Case report

Clinicopathological study of a patient with procainamide-induced systemic lupus erythematosus

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Levo, Y., Pick, A. I., Avidor, I., and Ben-Bassat, M. (1976), *Annals of the Rheumatic Diseases*, 35, 181–185. **Clinicopathological study of a patient with procainamide-induced systemic lupus erythematosus.** A patient who developed a multisystem involvement of systemic lupus erythematosus (SLE) after 9 years of procainamide therapy, during which time he ingested enormous amounts of the drug, is described. The patient first suffered from recurrent episodes of pleuritis and arthritis, after which he developed a characteristic SLE nephritis associated with a high level of antinative DNA antibodies and a low level of complement. He finally died from a complication of a nonbacterial endocarditis. Autopsy showed polyserositis and typical deposits of electron-dense material on the glomerular basement membrane, and confirmed the clinical diagnosis of Libman-Sacks endocarditis. The possibility that procainamide-induced SLE might have all the clinical, immunological, and pathological features of spontaneous SLE, especially in patients exposed to large doses of the drug for many years, is discussed.

Since the first description of procainamide-induced systemic lupus erythematosus (P-SLE) by Ladd (1962), about 100 cases have been described in the literature (Alarcón-Segovia, 1969; Blomgren, Condemni, and Vaughan, 1972; Blomgren, 1973; Dubois, 1969; Ladd, 1962; Swarbrick and Gray, 1972; Winfield and Davis, 1974). On the basis of these reports the following characteristics which distinguish this entity from spontaneous SLE (S-SLE) have been delineated: male predominance, older people being more frequently affected, common occurrence of lung involvement in the absence of kidney involvement, normal serum levels of complement and antinative DNA antibodies, and usually the remission of symptoms upon withdrawal of the drug.

In spite of the large body of clinical data, pathological documentation in P-SLE is meagre. Autopsy findings have been described in a few patients only and no evidence of SLE was seen in any (Blomgren and others, 1972; Dubois, 1969; Swarbrick and Gray, 1972).

We describe a patient with P-SLE with some unusual clinical and pathological findings.

Case report

A 63-year-old male suffered for the past 30 years from paroxysmal supraventricular tachycardia. Until 1965 his cardiac arrhythmia was reasonably controlled with quinidine, but since then it could be suppressed only by procainamide 4–5 g/day. In 1968 he began to suffer from arthralgia, but overt arthritis was not observed until one year afterwards when he was first hospitalized. At that time, apart from severe arthralgia which affected most of the peripheral joints and frank arthritis of his wrists and right ankle, he suffered from severe pleuritic pains of the left lateral side of his chest. The relevant laboratory data were a Westergren erythrocyte sedimentation rate of 100 mm/h, positive LE prep. and ANF (antinuclear factor) test, blood urea 8.6 mmol/l (52 mg/100 ml) with a normal urinary sediment. Chest x-ray showed an obliterated left sinus; skeletal survey was normal; intravenous pyelography showed bilateral minimally contracted kidneys. A trial substituting ajmaline (Gilurytmal) for procainamide failed, and upon starting prednisone treatment

pleural and joint symptoms abated. He was then discharged on a maintenance dose of 20 mg prednisone/day.

During the next 3 years he suffered from recurrent episodes of pleuritis and arthritis necessitating temporary increments in prednisone dosage. In December 1972 another trial substituting quinidine for procainamide failed.

In February 1973 he was again hospitalized because of severe *E. coli* and *Klebsiella pneumoniae*. Parenteral cephalothin and gentamicin treatment was begun and the pneumonia cleared. He soon became minimally jaundiced and his liver enlarged to 3 cm below the costal margin. The relevant laboratory data at that time were blood urea rising from 9.6 to 26.5 mmol/l (58–160 mg/100 ml); urinary sediment containing erythrocytes and granular casts; proteinuria 500 mg/24 h; haemoglobin 10 mg/dl; sedimentation rate 120 mm/h; transaminase (SGOT) 47 units (normal up to 36); lactic dehydrogenase 180 units (normal up to 90); alkaline phosphatase 7.2 units (Bessey–Lowry); serum albumin 21 g/l (2.1 g/100 ml) and globulin 49 g/l (4.9 g/100 ml); positive LE prep.; 1/1280 positive ANF test and 1/320 positive latex test. C3 complement levels were 38% and C4 34%, as determined by the method of Carpenter (1967). Titre of antinative DNA antibodies, as determined by the method of Farr according to the modification of Pincus and others (1971), was 36% (normal $\leq 20\%$). These clinical and laboratory findings established the diagnosis of hepatitis. The patient was treated with prednisone and parenteral fluids; within 3 weeks all evidence of hepatitis and nephritis disappeared and he was discharged on his usual maintenance dose of prednisone and procainamide.

In May 1973 he was seen again because of a diffuse maculopapular rash, by that time the titre of anti-DNA antibodies had dropped to 16%. In December 1973 the patient was hospitalized because of severe dyspnoea, chest pain, and bloody sputum. Chest x-rays and lung scan confirmed the clinical diagnosis of pulmonary embolism and heparin treatment was begun. Several days afterwards

the intensity of his previously noted cardiac systolic murmur increased and severe rhythm disturbances were noticed. The next day he suffered from an acute abdominal episode manifested by abdominal pain and distension, haematuria, and hypotension. Blood urea rose to 33.2 mmol/l (200 mg/100 ml); leucocyte count to $30 \times 10^9/l$ (30000 mm³); transaminase (SGOT) 46 units and lactic dehydrogenase 213 units. The clinical and laboratory data were consistent with an episode of renal and possibly mesenteric emboli complicated by a hypotensive shock and possibly an acute myocardial infarction. Three days afterwards the patient died suddenly.

Autopsy showed the following characteristics of SLE. (a) Chronic polyserositis associated with pleural, pericardial, and peritoneal fibrous adhesions. (b) Verrucous endocarditis which affected both the mitral and aortic valves and the right atrium. It consisted of few, 3×4 mm, verrucae on the atrial surface of the mitral cusps and on the ventricular surface of the aortic cusps; some of them were near the closure line and some along the free margin. In the right atrium they formed grey-yellowish, irregular, up to 10 mm endocardial vegetations. Microscopical examination of these verrucae showed that they were mainly formed by a fibrinoid degeneration of the ground substance of the superficial connective tissue layer of the involved valves and endocardium. In some places there were superimposed thrombi; however, bacteria and proliferative changes were not seen (Figs. 1, 2). These histological findings established the diagnosis of Libman-Sacks endocarditis. (c) Lupus nephropathy. Although the microscopical examination of the kidneys provided no evidence of lupus nephritis, ultrastructural study showed the typical deposits of electron-dense material on the endothelial side of the glomerular basement membrane (Fig. 3).

No further evidence of SLE was found in any other organ; however, the following non-SLE changes were found. (a) Generalized atherosclerosis mainly affecting the aorta and the coronary arteries, associated with an

FIG. 1 Verruca from the closure line of the mitral valve. Marked fibrinoid degeneration, P.A.S. stained, is seen (arrow) involving the subendocardial connective tissue. $\times 40$

FIG. 2 Vegetation of the mural endocardium of the right atrium. P.A.S.-stained clumps consisting of altered ground substance are seen in the connective tissue layer of the endocardium. The intact endocardium (arrow) is raised by these clumps. $\times 200$

organizing myocardial infarction and hypertrophy of the left cardiac ventricle. (b) Pyelonephritic scars and retention cysts in both kidneys. (c) Cystitis and prostatitis. (d) Bilateral atrophy of the adrenals.

Discussion

The patient had ingested 1.5 kg procainamide every year for 9 years. Although no correlation has yet been found between the severity of P-SLE and the amount of procainamide ingested, the fact that the relentlessly progressive course of the disease observed in this patient was related to lengthy exposure to vast amounts of the drug cannot be excluded. The first symptoms were noted after 4 years of drug ingestion at which time he suffered from arthralgia only. He had frequent episodes a year later of arthritis and occasionally of pleuritis which were partially controlled by corticosteroid treatment. Four years later he developed hepatitis, nephritis, and dermatitis, and several months afterwards he died as a consequence of a nonbacterial endocarditis. It seems that in this patient more and more organs became involved as the exposure to the drug increased in time.

Nephritis and nonbacterial verrucous endocarditis are typical features of S-SLE which distinguish it from P-SLE (Blomgren and others, 1972; Dubois, 1969; Swarbrick and Gray, 1972). According to current concepts the nephritis in S-SLE is caused by the deposition of immune complexes which consist of native DNA and its antibody in the kidneys (Koffler and others, 1971). The absence of nephritis in P-SLE could possibly be attributed to the fact that

patients with P-SLE do not form complement-fixing antinative DNA antibodies (Blomgren and others, 1972). However, such antibodies have been described in P-SLE (Blomgren and others, 1972; Molina and others, 1969).

In this patient all the clinical, laboratory, and ultrastructural features of a classical SLE nephritis were present. The clinical picture of nephritis was accompanied by a rise in antinative DNA antibodies and a drop in complement levels, and electron-dense material, the ultrastructural evidence of immune complexes, was found at autopsy. The terminal clinical picture suggested thrombotic endocarditis since a change in cardiac murmurs was observed and embolic phenomena occurred. Indeed, autopsy showed atypical nonbacterial verrucous endocarditis. This endocarditis was primarily the result of fibrinoid degeneration, it involved the mural endocardium and affected both the right side and the left side of the heart; therefore, it is more compatible with the endocarditis of SLE (Libman-Sacks endocarditis) than the so-called marantic-nonbacterial thrombotic endocarditis (Friedberg, 1966).

P-SLE is rarely fatal because procainamide is usually stopped whenever symptoms aggravate and long before they endanger the patient's life, and this alone or together with corticosteroids reverses the symptoms (Blomgren and others, 1972; Dubois, 1969; Swarbrick and Gray, 1972). Autopsy therefore has been performed in very few patients with active P-SLE. None of the reported cases actually died of SLE and hence it is not surprising that autopsy did

FIG. 3 *Electron micrograph of a glomerular capillary, stained by uranyl-acetate and lead citrate. Subendothelial electron-dense material (between arrows) is seen under a glomerular basement membrane of normal width. $\times 20\,000$*

not show any features of SLE (Blomgren and others, 1972; Dubois, 1969; Swarbrick and Gray, 1972). In our patient procainamide could not be withdrawn and his death can most probably be attributed to a complication of SLE. Thus it was not surprising to find at autopsy the typical multisystem involvement of SLE which included pleural and peritoneal adhesions, remnants of recurrent episodes of pleuritis, electron-dense material in the kidneys, and characteristic endocarditis. The possibility that our patient actually suffered from classical SLE which either was spontaneous or was only activated by procainamide cannot be ruled out. However, the occurrence of the

disease in a 63-year-old male, the predominance of the pleural involvement, and the progressive rather than intermittent course of the disease over so many years, together with the exposure to the extremely large dose of procainamide favour the possibility of procainamide-induced SLE.

We suggest that P-SLE, especially in patients exposed to large doses of procainamide for many years, might have all the clinical, immunological, and pathological features of the spontaneous disease. More autopsy and ultrastructural studies are required to further elucidate the connexion between P-SLE and S-SLE.

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