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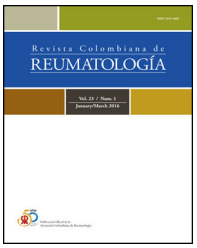

Case report

Scleromyxoedema with extracutaneous pulmonary manifestation: A case report and review of the literature

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ABSTRACT

Scleromyxoedema is a cutaneous fibromucinosis of unknown aetiology. It is associated with haematological dyscrasias and quite diverse manifestations. Pulmonary vascular involvement is rare and requires a differential diagnosis approach with systemic sclerosis. The case of a patient with scleromyxoedema with an extracutaneous pulmonary manifestation is described.

Escleromixedema con manifestación extracutánea pulmonar: reporte de un caso y revisión de la literatura

Palabras clave:
Escleromixedema
Hipertensión pulmonar
Gammapatía monoclonal de significado inciertoribed

RESUMEN

El escleromixedema es una fibromucinosis cutánea de etiología desconocida. Se asocia a discrasias hematológicas y a manifestaciones sistémicas muy diversas. El compromiso vascular pulmonar es poco frecuente y requiere un abordaje de diagnóstico diferencial con la esclerosis sistémica. Se describe el caso de un paciente con escleromixedema con manifestación extracutánea pulmonar.

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Introduction

Scleromyxedema (SM), also known as lichen sclerodermoid, myxedematous, or Arndt–Gottron syndrome, is a chronic, progressive, rare, unpredictable, and sometimes lethal idiopathic and systemic disease of chronic course, characterized by a generalized papular, scaly, dermiform rash accompanied by monoclonal gammopathy and showing mucin deposition, proliferation of fibroblasts, and fibrosis on histopathology.[1–3]

This disease mainly affects adults between the fifth and sixth decade of life, regardless of gender or ethnicity.[4–7] It is associated with hematologic dyscrasias and a wide range of systemic manifestations. About 70% of patients present with extracutaneous manifestations.[6–8] Pulmonary involvement (with restrictive or obstructive patterns) occurs in 17% of cases, with pulmonary arterial hypertension being an exceptional manifestation.[9,10] At the moment there is no specific treatment consensus. The case of a patient with scleromyxedema with pulmonary extracutaneous manifestation is described below.

Case presentation

A 64-year-old male patient from Cali, Colombia, with a history of arterial hypertension and a seven-year history of generalized papular lesions associated with distal cutaneous thickening with sclerodactyly and proximal involvement of the skin of the extremities, trunk, and face, of progressive course, being managed with azathioprine and colchicine. At the time of admission, he had been presenting for three months with mixed dysphagia, nasal regurgitation and dyspnea, especially on exertion. Physical examination revealed a significant cutaneous involvement of the skin (Fig. 1).

A chest CT scan was performed, which ruled out interstitial lung disease or other lesions. However, an enlargement of the pulmonary artery trunk was evident, and the transthoracic echocardiogram showed the presence of concentric remodeling of the left ventricle with slightly thickened walls, high probability of pulmonary hypertension (pulmonary systolic pressure 58 mmHg), maximum tricuspid regurgitation velocity (TR V_{max}) of 3.47 m/s, and a pressure gradient (TR PG_{max})

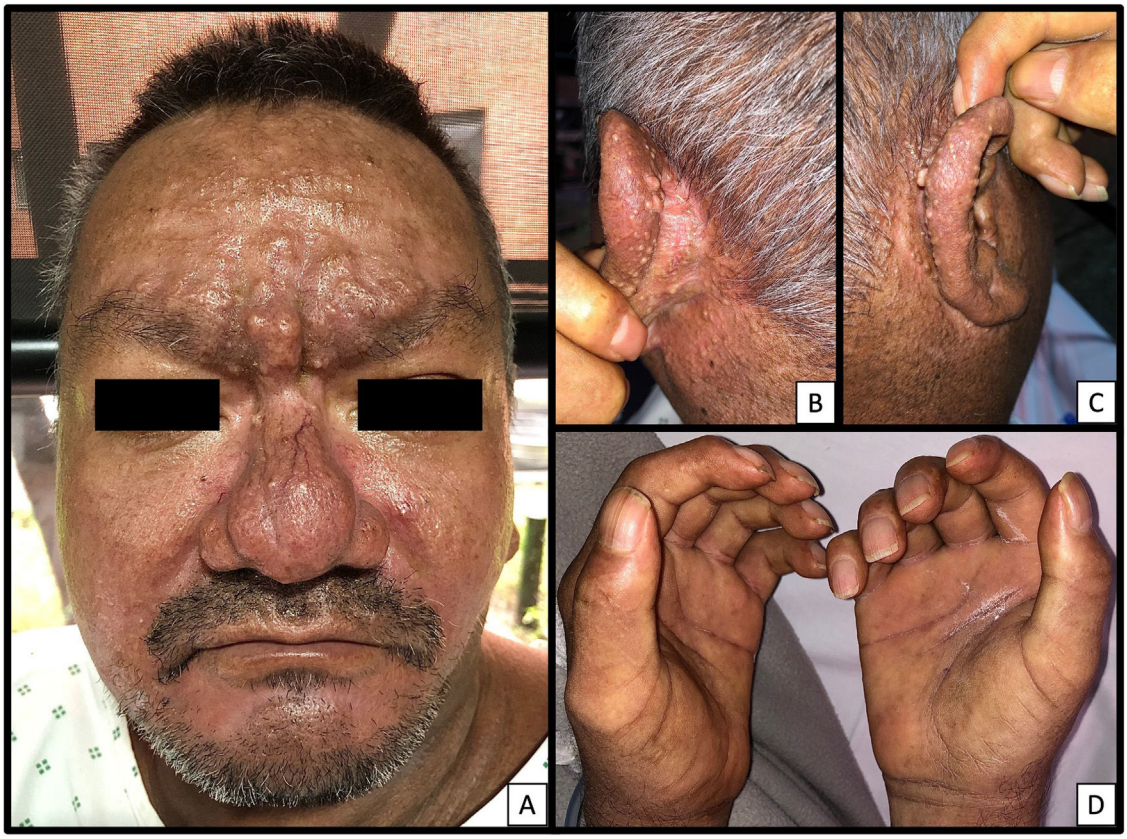

Fig. 1 – Skin lesions in a patient with scleromyxedema. (A) Diffuse shiny and indurated skin on the face. Waxy, confluent papules and some subcutaneous nodules are seen in frontal, glabellar, ciliary and nasal dorsum region. Deep longitudinal fold in glabellar region, madarosis. Leonine facies. (B and C) Posterior region of both auricular pavilions with monomorphous, euchromic, firm consistency, dome-shaped, linearly arranged papules. (D) Sclerodactyly without Raynaud's phenomenon with shiny-appearing skin and fixed flexion contractures.

of 48.16 mmHg. There was no evidence of ventricular function deterioration (left ventricular ejection fraction 60%–65%).

The six-min walk test (*6-min walk test* [6MWT]) was performed, in which the patient covered a distance of 270 m (53% of the predicted value), for a predicted value of normality 504 m. During the test, the patient presented desaturation but at the final had an SpO_2 95% with FC 67 beats per minute, which corresponded to 42% of the maximum heart rate, perceived dyspnea 0 (none) and MMII 2 (mild) fatigue. Spirometry reported a restrictive pattern and moderate alteration in the diffusion capacity of carbon monoxide (DLCO). He was taken to right heart catheterization with hemodynamic parameters with normal pulmonary wedge pressure (PCWP), elevated pulmonary vascular resistance and elevated mean pulmonary artery pressure (mPAP),compatible with group I pulmonary hypertension (systolic pulmonary artery pressure (sPAP) 63 mmHg, diastolic pulmonary artery pressure (dPAP) 22 mmHg, mean pulmonary artery pressure (mPAP) 35.7 mmHg, pulmonary vascular resistance 247.6 dyn/s/cm 5–3.1 Wood units, transpulmonary gradient (TPG) 21.7 mmHg).

In addition, deficits in oral motor control were confirmed, with inadequate bolus formation in the oral cavity, reduced lingual propulsion, and pharyngeal contraction during swallowing with solids.

Laboratory studies for autoimmunity were: complement C3 125.59 mg/dL and C4 23.99 mg/dL, antinuclear antibodies (ANAS) negative, rheumatoid factor 73.8 IU/mL, anti-citrullin 5.2 U/mL, IgG cardiolipin 2.2 GLP-U/mL, IgM cardiolipin 1.4 MPL-U/mL, IgG 2 glycoprotein I 1.4 U/mL, IgM 2 glycoprotein I 1.7 U/mL, anti-SSA (Ro) 2 U/mL, anti-SSB (La) <0.1 U/mL, anti-Sm 3.9 U/mL, anti-RNP 1.1 U/mL, anti-proteinase 31.3 U/mL, anti-myeloperoxidase 1.2 U/mL, anti-DNA 11.5 IU/mL by enzyme immunoassay and negative by indirect immunofluorescence, anti-Scl 70 3.2 U/mL. In protein electrophoresis, a small monoclonal peak corresponding to 4.2% was identified for the gamma region. Serum protein immunofixation suggested the presence of IgG lambda-type monoclonal gammopathy. A bone marrow aspirate-biopsy was performed in which 0.06% of plasma cells with pathologic phenotype were detected, compatible with plasma cell neoplasia, so the patient was considered to have a monoclonal gammopathy of uncertain significance (MGUS).

Finally, skin biopsies were taken from the left auricular pavilion and the ipsilateral hand, where the presence of mucin deposition, fibroblast proliferation, and fibrosis consistent with the diagnosis of scleromyxedema was confirmed (Fig. 2).

Pharmacologic management was initiated with ambrisentan (10 mg daily), sildenafil (50 mg twice daily), and cyclophosphamide (500 mg monthly). At two years of follow-up in the rheumatology unit, the patient remains without clinical deterioration.

Discussion

We present a case of scleromyxedema with a rare extracutaneous pulmonary manifestation. The patient presented with the typical skin lesions of scleromyxedema in the absence of thyroid disease, and a histopathologic skin specimen was obtained, in which the typical microscopic triad was observed (diffuse mucin deposition of varying intensity between the collagen fibers of the upper and middle reticular dermis, proliferation of fibroblasts irregularly dis-posed with large star-shaped nuclei, and fibrosis with increased collagen deposition).

Multiple entities associated with dermal fibrosis can mimic the cutaneous involvement of scleromyxedema. In the case of our patient, the main differential diagnosis was carried out with systemic sclerosis given the cutaneous, gastrointestinal, neoplastic, and pulmonary involvement (Table 1).

In the skin, the presence of disseminated papules, especially in a linear arrangement, is a very useful clinical sign to distinguish scleromyxedema.

The papules may evolve into hardened plaques, with marked sclerosis and hardening of the skin on the face, neck, trunk, hands, and extremities.[11] The mucous membranes and scalp are usually spared.[12] Mucin deposition within the dermis is responsible for cutaneous findings such as a leonine facies, given by the presence of papular induration on the glabella, and Sharpei's sign, given by deep longitudinal grooves on the trunk or extremities.[6,8] The distribution of cutaneous involvement in our patient is congruent with that described in the literature.[6,7]

As the disease progresses, engorgement and stiffness of the skin with sclerodactyly is observed leading to decreased joint mobility and difficulty in oral opening.[13] The skin in scleromyxedema moves over the subcutaneous tissue, unlike scleroderma.[14] Telangiectasias in nail folds and calcinosis as seen in systemic sclerosis are absent in our patient. Regarding gastrointestinal involvement, dysphagia is a shared systemic manifestation for both scleromyxedema and systemic sclerosis. After the skin, the gastrointestinal tract is the most affected organ in systemic sclerosis, with a frequency of 75%–90%.[15]

Dysphagia is not always associated with strictures and when it is intermittent it indicates gastroesophageal reflux disease, as a manifestation of hypomotility.[16] In the case of our patient, dysphagia is anchored to esophageal dysmotility predominantly in the upper esophagus.[6,11,12]

By definition, scleromyxedema has been described to be associated in almost all patients with the development of a hematologic dyscrasia. These disorders include MGUS, multiple myeloma, Waldenström macroglobulinemia, heavy chain diseases, plasmacytoma, and primary amyloidosis. The monoclonal gammopathy is usually IgG and the light chains are most frequently lambda (λ), although mild plasmacytosis may be observed in bone marrow biopsies, as seen in our patient. The pathogenesis of scleromyxedema is currently unknown. The most accepted hypothesis is that circulating cytokines such as IL-1, TNF- and TGF- stimulate glycosaminoglycan synthesis and fibroblasts proliferation. In vitro serum from patients with scleromyxedema can stimulate DNA synthesis by the fibroblasts. Monoclonal gammopathy is seen more frequently in patients with disseminated disease, and paraprotein concentrations do not correlate with the extent or progression of the disease.[17] In addition, tissue mucin deposition at autopsy does not correlate with clinical findings. About 10% of patients with scleromyxedema progress to symptomatic myeloma, so follow-up is essential.[5,18–20]

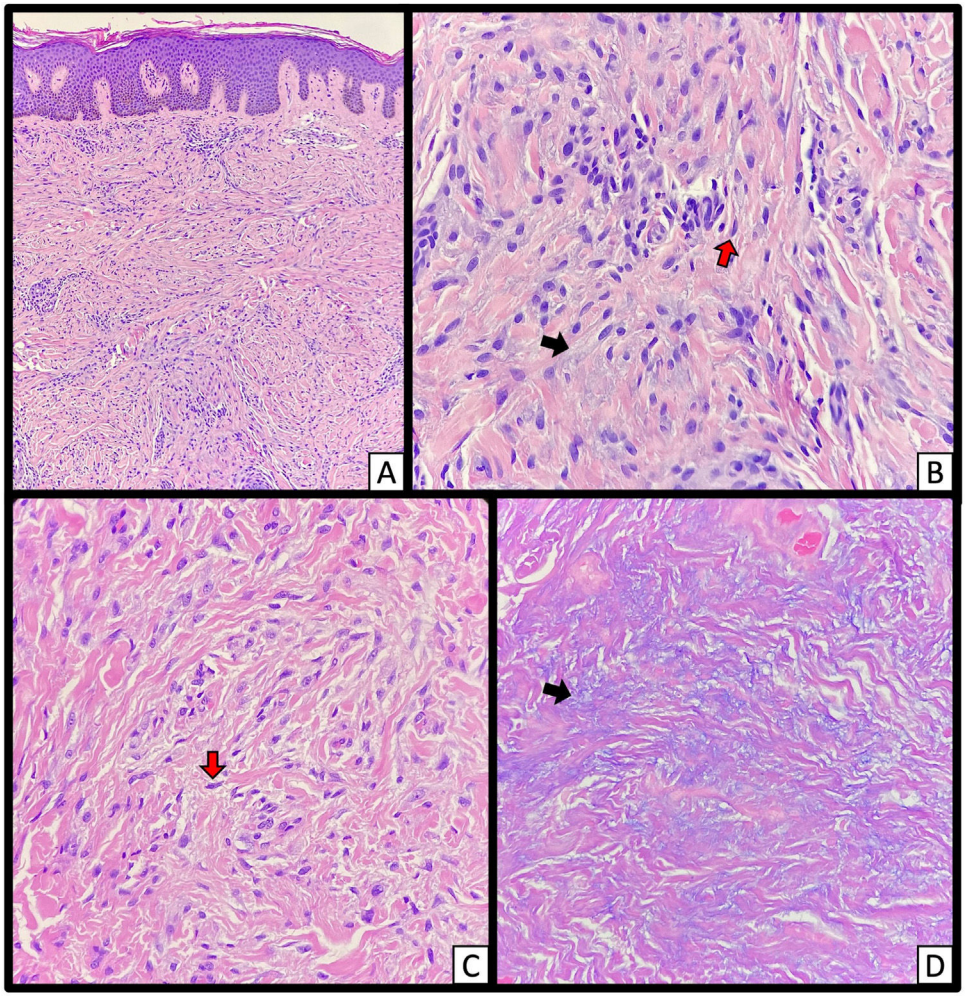

Fig. 2 – Typical triad in skin histopathology in scleromyxedema. (A and B) Hematoxylin and eosin — papule in left auricular pavilion: fibrosis, proliferation of fibroblasts with an elongated or stellate appearance (red arrows), irregularly arranged and interstitial mucin deposits in the upper and middle reticular dermis (black arrows). Images taken at 4× (A) and 40× (B). (C) Hematoxylin and eosin — left hand skin at 40×. (D) Alcian blue showing interstitial mucin deposition in the middle of the collagen fibers (black arrows) at 40×.

The greatest diagnostic challenge in our patient was given by pulmonary involvement, consisting of group I pulmonary hypertension, confirmed by right heart catheterization. Pulmonary involvement in systemic sclerosis most often consists of interstitial fibrosis and pulmonary vascular disease leading to pulmonary arterial hypertension. The prevalence of interstitial lung disease (ILD) in patients with systemic sclerosis varies according to the method of diagnosis (100% in a series of autopsies, 90% by high-resolution computed tomography, and between 40%–75% by pulmonary function tests). ILD occurs more frequently in the diffuse systemic sclerosis phenotype than in limited systemic sclerosis (42% vs. 22%, $p < 0.001$). The prevalence of pulmonary arterial hypertension in systemic sclerosis also varies according to the detection method used (between 13% and 35% by transthoracic echocardiography and between 12% and 16% by right heart catheterization).

Pulmonary arterial hypertension associated with ILD is the most common subphenotype (79.4%) in systemic sclerosis.[21] Our patient did not present pulmonary parenchymal involvement. So far, the prevalence of pulmonary arterial hypertension in scleromyxedema is unknown. Pulmonary arterial hypertension, defined by a mean pulmonary arterial pressure of ≥25 mmHg at rest,[22] can occur in patients with myeloproliferative neoplasms and other paraneoplastic conditions as in the case of our patient. Kreidy et al.[22] described a case of severe but reversible pulmonary hypertension in scleromyxedema and plasma cell dyscrasia. It has been described that pulmonary vascular cells of patients with pulmonary arterial hypertension have a dysregulated metabolism, with increased cell proliferation and resistance to apoptosis.[23,24] Multiple case reports have reported a favorable response to treatment with immunosuppressants and antiproliferative agents with improvement in hemodynamic parameters.[18,19]

So far there is no definitive specific treatment despite its chronic nature and guarded prognosis.[5,6,17,25] The treatment of scleromyxedema has a variable response. Therapies with cyclophosphamide, methotrexate, thalidomide, prednisolone, intralesional corticosteroids, and phototherapy have been

Table 1 – Differential diagnosis of systemic manifestations of scleromyxedema and systemic sclerosis.

Manifestations	Scleromyxedema	Systemic sclerosis
Cutaneous	Firm, waxy papules on the face, head, auricular pavilions, neck, hands, forearms, forearms, upper trunk and thighs. Deep, longitudinal grooves on glabella (leonine facies) and on trunk or extremities ("Shar-Pei sign").	Thickened, shiny and indurated skin on fingers, hands, extremities, face and thorax. Hyperpigmentation, hypopigmentation or patches of depigmentation with preservation of perifollicular pigmentation ("salt and pepper" appearance), usually on the face, arms and trunk.
	Sparse hair on eyebrows, axillae and genitalia.	General tanning of the skin in the absence of sun exposure.
	Mucin deposits in the dermis and proliferation of fibroblasts in the reticular dermis with a mild perivascular inflammatory infiltrate.	Thickened dermis with collagen, extracellular matrix and dense connective tissue. The perivascular lymphocytic infiltrate is minimal. Mucin absent or very scanty.
Gastrointestinal	Dysphagia, esophageal dysmotility, aperistalsis, esophagitis, nasal regurgitation	Dysphagia, esophageal dysmotility, gastroesophageal reflux disease, heartburn, esophageal stricture, Barrett's esophagus, gastroparesis, dyspepsia, gastric antral vascular ectasia of the gastric antrum, intestinal hypomotility, constipation, bacterial proliferation, diarrhea
Immunological	Uncommon	Anticentromere Anti-topoisomerase I or Scl70 anti-RNA-polymerase III
Neoplastic	Multiple myeloma, monoclonal gammopathy, Hodgkin's or non-Hodgkin's lymphoma, Waldenström's disease and leukemia.	Increased risk of malignancy with RNA polymerase III positivity
Pulmonary	Dyspnea on exertion, restrictive or obstructive compromise, decreased DLCO, pleural effusion, hoarseness, bronchial aspiration, pulmonary arterial hypertension (exceptional)	Interstitial lung disease, pulmonary arterial hypertension, decreased DLCO

DLCO: diffusing capacity of the lungs for carbon monoxide.

described in the literature with improvement, but not complete resolution of cutaneous findings.[6,7] Targeted treatment of monoclonal gammopathy with melphalan, bortezomib and autologous hematopoietic stem cell transplantation has been shown to induce clinical remission.[18,19] Scleromyxedema usually responds well to intravenous immunoglobulin when associated with systemic manifestations.[25] The patient received management with cyclophosphamide associated with ambrisentan and sildenafil, with no evidence of disease progression during follow-up in the rheumatology unit. Randomized studies, multicenter registries, and larger groups of patients are needed to optimize immunosuppressive management in this type of patients and thus improve their quality of life and decrease their morbidity and mortality.

Conclusions

Pulmonary vascular involvement in scleromyxedema is rare. Pharmacologic management with cyclophosphamide was successful in preventing multisystem disease progression during follow-up. More information is needed on how to manage these cases to decrease morbidity and mortality and improve the quality of life of these patients.

Ethical responsibilities

Protection of humans and animals. The authors declare that no experiments on humans or animals have been performed for this research.

Confidentiality of the data. We the authors declare that we have followed the protocols of the work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patient referred to in the article. This document is in the possession of the corresponding author.

Declaration of informed consent

I confirm that I have obtained all consents required by the legislation in force for the publication of any personal data or images of patients, research subjects, or other individuals appearing in materials submitted to Elsevier. I have retained a written copy of all such consents and, if requested by Elsevier, I agree to provide copies or evidence that such consents have been obtained.

Conflict of interests

The authors declare that they have no conflict of interest.

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