Coexistence of scleromyxedema and Sneddon syndrome

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INTRODUCTION

Scleromyxedema is a rare mucinosis characterized by a generalized, papular, sclerodermoid cutaneous eruption often accompanied by extracutaneous manifestation and associated with paraproteinemia.[1] Sneddon syndrome is a progressive disease characterized by generalized livedo racemosa and recurrent cerebrovascular events with an autoimmune or thrombophilic base.[1] To our knowledge, no cases of coexistence of these two disorders in the same patient have been reported. Herein we report the clinical, pathological, and laboratory findings of a patient with both scleromyxedema and Sneddon Syndrome.

CASE DESCRIPTION

A 62-year-old patient presented to our attention for diffuse livedo racemosa accompanied by asthenia, difficulty walking, paresthesia, confusion, and a two-year history of tingling in the limbs and lip. Cutaneous examination showed reticular-patchy, violaceous discoloration on the abdomen, trunk, and upper and lower limbs, together with widespread skin induration, difficulty in joint movements, and waxy papules with linear or patchy distribution on the front, trunk, thighs, limbs, and hands (Fig 1, *A* and *C*). The hands had the typical "doughnut sign" (Fig 1, *B*). These sclerodermoid alterations had been present for about one year. The patient had a history of type II diabetes mellitus, hepatitis C virus-related liver disease, arterial hypertension, IgG lambda monoclonal gammopathy of undetermined significance, and benign prostatic hypertrophy, and was under treatment with cardioaspirin, metformin, olmesartan, alfuzosin, and alendronic acid. Histological examination (6-mm punch biopsy at the center of a livedo racemosa area) showed dilated superficial vessels with a moderate perivascular and interstitial lympho-histiocytic infiltrate. A biopsy of a papule on the left thigh showed a proliferation of irregularly arranged fibroblasts, moderate mucin deposits, and fibrosis in the papillary and superficial dermis in association with interstitial CD68+ and CD163+ dendritic and epithelioid histiocytes. A mild perivascular lymphohistiocytic infiltrate with occasional eosinophils was also present (Fig 2). Renal and liver function tests were within the normal range. IgG lambda monoclonal gammopathy was present at 5 g/L. Serum antibodies against nuclear, extractable nuclear antigen, and double stranded DNA, cardiolipin, and beta-2 glycoprotein were absent. Lupus anticoagulants and cryoglobulins were also absent. No alterations in coagulation tests were found, including prothrombin time, activated partial thromboplastin time, fibrinogen, coagulation factor II, factor IX, and factor XI levels. Antithrombin, protein C, and protein S activities were within the normal range. Factor V Leiden and Prothrombin 20210 (factor II) mutation were absent, whereas

Abbreviation used:

MTHFR: methylenetetrahydrofolate reductase

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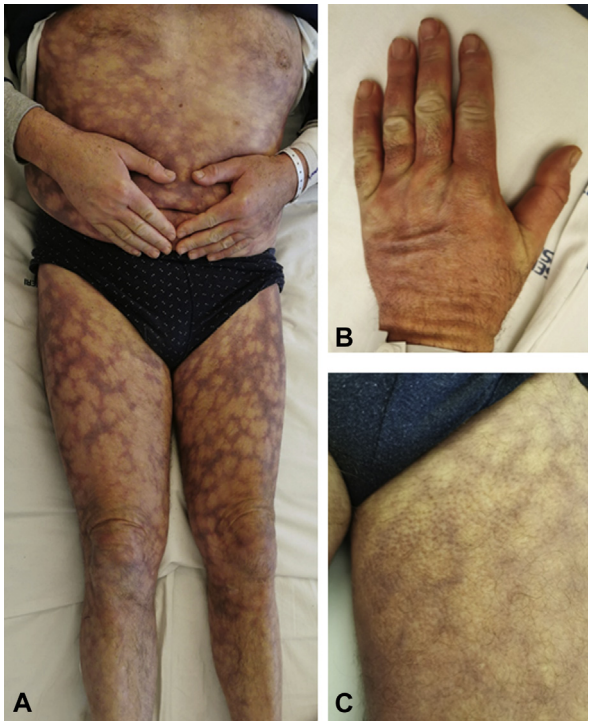

Fig 1. A, Reticular-patchy, violaceous discoloration on the abdomen and lower limbs, together with widespread skin induration and difficulty in joint movements. **B**, Doughnut sign on the hand. **C**, Waxy papules on the left thigh.

analysis of the methylenetetrahydrofolate reductase (*MTHFR*) gene revealed a compound heterozygosity with C677T and A1298C polymorphisms. Homocysteine levels were slightly elevated, 20 mcmol/L (normal value <15 mcmol/L). T2-weighted axial magnetic resonance image revealed lacunar infarcts in the nuclei of the base and in the semi-oval centers on both sides (Fig 3). Chest X-ray showed reinforcement of the interstitial texture, and a CO_2 diffusion test revealed a reduction of 70% in alveolar-capillary diffusion. Echocardiography revealed hypertensive heart disease with preserved systolic function and mild mitral insufficiency. The patient was treated with monthly intravenous infusions of immunoglobulins 2 g/kg/month and warfarin daily with international normalized ratio >2, with good response in both clinical symptoms and skin manifestations after four months (Fig 4). The patient reported an improvement of skin elasticity, an increase in facial mimetic movement and restoration of joint function, a decrease of asthenia and paresthesia, reacquiring mental concentration and better walking ability. No side effects were reported. At 9-month follow-up, the patient was still in remission with a maintenance of intravenous immunoglobulins 1 g/kg once a month.

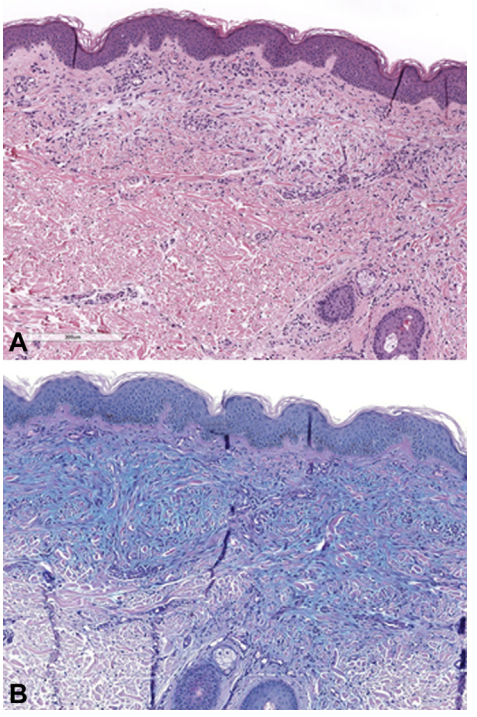

Fig 2. A, Biopsy of a papule showing a poorly circumscribed area of mucin deposition in the papillary and superficial dermis, with an increased number of fibroblasts, thickened collagen bundles, and sparse dendritic histiocytes (hematoxylin-eosin stain; original magnification, x100). **B**, A PAS-Alcian Blue stain confirmed the presence of mucin in the papillary and superficial reticular dermis (PAS-Alcian Blue stain; original magnification, x200).

DISCUSSION

Scleromyxedema and Sneddon syndrome are two rare diseases, and to our knowledge, their coexistence has never been reported. Scleromyxedema is a cutaneous mucinosis characterized by generalized or localized papular eruptions with sclerodermoid induration of the skin. Histopathology of the classic form is characterized by a triad of microscopic features, including mucin deposition, proliferation of fibroblasts, and increased collagen deposition in the dermis.[1-3] Histologically, our cases exhibited an interstitial granuloma annulare-like pattern with many CD163+ and/or factor XIIIa+ macrophages resembling an unusual histological variant of scleromyxedema, with interstitial histiocyte components in addition to classic signs.[4] Scleromyxedema is associated with paraproteinemia in more than 80% of the cases—more often IgG lambda, as in our case. Extracutaneous manifestations include cardiovascular, gastrointestinal, pulmonary, articular, and neurological involvement.[1] Intravenous immunoglobulins are considered the treatment of choice for both skin lesions and systemic manifestations.[1,3] Sneddon

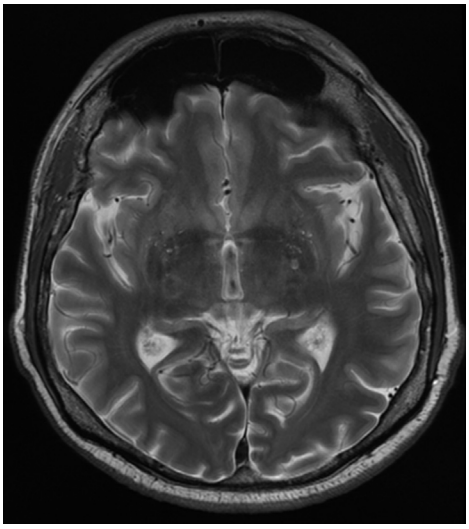

Fig 3. T2-weighted axial magnetic resonance image showing lacunar infarcts in the nuclei of the base and in the semi-oval centers on both sides.

syndrome is a rare neurocutaneous syndrome, characterized by generalized livedo racemosa and frequent cerebrovascular events.[5] Livedo racemosa generally precedes neurological manifestations by years. Neurological symptoms range from headaches, dizziness, vertigo, recurrent strokes, and finally dementia. Sneddon syndrome may be classified as antiphospholipid-positive or -negative, depending on the presence of anticardiolipin, lupus anticoagulant, or anti-beta 2-glycoprotein I antibodies. In this patient group, the reason for the increased risk of cerebrovascular disease remains unknown.[6] Patients affected by Sneddon syndrome may present with hypertension and other heart valve diseases, as well as impaired renal function and ophthalmological complications. Cutaneous and brain histopathology are characterized by a pauci-inflammatory thrombotic vasculopathy, involving medium and small-sized arteries. Antiplatelet and antithrombotic agents are generally used to prevent stroke.[7] In our patient, we could not find thrombotic occlusion of dermal vessels, but this is documentable in only 80% of cases, even when biopsy is taken in a relevant area,[8] and the patient refused an additional biopsy. Antiphospholipid antibodies were absent in our case; therefore, we hypothesized that the prothrombotic state could be sustained by polymorphisms in the *MTHFR* gene, which influences the homocysteine-lowering effect of folates.[9] Very few cases of neurological involvement (*e.g.*, altered sensorium, confusion, and dysarthria) during scleromyxedema have been reported, and they did not present as Sneddon syndrome. Indeed, the presence of paraproteinemia can trigger transient focal

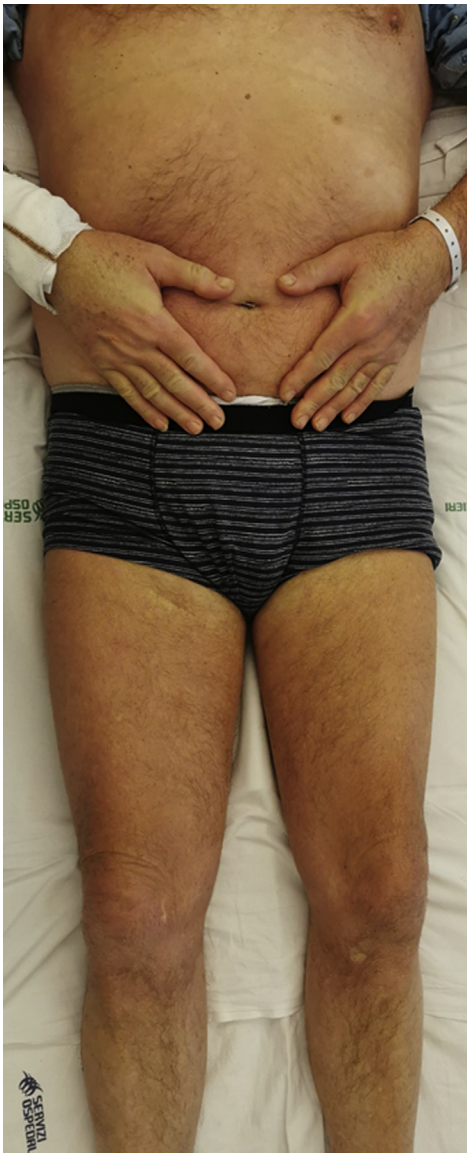

Fig 4. Disappearance of livedo racemosa after four months of treatment with monthly intravenous infusions of immunoglobulins 0.4 g/kg and warfarin daily.

neurological involvement, mainly through hemodynamic mechanisms due to hyperviscosity.[10] The neurological symptoms presented by our patient were possibly the result of several factors, including Sneddon syndrome, scleromyxedema-associated paraproteinemia, and *MTHFR* gene mutation, defining an exceptional clinical presentation in the context of two rare diseases.

Conflicts of interest

None disclosed.

REFERENCES

1. Rongioletti F. Lichen myxedematosus (papular mucinosis): new concepts and perspectives for an old disease. *Semin Cutan Med Surg*. 2006;25(2):100-104.

2. Samanta D, Cobb S, Arya K. Sneddon syndrome: A comprehensive overview. *J Stroke Cerebrovasc Dis*. 2019;28(8):2098-2108.
3. Arginelli F, Rongioletti F, Girolomoni G, Pellacani G, Guardoli D, Conti A. Long-term efficacy of high doses of intravenous immunoglobulins in generalized scleromyxoedema: Case report. *J Int Med Res*. 2016;44(1 suppl):109-112.
4. Rongioletti F, Cozzani E, Parodi A. Scleromyxedema with an interstitial granulomatous-like pattern: a rare histologic variant mimicking granuloma annulare. *J Cutan Pathol*. 2010;37(10):1084-1087.
5. Flöel A, Imai T, Lohmann H, Bethke F, Sunderkötter C, Droste DW. Therapy of Sneddon syndrome. *Eur Neurol*. 2002;48(3):126-132.
6. Tourbah A, Piette JC, Iba-Zizen MT, Lyon-Caen O, Godeau P, Francès C. The natural course of cerebral lesions in Sneddon syndrome. *Arch Neurol*. 1997;54(1):53-60.
7. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med*. 1995;332(15):993-997.
8. Zelger B, Sepp N, Schmid KW, Hinter H, Klein G, Fritsch PO. Life history of cutaneous vascular lesions in Sneddon's syndrome. *Hum Pathol*. 1992;23(6):668-675.
9. Schwahn B, Rozen R. Polymorphisms in the methylenetetrahydrofolate reductase gene: clinical consequences. *Am J Pharmacogenomics*. 2001;1(3):189-201.
10. Kwaan HC. Hyperviscosity in plasma cell dyscrasias. *Clin Hemorheol Microcirc*. 2013;55(1):75-83.