BRIEF REPORT

PROLONGED IMPROVEMENT OF RAYNAUD'S PHENOMENON AND SCLERODERMA AFTER RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR THERAPY

MARVIN J. FRITZLER and DAVID A. HART

We describe a patient with systemic sclerosis (SSc; scleroderma) characterized by severe Raynaud's phenomenon, cutaneous sclerosis, and digital ulceration and subsequent amputation who was treated with recombinant tissue plasminogen activator (rt-PA) after acute myocardial infarction. She showed prompt improvement of the Raynaud's phenomenon and healing of the digital ulceration. After 18 months of followup, the Raynaud's phenomenon has remained mild, and there has been improvement in the cutaneous sclerosis. Since the pathophysiology of SSc has been associated with disorders of fibrinolysis and coagulation, this patient represents an interesting index case that might prompt further evaluation of rt-PA therapy in carefully selected patients.

The treatment and management of systemic sclerosis (SSc; scleroderma) is limited by a lack of specific knowledge of the pathophysiology of the disease. The earliest manifestations of SSc are changes in the vascular and microvascular compartments, characterized by injury to endothelial cells. These changes are associated with circulating "factors" that have been shown in vitro to contribute to the fibrotic reaction that is a hallmark of the disease (1–3). This so-called "vascular hypothesis" was proposed in the 1970s (4), and continues to attract the interest of clinicians and investigators. Other relevant observations associated with SSc include coagulation abnormalities, characterized by thrombotic episodes, fibrin deposition, increased rates of fibrinogen breakdown, endothelial cell aberrations, and altered regulation of plasminogen activator (PA) and plasminogen activator inhibitors (PAI) (5–9). These regulatory alterations have the potential to cause circulatory abnormalities that can lead to Raynaud's phenomenon, pulmonary hypertension, autoamputation of fingers and toes, and abnormalities in the vasculature of multiple organs.

We describe an SSc patient who received the thrombolytic agent recombinant tissue plasminogen activator (rt-PA) for treatment of acute myocardial infarction. This patient subsequently showed a dramatic and prolonged improvement of complicated Raynaud's phenomenon and cutaneous sclerosis.

Case report. The patient, a 44-year-old white woman, had a 15-year history of SSc, but had no previous history of heart or coronary artery disease. She developed sudden, progressively increasing pain in both arms that radiated to the back. Nausea and vomiting were also present. The patient was treated at a hospital emergency room, and the clinical, laboratory, and electrocardiograph findings confirmed a diagnosis of acute, inferolateral, posterior myocardial infarction. At the time of admission, her medication regimen included D-penicillamine, levothyroxine, ranitidine domperidone, and nifedipine.

She was admitted to the coronary care unit and was given an intravenous infusion of rt-PA (100 mg) over a 4-hour period, followed by therapeutic doses of heparin for 24 hours. An angiogram revealed an ec-

From the Joint Injury and Diseases Research Group, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada.

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Marvin J. Fritzler, PhD, MD; David A. Hart, PhD.

Address reprint requests to Marvin J. Fritzler, PhD, MD, Department of Medicine, University of Calgary, 3330 Hospital Drive, NW, Calgary, Alberta, T2N 4N1, Canada.

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centric, 90% stenosis of the principal obtuse marginal branch of the circumflex coronary artery. The patient was discharged within 12 days and was maintained on the same therapeutic regimen described above, with the addition of acetylsalicylic acid, 325 mg/day. She has remained free of cardiovascular complications for 18 months.

Prior to the myocardial infarction, the patient was undergoing followup for a diagnosis of SSc. Her disease was characterized by the early onset of Raynaud's phenomenon, complicated by digital ulceration and gangrene, distal phalangeal tuft resorption, and calcinosis cutis. She had diffuse skin involvement of the extremities, face, and trunk. There was no history of polyvinylchloride exposure, fetal wastage, recurrent thrombosis, or pulmonary emboli. Prior to the myocardial infarction, there was no evidence of cardiac, pulmonary, or renal disease. She had a history of esophageal dysmotility and stricture that required repeated dilatation.

A subtotal thyroidectomy was performed 10 years earlier, after the detection of a thyroid nodule that contained cells suggestive of papillary carcinoma. An antinuclear antibody test result was positive (titer 1:1,280 with a homogeneous and speckled pattern). Further analysis of the autoantibody profile identified antibodies directed against the centromere/kinetochore and histones. Test results for the presence of antinucleolar or anti–Scl-70 (topoisomerase I) antibodies were negative.

Within hours of the rt-PA infusion, a dramatic improvement of the Raynaud's phenomenon was noted by the patient, her husband, and the attending physicians. In the patient's own words, "My fingers hadn't been this pink and warm for years."

Over the next 4–6 weeks, the patient noted progressive and sustained softening of the skin, including that of the distal extremities. The open ulcers of the fingers had healed. The most obvious skin changes occurred on the patient's trunk, neck, and arms, as evidenced by a modified skin score (10) that changed from 44 to 38 over the 18-month followup period. In addition, the Raynaud's phenomenon has remained mild, and there has been no evidence of new digital ulceration or progression of acroosteolysis. The specificity and titer of the autoantibody profile has remained unchanged in subsequent followup visits.

Discussion. The patient described has shown a sustained and dramatic improvement of severe Raynaud's phenomenon complicated by multiple digital ischemic events. In addition, we noted a modest improvement in the sclerodermatous skin changes beginning 4–6 weeks after rt-PA therapy was initiated and continuing for 18 months. Although it is known that spontaneous remission of scleroderma can occur (11), the patient's temporal improvement with rt-PA therapy is noteworthy.

To better understand the potential therapeutic benefits of rt-PA in SSc, a greater appreciation of the role of PA/PAI in the pathogenesis of scleroderma is required. Our understanding of PA/PAI regulation has increased rapidly over the past few years (for review, see ref. 9). It is known that inflammatory processes are intimately associated with the coagulation, fibrinolytic, complement, and kinin systems of plasma. A number of reports have indicated that alterations in PA/PAI regulation occur in rheumatic diseases (for review, see refs. 9 and 12). However, abnormalities of PA/PAI regulation may not be directly involved in the circulatory alterations, since t-(tissue)PA/PAI-1 levels have not been reported to be abnormal in SSc patients (13). Other observations of SSc that may be related to abnormalities of coagulation include altered cutaneous fibrinolytic activity and the identification of a serum fibroblast mitogenesis factor whose presence precedes endothelial damage (9).

It is clear that abnormalities of coagulation-fibrinolysis regulation are not unique to SSc because they occur in other rheumatic diseases (9). While some abnormalities are likely to be the result of the chronic inflammatory nature of the diseases, it is likely that some parameters are unique to specific diseases or subsets of diseases.

These observations have suggested the use of new therapeutic approaches. For example, the use of purified PA/PAI proteins to alter disease activity and progression is one area that can now be investigated more extensively. Recombinant human t-PA, urokinase, and plasminogen activator inhibitors PAI-1 and PAI-2 are being developed commercially, and t-PA is being used in clinical settings as a treatment for acute myocardial infarction (for review, see ref. 14). The use of rt-PA for rheumatic disease therapy has yet to be approved and has not been investigated very thoroughly. However, the rigorous clinical trials implemented to gain approval of rt-PA for treatment of myocardial infarction have indicated that this "drug" is relatively safe, even at the high doses required to initiate reperfusion. In addition, since rt-PA is essentially a human protein, this enzyme should not be immunogenic and could therefore be given repeatedly in a disease-modifying regimen.

These observations suggest that SSc is a prime candidate for initial trials of rt-PA therapy. Since the effectiveness of current therapeutic modalities is limited in advanced SSc complicated by Raynaud's phenomenon and pulmonary and/or renal hypertension, this disease subset would be a good candidate for these initial studies. Although there was a prolonged response in the patient described here, treatment of SSc may require repeated drug administration in order to effectively interfere with the disease progression and improve the patient's condition.

The experience acquired with rt-PA trials for treatment of myocardial infarction (14) and with a preliminary trial in SSc patients (15) has illustrated that such a proposal is not without risks. For example, bleeding complications were encountered when 6 patients with the CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias) variant of SSc were treated with rt-PA (15). However, the rt-PA was administered using a protocol that differs from most, including the one used in our case report. If clinical trials of rt-PA are being considered, carefully formulated exclusion criteria and modalities of drug administration will be required.

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