Anti-NXP2 antibody positive dermatomyositis presenting as unilateral heliotrope rash

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Key words: anti-MDA5 antibody; anti-NXP-2 antibody; dermatomyositis; heliotrope rash.

INTRODUCTION

Heliotrope rash is one of the early cutaneous manifestations of dermatomyositis (DM). Unilateral heliotrope eruption has been previously reported in positive anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody individuals who tend to develop painful skin ulcers, absent or minimal inflammatory myopathy and, often, a rapidly progressive interstitial lung disease (ILD). In this article, we present a case of unilateral heliotrope rash in an antinuclear matrix protein 2 (anti-NXP2) positive DM patient.

Abbreviations used:

DM:	dermatomyositis
ILD:	interstitial lung disease
MDA5:	melanoma differentiation-associated gene 5
NXP2:	nuclear matrix protein 2

CASE REPORT

A 58-year-old woman presented with a 1-month history of muscle weakness, difficulty swallowing, and right periorbital erythema. She denied any fever or shortness of breath. Physical examination revealed a well-demarcated, erythematous and edematous plaque on the right periorbital skin with slight scaling on the upper eyelid (Fig 1). She also had an erythematous scaly rash over the metacarpophalangeal and proximal interphalangeal joints bilaterally consistent with Gottron's papules. Three firm nodular subcutaneous calcifications, consistent with calcinosis cutis, were palpable on the left hip and lateral aspect of the right thigh. Her muscle strength was 2/5 in the proximal upper and lower muscle groups. Work-up revealed a normal complete blood count and renal and thyroid function tests. Erythrocyte sedimentation rate was mildly elevated at 42 mm/hour. C-reactive protein was normal at 0.5 mg/dl. Her muscle enzymes were elevated: creatine kinase 2821 U/L (normal < 180 U/L), aldolase 17 IU/L (normal < 7 IU/L), aspartate aminotransferase 453 IU/L (normal < 34 IU/L), and alanine aminotransferase 129 IU/L (normal < 49 IU/L). Antinuclear antibody was borderline positive 1:80 with a speckled pattern. Extractable nuclear antigen test was negative. Her myomarker panel was positive for anti-NXP2 antibody and negative for anti-MDA5 antibody.

Computed tomography of the orbits showed the presence of asymmetric contrast enhancement and soft tissue swelling involving the preseptal soft tissues of the right orbit. The globes, extra-ocular muscles, and retro-ocular fat appeared normal and symmetric. A four-mm punch biopsy from the right upper eyelid revealed the presence of vacuolar interface dermatitis with thickened basement membrane, epidermal atrophy, and parakeratosis (Fig 2).

Magnetic resonance imaging of the femurs revealed diffuse and increased T2-weighted signal/edema throughout all musculature of the thighs and portions of the pelvis suggestive of an inflammatory myopathy. Muscle biopsy noted the presence of perivascular and perimysial inflammation, as well as perifascicular atrophy and fibrosis.

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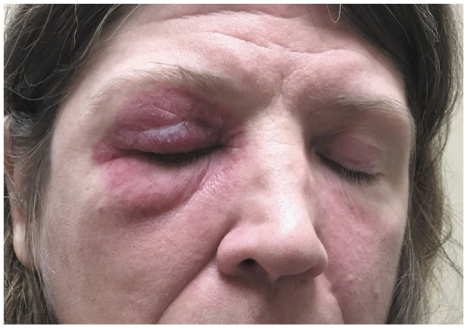

Fig 1. Unilateral heliotrope rash.

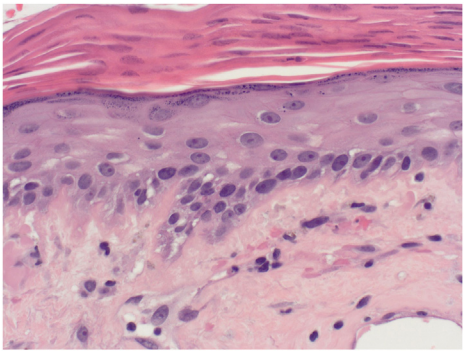

Fig 2. A skin biopsy of the erythematous lesion revealed vacuolar interface dermatitis with lymphocytes at the dermo-epidermal junction (hematoxylin and eosin stain, 400 × magnification).

Three-phase swallowing study showed normal caliber esophagus with delayed passage of contrast into the stomach suggestive of esophageal dysmotility.

Malignancy work-up was negative. High-resolution computed tomography of the chest was negative for ILD.

Our patient was diagnosed with DM with skin and muscle involvement. She was started on oral prednisone 40 mg daily; higher doses were avoided due to her history of poorly controlled diabetes mellitus. Two infusions of rituximab 1 gram IV each, 2 weeks apart, were administered. Given her dysphagia and risk of glucocorticoid toxicity, intravenous immunoglobulin 1 g/kg per day on 2 consecutive days every 4 weeks was added for 6 months. Prednisone was tapered off completely within 5 months. At her sixth month follow-up, the patient had normalization of her muscle strength and muscle enzymes as well as near resolution of her heliotrope rash (Fig 3). A plan was made to give her another course of rituximab and decrease her intravenous immunoglobulin dose to 1 g/kg per month for the following 6 months.

DISCUSSION

Heliotrope eruption is a violaceous rash of the eyelids that is usually bilateral and is associated with scaling and edema. It is one of the 3 pathognomonic cutaneous features of DM that also include Gottron's papules and Gottron's sign.[1]

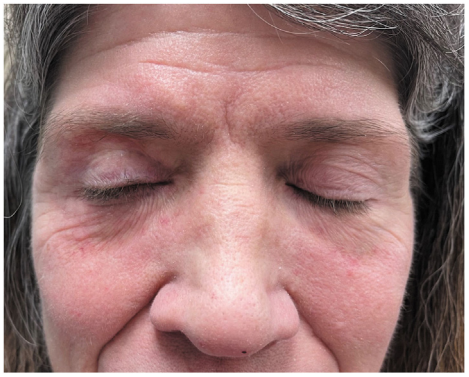

Fig 3. Near resolution of the heliotrope rash at 6-month follow-up.

Unilateral eyelid involvement is a rare variation of the classical heliotrope rash. To date, 8 cases have been reported in the literature (Table I). Its differential diagnosis includes eyelid dermatitis, cellulitis, sarcoidosis, and neoplastic conditions such as angiosarcoma.

Interestingly, all previously reported cases of unilateral heliotrope rash have positive anti-MDA5 antibody. Anti-MDA5 DM individuals usually present with a distinctive mucocutaneous and systemic phenotype. In addition to the typical DM rash (heliotrope rash, Gottron, and Shawl sign), these patients tend to develop painful cutaneous ulcers and have an elevated risk of developing ILD. This subset can be amyopathic and does not carry an increased risk of malignancy.[1]

To our knowledge, this is the first reported case of unilateral heliotrope rash with a positive anti-NXP2 antibody. Anti-NXP2 is a myositis-specific autoantibody that is associated with disabling myopathy, calcinosis cutis, dysphagia and an increased risk of malignancy. ILD is not an associated clinical feature of anti-NXP2 antibody-positive DM.[1] Similar to this subset of DM individuals, our patient presented with significant myopathy, calcinosis cutis, dysphagia, and did not develop ILD. However, our patient had no detected malignancy through her follow-up at 6 months.

In conclusion, early recognition of the unilateral heliotrope rash is important in order to avoid delay in diagnosing DM. This article highlights a new clinical profile of a DM patient with unilateral heliotrope eruption and positive anti-NXP2 antibody. Bilateral heliotrope rash is not associated with any myositis-specific antibody. Although, the unilateral variant has been previously linked exclusively to anti-

Table I. Dermatomyositis patients presenting with unilateral heliotrope rash

Case number	Author, year[Ref]	Age, sex	Unilateral heliotrope rash as a first symptom	Associated manifestations	Muscle symptoms	ILD	Autoantibodies	Therapy	Outcome
Case 1	Present	58 F	Yes	Trouble swallowing Gottron's papules Calcinosis cutis	2/5 weakness in upper and lower proximal muscles	No	ANA NXP-2	Prednisone 40 mg/d + rituximab + IVIG	Skin and muscles recovered at 6 mo
Case 2	Bhandari et al, 2022[2]	39 F	Yes	Gottron's papules (typical and inverse) Shawl sign Holster sign	Amyopathic	Yes	MDA5	Prednisone 60 mg/d + topical mometasone	Improved over 2 mo
Case 3	Kusano et al, 2021[3]	45 F	Yes	Shawl sign Gottron's papules (typical and inverse)	Amyopathic	Yes	ANA MDA5	Prednisolone + CYC	Stable heliotrope rash at 3-mo follow-up
Case 4	Kume et al, 2021[4]	74 F	Yes	Gottron's and palmar papules Periungual erythema V sign Flagellate erythema of the limbs Antihelix/helix macules	Amyopathic	Yes (RP-ILD)	MDA5	Methyl-prednisolone + CYC Followed by: prednisolone + CSA + MMF	Skin improved ILD worse Died after 3 mo
Case 5	Kume et al, 2021[4]	49 F	Yes (progressed to bilateral)	Palmar and Gottron's papules	Amyopathic	Yes	MDA5	Prednisolone + tacrolimus + CYC + IVIG	"Successfully treated"
Case 6	Kume et al, 2021[4]	66 M	Yes	Gottron's and palmar papules	Slight weakness proximal upper extremities	Yes (RP-ILD)	MDA5	Prednisolone + tacrolimus + CYC + IVIG + methyl-prednisolone	Died after 1 mo
Case 7	Chen et al, 2020[5]	48 F	Yes	Inflammatory arthritis Dorsal hand papules Mechanic's hands Fever Dactylitis	Proximal leg weakness	Yes (RP-ILD)	ANA SSA>8 SSB>8 MDA5	Prednisone + HCQ + MMF	Eyelid and ILD improved

Continued

Table I. Cont'd

Case number	Author, year[Ref]	Age, sex	Unilateral heliotrope rash as a first symptom	Associated manifestations	Muscle symptoms	ILD	Autoantibodies	Therapy	Outcome
Case 8	Lam et al, 2018[6]	40 F	Yes (progressed to bilateral)	Skin rash over the knees Oral ulcers Hand plaques and papules Skin ulcers on elbows	Bilateral upper limb weakness	No	SSA MDA5	Prednisolone 1 mg/kg/d CSA (stopped due to cytopenia) Tacrolimus+ Rituximab + IVIG	Periorbital swelling and skin ulcers improved markedly
Case 9	Al-Janobi et al, 2014[7]	14 M	Yes	Gottron's papules	Proximal > distal muscle weakness	N/S	N/S	Prednisone 50 mg/d + MTX	Resolution of the rash and normalization of muscle power at 6 mo

ANA, Antinuclear antibody; *CSA*, cyclosporine; *CYC*, cyclophosphamide; *F*, female; *HCQ*, hydroxychloroquine; *IVIG*, intravenous immunoglobulin; *M*, male; *MDA5*, melanoma differentiation-associated gene 5; *MMF*, mycophenolate mofetil; *MTX*, methotrexate; *N/S*, not specified; *NXP2*, nuclear matrix protein 2; *RP-ILD*, rapidly progressive interstitial lung disease; *SSA*, anti-Sjogren syndrome antibody A; *SSB*, anti-Sjogren syndrome antibody B.

MDA5-positive disease, our patient challenges this association. Further studies and reports of similar cases are necessary for further elucidation.

Conflicts of interest

None disclosed.

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