Scleroderma

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Scleroderma is a disease of unknown cause characterized by the fibrosis of connective tissue. The involvement in this disease of small arterioles and capillaries tends to produce vascular insufficiency. It may be localized to the skin, as in linear scleroderma or morphea. If other organs or organ systems are involved, the disease is called progressive systemic sclerosis (PSS). The disease may be mild or very severe and life-shortening. However, in almost all patients it is slowly progressive.

The disease usually begins insidiously with symptoms of Raynaud's phenomenon, vague weakness, weight loss, edema of the hands, polyarticular arthalgia, and diffuse stiffness and aching.

In a histologic examination, the skin shows loss of subcutaneous fat and replacement by dense thickened collagen bands. Systemic findings are analogous to dermal changes and include progressive fibrosis of the esophagus, small and large bowel, lungs, and heart.[1] Renal changes are primarily vascular. There are significant variations from one system to another; and all loci, even in the same organ, may not be involved to the same degree. There is a unique form of PSS known as the CRST syndrome, which is manifested by calcinosis, Raynaud's phenomenon, esophageal dysfunction, and telangectasia.

According to Harris,[2] the various manifestations include the following.

Cutaneous

With classic acrosclerosis the skin is taut, thickened, or edematous, bound tightly to subcutaneous tissues in the hands and fingers. Normal skin folds at the knuckles disappear. Chronic recurrent painful ulcerations may develop at the ends of the digits, and the fingers may be shortened by progressive resorption of the terminal phalanges. The joints become immobilized from encasement by thickened skin as well as contractures of muscles, tendons, or palmar fascia. Telangectasia, changes in pigmentation, and subcutaneous calcification are common. The hair becomes thin, and the skin of the face appears smooth and waxy. The skin around the mouth may constrict and thereby restrict lip movement, which can prevent adequate dental hygiene. The sweating mechanism is often impaired; the involved skin feels leathery and dry and may scale and itch.

Clinical Obstetrics and Gynecology, Vol. 26, No. 3, September 1983

Musculoskeletal

About half the patients present with joint pain or develop it within the first year. Small joints are involved more often than large. Joint involvement is from encasement, not from invasive erosive synovitis, as in rheumatoid arthritis. Muscle wasting is often severe in the hands.

Gastrointestinal

Of the internal viscera, the gastrointestinal system is the one most frequently involved. Oral symptoms include xerostomia and a progressive decrease in the size of the mouth. Patients with Sjögren's syndrome are seen frequently. Symptoms referable to the esophagus range from simple dysphagia to heartburn, nausea, and substernal fullness and are found in about half the patients. If reflux esophagitis becomes a persistent problem, stricture may develop. Vomiting, abdominal distention, and pain or diarrhea may indicate involvement of the small intestine. The mobility of the small bowel is decreased, and malabsorption may result. Functional bowel complaints secondary to changes in the colon are common. Disease of both large and small bowel may produce a clinical picture identical to paralytic ileus with incomplete obstruction at any level.

Heart and Lungs

Dyspnea is the most common cardiorespiratory symptom in PSS and is present in about 50%. Some patients suffer from progressive pulmonary fibrosis. Signs of elevated pulmonary vascular resistance may develop independent of parenchymal lung changes and lead to cor pulmonale and congestive heart failure. Scleroderma heart disease is an occasional cause of heart failure.

Kidneys

The sudden development of malignant hypertension resistant to therapy, with associated uremia, progressing rapidly to death, is a dreaded complication of systemic sclerosis.

Diagnosis

Hematologic, serologic, electrocardiographic, and roentgenographic studies are useful.[2]

In most patients with PSS the erythrocyte sedimentation rate is elevated, and a mild anemia of chronic disease may be present. Iron deficiency anemia may develop through bleeding from esophagitis, and there may be evidence of folic acid or vitamin B_{12} deficiency associated with malabsorption. Although hemolysis is uncommon, microangiopathic hemolytic anemia has been described.

Serologic abnormalities, as seen in other autoimmune diseases, may be expressed as mild hypergammaglobulinemia (30–50%) and through the presence of rheumatoid factor (25–30%) and antinuclear antibodies (30–40%).

The electrocardiogram shows nonspecific abnormalities in about half the patients. Conduction defects are rare and seen in those patients with marked myocardial replacement with fibrous tissue.

Roentgenography is useful in demonstrating soft tissue atrophy, calcinosis, and absorption of terminal phalanges without loss of joint space between phalanges. Studies of the gastrointestinal tract reveal a dilated atonic esophagus in 60% of the patients. Small bowel studies may show segmental atony, dilatation, and sacculation in the duodenum and jejunum. Barium studies of the colon may reveal wide-mouth, asymetrical diverticulae in 20–40% of patients. Chest studies reveal a diffuse reticular pattern with a honeycomb appearance in the lower lung fields. Serial films may reveal progression to a picture of dense interstitial fibrosis.

Differential diagnosis includes rheumatoid arthritis, systemic lupus erythematosus, and mixed connective tissue disease, which have a number of common clinical and serologic features. "Overlap" syndromes are being described with increasing frequency.

The course of untreated PSS is variable, and those patients with only acrosclerosis

and decreased esophageal motility often have slowly progressive disease with no significantly increased probability of early death. However, those with cardiac, pulmonary, or renal involvement may progress rapidly to their demise.

No specific treatment is known; however, D-penicillamine is being tried. Adrenal steroids are not helpful. Other therapy depends on the organ systems involved and the specific problems that arise—physiotherapy, protection of skin, and, especially, the hands from environmental- and employment-related trauma, iron, folate and vitamin B_{12} replacement, tetracycline for malabsorption syndromes, antihypertensives, etc.

Some patients with PSS renal disease have been dialyzed until transplantation could be performed. While some of these patients have done well, recurrence of the vascular lesions in the grafts has been reported.[3]

Pregnancy

PSS is three to four times more common in females than in males. Because it is most often diagnosed between the ages of 35 and 55, PSS is not usually associated with pregnancy.

Consideration of the pathophysiology of PSS and the physiologic and anatomic changes of pregnancy leads to concern about the effect of the enlarging uterus on abdominal skin, as well as delivery and the potential changes in the birth canal and perineum. Since the disease usually affects the skin of the upper extremities, thorax, neck, and face and not that of the abdominal wall and perineum, there is rarely a problem. Certainly, reflux esophagitis can present significant difficulty but can usually be controlled with appropriate dietary advice and antacids. Small bowel involvement and malabsorption potentially could present difficulty, but there are no reports of complications from nutritional deprivation during pregnancy. Should there be decreased colonic motility from the disease, the added changes of pregnancy might result in a greater problem with constipation. PSS renal disease can be a disasterous complication;[4-6] and pulmonary hypertension, no matter what the cause, carries a formidable maternal mortality rate.

Johnson et al.[7] reported 36 instances of concomitant PSS and pregnancy. Although one patient had had three spontaneous abortions and one stillbirth, no specific deleterious effects due to scleroderma were observed. All of the patients had the acrosclerotic form of the disease, although some had esophageal involvement as well. The disease remained the same or continued to progress at an unchanged rate in 39%. In an additional 39%, pregnancy was associated with some adverse effects on the scleroderma, but none involved the viscera or were life-threatening. In the remaining 22%, the patients noted marked relief of symptoms or signs of the disease during pregnancy. In the patients who were observed to have favorable skin changes, there was regression by 1 year following delivery. There were no maternal deaths in this series, and the perinatal mortality rate was not increased over normal.

Slate and Graham[8] described seven patients in whom pregnancy and scleroderma coexisted. One had the localized form of the disease. In the six patients who had PSS, there were 13 abortions and four premature deliveries. Two of the premature deliveries were stillborns, and the others survived. This fetal wastage is in marked contrast to the finding of Johnson et al.[7] Slate and Graham[8] reported one maternal death from bronchopneumonia and congestive heart failure.

Spellacy[9] presented one patient who had two pregnancies following the diagnosis of PSS. One pregnancy ended in spontaneous abortion, and the other ended with premature labor and the delivery of a 900-g infant who survived for 3 days. An autopsy was performed on the baby, and there was no evidence of scleroderma. This was noted specifically, because in his literature review Spellacy found two case reports of infants with stigmata of scleroderma. This might have been sclerema, however.

Knupp and O'Leary[10] reported a 40-year-old patient whose PSS was of 8 years' dura-

tion when she conceived. She proceeded through her pregnancy with minimal problems and was delivered by cesarean section for midpelvic dystocia. Both the mother and the infant did well.

Fear[4] reported a 26-year-old patient who had PSS for 6 years before conception. An evaluation 1 year before pregnancy had revealed dermal, esophageal, and pulmonary involvement, but renal function was normal. At twelve weeks' gestation the blood pressure was 130/90, but there was no proteinuria. At the 30th week proteinuria suddenly developed, and 2 days later the blood pressure was 200/110. The patient's condition was progressive, and the following day she convulsed. The fetus died during induction of labor. The patient was treated heroically but died 3 weeks after the proteinuria was first noted. This probably represents the acute development of PSS renal disease during pregnancy.

Sood and Kohler[5] reported the maternal death of a patient with PSS of about 2 years' duration. Before the pregnancy the only visceral involvement was esophageal, and renal function studies were normal. At 27 weeks' gestation she developed hypertension and proteinuria. She was treated with bedrest and barbiturate sedation. Nine days later acute pulmonary edema developed. The patient responded to therapy initially but died the following day. In addition to the expected findings in the skin, autopsy revealed typical changes in PSS renal disease. The author concluded that the PSS renal disease had developed acutely during the pregnancy.

Karlen and Cook[6] also have reported a death from PSS renal disease. Their patient was examined 6 months before conception, and her condition was diagnosed as the cutaneous form of scleroderma. At the time of diagnosis she was normotensive and had no proteinuria. At 31 weeks the patient exhibited proteinuria and mild hypertension for the first time. On admission to the hospital there was evidence of nitrogen retention. Two days later she went into congestive heart failure. With appropriate therapy she improved slightly for a short while. One week after admission, the membranes ruptured spontaneously and labor ensued. After a 4-hour labor she was delivered of a healthy infant, who subsequently did well. But the 7th postpartum day the patient was in severe renal failure and died during preparations for hemodialysis. Autopsy revealed classic findings of PSS renal disease.

These last three case reports are all very similar and demonstrate the remarkably rapid course from onset to death when PSS renal disease develops in pregnancy.

Ehrenfeld et al.[11] reported the case of a patient in whom scleroderma had been diagnosed about 9 months before conception. Early in the third trimester she developed hypertension and proteinuria and showed evidence of nitrogen retention. She was delivered of a normal infant by cesarean section. Following delivery, her blood pressure returned to normal, but the urinary findings persisted, as did the nitrogen retention. Six weeks postpartum she was hospitalized in early renal failure with malignant hypertension. Because of the inability to control her hypertension by medication and hemodialysis, she underwent bilateral nephrectomy. Subsequently she became normotensive and was treated by chronic dialysis for 17 months until her death. The histologic appearance of the kidneys was compatible with nephrosclerosis or PSS. This was probably renal PSS with onset early in the third trimester of pregnancy.

During the last 15 years we have delivered only one patient with PSS. Her disease was manifested by the CRST syndrome. She had periodic problems with nausea and vomiting. Her weight gain was inadequate. Following premature spontaneous rupture of the membranes and premature labor, she delivered a normal infant at 35 weeks.

From the foregoing review one must conclude that pregnancy complicated by PSS carries an increased rate of abortion, premature labor, and perinatal mortality. However, in contrast to such autoimmune diseases as systemic lupus erythematosus, immune thrombocytopenic purpura, myasthenia

gravis, and hyperthyroidism, babies born to mothers with any of the forms of scleroderma do not manifest the stigmata of the maternal disease.[12]

D-Penicillamine, which has been used in the treatment of PSS, is also used in patients with cystinuria and Wilson's disease. Some patients with the latter diseases have been followed through pregnancy while therapy was continued. Endres[13] has reported severe connective tissue defects in two newborns and feels D-penicillamine may be teratogenic.

With regard to antenatal care, it is recommended that complete evaluation be made as early in the pregnancy as possible. If there is evidence of pulmonary hypertension, myocardial fibrosis, or renal disease, therapeutic abortion should be offered. In the absence of significant pulmonary, cardiac, or renal impairment, the patient should be informed that the possibility of the development of such complications of PSS is always present and cannot be predicted. With this knowledge, the patient may elect to terminate the pregnancy. If the patient chooses to proceed with the pregnancy, antenatal examinations should be frequent, and at each examination the cardiopulmonary and renal status should be assessed. Careful attention should be paid to weight, esophageal and intestinal symptoms, and the hematologic status of the patient. Symptomatic treatment for integumental and musculoskeletal problems and appropriate nutritional supplements should be provided for the patient. Though intrauterine growth retardation does not seem to be increased in PSS, premature labor is common, but apparently not if only the skin, musculoskeletal tissues, or esophagus is involved. Fetal surveillance is indicated if renal or cardiopulmonary complications arise. Electronic monitoring is advised during labor, and the method of delivery should be dictated by obstetric events.

Patients with PSS should be advised against pregnancy and offered surgical sterilization. Those patients with milder forms of the disease should be advised of the potential problems and provided with secure contraception or offered sterilization.

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