Points of View

The diagnosis and classification of scleroderma (systemic sclerosis)

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Summary: Difficulty in the diagnosis of the disease scleroderma may occur at the early stage prior to the development of obvious skin sclerosis. A presumptive diagnosis may be made if Raynaud's phenomenon is accompanied by a positive 'neck test', 'scleroderma' capillary changes in the nailfolds or antinuclear antibodies. Definitive diagnosis may have to be delayed for several years from the onset of Raynaud's phenomenon until definite characteristic skin changes are seen. Ten cases in which an earlier diagnosis of scleroderma was not substantiated are listed. The earlier incorrect diagnosis would have been avoided by use of the methods described in this paper.

Various terms have been used to denote subdivisions of scleroderma. These include acrosclerosis, diffuse scleroderma and CREST. We have used the terms Type 1, Type 2 and Type 3 based on the early extent of the skin sclerosis where Type 1 (limited extent) indicates sclerodactyly only, Type 2 (moderate extent) indicates sclerosis proximal to the metacarpophalangeal joints but excluding the trunk and Type 3 (extensive) indicates diffuse skin sclerosis including the trunk. The clinical value of this simple classification is reviewed and contrasted to other classifications which appear to be poorly defined and of limited use.

Diagnosis of scleroderma

For many years there have been problems with the diagnosis of scleroderma, largely due to the use of this term for two different groups of conditions. On the one hand there are various dermatological conditions characterized by thickened skin, such as morphea, linear scleroderma, scleroderma *en coup de sabre*, or scleroderma with hemiatrophy, and on the other hand there is a systemic disease characterized by symmetrical stiffness of the skin, vascular insufficiency and disturbance of function of various internal organs. This latter disease was designated by Goetz¹ 'progressive systemic sclerosis', later shortened because it is not persistently progressive, to 'systemic sclerosis'. It is this latter condition which will be considered in

more detail, in the light of experience with patients with scleroderma seen over a period of 30 years.

Definition

It is first necessary to define scleroderma. As the cause is not known, it can only be defined in terms of its clinical manifestations. The following definition applies to the patients we regard as suffering from this disease and probably most of those described by recent writers: 'a condition of obscure origin characterized by symmetrical stiffness of the skin, vascular insufficiency and various characteristic forms of systemic involvement'. Commonly accepted features are listed in Table I. Stiffness of the skin during at least one stage of the clinical course is an essential component of the illness. This avoids including patients with some features of scleroderma but without skin sclerosis, which we have placed in a separate category called 'atypical scleroderma'. Our diagnostic criteria are somewhat more liberal than those of the American Rheumatism Association²

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Accepted: 10 September 1987

Table I Criteria for diagnosis of scleroderma

1. Typical scleroderma	
Feature	
(i) Symmetrical skin thickening	All cases over 90% of cases
(ii) Raynaud's phenomenon, acrocyanosis	
(iii) Characteristic nail-fold capillary changes	
(iv) Typical antinuclear antibodies	variable
(v) Characteristic systemic organ involvement	
2. Atypical scleroderma	
Various combinations of above with <i>no</i> skin changes or with finger swelling only.	
3. Exclusions	
(i) Other identifiable connective tissue disease such as systemic lupus erythematosus.	
(ii) Drug or chemical related scleroderma.	

who listed as a 'major criterion' sclerosis proximal to the metacarpo-phalangeal joints, although they accepted the diagnosis in the absence of this in the presence of certain 'minor criteria'. However, even using the simple diagnostic criteria in our definition, there may sometimes be difficulties with diagnosis. Skin stiffness may sometimes first appear several years after the onset of Raynaud's phenomenon. Other conditions such as dermatomyositis and systemic lupus erythematosus may develop skin stiffness together with Raynaud's phenomenon.

Difficulty in diagnosing early cases, before the development of skin sclerosis

A major problem is differentiation from primary Raynaud's disease. This is stated to affect almost exclusively women and the age of onset is usually under 40 years.³ Scleroderma affects both females and males with a female to male ratio of about 3 to 1 and may occur at any age although the onset is usually after 40 years.⁴ There can obviously be overlap of early onset scleroderma and late onset Raynaud's disease. In some cases we have obtained help from the 'neck test' of extending the head and looking for tightness of the skin of the neck; this test is positive in patients with scleroderma but negative in those with primary Raynaud's disease. Skin biopsy has not helped much, as we have found that skin stiffness could be observed by the physician before the microscopic changes were obvious to the pathologist.

Are special tests of any value? Nailfold capillaroscopy shows a characteristic pattern – sparseness of the capillaries with dilated, irregular loops – present

in over 80% of patients with scleroderma⁶ but absent in patients with primary Raynaud's disease. It is not certain how early the changes develop in scleroderma. However, Maricq *et al.*⁷ have reported on a patient with apparent primary Raynaud's disease who had scleroderma nailfold capillaries pattern and who later developed clinical scleroderma. We have also seen such a case.

Antinuclear antibodies of various types can be detected by current techniques in over 90% of patients with scleroderma⁸ and we have found them to be absent in all of 7 cases of primary Raynaud's disease who had been followed over several years. However, it is not certain that the antibodies always precede the skin sclerosis in scleroderma. Several studies from the onset of Raynaud's phenomenon will be necessary to establish this point. Nevertheless, the presence of antinuclear antibodies in a significantly raised titre in a patient with Raynaud's phenomenon would suggest that the condition is not primary Raynaud's disease.

The findings presented above suggest that a presumptive diagnosis can be made with reasonable confidence in most early cases, although a definitive diagnosis may sometimes have to be postponed for several years pending the development of definite skin stiffness.

Problem of skin stiffness in other illnesses

Some patients with other connective tissue diseases, particularly dermatomyositis and systemic lupus erythematosus may develop stiffness of the skin of the fingers or across the front of the chest suggestive of scleroderma. Diagnosis is based on the major clinical features which are predominantly those of the other disease. Sometimes the symptoms are almost equally those of scleroderma and of the other disease, in which case an 'overlap syndrome' appears to be the most appropriate diagnosis. The outcome of such patients is determined by the dominant clinical syndrome, be it scleroderma, polymyositis or systemic lupus erythematosus.

Diagnostic problems in our series

In the course of a follow-up study of 185 patients whom we had diagnosed as suffering from scleroderma over a period of 30 years⁹ we found that in 99 survivors reviewed this diagnosis was accepted in 89, but in 10 another diagnosis was made. The initial diagnosis was generally made on the basis of the criteria given in our definition but we included some presumptive cases with late onset Raynaud's phenomenon or with other features believed at the time to be indicative of scleroderma in the absence of definite skin stiffness.

Over-diagnosis The ten patients who were initially diagnosed as suffering from scleroderma and who did not meet the current criterion of 'symmetrical stiffness of the skin' when seen at review are summarized in Table II. These patients had late onset of Raynaud's phenomenon or some symptoms commonly found in scleroderma. Cases 1, 2 and 3 are now regarded as late onset Raynaud's disease and not scleroderma. Case 4 had La and Ro antibodies, which are regarded as markers for Sjögren's syndrome.¹⁰ Cases 5 and 6 had U₁RNP antibody which is regarded as a marker of mixed connective tissue disease.¹¹ Cases 7, 8, 9 and 10 had other clinical features and antibodies commonly found in scleroderma. They have been diagnosed as 'atypical scleroderma' and probably correspond to those diagnosed in the past to 'progressive systemic sclerosis *sine* scleroderma'.¹²

Under-diagnosis Our review study did not allow us to be sure that the diagnosis of scleroderma had been missed in some patients initially referred to one of us (AJB) with Raynaud's phenomenon or other symptoms. However, this probably occurred in few, if any, cases because, in view of this author's 30 year interest in scleroderma, patients who later developed stiffness of the skin would most likely have been referred back to him.

Comments

From our observations it appears that the diagnosis of scleroderma should be made readily from the presence of vascular insufficiency of the digits plus symmetrical stiffness. The presence of antinuclear antibodies and of typical scleroderma nailfold capillary changes are confirmatory and it is

recommended that all patients with Raynaud's phenomenon should have these tests. However, our observations do not allow us to be sure that these features are present in all early cases. A positive 'neck test' (tightness of the skin of the neck on extending the head) is a helpful confirmatory sign.

Scleroderma was initially overdiagnosed in our series and we did not substantiate the diagnosis in 10 of the 99 patients reviewed. This was due to making the initial diagnosis in the absence of skin stiffness.

A diagnosis of 'atypical scleroderma' was made in certain patients with Raynaud's phenomenon, some other features commonly found in scleroderma and the presence of scleroderma type antibodies. We believe it is preferable to include these few patients in this separate category as they do not have 'hard skin' and one avoids the risk of including patients who would be shown eventually to have some non-scleroderma condition.

Classification of the subdivisions of scleroderma

It has been recognized for a long time that scleroderma (systemic sclerosis) presents a very wide clinical picture – with at one extreme Raynaud's phenomenon and sclerodactyly and long survival and at the other extreme widespread skin involvement and a severe illness causing early death. The extremes are so different that one may question whether they are varieties of the same disease or different diseases which happen to share two symptoms – vascular disturbance and stiffness of the skin.

These differences in clinical picture have led to the use of different terms for the particular

Table II Patients in whom diagnosis of scleroderma was not accepted at review

Patient	Sex	Age		Sicca	Arthralgia	Telang- iectasia	Stiffening of fingers	Neck sign	Nailfold scleroderma findings	Autoantibody findings
		Onset	Current							
1	M	40	55	0	0	0	±*	0	0	neg
2	F	44	70	0	+	0	0	0	0	neg
3	F	47	69	+	+	+	0	0	0	neg
4	F	39	56	+	0	0	0	nd	nd	La, Ro
5	F	41	50	0	+	+	0	±	nd	U ₁ , RNP
6	F	59	61	+	+	+	0	0	+	U ₁ , RNP
7	F	61	64	+	+	0	Puffy	0	0	Nucleolar Scl 70
8	F	51	57	+	+	0	0	+	+	Nucleolar
9	M	56	58	0	0	+	0	0	+	Nucleolar
10	F	26	33	0	+	+	Puffy	0	+	Anti- centromere

0 = absent; + = present; nd = not done; *patient acromegalic.

varieties. These include acrosclerosis¹³ when the sclerosis of the skin is confined to the extremities, and diffuse scleroderma when the sclerosis of the skin is more widespread and involves the trunk. In general, patients with acrosclerosis have a better prognosis as regards life expectancy than those with diffuse scleroderma.^{4,14} Some writers have considered acrosclerosis and diffuse scleroderma to be different diseases^{15,16} but others have found similar visceral disturbances in the two forms and have regarded them as variants of the same disease.¹⁷⁻²²

In 1964, Winterbauer²³ introduced a new term 'CRST syndrome' to denote a combination of calcinosis, Raynaud's phenomenon, sclerodactyly and telangiectasia and considered that this was a benign form of scleroderma. Others have criticized this term. Rowell²⁴ found that the features denoted by the letters were common in scleroderma generally. Barnett²⁰ found that telangiectasia and calcinosis were common in various types of scleroderma. The acronym CRST has since been expanded to the more euphonic CREST to include oesophageal involvement, which also is common in scleroderma generally. The diagnosis of CRST (or CREST) has become imprecise and some writers include patients with only three of the components.²⁵ The old term acrosclerosis seems to have disappeared from current literature. The term diffuse has acquired a new meaning of non-CREST without the requirement that the sclerosis include the trunk.

Because of the apparent inconsistency of terms used by other writers Barnett & Coventry⁴ classified cases of scleroderma according to the extent of early skin involvement (within one year of presentation) as follows: Type 1 (limited) – sclerosis of the fingers only, Type 2 (moderate) – sclerosis of the limbs and face but excluding the trunk, and Type 3 (extensive) – diffuse sclerosis including the trunk. This classification is simple, reproducible and has proved useful as a shorthand description of cases. Patients do not change types unless skin thickening improves spontaneously or with treatment. It is also an aid to prognosis: in general Type 1 and Type 2 cases have a favourable prognosis in respect to life expectancy and Type 3 cases have a much worse prognosis^{4,26} although current treatment of renal hypertensive crisis has improved survival of Type 3 patterns.

The term CREST does not fit comfortably with the acrosclerosis-diffuse or the Type 1, 2 and 3 classifications. The incidence of CREST features and of the presence of anticentromere antibody (ACA) in 74 of our 89 scleroderma survivors who were examined in detail for these features is shown in Table III. It is seen that more than 50% of

Table III Relationship of scleroderma type to incidence of CREST features and ACA in authors' series.

Type of scleroderma*	Presence (percentage of type) of >4 CREST features							ACA
	n	C	R	E	S	T		
Type 1	45	40	100	78	100	87	51	71
Type 2	22	36	100	95	100	86	77	23
Type 3	7	29	100	86	100	86	71	0

*As defined in the text.

C=calcinosis, R=Raynaud's phenomenon, E=(o)esophageal or gastro-oesophageal reflux symptoms, S=sclerodactyly, T=telangiectasia. ACA=anticentromere antibody.

patients of each type have more than 4 CREST features. The incidence of ACA was highest in Type 1 cases, intermediate in Type 2 cases and nil in Type 3 cases. The presence of this antibody is stated to be associated with a good prognosis.^{27,28}

Comments

There is widespread agreement that scleroderma varies greatly in severity and prognosis and that some system of subdivision is required. The old classification into acrosclerotic and diffuse was not helpful in this respect. The current use of CREST is not helpful as CREST features are spread over the whole range of scleroderma and there is no suitable name for non-CREST. The subdivision into Types 1, 2 and 3 according to the early extent of skin involvement has the advantage that these types are easy to define and is useful in prognosis. The presence of anticentromere antibody may also be associated with a good prognosis, but it is not possible to state whether this is a primary factor in prognosis or a secondary factor related to other clinical features.

The scleroderma type is not the only factor in prognosis. Occasionally Type 1 or Type 2 patients have a severe life-shortening manifestation such as severe small bowel involvement, pulmonary hypertension or primary biliary cirrhosis and, on the other hand, a Type 3 patient may sometimes show a remarkable remission. It is thus apparent that prognosis ultimately depends on response to treatment of particular manifestations of the disease and current subdivisions of scleroderma merely act as guidelines for groups of patients rather than precise prognostic indices for the individual. Continued study of clinical and laboratory features is needed in order to establish an improved classification and clinically useful indices of prognosis.

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