Scleredema in Chinese patients: a local retrospective study and general review

CS Leung, LY Chong

The records from 12 Chinese adult patients with scleredema, who had attended the Social Hygiene Service of the Hong Kong Department of Health between 22 January 1990 and 19 March 1996, were retrieved and analysed. The neck was the commonest site of involvement (75%), followed by the back (42%), and the shoulder (17%). The vast majority (83%) of scleredema cases were associated with diabetes mellitus; half of these were insulin-dependent. Most of the patients (92%) had hypertension for which medical treatment was needed. No cases of skin disease were preceded by acute infection, and none had any associated paraproteinaemia. The degree of skin involvement did not affect the daily activities of most of the patients. This study revealed differences between the disease in our locality and those described in the western literature.

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Introduction

Scleredema is an uncommon connective tissue disease; it mainly presents as a wooden-like, non-pitting induration of the skin. The induration usually starts on the back or sides of the neck, and spreads to the face, shoulder, arm, and thorax. Sometimes it is preceded by an upper respiratory tract infection, while at other times, it is associated with diseases such as diabetes mellitus or paraproteinaemia. There is as yet no local data concerning this skin condition. To our knowledge, this is the first local survey of this disorder in Hong Kong.

Materials and methods

The records of all patients who were diagnosed as having scleredema at the Social Hygiene Service (dermatology division) of the Hong Kong Health Department between 22 January 1990 and 19 March 1996 were retrieved. The case records were reviewed in detail and analysed with respect to the demographic data, age of onset, site and extent of disease involvement, precipitating factors or associated systemic illnesses, and skin biopsies. Patients were traced for interview or investigation if their records were incomplete. All cases were diagnosed clinically and confirmed by skin biopsy.

Results

A total of 12 cases were reviewed. All skin biopsy findings were compatible with the diagnosis of scleredema. The biopsies showed unremarkable epidermis; the collagen bundles were swollen and thickened, and had clear spaces or 'fenestrations' between them. Mucin deposits, consisting largely of hyaluronic acid, were present in the ground substance of the dermis.

The data regarding age, sex, and site of disease involvement were analysed, and the results are shown in Table 1. Associations with diabetes and other related medical illnesses are shown in Table 2.

Among the 12 patients studied, there were seven (58%) men and five (42%) women. The mean age when first seen was 58 years (range, 47 to 71 years). The neck, particularly the nape, was the commonest site of involvement (n=9, 75%) The second most common site was the back (n=5, 42%), usually the upper back; and the third most common was the

Social Hygiene Service (Dermatology), Department of Health, Yung Fung Shee Social Hygiene Clinic, Cha Kwo Ling Road, Kowloon, Hong Kong
CS Leung, FHKCP, FHKAM (Medicine)
LY Chong, FRCP (Edin, Glas), FHKAM (Medicine)

Correspondence to: Dr CS Leung

Table 1. Patient age, sex, and site of scleredema involvement

Patient	Age (years)	Sex	Site of involvement
1	55	M	Nape of neck
2	47	M	Back
3	55	M	Shoulder and interscapular areas
4	70	F	Nape of neck, then upper back and left shoulder
5	53	M	Nape of neck
6	64	F	Neck, upper back
7	64	M	Nape of neck
8	57	F	Nape of neck
9	48	M	Upper back
10	71	F	Nape of neck
11	53	M	Neck
12	58	F	Nape of neck

shoulder (n=2, 17%). The duration of scleredema among the 11 patients whose time of disease onset was known ranged from 2 months to 10 years (median, 1 year; interquartile range 0.998 year).

Ten (83%) of the 12 patients had diabetes mellitus; eight (80%) of them developed diabetes as adults. Five (50%) of the 10 patients were treated using insulin, four (40%) were treated with oral hypoglycaemic drugs, and one (10%) was treated by dietary control. In our series, there were 11 (92%) cases of hypertension which needed medical treatment. None of the scleredema cases were preceded by an upper respiratory tract infection or any other type of infection.

Electrophoresis of immunoglobulin (Ig) was done for eight (67%) of the 12 cases and results for all except one (patient 10) were normal. Patient 10 showed a rise in IgA level but the IgG and IgM levels were within normal limits. The serum protein electrophoresis pattern of this patient was normal and did not show monoclonality; the urine was negative for Bence-Jones protein.

There were two (17%) cases in which the scleredema was of spontaneous onset, not preceded by any infection, and not associated with diabetes mellitus. Four (33%) patients were given a topical steroid and eight (67%) patients were placed under observation. All 12 patients, despite receiving treatment, showed no improvement.

Discussion

Scleredema is an uncommon connective tissue disease that is sometimes misdiagnosed as scleroderma or scleromyxoedema. In a report by Greenberg et al, 29% of 209 patients were children aged below 10 years, 22% were aged between 10 and 20 years, and 49% were adults.[1] In our series of patients, all 12 were adults, the youngest of whom was 47 years old;

Table 2. Association of scleredema with diabetes mellitus and other medical illnesses

Patient	Duration of scleredema	Diabetes status	Other associated medical illnesses
1	1 year	Diabetes, unspecified duration; given insulin	HT*, treatment unspecified
2	1 year	Diabetes, 3 years; given oral hypoglycaemic	HT, given methyldopa, metoprolol, prazosin
3	6 years	Diabetes, unspecified duration; given insulin	Nil
4	10 years	Diabetes, 23 years; given insulin; also with diabetic retinopathy	HT, given nifedipine; also ischaemic heart disease, congestive heart failure
5	6 months	No diabetes	HT, given atenolol
6	6 months	Diabetes, 7 years; given insulin; also with diabetic retinopathy, cataract, glaucoma	HT, treatment unspecified
7	6 months	Diabetes, 3 years; given glibenclamide	HT, given cyclopenthiazide
8	Many years (unspecified)	Diabetes, 8 years; given glibenclamide	HT, given atenolol
9	1 year	Mild diabetes detected at first consultation; dietary control	HT, given indapamide
10	2 years	Diabetes, 20 years; given insulin	HT, treatment unspecified
11	2 months	Mild diabetes detected at first consultation; dietary control	HT, given atenolol
12	2 months	No diabetes	HT, treatment unspecified

*HT hypertension

Table 3. The three subgroups of scleredema

	Group 1	Group 2	Group 3
Age of onset	All age groups	Usually >15 years	Usually >40 years
Reported associations	Usually preceded by streptococcal infection	Paraproteinaemia, multiple myeloma, rheumatioid arthritis, Sjögren's syndrome, primary hyperthyroidism, insulinoma	Preceded by maturity-onset diabetes mellitus
Nature of onset	Usually several days to 3 months after bacterial infection	Insidious	Insidious
Duration/course	Usually less than 2 years	Slow, progressive	Unremitting
Visceral involvement	Not uncommon; carditis, myositis, heart failure	Not uncommon	Rare

in this patient, the disease was detected 1 year prior to consultation.

Scleredema usually presents with induration of the skin, which first appears on the nape of the neck; it then spreads to the anterior aspect of the neck, face, upper chest, and back. In our series, the majority of patients had their neck and/or back affected. On palpation, the affected skin is firm with a wooden-like consistence and non-pitting swelling. In severe cases, the face may lose its expression and the tongue and pharynx may be involved, which results in difficulty in swallowing. It rarely involves the extremities and abdomen; pleural and pericardial effusion may occur. If cardiac muscle is involved, there may be tachycardia, unexplained diastolic murmurs, and electrocardiographic changes such as prolonged QT intervals, and changes in the ST segment and T wave. Skeletal muscle may also be involved. In our series of patients, however, none had symptoms or signs of systemic involvement.

Although scleredema can occur spontaneously, it can be classified into three broad groups according to the associated causes (Table 3).[2] In the first group, the disease arises after an acute infection, usually bacterial in origin and commonly due to streptococci. Examples of such infections are tonsillitis, pharyngitis, scarlet fever, and cellulitis. Sometimes, scleredema may follow a viral infection such as influenza. This first type of scleredema accounts for about 60% of cases according to one study[1] and is predominant in children; the scleredema is usually expected to resolve spontaneously within 2 years. In the second group, the onset of the disease is more insidious, and the scleredema lasts longer. It is not preceded by infection, but instead may be associated with a variety of disorders such as paraproteinaemia, multiple myeloma, Sjögren's syndrome, rheumatoid arthritis, or hyperparathyroidism. The third type of scleredema is associated with diabetes mellitus, and the course is unremitting. This group comprises about 20% of all cases.[3]

None of the patients in the present series had scleredema in which the onset was preceded by any known episodes of infection, or associated with paraproteinaemia. On the other hand, most of the 12 patients (83%) belonged to the third group of disease classification, in that their disease had a strong association with diabetes mellitus. The disease pattern thus shows a significant difference from that described in the western literature.[1-3]

According to the literature, diabetes-associated scleredema is more common in males while scleredema that is not associated with diabetes is more common in females. Furthermore, most diabetic patients who have scleredema are obese.[4] Our series of scleredema patients showed a similar trend, in that the ratio of male to female diabetic patients was 3:2. It has been reported that most cases of diabetes in scleredema patients start in adulthood and are difficult to control.[4] These patients have a high incidence of development of cardiovascular complications and retinopathy, and in one series, reported by the Mayo Clinic, all patients with diabetes were treated with insulin therapy.[4] In our series, all the patients with diabetes developed it during adulthood. Fifty percent of the patients with diabetes required insulin therapy; the others were treated with oral hypoglycaemic drugs (40%) or by dietary control alone (10%). All except one of the 12 patients (92%) suffered from hypertension; this is not surprising, since it is one of the common cardiovascular complications of diabetes.

In addition to diabetes mellitus, monoclonal hypergammaglobulinaemia, usually of the IgG or IgA type, has been found to be associated with scleredema, and more than 20 cases have been reported.[3] Hypergammaglobulinaemia usually appears several years after

the scleredema, and the subsequent progression to multiple myeloma is common.[3] There have been five cases of frank multiple myeloma[5] and four latent cases with >10% plasmacytosis in the bone marrow.[3] In our series, however, none of the patients who were tested by serum protein electrophoresis demonstrated monoclonal gammopathy.

The aetiology of scleredema remains unclear. Several suggestions have been made with regards to its pathogenesis, such as streptococcal hypersensitivity and an autoimmune mechanism.[6] The former suggestion is based on observations that scleredema may be preceded by streptococcal upper respiratory tract infection. Autoimmunity, on the other hand, is a candidate because of its association with other diseases such as diabetes mellitus and monoclonal gammopathy.[6]

As detected by the histochemical analysis of skin biopsies in the present study, scleredema involves thickening of the dermis and collagen bundles; the latter also become separated by large 'fenestrations' that fill with variable amounts of mucin.[7] It is uncertain whether the disease is caused by the overproduction of collagen or glycosaminoglycan or both. Several studies have been performed to test this. A study in diabetic patients with scleredema showed that the glycosaminoglycan level was sometimes increased in fibrotic skin while collagen synthesis was unchanged.[8] Another study, however, has shown an increase in the production of type I collagen and its mRNA in fibrotic skin fibroblasts in vitro.[9] A second in vitro study of affected fibroblasts has shown a 44% to 97% increase in total protein production, glucosamine incorporation, and collagen synthesis.[10] The levels of mRNA for α-1(I) procollagen, α-1(III) procollagen, and fibronectin were also elevated.[10] Alpha-1(I) procollagen and α-1(III) procollagen are the constituent components of type I and type III collagens respectively—these are the major interstitial collagens of skin. In situ hybridisation in dermal fibroblasts taken from a non-diabetic patient with scleredema has also demonstrated an increase in the level of type I collagen mRNA. Thus, it seems likely that a degree of activation of selected genes that code for components of connective tissue is one of the important pathogenetic mechanisms for scleredema.

Differential diagnoses of scleredema include the early oedematous stages of systemic sclerosis; trichinosis; dermatomyositis when associated with cutaneous oedema; scleromyxoedema; and localised myxoedema. In the newborn, scleredema neonatorum and subacute fat necrosis are the two main differential diagnoses. Unfortunately, there is currently no effective therapy available for scleredema, although systemic corticosteroid, intralesional corticosteroid, and hormones (eg thyroid and pituitary hormones) have been tried. One patient, with associated multiple myeloma, was treated with pulse therapy of cyclophosphamide and prednisone.[11] Another, with associated benign gammopathy, was treated with electron beam therapy.[3]

The prognosis of patients with infection-linked scleredema is generally expected to be good and the disease usually resolves within 2 years. In the series from the Mayo Clinic, however, not all patients had a short duration of illness.[4] For patients with non–infection-linked scleredema, the disease usually has a longer duration. A patient who had scleredema of this class, which was associated with benign gammopathy, subsequently developed myeloma and extensive skin disease[12]; the patient died of bronchopneumonia as a result of difficulty in breathing due to a stiff chest. In contrast, another patient with extensive skin disease from scleredema that was associated with monoclonal hypergammaglobulinaemia responded dramatically to electron beam therapy.[3] In patients with diabetes-associated scleredema, the disease usually has poor resolution. There has recently been a report in the Chinese literature of 60 scleredema cases.[13] The prognosis of some cases was poor, and some patients with severe disease died. One patient, for example, developed severe dysphagia and died of prostration.[13] In our series, the scleredema in all 12 patients showed no sign of resolution. The duration of the scleredema varied from 2 months to 10 years from the time of consultation. Nevertheless, most of the patients only showed localised skin disease which did not affect their daily activities.

In conclusion, our study has discussed some of the characteristic features of scleredema in adult Hong Kong Chinese patients, who had skin but not systemic involvement. The majority of cases were associated with diabetes mellitus and, in contrast to other studies, only half of them required insulin therapy. The majority also had hypertension, but there were no cases associated with paraproteinaemia or streptococcal infection. Although this study consisted of a small number of patients, it reveals some differences in the local disease pattern of scleredema compared with that recorded in western literature.

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