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ORIGINAL COMMUNICATION

Myopathy and scleromyxedema

Antoine Soulages[1] · Hoang Marie-Ange Tang[1] · Anne Pham-Ledard[2] · Marie-Laure Négrier-Leibreich[3] · Alexandre Cosnard[1] · Fanny Duval[1,4] · Guilhem Solé[1,4] · Louis Carla[1] · Gwendal Le Masson[1,4] · Stéphane Mathis[1,4]

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Abstract
Scleromyxedema is a chronic, idiopathic disorder associated with monoclonal gammopathy, and characterized by dermal mucin deposition. However, systemic manifestations are frequent, including neuromuscular symptoms. We herein present a 71-year-old man who developed a vacuolar myopathy in a context of a known scleromyxedema, and we compare our observation with the nineteen other cases found in the medical literature. Such an association (especially with suggestive skin abnormalities) has to be known for two reasons. First, this diagnosis might be quite challenging because the myopathy may precede the typical skin changes. Secondly, conversely to other forms of vacuolar myopathy, some of the symptoms may respond (even partially) to immunomodulatory and/or immunosuppressant therapeutics.

Keywords Scleromyxedema · Myopathy · Inflammation · Vacuole · IVIg

Background

Scleromyxedema belongs to a heterogeneous family of skin disease called 'cutaneous mucinoses', all characterized by abnormal mucin deposition in the skin. As a protein–hyaluronic acid complex (jelly-like amorphous mixture of acid glycosaminoglycans), mucin (produced by fibroblasts) is a normal component of the dermal extracellular matrix: mucin may be observed on hematoxylin and eosin stains, although special stains are usually needed (Alcian blue staining) [1]. We herein described the observation of a patient with scleromyxedema associated with myopathy, and we compare it to the few similar cases reported in the medical literature.

✉ Stéphane Mathis
stephane.mathis@chu-bordeaux.fr

1 Department of Neurology, Nerve-Muscle Unit, CHU Bordeaux (Groupe Hospitalier Pellegrin), University of Bordeaux, Place Amélie Raba-Léon, 33000 Bordeaux, France

2 Department of Dermatology, CHU Bordeaux, 33000 Bordeaux, France

3 Department of Pathology, CHU Bordeaux, 33000 Bordeaux, France

4 Centre de Référence Des Pathologies Neuromusculaires, CHU Bordeaux (Groupe Hospitalier Pellegrin), University of Bordeaux, Place Amélie Raba-Léon, 33000 Bordeaux, France

Methods

Case report

A 71-year-old man complained of proximal and distal progressive muscle weakness of the four limbs for two years, progressive dysphagia for one year, as well as loss of weight (4 kg) since four months. His past medical history included prosthetic cardiac valve and oral anticoagulation, arterial hypertension (treated with lisinopril), dyslipidemia (treated with ezetimibe), as well as severe dental post-surgery sepsis (endocarditis, then bacterial meningitis) ten years ago. Clinical examination showed atrophy of the forearms and brisk reflexes, without Babinski sign. Muscle weakness was observed at proximal (MRC, Medical Research Council, was graded 3/5) and distal parts (MRC: 3/5) of the upper limbs, as well as at the proximal part of the lower limbs (MRC: 4/5). There was no sensory disturbance, no cerebellar symptom, and no parkinsonism. He did not have any pain, but complained of chronic fatigue for several months. Except swallowing impairment for both liquid and solid, he presented no cranial nerve palsy. He had no skin abnormalities at that time. Laboratory studies only showed mild elevated serum creatine kinase (CK: 480 IU/L) level and IgG monoclonal gammopathy with lambda light chains. Thyroid function was normal. Immunological tests were negative, especially for anti-neural and anti-ganglioside antibodies,

classical myositis-associated antibodies, as well as anti-acetylcholine receptor and anti-muscle specific kinase antibodies. Serologic tests (including Lyme disease) were negative. Brain and spine MRI were normal, as well as lumbar puncture (no cell; protein level: 40 g/dL). Electrophysiological test showed normal sensorimotor nerve conduction studies; by needle electromyography, we observed diffuse spontaneous fibrillation potentials with short duration and polyphasic motor unit potentials in proximal muscles in the four limbs, suggestive of a myogenic pattern. Muscle biopsy was performed, showing severe atrophic angulated muscle fibers with perifascicular distribution, large vacuoles in some fibers, a few ragged-red fibers, but no sign of muscle inflammation; immunohistochemistry was normal (Fig. 1). The search for mutations of the *VCP* (valosin-cantaining protein) gene was negative. At that time, the diagnosis of 'vacuolar myopathy' was proposed; no specific treatment was begun.

Less than three years later, he developed painless macular skin lesions (without prurit) on the back of the fingers, axilla, and retroauricular area (on both sides); he still complained of the same myopathic symptoms. A skin biopsy was performed and showed cellular dermis with proliferation of fibroblasts in the interstitium, mild dermal sclerosis, perivascular lymphocytic inflammatory infiltrate, and deposits of mucinous material within the dermis (Alcian blue staining); we also decided to test staining for mucin in the former muscle biopsy (Alcian blue staining), without positive result. In this context of monoclonal gammopathy with lambda light chains, the diagnostic of papular mucinosis (scleromyxedema) associated with myopathy was finally proposed. He was started on intravenous immunoglobulin (IVIg: 2 g/kg divided over five consecutive days): after three courses, his skin improved dramatically with softening of the face, arms, legs and trunk; we also observed the total regression of myopathic symptoms (except for persistent dysphagia) within two years after regular courses of IVIg (2 g/kg during 5 days, every 4–6 weeks); so the frequency of IVIg was decreased and then IgIV was finally stopped.

One year later, he was admitted in our hospital for flu-like syndrome and confusion. Upon admission to the hospital, he was febrile and in a stuporous state, with normal oculomotor function but bilateral Babinski sign. For six months, he also complained of myalgia and progressive motor weakness of the four limbs; he still had dysphagia. Brain and spine MRI, whole-body CT scan and lumbar puncture were unremarkable. Electroencephalogram showed symmetric theta activity over the frontal regions. Antineural antibodies, angiotensin-converting enzyme and all the serologic studies (in both serum and cerebrospinal fluid) were negative. Creatine kinase was normal, as well as thyroid and hepatic function. Based on his past medical history (scleromyxedema and myopathy), we made the diagnosis of dermato-neuro syndrome (DNS). We observed total regression of the acute neurological manifestations and again stabilization of myopathic symptoms (with persistent dysphagia) after regular courses of IVIg (2 g/kg during 5 days, every 4–6 weeks).

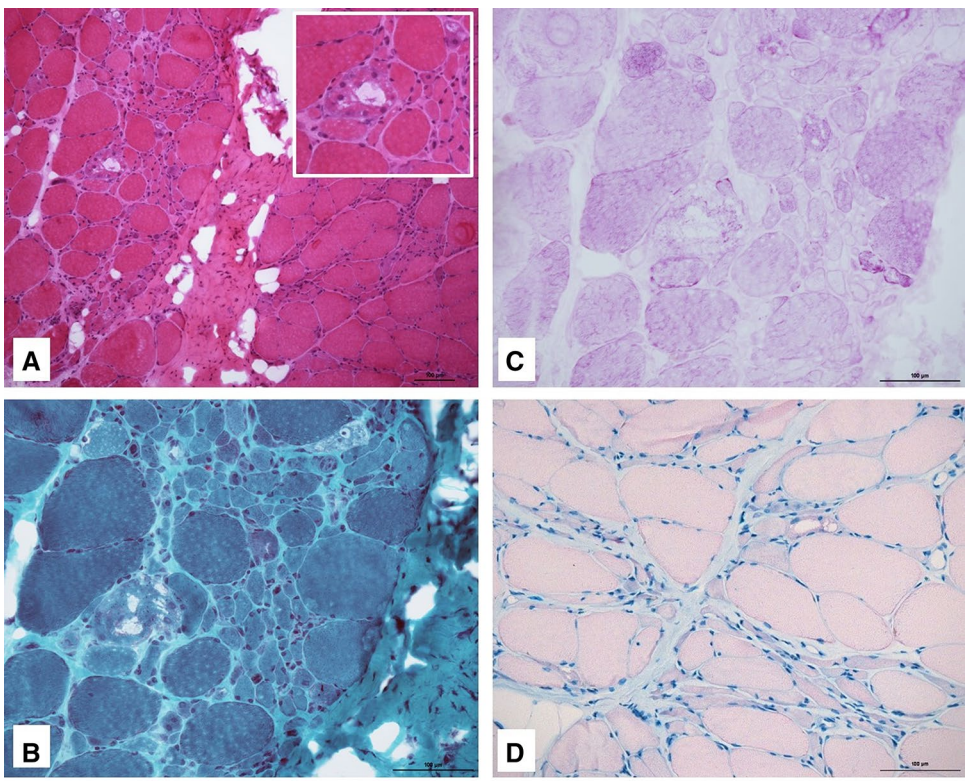

Fig. 1 Deltoid muscle biopsy showing atrophic angulated fibers clustered into groups and large vacuoles without blue rim in some fibers (inset) (**a** hematoxylin and eosin stain). No red stained material was detected around vacuoles (**b** Gomori trichrome stain). These vacuoles are unstained with periodic acid-Schiff (**c**) and Alcian blue stain (**d**). Scale bar 100 µm

Review of the literature

We have performed a review of the literature of the cases of scleromyxedema associated with myopathy (confirmed by muscle biopsy) by searching in Pubmed, Google Scholar, and ScienceDirect using the following terms: [scleromyxedema AND myopathy], [dermatoneuro syndrome AND myopathy] and [papular mucinosis AND myopathy]. Among all the case reports and short series of cases found, we have selected only those with myopathy demonstrated by muscle biopsy, with enough clinical (sex and age of the patient, description of myopathic and skin signs, onset of myopathic and skin signs), biological (maximum serum CK level), and electrophysiological (electromyography) data, if possible.

Results

With our case, we found 20 patients with myopathy and scleromyxedema (Table 1) [2–19]. There were 13 men and 7 women: sex ratio M/F was 1.85. The average age at diagnosis of myopathy was 47.8 (range 27–70): for men, the average age was 46.7 (range 27–69); for women, the average age was 49.8 (range 38–70); there was no significant statistical difference between the two groups.

Skin manifestations of scleromyxedema (no data for one patient) were observed before the diagnosis of myopathy in more than half of the patients (10/19), after the diagnostic of myopathy in a third of the patients (6/19), and were concomitant to myopathy in only 2/19 patients. When skin manifestations were first diagnosed, the average delay for the onset of myopathy was 36 (range 3–108) months. When myopathy was first diagnosed, the delay for the onset of skin manifestations was 19.5 (range 1–36) months.

All patients had a myogenic pattern on electromyography. Most of patients (17/20) presented with muscle weakness: motor weakness was proximal in 14/17 patients, myalgia was reported in only 5/20 patients, but dysphagia was observed in more than half of the patients (12/20). Serum CK level was increased in almost two thirds of the patients, with an average value at 3147 (range 247–9920) IU/L.

The most frequent pathological signs observed on muscle biopsy were inflammation (12/20) atrophy/degeneration (12/20), vacuoles (5/20), and necrotic fibers (4/20); mucin deposition was found in the muscle biopsy of only 2/20 patients.

Various treatments were used, but corticosteroids were first tried in most patients. Finally, muscle improvement (at least partial) was reported in most of the cases (15/18).

Discussion

Cutaneous mucinoses are divided into primary (idiopathic) mucinoses (such as lichen myxedematosus, or LM) or secondary mucinoses (in which mucin deposition simply represents an additional histological finding and not the main feature) [20]. Despite LM was first reported in the beginning of the twentieth century [21, 22], it was clearly distinguished from scleroderma and generalized myxedema only in the middle of the twentieth century [23]: the term ‘scleromyxedema’ (or Arndt-Gottron disease) was created to distinguish the sclerotic and generalized variant of LM [24]. Lichen myxedematosus is characterized by lichenoid papules, nodules and/or plaques due to mucin dermal deposition, and a variable degree of fibrosis (without thyroid dysfunction). In the 1950s, four patterns were distinguished: generalized lichenoid papular eruption (or ‘scleromyxedema’), discrete popular form, localized to generalized lichenoid plaques, and urticarial plaques with nodular eruptions [23]. Nowadays, only two patterns exist: the localized form (including four subtypes) and the generalized form (scleromyxedema) [25].

Scleromyxedema is characterized by the association of generalized papular (1–3 mm white or skin-colored waxy papules) and sclerodermoid (marked skin thickening resulting in decreased mobility of the joints and of the mouth.) eruption, mucin deposition (hyaluronic acid) in the skin, fibroblast proliferation and fibrosis (irregular collagen deposition, often with perivascular lymphoplasmacytic inflammatory infiltrates) in the skin, and monoclonal gammopathy (always in the absence of thyroid disease); other clinical signs are erythema and edema; a central depression (surrounded by an elevated rim due to the skin thickening) may also be observed over the proximal interphalangeal joints, described as the ‘doughnut sign’ [20]. Scleromyxedema is generally developing during middle age and equally distributed in males and females [1, 26]. Its incidence varies from 7 to 489 per million people [27]. It is not a disease purely restricted to the skin, but with many possible systemic implications. For example, rheumatological (arthralgia/arthritis), hematological (myeloma, lymphoma, Waldenström’s macroglobulinemia), cardiopulmonary (myocardial ischemia, congestive heart failure, pericardial effusion, obstructive or restrictive lung involvement) and renal (acute renal failure) manifestations can be observed [1]. Neurological manifestations are also frequently observed (30%), such as sensorimotor peripheral neuropathy, carpal tunnel syndrome, stroke, seizure, memory loss, dermato-neuro syndrome) [1]. Finally, a few cases of muscle disorder were observed (only 20 patients in the medical literature), showing non-specific inflammatory (sometimes vacuolar) myopathies in most of the cases, but with dysphagia in more than half of the patients.

Table 1 Main clinical, biological, electrophysiological and pathological characteristics of myopathy related to scleromyxedema

References	Patient	Sex	Age at diagnosis of myopathy	Skin manifestation diagnosed before myopathy	Muscular symptoms	Dysphagia	CK[a]	EMG	Muscle biopsy	Treatment of myopathy	Muscle impr.
Johnson et al. [2]	01	M	35	ND	Prox. MW	Yes	Increased	Myogenic	Perifascicular atrophy Vacuoles PV inflammation	Corticosteroids	Yes
Kubba et al. [3]	02	M	63	Yes (−108 months)	Myalgia Prox. MW Dist. MW	No	Normal	Myogenic DBN	Mild, non-specific degenerative changes	Corticosteroids Melphalan	ND
Verity et al. [4]	03	F	58	Yes (−60 months)	Prox. MW	Yes	Increased	Myogenic FP	Necrotizing myopathy PV inflammation Vacuoles Severe preferential type II fiber atrophy	Corticosteroids Cyclophosmamide 6-Mercaptopurine Methotrexate	Yes
Harris et al. [5]	04	F	39	Yes (−84 months)	MW	No	ND	Myogenic (IFM)	Myositis (inflammation)	Corticosteroids Melphalan	Yes
Harvey et al. [6]	05	F	70	No (concomitant)	Prox. MW Dist. MW	No	Normal	ND	Severe myositis (inflammation) Vasculitis	Corticosteroids Methotrexate (IM)	Yes
	06	M	43	No (+8 months)	Myalgia Prox. MW	Yes	Increased (835 IU/L)	Myogenic FP	Perifascicular atrophy Single fiber necrosis Inflammation	Corticosteroids	Yes
Fudman et al. [7]	07	M	27	No (+3 months)	Prox. MW	Yes	Increased (8400 IU/L)	Myogenic (IFM)	Atrophic and hypertrophic fibers Vacuoles No inflammation	ND	ND
Helfrich et al. [8]	08	F	56	Yes (−3 months)	Prox. MW	Yes	Normal	Myogenic (IFM) FP	Degeneration of both type I and II fibers Vacuoles Inflammation	Corticosteroids Methotrexate	Yes
Harris et al. [9]	09	M	61	No (+36 months)	MW	Yes	Increased (586 IU/L)	Myogenic (IFM)	Mild atrophy	Corticosteroids Methotrexate (IV)	Yes

Table 1 (continued)

References	Patient	Sex	Age at diagnosis of myopathy	Skin manifestation diagnosed before myopathy	Muscular symptoms	Dysphagia	CK[a]	EMG	Muscle biopsy	Treatment of myopathy	Muscle impr.
Rothe et al. [10]	10	F	38	Yes (−6 months)	Prox. MW	Yes	Increased (7709 IU/L)	Myogenic (IFM)	Necrotizing myopathy Marked type II atrophy Inflammation Positive staining for mucin	'Intravenous fluids' Methotrexate	Yes
Hisler et al. [11]	11	M	30	No (+36 months)	MW	Yes	Increased (9920 IU/L)	Myogenic (IFM)	Severe degeneration, with regeneration No inflammation	Corticosteroids Azathioprine Isotretinoin	Yes
Taylor and Owen [12]	12	F	48	Yes (−36 months)	Prox. MW	No	Increased (333 IU/L)	Myogenic	Mild degeneration with regeneration Some necrotic fibers	Corticosteroids D-Penicillamine	Yes
Bata-Csorgo et al. [13]	13	M	50	No (concomitant)	Prox. MW	Yes	Increased (1862 IU/L)	Myogenic (IFM)	Myositis (diaphragm) at autopsy	Cyclosporine	No (sudden death)[b]
Rayson et al. [14]	14	F	40	No (+1 month)	Myalgia Prox. MW	Yes	Increased (648 IU/L)	Myogenic (IFM) FP	Myositis	Corticosteroids Isotretinoid	yes
Lister et al. [15]	15	M	30	Yes (−12 months)	Prox. MW	No	Normal	Myogenic	Myositis Marked fiber atrophy	IVIg	No
Prasad et al. [16]	16	M	49	Yes (−36 months)	No	No	Increased (247 IU/L)	Myogenic (IFM) FP	Myositis	Corticosteroids Cyclophosphamide	Yes
Wu et al. [17]	17	M	64	Yes (−12 months)	Prox. MW	No	Normal	Myogenic	Scattered degenerated and atrophic fibers No inflammation Positive staining for mucin	Thalidomide	No
Tan et al. [18]	18	M	44	No (concomitant)	Myalgia	No	Increased (3600 IU/L)	ND	Myositis CD68+; CD3+ Negative staining for mucin	ND	Yes
Dolenc-Voljč et al. [19]	19	M	42	Yes (−3 months)	Myalgia	Yes	Normal	Myogenic	Mild myopathy with atrophy No inflammation	Corticosteroids Thalidomide IVIg	Yes

Table 1 (continued)

References	Patient	Sex	Age at diagnosis of myopathy	Skin manifestation diagnosed before myopathy	Muscular symptoms	Dysphagia	CK[a]	EMG	Muscle biopsy	Treatment of myopathy	Muscle impr.
Our case	20	M	69	No (+33 months)	Prox. MW Dist. MW	Yes	Increased (480 IU/L)	Myogenic FP	Perifascicular atrophy Vacuoles Ragged-red fibers No inflammation Negative staining for mucin	IVIg	Yes

CK creatine kinase (normal < 235 IU/L), *DBN* 'dive-bombing' noises, *Dist.* distal, *EMG* electromyography, *F* female, *FP* fibrillation potentials, *IFM* suggestive of inflammatory myopathy, *IM* intramuscular, *impr.* improvement, *IU/L* international unit per liter, *IV* intravenous, *IVIg* intravenous immunoglobulin, *M* male, *MW* muscle weakness, *ND* no data, *Prox.* proximal, *PV* perivascular, *SM* skin manifestation

[a]Higher value

[b]Bronchopneumonia

It was suggested that "slight or severe proximal muscle weakness is found in 27% of the patients and is occasionally associated with slight elevation of muscle enzymes and inflammatory electromyographic findings" [28]. However, regarding the few cases reported in the medical literature, myopathy seems to be unfrequent in scleromyxedema. The twenty cases reported in our paper (representing the largest series reported to date) allow us to better understand the characteristics of this condition, although a prospective series would probably be more appropriate. Although the mean age upon diagnosis of scleromyxedema is 30 years (18 years for the linear form) [27], the combination of myopathy and scleromyxedema usually develops later, around the age of 50. Indeed, the male/female ratio seems to be lower for patients with myopathy (1.85:1) than for those in the general population of scleromyxedema (2.6:1) [27]. It is important to highlight that more than half of these patients develop skin manifestations before the first myopathic symptoms, usually during the three years before. So the occurrence of skin manifestations in a patient developing muscle weakness has to make the practitioner to think about the diagnosis of 'scleromyxedematous myopathy', in addition to other classical conditions such as dermatomyositis. As for other forms of myopathy, the muscle weakness may be also distal, as observed in 3/13 patients (in association to proximal weakness). The other important clinical symptom is the frequent occurrence of dysphagia, observed in more than half of the patients. Thus, the combination of dysphagia and skin abnormalities seems to be a good diagnostic argument to suggest the possibility of scleromyxedema. Moreover, CK level may be higher than that previously been suggested [28], with a mean of 3147 IU/L. In addition to myopathy, our patient also developed 'dermato-neuro syndrome' (DNS), a rare neurological complication of scleromyxoedema characterized by a triad of fever, coma and seizures (preceded by a flu-like prodrome). If mucin deposition has been observed within some blood vessels and in the perivascular connective tissue of various organs, they have never been identified within brain and rarely in muscles. So mucin deposition is probably not the cause of DNS, and even myopathy in scleromyxedema. In DNS, the cause of neurological manifestations is still uncertain, but a role of the paraproteinemia (hyperviscosity, leukocyte aggregation, or even pathologic role of IgG crossing the blood–nerve barrier) has been proposed. Because the sera from patients with scleromyxoedema are able to stimulate in vitro proliferation of fibroblasts (even after removal of IgG) [29], it was suggested that a factor other than paraproteinaemia may be the cause of the extracutaneous features. For example, interleukin-6 (IL-6) is known to be high in both serum and CSF of patients with DNS [30]. Blood–brain barrier disruption (possibly mediated by IL-6) was also pointed as a potential cause of the neurological symptoms of DNS, due to the high

level of CSF protein level observed in some DNS patients [18, 30, 31], but our patient had normal protein CSF level.

Muscle biopsy of patients with myopathy and scleromyxedema shows inflammatory signs in two-thirds of the patients, giving the possibility of an immune-mediated mechanism. For example, IL-6, acting as both a pro-inflammatory and an anti-inflammatory cytokine, plays a central role in the transition from the acute to the chronic phase of the inflammatory process [32], and elevated levels of IL-6 have been documented in a variety of autoimmune diseases, including inflammatory myopathies such as dermatomyositis [33]. The good response for IVIg seems also a good argument for an immune-mediated process. However, our patient, as the other third, had no sign of inflammation in the muscle. One explanation may be that muscle inflammation, in some cases, may be mild and patchy, so not always observed in muscle biopsy. Another explanation could be another mechanism such as mucin deposition, but it has rarely been searched or even observed in muscle. Finally, we can also consider that, if the muscle biopsy is performed after many years (as in our case), there is more atrophy and degeneration than inflammation. For example, similar features may be observed in inclusion body myositis where IVIg may sometimes give positive result (even transitory) despite the absence of clear inflammation in the muscle. Finally, it has been shown that normal skin fibroblast proliferation may be stimulated by the serum from patients with scleromyxedema [34], suggesting the presence of some factors able to induce changes in connective tissue metabolism. Indeed, the serum of such patients may stimulate both hyaluronic acid and prostaglandin E production by human fibroblasts [35]. In muscles, the proteoglycans and the glycosaminoglycans (including hyaluronic acid) of the extracellular matrix (ECM is an organized complex macromolecule network of proteins such as collagen and elastin) are main regulators of skeletal muscle development and repair; all these components, both in skin and muscle, are themselves regulated by biochemical mediators (interleukins, arachidonic acid and derivatives, interferons, platelet-derived growth factor, fibroblast growth factor, transforming growth factor, and epidermal growth factor) [36]. In muscles, ECM regulates the physiological processes of differentiation, proliferation, migration and cell adhesion, playing also a key role in muscle fibrosis [37]. For scleromyxedema, the exact connective tissue activator is unknown, but there is probably one that can activate both the bone marrow (giving paraproteinemia) and connective tissue such as skin and muscles.

We think that medical practitioners have to be aware of such a diagnosis because, as observed with our patient, good extra-cutaneous (especially for acute deterioration of the clinical condition with neurological symptoms) and cutaneous response may be observed with some therapeutics. Due to paraproteinemia (and in comparison to the approach used to treat myeloma), high-dose corticosteroids, melphalan, and thalidomide were first used in scleromyxedema, sometimes with success [26, 38, 39]. But, due to the limit of the use of such immunosuppressant treatments, hematopoietic stem cell transplantation [40, 41] and IVIg [42] were also tried with success for some years. Other systemic treatments used in scleromyxedema were plasmapheresis, extracorporeal photopheresis, α-interferon, and bortezomib [39, 43, 44]. Even if the treatment of scleromyxedema is not well defined, the management is usually the following [1]: IVIg are the first-line therapy, but the response is not permanent, so maintenance infusions are usually required every 6–8 weeks [45, 46]; the second-line treatment is based on thalidomide and corticosteroids [19, 47], usually in combination with IVIg [48]; the third-line treatment is based on autologous peripheral blood stem cell transplantation (sometimes followed by courses of bortezomib and dexamethasone). For myopathy, most of the patients were first treated with corticosteroids (as it is the case in inflammatory myopathy), but it was not the case in our patient where improvement was observed with IVIg (we used this treatment in first intention, based on some good results observed in the medical literature and the absence of clear muscle inflammation); however, there are two few cases of myopathy treated by IVIg (3 cases: one without improvement; two with improvement, whom one also treated by corticosteroids and thalidomide) to confirm this positive effect. For the neuro-dermato syndrome, IVIg is usually considered as first-line therapy. As for our patient, the onset of DNS sometimes coincided with the discontinuation of IVIg, increased intervals between IVIg infusions or reduced doses of IVIg [15, 31, 49]. Finally, the treatment of DNS remains empirical. Some good results have been observed with melphalan, thalidomide and, like in our case, IVIg.

In conclusion, myopathy, although rare, may be a treatable complication (at least partially) of scleromyxedema. As a consequence, in a context of non-specific inflammatory and/or vacuolar myopathy with dysphagia, the diagnosis of scleromyxedema has to be proposed, especially in case of suggestive skin lesions.

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Compliance with ethical standards

Conflicts of interest The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical standards The case study has been report in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from the patient.

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