**GRAND ROUNDS IN RHEUMATOLOGY**

**SYSTEMIC SCLEROSIS COMPLICATED BY PROCAINAMIDE-INDUCED LUPUS AND ANTIPHOSPHOLIPID SYNDROME**

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Procarainamide is one of the major causes of drug-induced lupus erythematosus (DIL) [1]. Patients taking procarainamide for prolonged periods often develop anticardiolipin antibodies, as well as anti-DNA and anti-histone antibodies [1–3]. Some of these patients manifest thrombosis, as a part of drug-induced antiphospholipid syndrome (Di-APS) [2–6]. However, the frequency of thrombotic events in these patients is considered to be less than that seen in antiphospholipid syndrome (APS) associated with systemic lupus erythematosus (SLE) [3–5, 7].

Systemic sclerosis (SSc) is another autoimmune disease of unknown aetiology. Its primary site of injury is the vascular system, especially at the microvascular level. Raynaud’s phenomenon and digital tip ischaemia are commonly seen [8]. However, digital gangrene which often requires amputation ensues in a few SSc patients [8], mainly in patients with limited cutaneous involvement [9].

We present a patient with SSc with diffuse cutaneous involvement (dcSSc) who later developed a toe gangrene, arthritis and pancytopenia as the manifestations of APS and lupus-like syndrome after the administration of procarainamide for the treatment of a ventricular arrhythmia.

**CASE REPORT**

A 51-yr-old Korean man had experienced Raynaud’s phenomenon since 1977 (at the age of 36 yr). He first visited our hospital in 1980 because of sustained Raynaud’s phenomenon. Physical examination revealed acrosclerosis with pigmentation and depigmentation; digital tip ulcers and pitting scars; telangiectasia in the face, V-neck area and palms; and shortening of the sublingual fold. Bilobar pulmonary fibrosis was recognized on chest radiographs. Serological tests demonstrated anti-DNA topoisoeraserase I (formerly Scl-70) antibodies (anti-DNA topo I), but not anti-DNA antibodies (Farr’s assay) or lupus erythematosus (LE) cells. He was diagnosed as having SSc according to the preliminary criteria of the ARA [10]. Skin sclerosis and pulmonary fibrosis progressed gradually during the next 5 yr. Treatment with 100 mg/day of d-penicillamine was begun in May 1990.

On 27 July 1991, the patient experienced anterior chest pain and was admitted to our hospital. An electrocardiogram showed monomorphic ventricular tachycardia (VT; heart rate 150/min), which was successfully treated with 600 mg of i.v. procarainamide. Echocardiogram and right ventriculogram with cardiac catheterization showed dilatation of the right atrium and right ventricle. A biopsy from the right ventricular myocardium revealed localized myocardial fibrosis. Treatment with 2000–3000 mg/day of procarainamide successfully suppressed ventricular arrhythmias.

In May 1993, he noticed a new skin ulcer on his left toe. Beraprost sodium (120 μg/day) and i.v. lipos-prostaglandin E1 (lipo-PGE1; 10 μg/week) did not improve the ulcer, and he was admitted to our hospital on 16 July 1993. Physical examination demonstrated skin sclerosis of the face, extremities and trunk. An ulcer with necrotic tissue on his left second toe was found (Fig. 1). Pulsion of dorsal pedal arteries was not palpable bilaterally. Tenderness was observed in his proximal interphalangeal and metacarpophalangeal joints. Facial erythema, alopecia and oral ulcers were not found. Laboratory testing revealed pancytopenia (white blood cell count 3600/μl, haemoglobin 8.6 g/dl and platelet count 80 000/μl), a prolonged activated partial thromboplastin time (aPTT > 150 s) and prolonged prothrombin time (PT, 26%) and decreased levels of several coagulation factors (both FXI and FXII 28% of normal controls). The plasma von Willebrand factor concentration was increased to 214% of normal controls. The serum creatinine concentration was increased (1.4 mg/dl) and the glomerular filtration rate was decreased (44 ml/min). The serum C-reactive protein (CRP) was elevated (6.22 mg/dl), with hyper-gammaglobulinaemia (IgG 2736 mg/dl) and hypocomplementaemia (C3 31 mg/dl, C4 13 mg/dl). Positive circulating immune complexes (24.1 μg/ml by anti-C3d methods; normal < 13 μg/ml) and mixed-type cryoglobulinaemia (IgG 3.0 mg/dl, IgA 0.3 mg/dl and IgM 2.7 mg/dl) were observed. The urinalysis was normal. At this point, antinuclear antibodies (ANA) and anti-DNA topo I were positive, and LE cell preparation was also positive. Moreover, the serum anti-DNA antibodies (Farr’s assay) were positive, with a high titre of anti-single-stranded DNA antibodies (anti-ssDNA; 452.9 AU/ml; normal < 10 AU/ml), whereas anti-double-stranded DNA antibodies (anti-dsDNA) were 76.3 AU/ml (normal < 10 AU/ml). Anti-U1 ribonuclear protein (RNP), anti-Sm and anticentromere antibodies were negative. A biological false-positive test for syphilis was observed, and β₂-glycopro-
tein I (\(\beta_2\)-GPI)-dependent IgG anticardiolipin antibodies (anti-\(\beta_2\)-GPI) were present in high titres (>100 U/ml by the conventional enzyme-linked immuno-sorbert assay). The lupus anticoagulant (LAC) was demonstrated by the cross-mixing test. Anti-histone antibodies were also detected by immunoblotting (Fig. 2). These serological abnormalities have not been observed before procainamide administration except for positive tests for anti-DNA topo I. The human leucocyte antigen (HLA) genotyping demonstrated HLA-DRB1*1502/0901, DQB1*0601/0303 and DPB1*0501/0901.

The diagnosis of DIL and DI-APS was made. Although procainamide was highly suspected to be the causative agent, there was a possibility of recurrent VT after the cessation of procainamide, which led us to continue it. Prednisolone (PSL) 30 mg/day and azathioprine (AZ) 50 mg/day were administered together in addition to daily infusion of lipo-PGE\(_1\). Angiography was performed, which showed occlusions of anterior tibial arteries bilaterally and narrowing of digital arteries. His digital ulcer and necrosis progressed, as did his renal dysfunction (serum creatinine 2.3 mg/dl) without hypertension, deterioration of thrombocytopenia, or increased plasma renin activity. Moreover, pancytopenia, especially thrombocytopenia, was sustained for over 3 months regardless of PSL and AZ therapy, although the titre of anti-ssDNA, anti-dsDNA and anti-\(\beta_2\)-GPI decreased (59.4 AU/ml, 14.7 AU/ml and 25.0 U/ml, respectively). Procainamide was withdrawn on 1 November 1993. Mexiletine was started, but was changed to propafenon because of an allergic skin reaction. After discontinuing procainamide, the patient’s general condition improved remarkably. His pancytopenia, coagulopathy and renal dysfunction resolved as well. Serum levels of anti-ssDNA as well as anti-dsDNA, anti-\(\beta_2\)-GPI and anti-histone antibodies finally decreased to normal levels (Fig. 2). Repeated angiographs showed narrow but patent anterior tibial arteries bilaterally. He was discharged on 26 January 1994, and has been doing well since then.

**DISCUSSION**

This is the first case report of a patient with SSc who developed DIL and DI-APS. In our patient, procainamide was used to treat VT which was attrib-
tuated to fibrosis in the right ventricle, possibly a cardiac manifestation of SSC. Procainamide is frequently associated with the development of a lupus-like syndrome [1]. ANA develop in 90% of procainamide-treated patients within 1 yr, and ~30% will subsequently develop procainamide-induced lupus (PIL) [1]. In patients with PIL, fever, serositis, leucopenia and positive test for the LE cell preparation are frequently found, while malar rash, renal and central nervous system (CNS) diseases are rare [1]. Anti-histone antibodies, especially anti-H2A-H2B complex, are usually found in PIL, and anti-ssDNA are more frequently detected than anti-dsDNA in DIL, although those findings cannot differentiate DIL from idiopathic SLE [1, 11, 12]. Our patient developed fever, arthritis, digital gangrene, pancytopenia and hypocomplementemia. Moreover, he had a positive test for the LE cell preparation, anti-DNA antibodies (the titre of anti-ssDNA was higher than that of anti-dsDNA) and anti-histone antibodies. However, he never displayed a rash, CNS involvement, proteinuria nor urinary casts. Finally, the clinical course of the lupus-like syndrome in our patient closely paralleled the administration of procainamide, not of penicillamine. Taken all together, the diagnosis of PIL was made.

There have been a number of reports of antiphospholipid antibodies (APA) appearing during procainamide treatment, although only a small portion of those patients actually manifested thrombotic events, and procainamide has been shown to be the most common drug implicated as being associated with the presence of APA [2–7]. Our patient developed lupus anticoagulants and extremely high titres of anti-β2-GPI in the setting of digital gangrene. Vasculopathy associated with SSc itself can develop digital gangrene typically due to intimal fibrosis of the digital arteries [8]. However, the occlusion of such large-sized arteries as anterior tibial arteries, which was demonstrated in our patient, is rare in SSc. Although sporadic reports of large-vessel involvement in SSc have been seen in the literature, most of those patients, including a patient we previously reported, had SSc with limited cutaneous involvement and anticientromere antibody [13–15]. Finally, while APA have been detected in low concentrations in 11 of 35 SSC patients [16], thrombotic events rarely occur in patients with SSc, in contrast to SLE with APA. Indeed, digital tip ulcers had been frequently observed in our patient, a digital gangrene which finally required amputation had never developed before the occlusion of tibial arteries occurred. Therefore, we concluded that his digital gangrene appeared as a manifestation of APS. Again, the exclusively close temporal relationship among the procainamide treatment, the appearance of anti-β2-GPI and arterial thromboses led us to the diagnosis of procainamide-induced APS.

As for the immunogenetics of APS, the association of APS with the HLA-DQB1 oligonucleotide allele that encodes seven consecutive residues (71–77, TRAELDT) in the third hypervariable region has recently been reported [17]. The fact that our patient also had this allele (HLA-DQB1*0303) suggests that there may be a common immunogenetic susceptibility between APS and DI-APS.

The most interesting point in this case is that drug-induced immune disorders (lupus and APS) overlapped with an idiopathic autoimmune disease (SSc). We have recently reported three cases having both serum anti-DNA top I and anti-Sm antibodies, all of whom had multiple serious organ involvements and thus poor prognosis associated with both of these two antibodies [18]. In the present case, likewise, both SSc vasculopathy in digital arteries and occlusions in anterior tibial arteries as a manifestation of APS seemed to have contributed additively to the development of a toe gangrene, which resulted in a digital amputation.

In summary, we presented the first case report of a patient with a 15 yr history of dcSSc who developed DIL and DI-APS after procainamide treatment. The combination therapy with PSL and AZ failed to resolve various manifestations such as pancytopenia, and the withdrawal of procainamide, in contrast, dramatically improved the clinical course. DIL and DI-APS should be taken into consideration, as well as the overlap syndrome with SLE and APS, in patients with SSc who develop lupus-like syndrome and thrombotic events.

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**References**