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Dermatoses that Present with Cutaneous Sclerosis

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The diseases which present with cutaneous sclerodermatous changes are scleroderma, eosinophilic fasciitis, mixed connective tissue disease, sclerederma adultorum, sclero-myxedema and cutaneous midline mucinosis.

This paper reviews the characteristics and differential diagnosis among of the above mentioned diseases.

Key Words: Scleroderma, Eosinophilic fasciitis, Mixed connective tissue disease, Sclerederma adultorum, Scleromyxedema, REM syndrome, Cutaneous midline mucinosis.

The dermatologist is asked to evaluate, to suggest therapy, and offer a prognosis on diseases with predominantly cutaneous involvement. Among such diseases are those presenting with sclerotic changes of the skin. These are rare diseases and personal experience for any one physician is limited. During this presentation, I would like to review with you concepts of some of these as they have evolved from my own experience and from that recently reported in the literature.

SCLERODERMA GENERALIZED AND LOCALIZED

Certainly, the disease, scleroderma, is the first one of the disease entities we might even think of when we talk about sclerosis of the skin. This classification evolved from one originally proposed by O'Leary is still a satisfactory means of clinically categorizing the different forms of scleroderma. From Table 1, one can see that facial hemiatrophy and the hemiatrophies are in an intermediate position between localized and generalized forms of the disease inasmuch as those patient do, at times, have systemic involvement with electroencephalographic changes and seizures. It is not entirely a benign cutaneous disease.

Table 1. Classification of scleroderma

Localized	Generalized
Morphea	Progressive systemic sclerosis
Guttate vs L.S. et A.	Acrosclerosis
Localized	
Generalized	
Linear	
En coup de sabre	
Facial hemiatrophy	
Hemiatrophy	

Patients with acrosclerosis present a characteristic facies with pinching and thinning of the

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nose, rhagades about the mouth, receding chin, and a skin otherwise free of wrinkles. Patients with acrosclerosis in addition, show hands that presents sclerosis of the soft parts with contracture deformities of the digits of a degree that a complete fist cannot be made. Severe limitation of function of the hands occurs and considerable disability oftentimes results. Ischemic ulcerations eventually develop due to vascular involvement. Loss of digits, whole or part, may occur.

All of you are aware of the multisystem organ involvement in systemic scleroderma with the gastrointestinal tract, particularly esophageal involvement, being common; pulmonary involvement occurs almost as frequently; and terminal involvement of the kidneys is a common complication. Cardiac involvement with conduction defects are a serious complication with which to contend.

The cause of the disease remains unknown with considerable thought given to its being a vascular disease, a purely collagen disease or an immunologic disease. In volume 3 of Progress in Cancer Research and Therapy, published in 1977 (Hecht, 1977), the authors state a clearly increased risk of cancer, particularly alveolar cell adenocarcinoma of the lung in patients with scleroderma. They state that more than 25 patients have been reported with this finding and note the striking features of the association that 7:1 are female/male and a positive correlation with the intensity of sclerodermal interstitial pulmonary fibrosis.

In contrast, Duncan and Winkelmann of the Mayo Clinic, reported in 1979 (Duncan and Winkelmann, 1979) a study in this regard and emphasized the fact that in a review of over 2000 cases, the incidence of malignancy was 4% and that the relative frequency of cancer types was the same as occurred in the general population. In their series, there was no increase of lung cancer and that their studies would seem to indicate this is a fortuitous association, not an etiologically important one.

In regard to localized morphea, all of us are aware of the isolated single plaque of the disease that might occur, either singly or multiply over the body. At times, these present only as hyperpigmented areas with very little sclerosis underlying the lesion and the differential consideration of atrophoderma of Pasini and Pierini must be considered. Whether the atrophoderma of Pasini and Pierini is really a separate entity is still discussed by many (Canizares, *et al*, 1958; Cunliffe, 1979).

The presentation of en coup de sabre as a form of morphea is a rare presentation and in some instances, we find even bilateral en coup de sabre with the sclerotic plaques in the paramedian area bilaterally. We had the occasion to report some of these cases in the past (Dilley and Perry, 1968). The usual patient with hemiatrophy eventuates into an individual who presents distortion of the tissues because of the sclerotic process that unilaterally involves the face with a lack of development of the hard and soft tissues of those parts. The psychological trauma associated with these developments is considerable and the cosmetic disfigurement of a considerable degree at times.

Not only the face but the trunk as well may be involved in this initial sclerotic pattern again with involvement of the deeper structures with the bones being shortened, the tendons involved and contracted.

The interrelationship of localized and systemic scleroderma has always been a confusing one. Christianson in revew published in 1956 (Dilley and Perry, 1968), reviewed 235 cases at Mayo Clinic and recognized that amongst 191 patients with linear lesions and plaques characterizing their scleroderma, none of them developed into systemic scleroderma. However, in 44 cases

of generalized morphea, 2 progressed to systemic scleroderma (Table 2).

Table 2. Progression of localized to systemic scleroderma

SCLERODERMA
1956 Christianson et al Arch Derm 74: 629
235 cases – Mayo clinic
Group 1 (191) linear lesions & plaques
No progression to systemic scleroderma
Group 2 (44) Generalized morphea
2 patients developed generalized scleroderma

This contrasts to information provided by Curtis and Jansen (Curtis and Jansen, 1958) a few years later when they, in a different manner, clinically designated their patients as having morphea, guttate forms of scleroderma or linear scleroderma. In those various categories, the progression of localized to generalized scleroderma was 4, 1 and 1, respectively. Six cases out of 106, a much higher incidence, showed progression of their localized disease to generalized disease (Table 3).

Table 3. Progression of localized to systemic scleroderma

SCLERODERMA
1958 Curtis and Jansen Arch Derm 78: 749
115 cases Univ. Hosp. Michigan
Localized Scleroderma
1) Morphea
4 pts. developed gen. scleroderma
2) Guttate
1 pt developed gen. scleroderma
3) Linear
1 pt developed gen. scleroderma

When this occurs, it is of rare occurrence but we must be aware such can occur from time to time.

Most of us feel comfortable with the classification of scleroderma as I have indicated here but there are always cases seen which provide a problem in classification.

A number of years ago under the title of "Familial" Scleroderma (Burge *et al*, 1969) I reported on two sisters who had the onset of their scleroderma in childhood. The older of these two sisters was seen as a 6-month-old infant with atopic eczema and then at the age of 2 years with asthma and hay fever. But it was not until she was 7 years of age that she experienced progressive stiffness and flexion contraction in most of the distal joints of both upper and lower extremities. From that time forward, there was continual progression of the cutaneous sclerosis so that by the time she was a young teenager, she presented with major deformities of all four extremities. Cutaneous sclerosis with the contracture deformities of joints was the major presentation in this girl.

This patient had difficulty with fine movements of her fingers, with making a fist or in some instances, even in moving her arms to any degree. There was severe involvement about the knees and feet which made walking difficult. Sitting was possible but mobility was otherwise very restricted. This patient was studied extensively at the age of 13 years. Because of total disability of her legs and the presence of recalcitrant ulcers of the feet and severe pain that required large doses of opium, bilateral mid-thigh amputations were performed. With the use of prostheses, she was able to ambulate and become active once again. The patient much preferred this situation to the disability she experienced without the prostheses.

A year later, however, additional sclerotic involvement developed on the face, back, breasts and abdomen and ulcers developed on the shoulders, elbows and hands. A progressive scoliosis

and flexion contractures of the hips then prevented ambulation altogether. There was a rapid course of deterioration of her condition and she died at the age of 16 years in 1967 of terminal bronchopneumonia.

This patient had a sister some 4 years younger. In 1965, two years before the older sister's death, this young patient began to develop stiffness of her fingers and joints with sclerosis of the palms and flexural surfaces of the dorsum of the hands and forearms that became more apparent at about the time of her sister's death. This sclerosis appeared to involve deep tissues and muscles with a lack of systemic involvement of any organ systems or of the presence of Raynaud's phenomenon.

No Raynaud's phenomenon was present. There were progressive sclerotic changes of the soft tissues with a decrease in the mobility in the joints of the fingers and the feet.

The patient was treated with a variety of measures that included thyroxine and topical steroids. With the death of her sister and the apprehension of the family, we felt that we should be more aggressive in her therapy. Thus, she was placed on Cytoxan with resolution of the skin lesions over the next year or so. Because of the development of persistent hematuria, the drug was discontinued and Penicillamine therapy instituted. This was continued for two years with a result that the deep sclerosis of the skin disappeared while she was on this therapy. Her most recent followup, two years ago, indicated that her skin has remained normal and the deep sclerosis had not recurred.

The exact classification of this type of sclerodermatous change to the skin is one that is difficult to specifically ascertain. One might question where such patients fit into the total scheme and classification of scleroderma.

To answer that dilemma, Dr. Diaz-Perez, Connolly and Winkelmann reviewed Mayo Clinic experience which included these patients, and collected a total of 14 children with problems similar to those just described. They classified them under the diagnosis of disabling, pansclerotic moprhea of children (Diaz-Perez *et al*, 1980). One should be aware in such classifications that this represents not only a cutaneous disease but there are systemic implications to the disease as well. This presence of various alterations in the globulins, the positive ANA, the elevated sedimentation rate and the systemic changes in the pulmonary and esophageal areas – all suggest the alteraton of systemic disease (Table 4). But again, the classification of patients who present with cutaneous sclerosis, is not easy.

But what about other types of subcutaneous involvement? Drs. Person, and Su of Mayo Clinic looked at some of our patients with similar problems (Person and Su, 1979) and they wondered about the diagnosis is of subcutaneous morphea as being appropriate for the designation of some of those patients. Here again, with the systemic implications of the patient (Table 5) and the recognition that not all patients with morphea are simple with extensive disease,

Table 4. Features of disabling pansclerotic morphea of children (Diaz-Perez *et al*, 1980)

14 children:	Onset 1-14 years of age	
Distribution:	Usually generalized	
Histology:	Lymphocytic inflammation	
	Hyaline panniculitis	
Lab data:	Polyclonal elev globulin	10/11
	Elevated IgG	10/11
	IgM	7/11
	Positive ANA	3/11
	Peripheral eosinophilia	8 pts
	ESR elevated	8 pts
Systemic changes:	Pulmonary	5
	Esophageal	1

Table 5. Features of subcutaneous morphea from Person and Su

Inflammatory sclerosis of panniculus and fascia, centrifugal spread of sclerosis	16 pts
Systemic associations:	
Digital vasospasms	4
Dermal morphea or LS&A	5
CO diffusing capacity	4
Pulmonary fibrosis	1
Esophageal involvement	3
Peripheral eosinophlia	3
Death	1

Inflamm. Morphea? Eo. fasciitis? Scleroderma?

there may be systemic involvement that complicates their problems. Thus, as we go back to the original papers of Christianson and his associates, Drs. Curtis and Jansen, perhaps we are seeing in a little different context, those patients which originally had localized disease but who are now presenting with systemic disease.

EOSINOPHILIC FASCIITIS

A new entity that has captured the imagination of the dermatologists is that of eosinophilic fasciitis. One might reasonably question whether this represents a distinct entity (Torres and George, 1977). There are those features which because of a cutaneous sclerosis, the rapid onset, the lack of systemic involvement, the presence of eosinophilia, the IgG alteration which is so common, all would speak against eosinophilic fasciitis being a form of scleroderma. In addition, the response of these patients to systemic steroids is quite in contrast to that which we have experienced in patients who have scleroderma (Robinson, 1979). Dr. John Doyle of our department has looked at patients with eosinophilic fasciitis. There is sclerosis throughout the dermis and alteration in the tissues with inflammation deep into the tissues, and those deeper areas have been studied in greater detail. He has felt that there is marked alteration of the fascial tissues with perhaps proliferation of blood vessels in the areas of involvement together with inflammation that suggests that prehaps the changes are due to a vascular involvement in this disease.

The relationship of eosinophilic fasciitis to scleroderma is one that becomes apparent clinically when one sees patients with sclerosis of the hands and forearms and of the lower legs in a patients who has eosinophilic fasciitis and whose disease has responded to the administration of corticosteroids. I had considered eosinophilic fasciitis separate and distinct from scleroderma. Yet, the recent report by Jarrat (Jarrat *et al.*, 1979) in which the patient originally had eosinophilic fasciitis and then more recently developed typical acrosclerosis is hard to say they are distinct.

MIXED CONNECTIVE TISSUE DISEASE

Not all firm, indurated changes of the skin fit into clear syndromes of scleroderma. I only need to emphasize the clinical features of the mixed connective diseases and all will recognize the scleromatous changes which are so common with this entity. Sharp in his review of the problem in the Bulletin on Rheumatic Disease (Rodnan, 1974-75) has indicated that sclerodermatous changes are the most common cutaneous change of this group (Table 6).

One must recognize that a diagnosis of mixed connective disease is predominantly that of a laboratory evaluation and not totally a clinical examination (Sharp and Anderson, 1980). The clinician, thus, may look at these patients from

Table 6. Clinical cutaneous changes in mixed connective tissue disease

Swelling of hands, sausage appearance of digits
Sclerodermatous changes
Ulcerative and necrotic lesions
Telangiectasias
Gottron changes
Nonspecific rashes
"LE" eruptions

the standpoint of firm skin and scleroderma, but the laboratory evaluation with the extractable nuclear antigen, places these patients within a special category of disease and management. Like some of these special forms of scleroderma, the use of corticosteroids is extremely beneficial in the treatment of that group of patients.

SCLEREDEMA ADULTORUM OF BUSCHKE

Firmness of the tissue may not all be on the basis of alteration of the collagen into firm sclerotic bundles. Edema may be a part of the presentation so great that the tissues do feel hard and firm and may be confused with scleroderma. Scleredema adultorum, a misnomer, because many of the patients involved are children. The signs and symptoms of the disease are listed in Tables 7 and 8. Although we have been inclined to believe that the hands and feet are not involved in this disease process, in about 10% of cases in large series, hands and feet are involved which makes the diagnosis of the disease more confusing for those not well acquainted with the process.

When one considers the characteristics of scleredema and differentiate it from scleroderma, the alterations can give some indication of the direction of the specific diagnosis. Although we

Table 7. Clinical signs of scleredema adultorum

Rapidly progressive, woody induration of skin; non-pitting
Waxy pallor of skin
Facies often mask-like
Onset over neck and shoulders; Spread to face, arms and trunk
Legs less commonly involved
Hands and feet in 10% of cases
No sharp delineation between involved and normal

Table 8. Symptoms encountered in scleredema adultorum

Symptoms:	
Skin	stiff, restricting motion
	rarely – an erythematous, roseolar, urticarial or annular rash
Eyes	motion restricted
Tongue	motion restricted
Joints	motion restricted; hydrarthrosis
Muscles	weakness, tenderness
Sign: Effusion-pleural, pericardial, peritoneal	

have indicated in the slide the usual duration of the disease is from 6 to 18 months, it is well to recognize that some patients with scleredema may have their disease persist for some 30 years.

Greenberg *et al* in their study of 209 patients (Greenberg *et al*, 1963) recognized that many of them had an antecedent illness usually a streptococcal sore throat preceding the onset of their disease. Today we still find this clinical feature to be common in the disease. The association of diabetes mellitus as originally delineated by Fleischmajer *et al* (1970) and Cohn *et al* (1970) were found in a proportion of the patients we have seen.

The sclerosis of the tissues is most confusing. One can appreciate the fact that diverse diagnostic considerations must be given to the differential considerations of these patients. Par-

ticularly noteworthy are those who may have edema of cardiac, renal or hepatic origin whose disease may be readily confused with those patients with scleredema who present pleural effusions of the pericardium or pleural cavities (Johnson and Ikram, 1970)

SCLEROMYXEDEMA

A disease which is of even rarer occurrence but may at times confuse physicians because of its sclerodermatous quality is that of scleromyxedema. The diagnostic terminology is difficult (Perry *et al*, 1960a) although the term scleromyxedema is at times applied only to the generalized lichenoid eruption which occurs in type 1 of this classification (Table 9). Appreciation that these other forms of the disease varying from discrete papules to urticarial and sclerotic plaques are considered a part of the total picture of mucinous deposits in the skin presenting at times with so much induration of the tissues, the patients are misdiagnosed as having scleroderma.

Table 9. Classification of papular mucinosis (lichen myxedematosus, scleromyxedema)

Classification
1. Generalized lichenoid eruption
2. Discrete papular eruption-trunk and extremities
3. Localized or generalized lichenoid plaques
4. Urticarial plaques
5. Confluent papular and sclerotic plaques

Scleromyxedema (papular mucinosis, generalized lichen myxedematosis) is a rare disease. The papular variety characterized clinically by the discrete papules may develop into plaque-like forms by confluence of lesions. Histologically, the disease is characterized by the deposition of mucinous material in the upper dermis. Although the serum protein electrophoretic pattern is normal, the presence of a monoclonal serum protein may be detected by a post-gamma peak, which is characteristic for this group of patients. Despite the presence of mucoid changes in the skin, thyroid dysfunction is not present but rather dermatomyositis, amyloid, pachydermal periostosis, coronary artery disease and cerebral vascular accidents have been associated with these cutaneous findings.

The form of therapy we have preferred for these patients has been that of Melphalan. The first such patient we treated in this manner, treatment was continued over many years. The usual dosage is 1 to 2 mg/day depending upon the hematologic tolerance of the patients. We have reported our findings in 8 patients in a paper published in the Archives of Dermatology (Harris *et al*, 1979).

After two years of therapy, she improved to a degree. Further improvement occurred in the next two years and the drug was discontinued by the patient on her own after some four years of treatment. She experienced a recurrence of the disease, this time associated with muscle weakness and swallowing difficulty. As we studied her in detail, she had the esophageal findings of scleroderma and a myopathic process present on electromyographic study of her muscles. Treatment with Melphalan was again instituted and continued for some two years with final resolution of the process. Now some 10 years later, her skin is soft and supple and essentially normal to touch.

In scleromyxedema, the biopsy on H&E staining shows perhaps a bit of bluish staining to the tissues but with an essentially normal appearing dermis. When one stains the slides with Alcian blue-PAS, the marked deposition of mucin that is present there is easily recognized.

Low-dose chemotherapy of scleromyxedema seems to us to be a reasonable way to manage

the patient with disabling disease. Certainly, we would not recommend such therapy for the patient with a minor papular quality to his skin. Whereas we employed Melphalan, others have employed methotrexate (Piper *et al*, 1967) or cyclosphamide (Howsden *el al*, 1975) as chemotherapeutic agents.

The employment of Melphalan in small doses over a long period of time in our experience is a very satisfactory therapy. The complications of this therapy have been minimal although we had one patient who died with a complication of leukemia and a second who died during the course of therapy. In the latter case, the patient had developed progressive disease before therapy had been instituted. Scleromyxedema is another of those diseases which present with cutaneous sclerosis which must be differentiated.

CUTANEOUS MIDLINE MUCINOSIS

A disease that interested me and which I describe in association with Drs. Kierland and Montgomery in the mid 50s was that of cutaenous midline mucinosis, a plaque-like form of induration of the chest, both anteriorly and posteriorly (Perry *et al*, 1960 b). In addition to the original three cases, we more recently have been three more cases (Table 10). One of these more recent cases also shows a question of an associated granuloma annulare. I have recently discussed this patient with Dr. Winkelmann who has seen that patient. He feels that she has both diseases, the mid-line mucinosis and granuloma annulare. Among those latter patients also, note the one who had had an adenocarcinoma of the right breast prior to the time that we had seen her for her midline musciosis.

Dr. Steigleder and his associates described the REM Syndrome: reticular, erythematous mucinosis, a disease very similar to that described by us (Steigleder *et al*, 1974).

Table 10. Patients seen initially and of more recent date, with cutaneous midline mucinosis

CUTANEOUS MIDLINE MUCINOSIS Plaque-Like Form		
Arch Derm 82: 980, 1960		
37 F	sun	urtication
39 F	sun	redness & burning
57 M	heat	redness
Recent Cases		
53 F (5/71)	Asymptomatic	
54 F (3/74)	? granuloma annulare	
55 F (8/74)	Gr III adenoca. rt breast 12/73	

After Steigleder's presentation for publication in 1974, a number of other cases have been presented; (Table 11) the most recently by Morrison (Morison *et al*, 1979) who believes firm indurated and sclerotic mucinous plaques of the anterior and posterior chest described by us and classified as the REM syndrome by Steigleder are in reality the same process.

Table 11. Recently reported cases of the REM Syndrome

REM SYNDROME Reported Cases		
1974 Steigleder, et al	48 M	No photosensitivity
1975 Steigleder	38 F	Transitional case
1977 Dal and Larsen	47 M	Asymptomatic
1977 Keckes and Jadhav	50 F	No photosensitivity
1979 Morison et al	34 F	Sun eruption
	40 F	Sun exacerbated

REFERENCES

Burge KM, Perry HO, Stickler GN: *"Familial" scleroderma. Arch Derm 99:681-687, 1969*

Canizares O, Sachs PM, Jaimovich L, Torres VM: *Idiopathic atrophoderma of Pasini and Pierini. Arch Derm 77:42-60, 1958*

Cohn BA, Wheeler CE, Briggaman RA: *Scleredema adultorum of Buschke and diabetes mellitus. Arch Derm 101:27-35, 1970*

Cunliffe WJ: *Disorders of connective tissue. In Rook A, Wilkinson DS, Ebling FJG(eds): Textbook of Dermatology. Colchester amd London: Spothiswoods Bullantyme, Ltd, 1979, vol. 1, chap 51, p1614-15*

Curtis AC, Jansen TG: *The prognosis of localized scleroderma. Arch Derm 78:749-757, 1958*

Diaz-Perez JL, Connolly SM, Winkelmann RK: *Disabling pansclerotic morphea of children. Arch Derm 116:169-173, 1980*

Dilley JJ, Perry HO: *Bilateral linear scleroderma en coup de sabre. Arch Derm 97:688-690, 1968*

Duncan SC, Winkelmann RK: *Cancer and scleroderma. Arch Derm 115:950-955, 1979*

Fleischmajer R, Faludi G, Krol S: *Scleredema and diabetes mellitus. Arch Derm 101:21-26, 1970*

Greenberg LW, Geppert C, Worthen HG, Good RA: *Scleroderma adultorum in children. Pediatrics 32:1044-1054, 1963*

Harris RB, Perry HO, Kyle RA, Winkelmann RK: *Treatment of scleromyxedema with melphalan. Arch Derm 115:295-299, 1979*

Hecht F: *Chromosome instability syndromes. In Mulvihill JJ, Miller RW, Fraumeni JF: Cancer research, vol. 3, Genetics of human cancer. New York: Raven Press, 1977, p 116*

Howsden SM, Herndon JH Jr, Freeman RG: *Lichen myxedematosus: A dermal infiltrative disorder responsive to cyclophosphamide therapy. Arch Derm 111:1325-1330, 1975*

Jarratt M, Bybee JD, Ramsdell W: *Eosinophilic fasciitis: An early variant of scleroderma. JAAD 1:221-226, 1979*

Johnson ML, Ikram H: *Scleroedema of Buschke. Brit J Derm 32:720-722, 1970*

Morison WL, Shea CR, Parrish JA: *Reticular erythematous mucinous syndrome. Arch Derm 115: 1340-1342, 1979*

Perry HO, Montgomery H, Stechney JM: *Further observations on lichen myxedematosus. Ann It Med 53:955-69, 1960a*

Perry HO, Kierland RR, Montgomery H: *Plaque-like form of cutaneous mucinosis. Arch Derm 82:980-985, 1960b*

Person JR, Su WPD: *Subcutaneous morphea: a clinical study of sixteen cases. Brit J Derm 100: 371-380, 1979*

Piper W, Hardmeier T, Schafer E: *Das Skleromyxodem Arndt-Gottron: Eine paraproteinamische Erkrankung. Schweiz Med Wochenschr 97:829-838, 1967*

Robinson JK: *Eosinophilic fasciitis: A problem in differential diagnosis. J Dermatol Surg Oncol 5:780-783, 1979*

Rodnan GP: *Bulletin on the rheumatic diseases. Published by the arthritis foundation, 1974-75, vol. 25, pp 828-831*

Sharp GC, Anderson PC: *Current concepts in the classification of connective tissue diseases. JAAD 2:269-279, 1980*

Steigleder GK, Gartmann H, Linker U: *REM syndrome: reticular erythematous mucinosis (round-cell erythematosis), a new entity? Brit J Derm 91:191-199, 1974*

Torres VM, George WM: *Diffuse eosinophilic fasciitis. A new syndrome or variant of scleroderma? Arch Derm 113:1591-1593, 1977*