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Case report

Pulmonary thromboembolism associated with procainamide induced lupus syndrome and anticardiolipin antibodies

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SUMMARY Procainamide is the commonest cause of a drug induced lupus syndrome. Long term administration of this compound may induce a variety of immunological abnormalities, including antinuclear antibodies. Uncommonly, 'lupus anticoagulants' have been demonstrated in the absence of other evidence of drug induced lupus. Details of a 67 year old man who developed not only drug induced lupus but also antiphospholipid antibodies which were associated with multiple pulmonary thromboemboli after the administration of procainamide are recorded.

It is well known that a variety of drugs, particularly chlorpromazine,[1 2] hydralazine,[3–5] and procainamide,[6–8] are responsible for the development not only of a variety of immunological abnormalities but also for the appearance of a drug induced lupus syndrome. Immunological abnormalities, in particular, positive tests for antinuclear antibodies, may be seen in 50–74% of asymptomatic patients treated with procainamide for longer than two months. With procainamide treatment a much smaller percentage of patients will develop drug induced lupus than those treated with chlorpromazine. The production of coagulation abnormalities such as 'lupus anticoagulants' is even rarer, particularly in the absence of other manifestations of drug induced lupus.[9–17]

We record a patient who developed drug induced lupus and anticardiolipin antibodies which were associated with multiple pulmonary thromboemboli. All evidence of the immunological disturbance disappeared when drug treatment was stopped.

Case history

This 67 year old Caucasian man was admitted to hospital for evaluation of fever, pleuritic chest pains with bilateral effusions, and weight loss. Three years before admission treatment with procainamide had been started for management of ventricular arrythmias. About one year later he developed symmetrical proximal myalgias and muscle weakness accompanied by inflammatory arthritis of the small joints of the hands. He was treated with several anti-inflammatory drugs, including naproxen, indomethacin, and ibuprofen, with no significant relief. Prednisolone was prescribed in doses up to 40 mg daily, with dramatic response. Two months before admission to hospital the prednisolone was discontinued because of the occurrence of hyperglycaemia. The patient then developed profound proximal muscle weakness, fever to 38·8°C accompanied by chills, a 20% weight loss over two months, fatigue, depression, and anorexia. Two weeks before admission to hospital the procainamide was discontinued. Because of severe pleuritic chest pains and chest *x* ray findings of bilateral pleural effusions with a minimal left lower lobe infiltrate the patient was admitted. While in hospital the patient was noted to have acute episodes of chest discomfort and shortness of breath, and on one occasion this was accompanied by peripheral cyanosis. A pulmonary perfusion scan showed multiple perfusion defects in both lungs, in areas where the chest *x* ray appeared normal. The study was incomplete as the patient was

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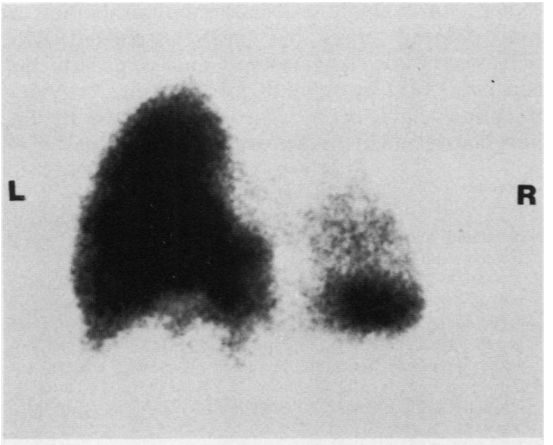

Fig. 1a

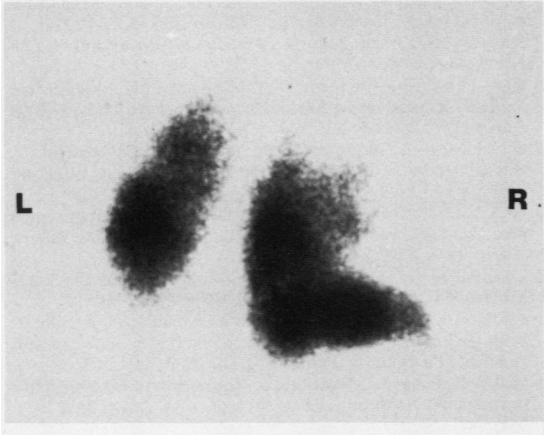

Fig. 1b

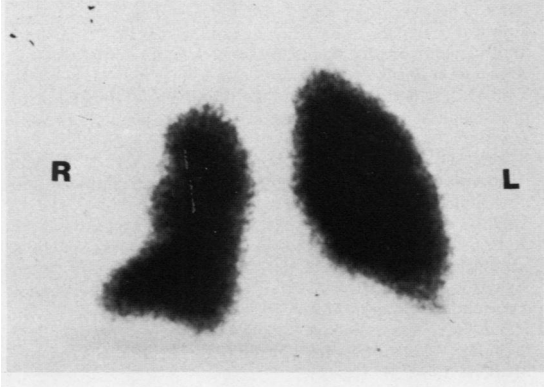

Fig. 1c

Fig. 1 *(a) Perfusion scan: left posterior oblique view; (b) right posterior oblique view; (c) view showing segmental perfusion defects in (R) lung.*

unable to tolerate the ventilation mask, but the radiological impression was of the high probability of multiple pulmonary emboli (Fig. 1). A blood chemistry screen was normal. The sedimentation rate on admission was 49 mm/h (Westergren) and fell to 29 mm/h before discharge. The antinuclear antibody test was positive in a diffuse pattern (1/2560). DNA binding was 14·7% (normal <10%). C3 was 1·27 g/l (normal range 0·9–1·82 g/l). C4 was 110 mg/l (normal range 160–450 mg/l). Rheumatoid factor was negative. A Venereal Disease Research Laboratory test was negative. Haemoglobin on admission was 105 g/l and rose to 125 g/l before discharge. Platelet count was normal and the Coombs' test was negative.

The patient was initially treated with heparin followed by warfarin sodium for three months. Within one day of the institution of heparin the patient noted improvement in the episodes of shortness of breath and chest pain. At this time prednisolone was restarted in a dose of 10 mg daily. With the reinstitution of prednisolone the symptoms of muscle weakness, pain, and synovitis resolved dramatically. He was discharged and treatment was continued with prednisolone 10 mg daily and warfarin sodium 5 mg daily. The warfarin sodium treatment was continued for three months and the prednisolone tapered and discontinued after six weeks. The patient has been monitored for four years since discontinuation of all drugs and has remained in excellent health without any symptoms or signs to suggest recurrence of his drug induced 'lupus-like' illness or of pulmonary thromboembolic disease.

Anticardiolipin antibodies were assayed on stored serum samples obtained at the time of admission and three months later by the method of Gharavi *et al.*[18] Both assays showed high positive IgM and negative IgG concentrations. Subsequent assays on serum samples obtained four months and three years after admission were negative. Antibodies to histones, single stranded DNA, and the lupus anticoagulant were not estimated.

Discussion

This patient had a drug induced lupus-like illness with high titres of anticardiolipin antibodies (IgM) associated with multiple pulmonary thromboemboli, positive antinuclear antibodies, and low positive DNA binding. He made a full recovery on withdrawal of procainamide combined with anticoagulation.

Antiphospholipid antibodies (lupus anticoagulant antibodies to cardiolipin) occur in approximately 30–40% of patients with systemic lupus erythematosus[19 20] and in a variety of other disorders, particularly with certain infections and autoimmune

diseases, as well as in patients with no underlying 'autoimmune' disease, recently defined as the 'primary' antiphospholipid syndrome.[21] Additionally, production of these autoantibodies may be induced by a variety of drugs, particularly those responsible for the drug induced lupus syndrome.[22] They may be present as an isolated immunological phenomenon as is the case in the primary antiphospholipid syndrome. There have been a number of reports of a lupus anticoagulant appearing during procainamide treatment,[3-17] in which its appearance has usually been accompanied by other clinical manifestations of drug induced lupus. Thrombotic events occurring with procainamide administration are, however, distinctly uncommon.[3 23 24]

Procainamide may be responsible for a wide spectrum of disease features of drug induced lupus, such as polyarthralgias, myalgias, fevers, pleurisy, and pericarditis, etc. Typical immune complex glomerulonephritis with mesangial deposition of immunoglobulins and complement[25] and a nephrotic syndrome[26] have been documented. Diffuse vasculitis,[21 27-29] immune complex deposition involving the pleura with local deposition of antinuclear antibodies,[30 31] and polyneuropathy[32] have also been reported. Although the antinuclear antibodies from most patients with drug induced lupus react with denatured single stranded DNA only, autoantibodies to native double stranded DNA may be detected in patients who develop drug induced lupus with procainamide treatment, as in our patient.[32-34] This has also been seen in patients treated with phenylbutazone.[35] Antibodies to ribonucleoprotein may be induced by procainamide in most patients soon after the start of treatment. These, however, disappear after long term treatment, and antibodies to extractable nuclear antigens never appear. The antinuclear antibodies are homogeneous in pattern and directed mainly at histones rather than at RNA/DNA and the wide variety of other non-histone proteins such as occur in idiopathic systemic lupus erythematosus. The antinuclear antibodies are specifically directed against the H_2A-H_2B complex in 50% of symptomatic patients.[36] Circulating immune complexes may be detected in a higher proportion of patients receiving procainamide even in the absence of drug induced lupus,[37] and hypocomplementaemia has also been noted. Hypocomplementaemia is not usually seen in drug induced lupus but has been recorded in patients receiving procainamide and in those receiving hydralazine.[38 39] This hypocomplementaemia has been shown to be due to the presence of null alleles at the C4 locus.[39 40] Our patient also developed hypocomplementaemia (low C4) Polycryoglobulinaemia may also occur.[41] Generally, the presence of antiphospholipid antibodies—for example, anticardiolipin antibodies, in drug induced lupus has been associated with increases of the IgM isotype and is usually not associated with thrombotic complications.[42] A few exceptions have been recorded as shown by the present case and in three previous case reports.[3 23 24]

References

1 Canoso R T, Sise H S. Chlorpromazine induced lupus anticoagulant and associated immunologic abnormalities. *Am J Hematol* 1982; **13:** 121-9.
2 Zarrabi M H, Zucker S, Miller F, *et al.* Immunologic coagulation disorders in chlorpromazine-treated patients. *Ann Intern Med* 1979; **91:** 194-9.
3 Mueh J R, Herbst K D, Rapaport S I. Thrombosis in patients with a lupus anticoagulant. *Ann Intern Med* 1980; **92:** 156-9.
4 Blumenkrantz N, Christiansen A H, Ullman S, Asboe-Hansen G. Hydralazine induced lupoid syndrome. *Acta Med Scand* 1974; **195:** 443-9.
5 Irias J. Hydralazine induced lupus erythematosus-like syndrome. *Am J Dis Child* 1975; **129:** 862-4.
6 Lee S L, Chase P H. Drug induced systemic lupus erythematosus: a critical review. *Semin Arthritis Rheum* 1975; **5:** 83-103.
7 Russell A S, Ziff M. Natural antibodies to procainamide. *Clin Exp Immunol* 1968; **3:** 901-9.
8 Blomgren S E, Comdeni J J, Vaughan J H. Antinuclear antibody induced by procainamide: a prospective study. *N Engl J Med* 1969; **281:** 64-6.
9 Schleider M A, Nachman R L, Jaffe E A, Coleman M. A clinical study of the lupus anticoagulant. *Blood* 1976; **48:** 499-509.
10 Nick J, Combrisson A, Reignier A, *et al.* Lupus introgene a la procainamide avec anticoagulant circulant. *Ann Med Interne (Paris)* 1978; **129:** 259-63.
11 O'Brien B C, Shimoura S K. Procainamide and the lupus anticoagulant. *Drug Intell Clin Pharm* 1984; **18:** 971.
12 Chokron R, Robert A, Rozenstein Z, Abuaf N, Dumoulin P, Valty J. Lupus induit par la procainamide avec anticoagulant circulant. *La Nouvelle Presse Medicale* 1982; **11:** 2568.
13 Bell W R, Boss G R, Wolfson J S. Circulating anticoagulant in a procainamide-induced lupus syndrome. *Arch Intern Med* 1977; **137:** 1471-3.
14 Davis S, Furie B C, Griffin J H, Furie B, Willey R. Circulating inhibitors of blood coagulation associated with procainamide induced lupus erythematosus. *Am J Hematol* 1978; **4:** 401-7.
15 Edwards R L, Rick M E, Whakem C J. Studies on a circulating anticoagulant in procainamide induced lupus erythematosus. *Arch Intern Med* 1981; **141:** 1688-90.
16 Day H J, Cherry R, O'Hara D, Carabello J. Incidence of procainamide induced lupus anticoagulant [Abstract]. *Thromb Haemost* 1987; **58:** 394.
17 Triplett D A, Brandt J T, Musgrave K A, Orr C A. The relationship between lupus anticoagulants and antibodies to phospholipid. *JAMA* 1988; **259:** 551-4.
18 Gharavi A E, Harris E N, Asherson R A, Hughes G R V. Anticardiolipin antibodies: isotype distribution and phospholipid specificity. *Ann Rheum Dis* 1987; **46:** 1-6.
19 Asherson R A, Harris E N. Anticardiolipin antibodies—clinical associations. *Postgrad Med J* 1986; **62:** 1081-7.
20 Harris E N, Asherson R A, Hughes G R V. Antiphospholipid antibodies—autoantibodies with a difference. *Annual Review of Medicine* 1988; **39:** 261-71.
21 Asherson R A. A 'primary' antiphospholipid syndrome? *J Rheumatol* (in press).
22 Denman A M, Pugh S. Drug induced systemic lupus erythematosus. In: Dukor P, Kallós P, Schlumberger H D, West O B, eds. *Pseudoallergic reactions. Involvement of drugs and chemicals.* Vol 3. Basel: Karger, 1982: 18-47.

23 Li G C, Greenberg C S, Currie M S. Procainamide-induced lupus anticoagulants and thrombosis. *South Med J* 1988; **81:** 262–4.

24 Schlesinger P A, Peterson L A. Procainamide-associated lupus anticoagulants and thrombotic events [Abstract]. *Arthritis Rheum* 1988; **31:** S54.

25 Whittle L E, Ainsworth S K. Procainamide-induced systemic lupus erythematosus. *Arch Pathol Lab Med* 1976; **100:** 469–74.

26 Zech P, Colon S, Labreu M, Bernheim J, Brunat N. Nephrotic syndrome in procainamide induced lupus nephritis. *Clin Nephrol* 1979; **11:** 218–21.

27 Ladd A T. Procainamide-induced lupus erythematosus. *N Engl J Med* 1962; **267:** 1357–8.

28 Rosin J M. Vasculitis following procainamide therapy. *Am J Med* 1967; **42:** 626–9.

29 Jackson C, Phillips P E. Procainamide induced lupus with vasculitis. *Clin Exp Rheumatol* 1986; **4:** 290–3.

30 Chandra A, Seckhar A J, Robinson J, Barr L. Antibody deposition in the pleura; a finding in drug-induced lupus. *J Allergy Clin Immunol* 1978; **61:** 399–402.

31 Caplain K, Zakher F, Sabin S. Drug induced lupus erythematosus with in vivo lupus erythematosus cells in pleural fluid. *Chest* 1978; **73:** 875–6.

32 Sahenk Z, Mendell J R, Rossio J L, Hartubise P. Polyradiculoneuropathy accompanying procainamide induced lupus erythematosus: evidence for drug induced enhanced sensitisation to peripheral nerve myelin. *Ann Neurol* 1977; **1:** 378–84.

33 Winfield J B, Davies J S. Anti-DNA antibody in procainamide induced lupus erythematosus. *Arthritis Rheum* 1974; **17:** 97–100.

34 Klajman A, Farkes R, Gold E, Ben-Efrain S. Procainamide induced antibodies to nuclear protein, denatured and native DNA in human subjects. *Clin Immunol Immunopathol* 1975; **3:** 525–30.

35 Grayson H R, Yartin Y M, Markham R L. DNA antibodies as a reaction to pyrazole drugs. *Ann Rheum Dis* 1975; **34:** 373–6.

36 Portanova J P, Rubin R L, Joslin F G, Agnello V D, Tan E M. Reactivity of anti-histone antibodies induced by procainamide and hydralazine. *Clin Immunol Immunopathol* 1982; **25:** 67–79.

37 Becker M, Klajman A, Moalem T, Yaretzky A, Ben-Efraim S. Circulating immune complexes in sera from patients receiving procainamide. *Clin Immunol Immunopathol* 1979; **12:** 220–7.

38 Utsinger P D, Zvaifler N J, Bluestein H G. Hypocomplementemia in procainamide associated systemic lupus erythematosus. *Ann Intern Med* 1976; **84:** 293–6.

39 Asherson R A, Benbow A G, Speirs C J, Jackson N, Hughes G R V. Pulmonary hypertension in hydralazine induced systemic lupus erythematosus: association with C4 null allele. *Ann Rheum Dis* 1986; **45:** 771–3.

40 Batchelor J R, Welsh K I, Tinoco R M, *et al.* Hydralazine-induced systemic lupus erythematosus: influence of HLA-DR and sex on susceptibility. *Lancet* 1980; **i:** 1107–9.

41 McLain D A, Hahn B N. Cryoglobulins in the procainamide induced lupus syndrome. *Arthritis Rheum* 1979; **2:** 305–7.

42 Gharavi A E, Harris E N, Asherson R A, Hughes G R V. Anticardiolipin (a-CL) isotypes: a study of their clinical relevance [Abstract]. *Clin Rheumatol* 1986; **5:** 154.