Case report

Effect of penicillamine treatment on immune complexes in two cases of seropositive juvenile rheumatoid arthritis

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Bresnihan, F. P., and Ansell, B. M. (1976). *Annals of the Rheumatic Diseases*, 35, 463–465. **Effect of penicillamine treatment on immune complexes in two cases of seropositive juvenile rheumatoid arthritis.** A correlation has previously been observed between the presence of enhancing complexes and cutaneous vasculitis in rheumatoid arthritis. Two patients with seropositive juvenile rheumatoid arthritis are described in whom enhancing complexes were detected before the appearance of cutaneous vasculitis. Their contrasting response to penicillamine is discussed in relation to the role of rheumatoid factor and antinuclear antibodies.

Penicillamine has been used in the treatment of rheumatoid arthritis for several years. Controlled trials suggest that it is as effective as gold in suppressing disease activity (Multicentre Trial Group, 1973; Huskisson and others, 1974). The mode of action of penicillamine is unknown; Jaffe (1970) has discussed some hypotheses. Circulating soluble immune complexes may play a pathogenic role in rheumatoid arthritis, particularly in patients with cutaneous vasculitis, and the effect of penicillamine could be through its action on such complexes.

A method of detecting soluble complexes in serum, based on the ability of guinea pig peritoneal macrophages to take up aggregated human IgG and immune complexes, provides a competitive radio-bioassay system for measuring the latter. In this system the sera of patients with systemic lupus erythematosus inhibit uptake of ¹²⁵I-labelled aggregated human IgG (Onyewotu, Johnson, and Holborow, 1974). In contrast, the sera of rheumatoid patients with vasculitis show a strong tendency to enhance rather than inhibit uptake. This is not solely dependent upon the presence of rheumatoid factor but appears to result from an interaction between rheumatoid factor and soluble immune complexes present in the sera (Onyewotu and others, 1975).

This short paper describes 2 patients with seropositive juvenile rheumatoid arthritis in both of whom enhancing complexes (EC), measured as described by Onyewotu and others (1975), were discovered before any clinical evidence of vasculitis. Their varying responses to penicillamine therapy are compared.

Case reports

CASE 1 (FIG. 1).

A 15-year-old girl developed polyarthritis in June 1973. Three weeks after the first symptoms the erythrocyte sedimentation rate (ESR) was 112 mm and differential agglutination titre (DAT) 1:128. Juvenile rheumatoid arthritis was diagnosed and therapy with aspirin started. Because of failure to improve, prednisone 20 mg daily was begun in August and gradually reduced to 7.5 mg daily. She continued to have an active polyarthritis and in January 1974 rheumatoid nodules developed. She was referred to this unit in February 1974, when erosions were noted in metacarpal and metatarsophalangeal joints. No cutaneous vasculitis was present. DAT at this time had risen to 1:512 and ESR was 47 mm/h. Tests on her serum gave the following results: IgG 1440 mg/100 ml (14.4 g/l); IgA 367 mg/100 ml (3.67 g/l); IgM 241 mg/100 ml (2.41 g/l); antinuclear antibodies (ANA) absent; C3 164 mg/100 ml (1.64 g/l); EC present. After conversion to an alternate-day prednisone regimen, in view of her severe and active disease, penicillamine 150 mg daily was started and the dose was

slowly increased to 600 mg daily. This led to a gradual clinical improvement, loss of synovitis, fall of ESR to normal and DAT to 1:4, and loss of serum EC. She has returned to normal schooling and now leads a fully active life.

CASE 2 (FIG. 2)

A 16-year-old girl developed polyarthritis in November 1971. Aspirin failed to control her symptoms and in September 1972, hydroxychloroquine was added, but did

not reduce disease activity. She was referred to this unit in February 1973, with severe polyarthritis, widespread nodule formation, and many small erosions on the radiographs of the hands. No vasculitis was present. ESR was 64 mm/h; DAT 1:32; ANA 158 units/ml; DNA binding capacity within normal limits; C3 82 mg/100 ml (0.82 g/l), IgG 2160 mg/100 ml (21.6 g/l), IgA 211 mg/100 ml (2.11 g/l), IgM 300 mg/100 ml (3.0 g/l), and EC were present in the serum. Gold therapy was started in April 1973, and by the end of August she had received 800 mg. There was no improvement in the joints, more nodules had developed, and erosions had increased in the hand and foot x-rays; ESR had risen to 88 mm/h and the DAT to 1:128; EC were still present but no cutaneous vasculitis was seen. Gold was discontinued and penicillamine 150 mg daily was begun and slowly increased to 1200 mg daily. Only slight reduction was seen in the degree of nodule formation. During treatment vasculitic lesions appeared intermittently in the nail folds and at nodule sites, and she had transient bouts of pleurisy and pericarditis. Corticotrophin 20 units (Acthar Gel) on alternate days started in August 1974 produced some clinical improvement, but she continued to have widespread synovitis, nodule formation, and intermittent vasculitis. The raised ESR persisted, and DAT rose to 1:512, remaining at this level for several months, and settling later to 1:32. During the same period the ANA rose to 1:1600 and has continued at this high titre. Serum C3 remains low (48 mg/100 ml; 0.48 g/l) and EC are consistently present in the serum.

Discussion

Onyewotu and others (1975) concluded that rheumatoid factor produces EC by interacting with soluble immune complexes in the serum. Both patients in this study had rheumatoid factor in high titre when enhancing complexes were first detected. On penicillamine treatment, EC rapidly disappeared from the serum in Case 1, DAT fell to normal levels, and clinical improvement occurred. In

FIG. 1 Course of Case 1. Onset of juvenile rheumatoid arthritis occurred at age 15 years

FIG. 2 Course in Case 2 showing steady deterioration despite increasing penicillamine, with persistence of enhancing complexes, development of vasculitis, and development of vasculitis. Onset of juvenile rheumatoid arthritis occurred at 16 years of age

Case 2, however, vasculitic lesions supervened with continued disease activity against a serological background of persistently positive tests for EC, raised DAT, and a titre of ANA rising to high levels. These findings suggest that in Case 2 antinuclear antibodies may have contributed significantly to the composition of pathogenetic immune complexes, and that penicillamine treatment did not prevent formation of the latter. If this interpretation is correct, a beneficial effect from penicillamine

therapy should be predicted with caution in rheumatoid subjects having or developing high titres of ANA.

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