

Thirty-two out of the 38 patients with EAFs (84%) and 38 of the 60 patients without EAFs (63%) were AKA positive and there was thus no significant difference in the overall incidence of AKA between the two groups. However, 90% (nine of 10) of patients with Sjögren's syndrome, 81% (21 of 26) of patients with nodules and 100% (all five) of patients with fibrosing alveolitis were AKA positive. Furthermore the intensity of the AKA reaction was significantly greater in the groups with nodules ($P < 0{\cdot}01$) and with Sjögren's syndrome ($P < 0{\cdot}01$) than in the group without EAFs (Fig. 1). Although there was a significant difference ($P < 0{\cdot}05$) in AKA intensity between patients with fibrosing alveolitis and those without EAFs, the number of patients (five) was too small to draw firm conclusions. As expected the titre of RF was significantly higher in patients with EAFs than in those without ($P < 0{\cdot}001$).

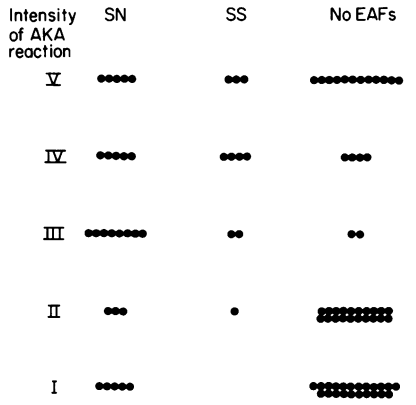

Fig. 1. Intensity of AKA staining reaction in RA patients with and without extra-articular features (EAFs). SN = subcutaneous nodules; SS = Sjögren's syndrome.

DISCUSSION

We have analysed here sera from a large group of well characterized patients with RA and shown that most of the indices of disease activity correlated significantly with the presence of AKA. A previous study (Scott *et al.*, 1981) failed to show such correlations. This may have been due to differences in technique and in interpretation of AKA reactions such as the absence of any grading of staining intensity. A significant association of AKA with RF has been reported previously (Johnson *et al.*, 1981; Scott *et al.*, 1981) and in this study we have shown a close correlation between the two and also between AKA and anti-ssDNA levels. The significance of either of these relationships is not clear. Previous absorption experiments with heat aggregated IgG and gel filtration chromatography showed that AKA is an IgG antibody unrelated to RF (Young *et al.*, 1979). Most patients with EAFs tend to have raised titres of RF and this was confirmed here.

The AKA reactions followed a similar pattern in patients with nodules and those with Sjögren's syndrome, suggesting the possibility that normal or structurally altered keratin may become immunogenic during the formation of subcutaneous nodules or during the development of Sjögren's syndrome. However, some patients without either of these complications also have AKA and may therefore also have altered keratin, whilst an alternative view is that AKA may play a pathogenetic role in development of nodules and/or Sjögren's syndrome. It is interesting to note that the parotid glands share an ectodermal origin with the skin. The presence of AKA has recently been reported in patients with scleroderma (Scott *et al.*, 1981). Whilst it is possible that patients with RA and those with scleroderma may both develop altered and therefore autoantigenic keratin, the mechanisms underlying appearance of these antibodies may be different in the two diseases. Further studies are required to answer these questions.

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