Case report

Antinative DNA antibodies as a reaction to pyrazole drugs

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Grayson, M. F., Martin, V. M., and Markham, R. L. (1975). *Annals of the Rheumatic Diseases*, 34, 373–375. Antinative DNA antibodies as a reaction to pyrazole drugs. A case history is presented of the occurrence of a high binding capacity for native DNA in the serum of a patient on phenylbutazone. This reverted to normal on stopping the drug. The patient also had a reversible neutropenia and leucopenia, and it is suggested that the high anti-DNA binding capacity was a feature of a drug-induced lupus-like phenomenon.

The development of a lupus erythematosus-like phenomenon as a reaction to the pyrazole drugs, phenylbutazone and oxyphenbutazone (Ogryzlo, 1956; Handley, 1971) and to many other drugs (Alarcón-Segovia, 1969) has been reported in the past. No report has yet appeared of a drug-induced lupus-like reaction in which a high titre of antibodies to native double stranded DNA (nDNA) was found, and it has been maintained that the absence of such antibodies is a feature of the drug-induced reaction (Hughes, 1973).

Case report

The patient, aged 49, with ankylosing spondylitis, was treated with phenylbutazone 100 mg three times a day intermittently since 1965 and continuously since September 1971. His haemoglobin in 1971 was 13.9 g/dl, white cell count $6.0 \times 10^9/l$ ($6000/mm^3$) (and in February 1972 $5.0 \times 10^9/l$ ($5000/mm^3$)), with a normal differential count, and platelets $128 \times 10^9/l$ ($128000/mm^3$).

In November 1972 he had a mild febrile illness, and phenylbutazone was changed to oxyphenbutazone in the same dose.

In January 1973, his Hb was 11.8 g/dl, WBC $2.6 \times 10^9/l$ ($2600/mm^3$), neutrophils 442 (17%), lymphocytes 1794 (69%), monocytes 208 (8%), eosinophils 156 (6%), and platelet count normal. Oxyphenbutazone was stopped and he was admitted to hospital 3 weeks later. His ESR was then 130 mm (55 mm one year before) in the first hour, Hb 11.5 g/dl, WBC $3.4 \times 10^9/l$ ($3400/mm^3$), neutrophils 850 (26%), lymphocytes 2312 (68%), eosinophils 204 (6%); no immature white cells were seen. Platelets were

'adequate'. Blood urea was 8.9 mmol/l (54 mg/100 ml). Total plasma proteins were 90 g/l (9 g/100 ml) (albumin 35 g/l (3.5 g/100 ml)) with a moderately raised IgG and IgM and slightly raised IgA. Bone marrow aspiration showed normal granulopoiesis. Antinuclear antibody (ANA) titre was 1 in 640 showing a rim pattern of fluorescence. LE cells were always absent and tests for rheumatoid antibody negative. Antibody binding of nDNA was 54% (normal range up to 25%) tested by the Farr precipitation method using a calf thymus antigen labelled with tritiated actinomycin-D (Carr, Koffler, Agnello, and Kunkel, 1969), and 71% using internally labelled antigen from a human source (Pincus, Shur, Rose, Decker, and Talal, 1969). C3 complement was above normal range. A 24-hour urine specimen contained 173 mg of protein. A few white and red blood cells were seen in the urinary deposit. Creatinine clearance was 72 and 62 ml/min. A renal biopsy showed a mild focal proliferative glomerulonephritis with occasional focal fibrinoid necrosis. There was also 'focal but considerable' cellular infiltration of the interstitial tissue with a predominance of plasma cells associated with tubular damage.

Antistreptolysin O titre was 400–600 units/ml, rising to over 800 units/ml 2 weeks later. A throat swab grew a group C streptococcus.

The provisional diagnoses were ankylosing spondylitis, possible postinfective focal glomerulonephritis, and probable systemic lupus erythematosus. The latter was based on the finding of a very high anti-nDNA binding, a high antinuclear antibody titre by immunofluorescence with a rim pattern, and leucopenia.

The patient remained off any pyrazole drug, receiving only indomethacin 50–100 mg daily, and the Figure shows

FIGURE Laboratory findings before and after stopping drug treatment. Conversion: Traditional to SI units— $WBC: 1000/mm^3 \approx 1.0 \times 10^9/l$

the subsequent course of the blood count and anti-nDNA binding. The leucopenia resolved, the neutrophils returned to his peripheral blood, and the capacity of his serum to bind the DNA gradually decreased. Furthermore, the antinuclear antibody reverted to a diffuse immunofluorescent pattern, with a titre of 1 in 40. By September 1973, there remained no evidence of systemic lupus erythematosus, nor even of a lupus-like reaction.

Antistreptolysin O titre fell gradually to a normal level of 50–200 units/ml. A renal biopsy 2 months after the first one was unchanged. The picture remained consistent with either postinfective glomerulonephritis or with lupus. Plasma level of C3 complement remained at or above normal values. Urinary deposit still showed a few white and red blood cells with a trace of protein in the urine. ESR remained at between 85 and 130 mm.

The patient's lymphocytes tested against phenylbutazone *in vitro* showed no evidence of transformation induced by the drug (Sarkany, 1967), and it did not induce toxic inhibition of phytohaemagglutinin stimulation of cell division of his lymphocytes (Gaylarde and Sarkany, 1972). Skin window tests *in vivo* using a cover slip over a solution of phenylbutazone failed to show eosinophilia on the cover slip (Fowler and Lowell, 1966), nor were any LE cells seen.

Discussion

This patient almost certainly experienced a reaction to phenylbutazone and oxyphenbutazone. He showed leucopenia with selective neutropenia and circulating antinuclear antibodies of the rim pattern usually associated with systemic lupus erythematosus (SLE) (Friou, 1967), with a high level of anti-nDNA antibodies. All these features reverted to normal after pyrazole drugs were stopped.

The presence of a high level of anti-nDNA antibodies in a drug-induced lupus syndrome has not previously been reported. Hughes, Cohen, and Christian (1971) and Hughes (1973) stated that patients with drug-induced lupus, for whom standard antinuclear antibody and LE cell tests were positive, did not show anti-nDNA antibodies.

Raftery and Denman (1973) failed to find anti-nDNA antibodies in their three cases of practolol-induced SLE. Blomgren, Condemi, and Vaughan (1972) found antibodies to denatured but not to nDNA in procainamide-induced SLE. Beer (1973) regarded the presence of anti-nDNA antibodies in a patient with coexistent rheumatoid arthritis and SLE as a pointer against phenylbutazone treatment having induced the latter, but it is possible that such a reaction was responsible.

Winfield and Davis (1974) have suggested that confusion may occur concerning specificities of anti-DNA antibodies, due to contamination of nDNA by denatured or single stranded DNA (dDNA). The level of binding given by the serum of our patient was too high to be explained by the presence of other than an improbably high level of DNA. In addition, the inability of actinomycin-D to form a stable complex with dDNA (Gellert, Smith, Neville, and Felsenfeld, 1965) lessens the influence of this antigen. Although exact knowledge of the antigen's configuration is lacking, it has been used in many hundreds of estimations on sera from a wide variety of diseases in which antibodies directed at nuclear material occur. Binding at high levels has occurred only in active

cases of SLE and a proportion of cases of active chronic hepatitis.

There is no reason to doubt a drug-induced lupus reaction in our patient because LE cells were not found; they have often been absent in cases reported by other authors (Blomgren and others, 1972).

The lymphocyte transformation tests suggest that there is no direct toxic effect of phenylbutazone on the patient's lymphocytes. In the practolol-induced SLE syndromes described by Raftery and Denman (1973), mitogen stimulated lymphocyte transformation was inhibited, and these authors postulated a mechanism for the SLE-like reaction. However, there are at least two different mechanisms involved in drug-induced SLE syndromes (Alarcón-Segovia, 1969), and the negative findings in the present case in no way lessen the probability of a drug-induced lupus reaction.

There seems little doubt that the patient described here also had an attack of poststreptococcal focal glomerulonephritis, probably from a group A strain causing his febrile illness in November 1972. The rise and subsequent fall of the antistreptolysin O titre points to this and the persistently high C3 complement level is compatible with it and does not suggest that SLE has affected the kidney. Renal biopsy findings were inconclusive.

Two years after stopping phenylbutazone the patient shows no signs whatsoever of SLE, either clinically or on laboratory testing. He still has peripheral joint inflammation from ankylosing spondylitis, and a small number of red and white blood cells in his urinary deposit. These two features are thought to explain the persistence of a very high ESR. It is only remotely possible that he does in fact have SLE. It is not felt justified to rechallenge him with phenylbutazone, but the evidence is strong that he had a lupus-like reaction to phenylbutazone which included the presence of a high titre of circulating antibodies to native DNA. A prospective study of the incidence of such antibodies in patients taking pyrazole drugs is in progress.

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