

Buschke's Scleredema and Concomitant Diseases: Report of Five Cases and Literature Review

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SUMMARY Scleredema adultorum or Buschke's scleredema is a rare disorder that belongs to the group of mucinoses. Diffuse, sudden swelling, hardening and induration of the skin can occur in children and younger women as well as in older men. The dermis is thickened because of the increased collagen glycosylation, like that in diabetic stiff skin syndrome. The face is most often involved. In older persons the trunk is usually first involved. There is relative sparing of the extremities, with no distal or Raynaud's phenomenon. Eosinophilic fasciitis, scleromyxedema, associated gammopathy, and other forms of edema and mucin deposition must be excluded on differential diagnosis. Antibiotics, sometimes high doses of intravenous penicillin, systemic corticosteroids, systemic PUVA and PUVA bath therapy seem most promising for the management of the disorder. Our patients were aged 27, 60, 64, 69 and 72 years, with typical skin lesions, thus that term "adultorum" does not appear to fit well.

KEY WORDS scleredema adultorum, Buschke's scleredema, scleredema, concomitant diseases

INTRODUCTION

This article about the rare skin disorder of Buschke's scleredema is dedicated to the 63rd anniversary of the death of great Jewish dermatologist.

Scleredema adultorum or Buschke's scleredema is a rare disorder that belongs to the group of mucinoses, and is characterized by diffuse non-pitting swelling and induration of the skin. Skin biopsies reveal marked thickening of the dermis due to collagenous replacement of the subcutis and deposition of hyaluronic acid between the collagen fibers. The disease classically affects exclusively the skin. However, in 1998, Umler *et al.* have reported on Buschke's scleredema with

a wide variety of extracutaneous manifestations on the tongue, pharynx and upper esophagus (1). Eponymously, many other scleredema-like diseases have been recognized since Buschke discovered this disease in 1902.

Scleredema and concomitant Diseases

Buschke-Ollendorff syndrome and nail-patella syndrome are rare connective tissue disorders inherited in an autosomal dominant pattern, characterized by cutaneous and bone lesions. Drouin and Grenon were the first to describe this disorder in a 3-year-old boy (2). This association had not been reported previously, suggesting that these two

connective tissue disorders may share the same gene location with different mutations or involve different mutated genes that share downstream segments of their signaling pathways. Chronic idiopathic neutropenia was also observed (2).

Buschke-Löwenstein tumor (BLT, giant condyloma) is a rare disease that arises on male and female external genitalia. BLT arises from the confluence of multiple condylomata acuminata and is induced by human papillomavirus (HPV) infection. BLT presents a clinical malignancy, yet it is known to be a histologically benign tumor, even if it carries a risk of malignant transformation (3,4). The role of HPV as a cofactor involved in carcinomatous transformation remains controversial (3). Some authors consider these tumors to be benign tumors or giant condylomata (non-metastatic, associated with HPV 6-11), while others consider them to be borderline malignant associated with oncogenic virus (HPV 16 and 18). This evolution follows the alteration by a viral protein of the functions of the tumor suppressor protein P53 (3). The surgery remains the reference treatment although there is a possibility of frequent recurrences. Radiotherapy and chemotherapy have been suggested as adjuvant treatments for complicated forms. It is advisable to treat it early. The treatment by combined CO₂ laser surgery excision-vaporization, with long-term follow-up has been described by Frega *et al.* (4).

Scleroderma-like disorders are widely disparate conditions mimicking either systemic sclerosis or cutaneous localized scleroderma, not infrequently displaying features of both. The recognition of scleroderma-like disorders is of practical importance because by establishing the cause of the disease, it is possible to introduce an effective therapy, as in scleredema Buschke or scleredema diabetorum, sclerodermiform porphyria, *Borrelia burgdorferi*-induced sclerodermiform acrodermatitis atrophicans, sclerodermiform phenylketonuria, drug-induced conditions, etc. (5). Scleroderma-like disorders suggest that the pathogenesis of skin sclerosis and internal involvement may be divergent, and of various causes. Some of them such as atrophoderma Pasini-Pierini or progressive facial hemiatrophy frequently overlapping with scleroderma make the differentiation very difficult, and the diagnosis is often arbitrary. Some, as sclerodermiform graft-versus-host-reaction, point to the autoimmune origin of scleroderma. The congenital sclerodermiform conditions present a large spectrum of still not widely known and extremely heterogeneous syndromes, associated with numerous anomalies and/or malignancies (5).

The first report of scleredema and the second of reticular erythematous mucinosis in three different HIV-infected patients seem to be more than coincidental (6).

Valente *et al.* reported on the association between acanthosis nigricans and scleredema in 1997. There are three clinical types of scleredema. The first is preceded by an upper airway infection and progresses rapidly before regressing spontaneously within a few months. The second type is associated with chronic diabetes. The third type is associated with monoclonal gammopathy, rarely of myelomatous type, and develops insidiously (7). A 56-year-old woman developed scleredema when acanthosis nigricans appeared together with IgA kappa multiple myeloma. Therapy with melphalan and prednisolone for myeloma proved effective also for scleredema and acanthosis nigricans (7). Only five cases of associated scleredema and multiple myeloma have been reported, four with kappa IgG myeloma and only one with IgA myeloma (7). An association with acanthosis nigricans and scleredema could be coincidental although the fact that the different manifestations regressed together after the myeloma treatment would suggest some relationship between these three diseases (7). Although scleredema of Buschke is a rare disorder that usually resolves spontaneously, Sansom *et al.* (1994) describe a fatal case of extensive skin changes and IgA myeloma in a 60-year-old woman who did not respond to conventional myeloma therapy and died from sequels of the progressive skin disease (8).

In 2000, Grudeva-Popova and Dobrev reported on Buschke's scleredema associated with multiple myeloma and IgG kappa monoclonal hypergammaglobulinemia. The bioengineering method proved useful for early detection and monitoring of skin involvement in the patient with this disease association (9). Systemic involvement in scleredema of Buschke associated with IgG-kappa paraproteinemia was first described in a 60-year-old man with scleredema and evidence of mucin deposition on biopsies from multiple extracutaneous sites (10).

Scleredema adultorum of Buschke as an unusual manifestation of diabetes mellitus that can result in painful indurations and thickening of the skin with associated limitation of motion, has been previously reported to be responsive to radiotherapy. Several patients were treated by photon fields and multiple electron fields encompassing the entire neck, arms and thorax, as reported by Tobler *et al.* (2000) (11).

Banney *et al.* (2000) report on a case of scleredema diabeticorum of Buschke associated with nuchal fibroma and organic solvent exposure. This is the first report on the association of these conditions, with increased and thickened collagen bundles without significant fibroblast proliferation in a patient with insulin-dependent diabetes mellitus with complications of retinal vessel thrombosis and peripheral neuropathy (12).

Stiff-man syndrome is a rare disorder of the central nervous system characterized by muscular rigidity and superimposed spasms. Happe *et al.* (1999) report on a 22-year-old male patient with stiff-man syndrome. He developed painful rigidity of the trunk, starting in the neck. Massive stiffness of the trunk with pale appearance of the skin and initial stage of swallowing and respiration impairment were observed. Skin biopsy presented typical characteristics of scleredema adultorum, a rare connective tissue disorder of unknown etiology. Scleredema adultorum should be regarded as a differential diagnosis of the stiff-man syndrome (13). In 1996, a 73-year-old retired truck driver was diagnosed with acute pericarditis, which responded well to steroid treatment. In January 1997, he noted a swelling of the abdominal skin, genitalia and limbs, sparing the feet. Echocardiography was consistent with infiltrative cardiomyopathy, and after his cardiac condition had suddenly worsened, he suffered a cardiac arrest and died. Autopsy findings revealed systemic scleredema adultorum of Buschke. Amyloid deposits were also found. There was a coexistence of systemic Buschke's scleredema with infiltrative cardiomyopathy, IgG kappa gammopathy and amyloidosis (14).

Ulmer *et al.* (1998) have noted 24 cases of associated monoclonal gammopathy in the literature. They describe a 75-year-old patient with a 19-year history of scleredema adultorum with monoclonal gammopathy and involvement of the tongue, pharynx and upper esophagus. Furthermore, polyneuropathy, ocular involvement with restricted eye movements and sicca syndrome were present. The simultaneous occurrence of cutaneous scleredema with any one of the above mentioned manifestations has been reported before. The wide variety of extracutaneous manifestations of scleredema as found in this patient has not been previously described (1).

Tate *et al.* (1996) describe seven adults with scleredema and diabetes mellitus for an average of 13 years prior to the onset of scleredema. They had complications of diabetes, especially retinopathy, neuropathy and peripheral vascular

disease. Scleredema did not resolve on therapy in any of these patients (15). In all of them histopathology revealed thickened dermal collagen with a mild infiltrate of mucin in deeper dermis. In case of one scleredema patient with insulin dependent diabetes without vascular complications, electron microscopy demonstrated heterogeneity in size and density of collagen fibrils and presence of filamentous material between them (16).

Scleredema adultorum or Buschke's scleredema belongs to the group of mucinoses. There are reports on many associations with scleredema adultorum, e.g., with diabetes mellitus and multiple myeloma. Jacob *et al.* (2002) have reported on a case of scleredema adultorum and secondary hyperparathyroidism in a 46-year-old patient. The increased levels of parathormone could have influenced the collagen metabolism (17). Koga (2001) described a 59-year-old woman with severe diabetic scleredema associated with heterozygous familial hypercholesterolemia treated with low-density lipoprotein apheresis therapy monthly or every 2 weeks in addition to drugs to lower serum lipids for hypercholesterolemia. Scleredema had not improved but after 3 years of treatment for hyperlipidemia the authors demonstrated histopathologic improvement in the dermis of cervical skin. They have concluded that weekly low-density lipoprotein apheresis therapy is effective for diabetic scleredema that is resistant to conventional treatments (18). Parmar *et al.* reported on a rarity of scleredema adultorum developing in an 8-year-old male child after chickenpox. The patient had a benign course and spontaneous recovery in two weeks (19). This was the first case of scleredema adultorum development after chickenpox. A 6-year-old female patient presented with a rapidly progressive scleredema-like syndrome involving almost the entire integument. Initially clinical pattern and histopathologic data of both eosinophilic fasciitis and scleredema adultorum were present. The authors concluded that eosinophilic fasciitis and scleredema adultorum might be subtypes of one disease entity (20).

Mechanical properties of the skin in a patient with scleredema of Buschke were investigated by Dobrev (1998) by a noninvasive *in vivo* method using a suction device. He made clinical scoring of the indurated skin, and measured skin elasticity and distensibility. Low values of skin distensibility correlated with a severe skin induration. The method applied can be used for objective and quantitative assessment of skin involvement in scleroderma of Buschke (21). A significant clinical improve-

ment was obtained with electron-beam therapy in a case of scleredema adultorum associated with IgA kappa monoclonal hypergammaglobulinemia (22). Scleredema seems to be linked to monoclonal hypergammaglobulinemia, but the relationship between the skin disorder and the immunoglobulin abnormality remains to be elucidated (22). A case of scleredema and smoldering myeloma has been reported by Schmidt *et al.* (1992) in a 46-year-old male Caucasian who subsequently had classic findings of scleredema, monoclonal immunoglobulin G lambda light chain in serum. Findings in a bone marrow biopsy specimen revealed an increased percentage of plasma cells, some of which were atypical (23). The success of extracorporeal photopheresis in a scleredema patient with paraproteinemia was described by Stables *et al.* in 2000 (24). In three patients clinical evolution of skin induration, thickness, and ultrasonography were evaluated at baseline and after PUVA-bath treatment (median - 59 expositions and a cumulative UVA dose of 245.7 J/cm²). Ultrasonography showed a significant reduction in both skin thickness and density. Hager *et al.* (1998) concluded that PUVA-bath therapy appears to be effective in the treatment of scleredema adultorum (25). Bowen *et al.* treated scleredema adultorum of Buschke with radiation therapy. Radiotherapy appears to be a viable therapeutic option in extreme cases of this difficult-to-treat disease (26). Konemann *et al.* proved that ionizing radiation is important, effective and well-tolerated therapy in the treatment of severe cases and may be a candidate first-line treatment of this disease (27). Eberlein-König *et al.* reported on scleredema adultorum showing striking clinical improvement to medium-dose UVA1 phototherapy (single dose-50 J/cm²; 35 expositions) (28).

Scleredema in children under 15 years of age was rare in Japan before 1996. A total of 166

cases of the disease were reported (29). A 3-year-old Japanese girl had had a bacterial infection of the tonsils three weeks before the skin lesions appeared, with induration of the skin of the face, shoulders, extensor aspect of the arms and proximal part of the forearms. Skin lesions expanded from the middle part of the forearms and gradually disappeared (29). Corn and Swetter (1994) reported on a case of 8-year-old boy with coincidental streptococcal colonization and relatively benign presentation of the disease, and the characteristic mucopolysaccharide intradermal staining of skin biopsy (30).

Buschke alone or in collaboration with his assistants has published numerous papers on various dermatological problems. Many of these papers dealt with the significance of the skin for immunity in syphilis (in 1929 with A. Joseph and B. Peiser), and the influence of arsphenamine on this immunity. Another entities were *keratoderma maculosa disseminata symmetrica* (in 1910, with H. Fischer) and *dermatofibrosis cuticularis disseminata* (in 1928, with Helen Ollendorff) (28).

REPORT ON FIVE CASES

The scleredema of Buschke (scleredema adultorum) (1900) was one of the dermatologic entities discovered by Abraham Buschke (1868-1943).

Between 1997 and 2003 only five cases of scleredema have been diagnosed out of the total 7648 of patients with scleredema consulted in our Department. Circumscribed scleroderma and progressive scleroderma have been diagnosed much more often (n=93 and n=33 respectively) (Table 1.). All our patients presented diffuse swelling and induration of the skin just like in case of scleredema described by Buschke in 1900. In all cases sudden hardening of the skin in the cervicothoracic region with extension to the trunk and proximal upper limbs were recorded (Fig. 1.). His-

Table 1. Number of patients with Buschke's scleredema hospitalized at University Department of Dermatology and Venereology, Zagreb University Hospital Center, Zagreb, Croatia, 1997-2002

Patient number	Year	Age	Gender	Diagnosis of Scleredema adultorum	Number of hosp. patients	Morphea	Scleredema Buschke	Lichen scler. et atrophy.	Graft versus host disease	Mixed connective tissue disease
1	1997	27	M	Yes	1588	23	6	2	2	
2	1997	64	M	Yes						4
3	1998	72	F	Yes	1494	11	3	2	0	4
4	1999	60	F	Yes	1295	15	5	0	1	2
5	2000	69	F	Yes	1097	15	9	1	1	0
	2001	0	0	0	1101	17	6	2	1	0
	2002	0	0	0	1073	12	4	1	1	0
Total number of hospitalized patients					7648					



Figure 1. Diffuse nonpitting swelling and induration of the skin in a patient with Buschke's scleredema.

tologically, skin biopsies revealed thickening of the dermis due to collagenous replacement because of increased collagen glycosylation. None of the patients had association with some other, extra-cutaneous disease. Only one middle-aged patient had insulin dependent diabetes mellitus without clinically relevant complications. The onset was subtle and the involvement persistent. The patients were aged from 27 to 74 years. There was relative sparing of the extremities and no Raynaud's phenomenon. Erythema and induration of the posterior neck and the back were commonly observed. None of the patients had systemic manifestations (serositis, dysarthria, dysphagia, myositis, etc.). The patients were treated with penicillin (n=3), PUVA-bath therapy (n=4), and one with oral corticosteroids. However, aggressive therapies were not introduced because the cases were not associated with myeloma or systemic disabling manifestations.

CONCLUSION

Although Buschke has been credited with the first description of scleredema, Pitford's description dates from 1867. Scleredema is an unusual disease that affects all races. A relationship with

diabetes mellitus was established in 1970 (32), and is considered to be a pathogenetic factor. During six years we have only five patients with scleredema. Abraham Buschke was an outstanding dermatologist and researcher who contributed significantly to the development of clinical and scientific dermatology. As Dr. A. Hollander wrote 20 years ago: "History happens; it records creation and destruction, generation and degeneration, joy and sorrow. Its facts can be recalled as lessons, but its events cannot be recalled to change" (33,34). Nothing could be more appropriate here.

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