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Title

Pansclerotic morphea associated with hypohidrosis and anti-M3 muscarinic acetylcholine receptor antibodies

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DEAR EDITOR, Pansclerotic morphea (PM) is a rare subtype of localized scleroderma (LS), accounting for 0·27-3·5% of all LS.[1,2] Autoantibodies to the extracellular domains of the M3 muscarinic acetylcholine receptor (M3R) are associated with the dysfunction of exocrine glands in several diseases[3,4]; however, their association with PM is unknown. Here we report a case of PM complicated with widespread hypohidrosis that was accompanied by elevated serum anti-M3R autoantibodies.

A man in his 50s was referred to our hospital due to a 3-month history of extensive hypohidrosis that he first realized in his upper trunk. He subsequently noticed tenseness of the skin on the hypohidrotic areas. He had a medical history of hyperlipidemia, duodenum ulcer and obsessive-compulsive disorder, but had not received drugs known to induce sclerosis or hypohidrosis. Physical examination showed diffuse, shiny, mildly sclerotic skin with a symmetrical distribution in the upper extremities and the trunk; however, the hands, axillae and lateral chest were spared (Figure 1a). His modified Rodnan total skin thickness score was 8. Analyses for antinuclear antibody and extractable nuclear antigen antibodies (ssDNA, ribonucleoprotein, Scl-70, SS-A, SS-B, centromere, and RNA polymerase III) were negative. Head magnetic resonance imaging and nerve conduction velocity measurement excluded neurological dysfunction. Fluorescein staining of the cornea and a lip biopsy were negative for signs of Sjögren's syndrome (SS). Computed tomography scans showed no findings indicative of systemic involvement. Skin biopsy samples taken from the lateral forearm and the abdomen showed sclerosis with thickened and homogenous collagen fibers in the dermis. Inflammatory cell infiltration was noted around the blood vessels and the appendages

(Figure 1b). The patient's effort-induced sweat secretion as assessed by iodine starch method revealed a striking distribution of hypohidrotic skin identical to the "tank-top sign", a hallmark of PM (Figure 1c).[5] Intradermal injection of acetylcholine failed to provoke sweating in the injected skin. The patient was diagnosed as having pansclerotic morphea complicated with hypohidrosis, because (1) the sclerotic skin showed a characteristic widespread, centrifugal distribution that spared the digits, without signs of the formation of any circumscribed, individual plaques, (2) systemic involvement was absent and (3) the hypohidrotic area corresponded closely to the sclerotic skin.[1,2]

Since anti-M3R autoantibodies are associated with exocrine gland dysfunction, we investigated their involvement in the present case.

We previously established a series of ELISAs to detect autoantibodies against each of the four extracellular domains of M3R[3]; in these assays, synthetic peptides encoding each extracellular domain of M3R were used as the antigens, and the serum was diluted to 1:50 when assayed. The cutoff values are determined as mean + 2 standard deviation values obtained from 42 healthy controls. The ELISA specific for the N-terminal region of M3R revealed an elevated titer at 0.107 optical density (OD) (cutoff: 0.074 OD) in the patient's sera. For the first, second and third extracellular loops, the ELISA titers were 0.051 OD (cutoff: 0.141 OD), 0.074 (cutoff: 0.103 OD) and 0.110 (cutoff: 0.145 OD), respectively.

The patient responded well to treatment of 20 mg prednisolone per day, which was discontinued after two years with restored sweating. The skin sclerosis persisted pathologically, although the skin tenseness as perceived by the patient was ameliorated.

Notably, titers of anti-M3R antibodies were all reduced to 0 OD. At 20 months after the cessation of treatment, no recurrence of hypohidrosis or progression of skin sclerosis has been observed.

To our knowledge, hypohidrosis associated with PM has not been reported to date. The present case is a notable example where the hypohidrotic skin showed the typical "tank-top" distribution of the sclerotic skin in PM. While most reported cases of PM show severe sclerosis involving deep subcutaneous tissues,[1,2] the fibrosis in the present case was relatively mild, which may be due to the early detection. Another possibility is that the patient had a clinically mild subset of PM.[1]

Anti-M3R antibodies are associated with the sicca symptoms of SS and gastrointestinal dysfunction of systemic sclerosis.[3,4] They may affect the expression of M3R or directly interfere with the M3R signaling pathway in salivary glands.[3,4] To our knowledge, their association with hypohidrosis have not been reported, and further studies are necessary to assess their presence and roles in hypohidrosis, especially those associated with morphea.

In summary, the present case indicates that hypohidrosis may accompany PM. Since the anti-M3R autoantibodies disappeared in parallel with the amelioration of hypohidrosis in the present case, it is possible that they may serve as a new marker in such cases, although the further accumulation of cases is warranted to test this hypothesis.

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Figure Titles and Legends

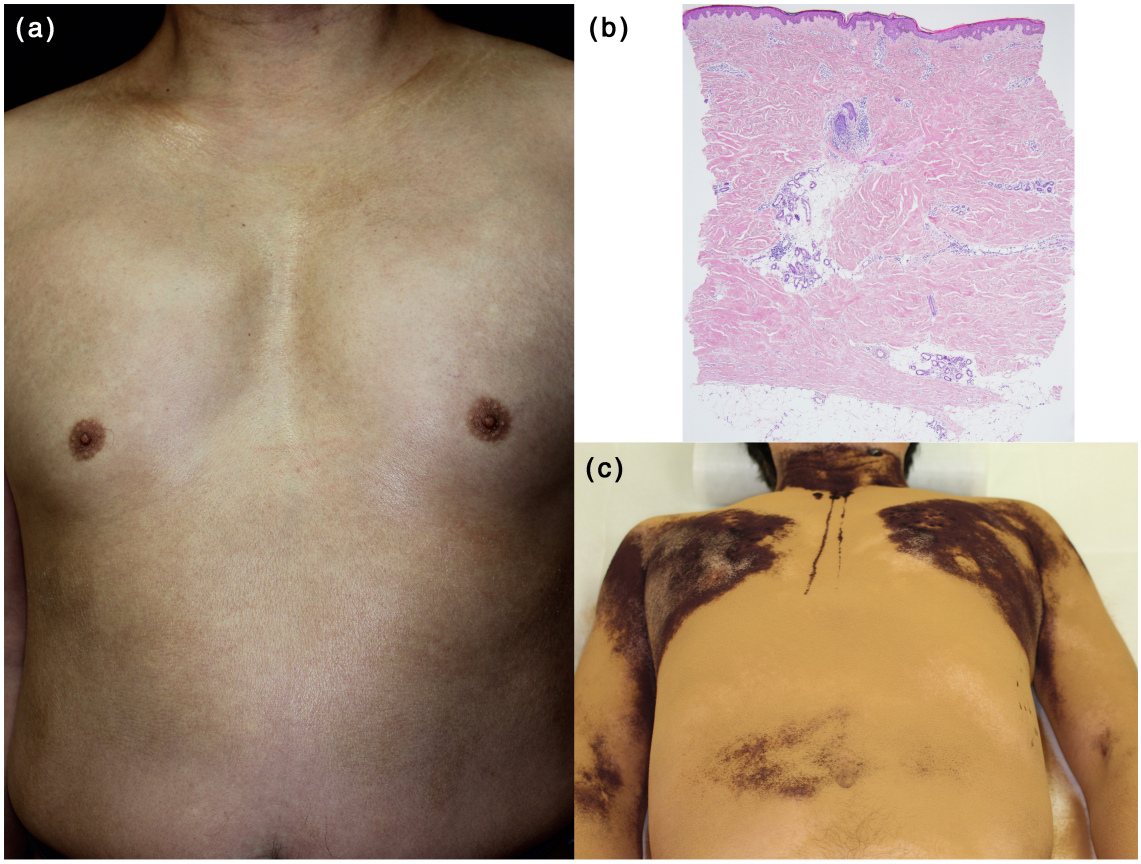

Figure 1. Hypohidrosis in a patient with pansclerotic morphea

(a) Sclerotic skin faintly shows “tank top sign”. Shiny, yellowish skin changes are seen in the bilateral clavicular lesions, the middle chest and the abdomen. (b) The distribution of the hypohidrotic area. Effort-induced perspiration is detected as purple staining of iodine-starch. (c) Histopathologic findings. Thickened homogenous collagen fibers are seen in the dermis. Infiltrating inflammatory cells are noted around the blood vessels and the appendages. (Original magnification ×40)