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CASE REPORT

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Localized scleroderma with pulmonary arterial hypertension and pulmonary interstitial fibrosis in a patient with positive Th/to antibodies: Case report and review of literature

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Abstract

Morphea is an auto-immune disease, and its association with other immune-mediated diseases should not come as a surprise. Dermatologists should be aware of its possible coexistence with severe systemic involvement.

KEYWORDS

clinical dermatology, morphea

1 | INTRODUCTION

We report an uncommon case of generalized morphea associated with pulmonary interstitial fibrosis, pulmonary arterial hypertension, and positive Th/To antibodies. Dermatologists should be aware of the possible coexistence of morphea with severe systemic involvement. In our patient, positive anti-Th/To antibodies may constitute the pathophysiological substratum of the fibrosing lung disease.

Morphea, also referred to as localized scleroderma, is an uncommon connective tissue disease characterized by sclerotic changes in the skin and subcutaneous tissue. It encompasses a wide spectrum of clinical variants.[1] Kreuter et al. distinguished the generalized, limited, linear, deep, mixed, and eosinophilic fasciitis of Shulman types.[2] Morphea mainly occurs with exclusive cutaneous changes and rarely affects internal organs. It is distinguished from systemic sclerosis (SSc) which presents with scleroderma-specific autoantibodies, Raynaud's phenomenon, sclerodactyly, and multiple organ dysfunction.[3]

Herein, we report an uncommon case of generalized morphea (GM) associated with pulmonary interstitial fibrosis (PIF), pulmonary arterial hypertension (PAH), and positive Th/To antibodies.

2 | OBSERVATION

A 79-year-old woman with no relevant medical history, presented with a 3-month history of itchy, diffuse hard skin. On physical examination, there was extensive hyperpigmentation and atrophy on the trunk (Figure 1A,B). Indurated confluent patches with an average size of 6 cm were noted on the chest, abdomen, and back, sparing the extremities (Figure 2). It was easy to pinch the skin of both the hands and the face. The skin temperature of the extremities was normal, and the patient did not have digital

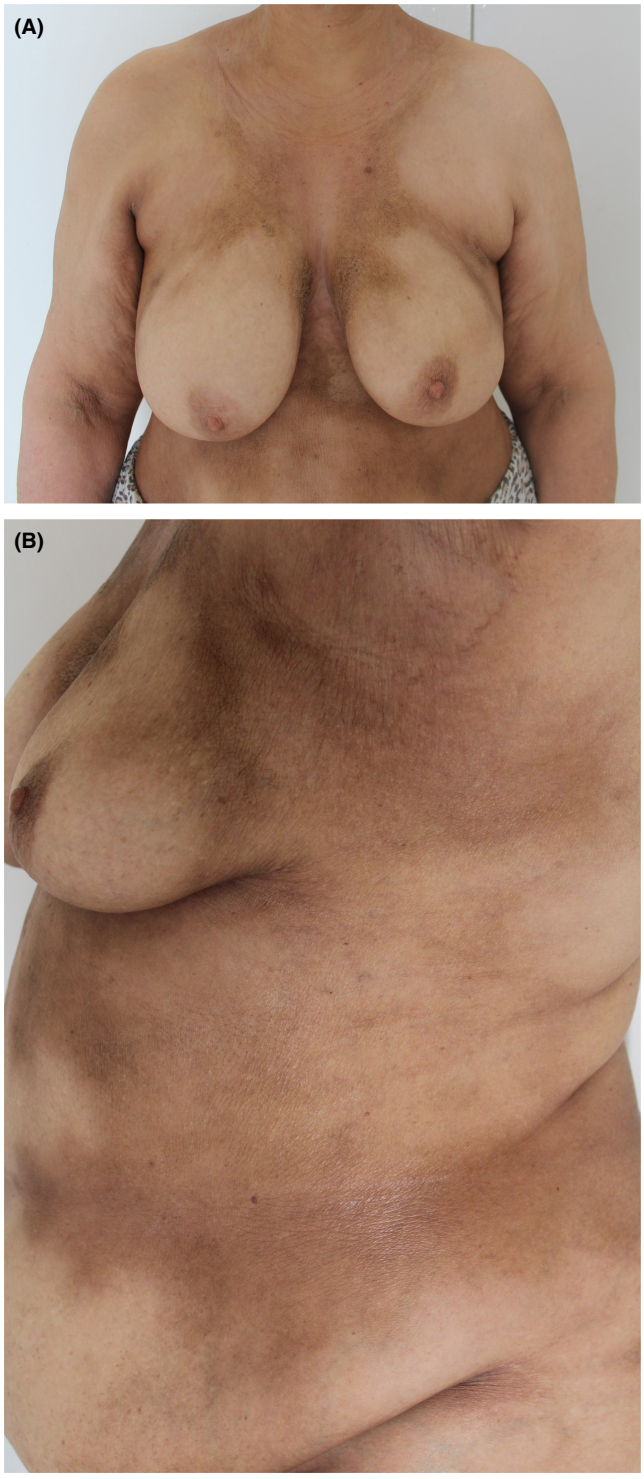

FIGURE 1 (A) Hyperpigmentation and atrophy on the trunk. (B) Extensive hyperpigmentation and atrophy on the trunk.

ulcerations (Figure 3). She had very few facial wrinkles and did not have limitations of mouth opening.

She was a housewife and was not exposed to any toxic substances. The patient was not taking any medications. She reported no discoloration of her fingers and/or toes when exposed to cold temperature, nor did she report dyspnea, dysphagia, arthralgia, or other systemic symptoms.

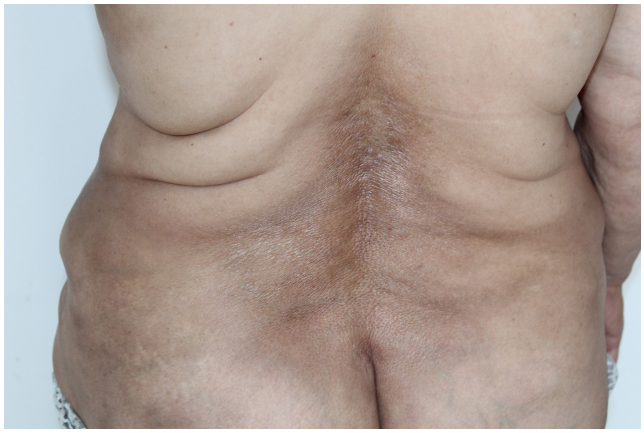

FIGURE 2 Indurated confluent patches of the back.

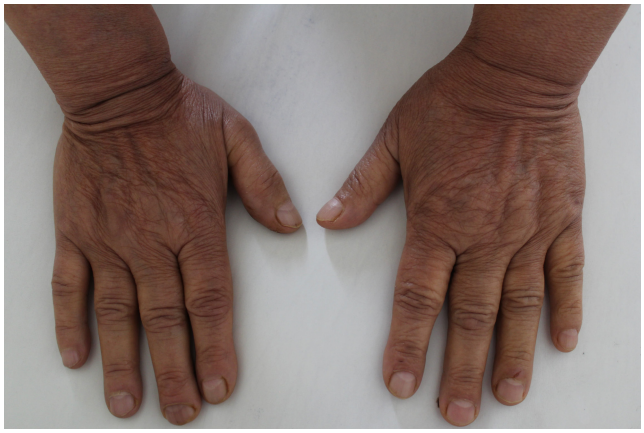

FIGURE 3 Absence of sclerodactyly and digital ulcerations.

Histopathology of a skin biopsy revealed a normal epidermis, homogenization of the whole dermal collagen with thick collagen bundles, and clear rarefaction of adnexal structures. The eccrine sweat glands were atrophic and "walled up" by newly formed collagen (Figure 4).

On the basis of clinical manifestations and histological examination, and according to the Laxer and Zulian classification, the diagnosis of GM was made. A blood test for antinuclear antibodies (ANAs) was positive at 1:200 with positive anti-Th/To antibodies. Systemic scleroderma-specific antibodies (Anti-centromere, anti-topoisomerase I (Anti Scl-70), and anti-RNA polymerase III) were negative. Serological tests for B and C hepatitis viruses were negative.

A treatment with 0,7 mg/kg/d of systemic prednisone and topical steroids was initiated with a very slight improvement within 2 months. Treatment with methotrexate was indicated. A pre-methotrexate chest x-ray was performed and revealed a bilateral interstitial infiltrate. Computed tomography of the lungs showed PIF of non-specific interstitial pneumonia type (NSIP). The echocardiography revealed PAH at 50 mmHg. Spirometry was normal. Gastrointestinal investigations revealed no abnormalities.

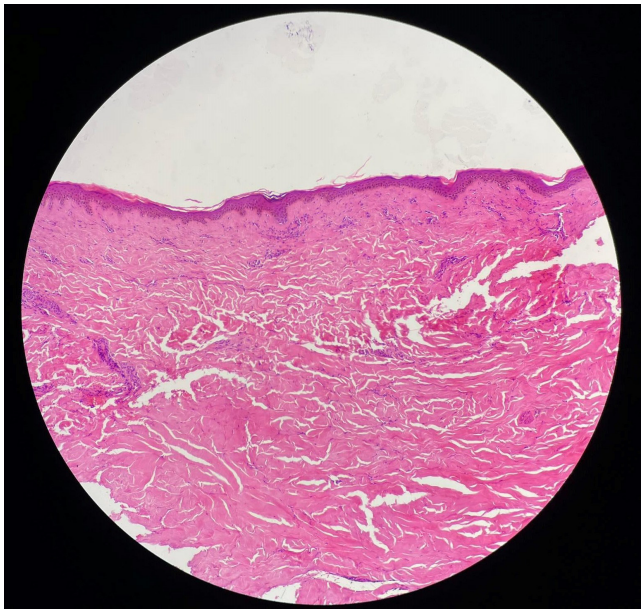

FIGURE 4 Histopathology showing homogenization of the whole dermal collagen with thick collagen bundles, and rarefaction of adnexal structures.

Given the clinical, histological, and radiographic data, the diagnosis of GM with PIF and PAH was established and treatment with a monthly pulse of 600 mg/m^2 cyclophosphamide was started.

3 | DISCUSSION

GM is defined as a subtype of localized scleroderma that displays widespread, multiple, well-circumscribed, and indurated patches with a lack of systemic manifestations.[4] Its incidence rate is rare, ranging from 7% to 9% of all morphea subtypes.[5]

Kreuter et al. consider that, depending on the subtype, morphea can also involve adjacent tissues such as the fat, fascia, muscle, and bone, but not internal organs.[2] Thus, screening for systemic damage in patients with morphea is not a common practice. Moreover, several authors have investigated the prevalence of systemic disease in patients with morphea and found that signs indicative of SSc are statistically not more frequent in patients with morphea than in controls, which supports the view that morphea and SSc are not part of a single disease continuum.[6–8] Also, none of the 82 patients with morphea included in a 33-year-period prospective study had evolved into SSc.[7] Last but not least, results of immunological studies demonstrate that specific HLA Class I and II alleles associated with morphea are different from those found in patients with SSc, which corroborates the fact that morphea is also immunogenetically distinct from SSc.[9] All these arguments support the consideration of morphea as an exclusive cutaneous disease that does not justify further investigations. In the present case, we report an unusual coexistence of GM, PIF, and PAH.

To the best of our knowledge, our patient represents the fifth reported case of GM with a respiratory involvement consisting of lung fibrosis (Table 1). The first case was described in a Japanese man with recurrent GM and SSc.[10] The authors noted that morphea and SSc activities were independent. Only the morphea lesions responded to systemic steroids. When the morphea recurred, manifestations of SSc did not worsen. They suggested, therefore, that the morphea lesions were not a skin manifestation of SSc and the case was diagnosed as a coexistence of SSc and morphea.[10] The second and third cases were those of two Tunisian women who had GM, sparing the extremities and without immunologic abnormalities. As in the present case, digestive investigations were normal but they both had PIF without PAH. Treatment with methotrexate in one of them and mycophenolate mofetil in the other was effective against the cutaneous sclerosis, but radiological examinations revealed persistent pulmonary involvement. The authors suggested that this association may be explained by a common cause that could have induced the pneumopathy and the GM such as exposure to silica or to infectious factor.[11] The fourth case is a Chinese man, who had GM with positive ANAs and negative specific SSc antibodies. He had no extracutaneous symptoms. In this patient, both skin lesions and PIF had improved after 2 months of oral steroids and monthly IV 0.8 g cyclophosphamide. The authors judged that the PIF was closely linked to the localized scleroderma and could not exclude the possibility that it may be the early phase of SSc. They concluded that a period of follow-up was needed to observe whether SSc-related symptoms would occur later.[5]

As in our case, specific SSc antibodies were negative in the above-mentioned reported cases. Interestingly, our patient was positive for Th/To antibodies, which was not investigated in the previously described patients. Fischer et al. evaluated the presence and clinical relevance of anti-Th/To-positivity in a cohort of 285 patients with idiopathic pulmonary fibrosis. They reported that positive ANAs are a common finding in these patients, and that anti-Th/To antibodies are responsible for the majority of ANAs.[12] More recently, Suresh et al. compared 204 anti-Th/To-positive patients with SSc to anti-Th/To-negative patients with SSc. They concluded that anti-Th/To antibodies represent an independent risk factor for PAH.[13]

In our patient, the presence of anti-Th/To antibodies may constitute the pathophysiological substratum of the fibrosing lung disease and the association of morphea and PIF may be so attributed to concurrent autoimmune diseases.

Morphea is an autoimmune disease, and its association with other immune-mediated diseases should not come as a surprise. Dermatologists should be aware of the possible

TABLE I GM with diffuse interstitial pneumonia in the literature.

Authors	Year	Country	Sex	Age	Exposure	Morphea plaques	TC (months)	SD	PAH	RP	ANA	Specific SSc antibodies	Anti-Th/To antibodies	Other internal organ involvement	TTT	Course
Hayashi et al.[10]	2008	Japan	M	66	No	Trunk	6	Yes	NM	No	1:640 (speckled)	(−)	NM	Esophageal	OS	ML: Response PL: No response
Nakouri et al.[11]	2017	Tunisia	F	52	NM	Trunk Limbs	3	No	No	NM	(−)	(−)	NM	No	MTX MMF	ML: Response PL: No response
Nakouri et al.[11]	2017	Tunisia	F	75	NM	Trunk Limbs	6	No	No	NM	(−)	(−)	NM	No	MTX MMF	ML: Response PL: No response
Chen et al.[5]	2019	China	M	70	NM	Trunk Limbs	1	No	NM	No	1:100	(−)	NM	No	OS CP	ML: Response PL: No response
Our case	2022	Tunisia	F	79	No	Trunk	5	No	Yes	No	1:200 (speckled)	(−)	(+)	No	OS CP scheduled	ML: Slight response PL: No response

Abbreviations: −, Negative; +, Positive; ANA, Anti-Nuclear Antibodies; CP, Cyclophosphamide; F, Female; M, Male; ML, Morphea Lesions; MMF, Mycophenolate mofetil; MTX, Methotrexate; NM, Non- mentioned; OS, Oral steroids; PAH, Pulmonary Arterial Hypertension Specific SSc antibodies; PL, Pulmonary lesions; RP, Raynaud''s phenomenon; SD, Sclerodactyly; TC, Time course of skin involvement before the diagnosis of the lung fibrosis.

association of morphea with severe internal organ involvement. Anamnesis and physical examination assessing disease activity, damage parameters, and looking for internal organ manifestations are crucial. According to a review article, up to 50% of patients with morphea have elevated levels of three main autoantibodies: antinuclear antibodies (ANAs); anti-histone antibodies (AHAs); and anti-single stranded DNA (a-ssDNA). These autoantibodies correlate positively with the severity of the disease and with extracutaneous manifestations.[14]

4 | CONCLUSION

In conclusion, we describe this case of a patient with GM and PIF simultaneously to highlight the pertinence of autoantibodies screening in patients with severe morphea phenotype and when concurrence with other autoimmune diseases is suspected. We also suggest that extracutaneous involvement may be predicted based on clinical findings and autoantibody profiles.

AUTHOR CONTRIBUTIONS

Dorsaf Elinkichari: Conceptualization; data curation; formal analysis; writing – original draft; writing – review and editing. **mariem tabka:** Conceptualization; data curation; validation. **Asmahane Souissi:** Conceptualization; data curation; supervision; validation. **Fatima Alaoui:** Formal analysis; resources. **Ines Chelly:** Data curation. **Slim Haouet:** Data curation. **Mourad Mokni:** Conceptualization; formal analysis; supervision; validation.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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