Response of Mucocutaneous Lesions to Rituximab in a Case of Melanoma Differentiation Antigen 5-Related Dermatomyositis

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Key Words

Dermatomyositis · Amyopathic dermatomyositis · Melanoma differentiation antigen 5 · Clinically amyopathic dermatomyositis 140 · Rituximab

Abstract

We report the first case in Western Europe of a person presenting with dermatomyositis associated with melanoma differentiation antigen 5 antibodies. She sequentially developed severe mucocutaneous erythematous and itchy lesions of the face, scalp, neck, knees and recurrent aphthae. In addition she presented painful, periungual, edematous digital lesions and small ulcers with digital necrosis. Her rapidly evolving, near-fatal interstitial lung disease responded to high-dose intravenous cyclophosphamide. However, her recurrent mucocutaneous manifestations improved only after rituximab administration.

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Introduction

Dermatomyositis (DM) is a primary inflammatory disease that typically affects skin and muscles frequently associated with interstitial lung disease (ILD). It en-

compasses a spectrum of clinical manifestations in which on the one hand myopathic manifestations (skeletal muscle weakness, and even swallowing and respiratory muscle involvement) may predominate with no or little skin involvement and on the other hand prototypic skin manifestations (heliotrope rash, periorbital edema, and Gottron's sign and papules) may be present with little or no muscular involvement. One extreme end of this spectrum is named clinically amyopathic DM (CADM) or dermatomyositis sine myositis [1]. Several antibodies, termed myositis-specific antibodies, have been associated with exquisitely specific myositic clinical patterns [2]. Such antibodies comprise the anti-aminoacyl-transfer RNA synthetase antibodies, the anti-Mi2, the anti-signal recognition particle (SRP), the anti-small ubiquitin-like modifier activating enzyme, the anti-155/140 (TIF1/), the anti-p140, and the recently identified autoantibody, named anti-CADM-140 also known as anti-melanoma differentiation antigen 5 (MDA5) [3, 4]. Here, we report a case of DM associated with anti-MDA5 antibodies to illustrate the peculiar clinical course of this condition, its response to treatment and in particular to B-cell-depleting therapy.

Case Report

A 68-year-old woman known for an inflammatory bowel disease currently in remission was hospitalized for erythematous and itchy lesions of the right jaw, scalp, face, neck, knees, and painful periungual erythematous and edematous digital lesions unresponsive to topical corticosteroids. The cutaneous lesions consisted in a diffuse, nonalopecic, scaly dermatosis with erythema on the scalp, widespread erythematous maculopapules of the face involving the upper eyelids, upper back, elbows and the right knee (fig. 1a) without poikiloderma. She presented with fever (38.5C), night sweats, loss of appetite, arthralgias, and generalized weakness. She reported severe aphthae, xerostomia, xerophthalmia, and mild Raynaud phenomenon. The muscular strength was normal in the lower limbs, and symmetrically diminished in the upper limbs without proximal predominance. Abnormal laboratory values included: increased C-reactive protein and erythrocyte sedimentation rate, anemia, lymphopenia, hyperferritinemia (805 g/l), hypoalbuminemia (27 g/l) and mild hepatic cytolysis. The creatine kinase and aldolase were within the normal limits. Serologies for cytomegalovirus, Epstein-Barr virus and parvovirus B19 (IgG) re-

vealed previous exposure. An interferon- γ -releasing assay, human immunodeficiency virus, hepatitis B and C virus and syphilis serology were negative. The sialometry and Schirmer test were pathological. A search for neoplasia performed twice, 2 years apart, was negative and included: an esogastroduodenoscopy, a colonoscopy, a thoracoabdominal CT scan, and a complete gynecological examination with screening for breast cancer. A blood smear performed once at the time of diagnosis was considered exempt of signs of hematological malignancy. An electroneuromyogram of the left deltoid muscle was compatible with myopathic lesions. A biopsy of this muscle showed a mild, perimysial, inflammatory infiltrate. A skin biopsy showed lichenoid interface dermatitis and the immunofluorescence displayed IgM large band granular deposits at the dermoepidermal junction. A capillaroscopy showed unspecific capillary changes. A diagnosis of DM was considered and high-dose prednisone (1 mg/kg) with a tapering scheme and monthly courses of high-dose intravenous immunoglobulin (IVIG, 3 mg/kg) were administered resulting in improved skin lesions, upper limb weakness and arthralgias, but persistence of sicca symptoms.

Four months later, while being on monthly IVIG courses and prednisone (40 mg/day), in parallel with the resurgence of mild cutaneous lesions, but no articular or muscular complaints, the patient developed fever with cough and an unusual dyspnea (NYHA III) not responding to antibiotics. A thoracic CT scan (fig. 2a) revealed an interstitial infiltrate, ground glass attenuation predominating in the middle and inferior fields associated with subpleural reticulations, and bronchiectases. A surgical lung biopsy was consistent with non-specific interstitial pneumonia. Pulsed, intravenous cyclophosphamide was initiated while IVIG were discontinued with progressive improvement of her respiratory symptoms. Cyclophosphamide was continued for a total of 9 pulses (total dose: 5.4 g), after which mycophenolate mofetil (MMF, 1–2 g/day) was introduced with low-dose prednisone (10 mg/day) maintenance. A follow-up thoracic CT scan showed the resolution of ground glass attenuation (fig. 2b), paralleled by substantial improvement of the lung function tests (total lung capacity, forced expiration volume at 1 s and single-breath diffusion of carbon monoxide: 67, 49 and 29% of predicted value 12 days after discharge and 78, 82 and

Fig. 1. Typical skin lesions of our MDA5-positive patient before rituximab administration. **a** Erythematous maculopapules on the jaws and eyelids, refractory to classical treatment. **b** Erythematous lesions of the metacarpophalangeal articulations, finger tips and the periungual region.

Fig. 2. ILD in our MDA5-related CADM patient. **a** Before cyclophosphamide administration. **b** After cyclophosphamide administration.

49% one year after discharge). With MMF and prednisone the patient experienced clinical stability during 1 year, but later (2 years after the initiation of DM symptoms), she developed palmar and periungual painful erythematous papules with finger pulp inflammation and discrete superficial necrosis (fig. 1b) accompanied by resurgence of numerous and painful aphthae. These lesions were treated in sequence with topical tacrolimus, IVIG (2 g/kg) and cyclosporine A (150 mg/day) in conjunction with MMF (1–2 g/day) with

no response. Hydroxychloroquine (400 mg/day 5 days/week and 200 mg/day 2 days/week) resulted in gastrointestinal pain and diarrhea and was discontinued. A second cycle of intravenous cyclophosphamide consisting in 5 pulses of 600 mg each, resulted in only mild and transient improvement. However, a course of rituximab (2 $\times$ 1,000 mg 15 days apart) allowed a substantial improvement of these mucocutaneous lesions.

Three months later, her second left finger developed an ischemic lesion, which

rapidly led to pulpar necrosis (fig. 3a). An angio-MRI of the left hand showed an occlusion of the digital artery of the second left finger (fig. 3b). Skin biopsies revealed interface dermatitis, with no obvious vasculitis but with vascular obstruction due to endomyofibrosis. These severe lesions were aggressively treated with iloprost, sildenafil, and an increase in the dose of nifedipine (80 mg/day). After 1 month, with the gradual healing of the finger lesions, iloprost and sildenafil were discontinued, and MMF was reintroduced. Afterwards, the patient has remained clinically stable until the writing of this report.

The immunological screening performed on several occasions revealed low-titer (1/160) anti-nuclear antibody positivity once, intermittently positive SSA antibodies and β_2 -glycoprotein I IgG at low to medium titers while the following antibodies were all negative: antineutrophil cytoplasm, antinucleosome, anti-U1RNP, anti-Sm, anti-SSB, antimitochondria, anti-LKM, anti-Jo1, anti-PL12, anti-PL7, anti-Mi2, anti-PM-Scl, anti-SRP, anti-Scl-70, anti-smooth-muscle, antitransglutaminase, and anticardiolipin.

As our patient's symptoms were predominantly cutaneous with a minimal muscular involvement associated with rapidly progressive interstitial pneumonia and pulpar necrosis, we retrospectively searched for anti-MDA5 antibodies and found them positive in 2 of 2 serum samples 2 years apart (at the time of ILD worsening and 2 years later when the skin disease worsened).

Discussion

We report a case of anti-MDA5 autoantibody-associated DM to illustrate the prototypical clinical evolution of this condition. In addition, for the first time, we document the response to the B-cell-depleting strategy adopted to control its characteristic mucocutaneous lesions.

Our patient presented DM lesions associated with transient muscle abnormalities with little clinical impact. These features are consistent with CADM, reported to account for 10–20% of DM cases [1]. Alternatively this clinical presentation could be defined as DM with predominant skin involvement. However, the mucocutaneous lesions in our patient had some particularities as she experienced dreadful, recurrent aphthae, associated with painful

Fig. 3. Digital necrosis in our MDA5 patient 3 years after the onset of CADM. **a** Pulpar necrosis of the distal phalanx of the second left finger. **b** Angio-MRI of the left hand showing obliteration of the second left finger's digital artery, from the distal interphalangeal articulation onwards.

nail fold lesions, skin ulcers especially on the fingers and ears, as well as digital necrosis, which are unusual in classical DM. Fiorentino et al. [5] and Chaisson et al. [6] have described such skin manifestations as characteristic of anti-MDA5-positive patients in conjunction with small and medium vessel vasculopathy, either pauc-inflammatory or with mononuclear infiltrates. Consistently with these reports, the skin biopsies in our patient revealed interface dermatitis with vascular obstruction due to endomyofibrosis (confirmed by α -actin immunodetection), thickening of the basal membrane, and numerous telangiectasias with no signs of thrombosis or vasculitis. Notably, in our patient, digital necrosis due to macrovascular acute abnormalities occurred 4 months after rituximab administration. This may suggest that B-cell depletion is not efficacious to attenuate the vascular changes observed in MDA5-positive CADM. The possible contribution of an acute thrombotic event superimposing to preexistent vasculopathy cannot be, however, dismissed, and the beneficial effects of rituximab on the mucocutaneous manifestations could have been associated with reduced microvascular disease.

ILD is classically associated with either polymyositis or DM with a prevalence of 5–65%, higher in the antisynthetase subset. Of interest, the rate of ILD is particularly high in CADM patients, with a more severe, corticoreistant, potentially fatal, rapidly progressive course [7]. The anti-MDA5 specificity appears to be associated with a prevalence of ILD variably reported

between 22 and 93% [3, 5, 8–11] and with a high mortality, with death rates around 70% [10, 12]. In this respect, luckily, our patient responded to a regimen of high-dose steroids and pulsed intravenous cyclophosphamide. It should be stressed that most (but not all) reports of rapidly progressive ILD in DM come from Asia, suggesting a genetic or environmental contribution to this aspect of the disease.

Our patient had Raynaud phenomenon and ILD, but no mechanic's hands or polyarthritides. Moreover, she was tested negative for anti-Jo1, anti-PL7 and anti-PL12, making it unlikely that her disease was consistent with antisynthetase syndrome. Furthermore, an extensive search for the presence of neoplasia performed twice was negative in our patient. This is consistent with the absence or low prevalence of neoplastic diseases in anti-MDA5-associated DM [9, 13]. Anti-SSA and Sjögren syndrome are known to be often associated with other connective tissue diseases. Our patient had positive anti-SSA antibodies and experienced sicca symptoms. Curiously, she had fluctuating anti-SSA titers, in parallel with the remissions and recurrences of her disease, which practically is never observed in primary Sjögren syndrome and rarely in systemic lupus erythematosus [14]. The coexistence of MDA5 and SSA antibodies was found in about 30% of the cases reported by Fiorentino et al. [5]. Finally, the absence in our patient of U1RNP antibody allowed to rule out mixed connective tissue disease.

MDA5 (also known as Helicard or IFIH-1) is a cytoplasmic RNA helicase, the

levels of which increase in response to type I interferon. It plays an important role in the recognition of double-stranded RNA viruses and mediates the induction of antiviral genes and type I interferon [15]. It has been shown that MDA5 is overexpressed in skin lesions of chronic discoid lupus erythematosus, DM and lichen planus [16]. These data implicate MDA5 in autoimmunity, even if the precise mechanism of its involvement remains unclear. Current hypotheses propose that increased interferon production may play a crucial role in vascular and skin lesions [17, 18]. Tissue damage would then either result in intracellular antigen release or increase MDA5 expression, resulting in loss of tolerance to MDA5 followed by the production of anti-MDA5 antibody [6, 16, 19]. Alternatively, anti-MDA5 autoantibody could be an epiphenomenon during viral infections associated with CADM [10].

Anti-MDA5 seems to be preferentially present in CADM, when searched in patients with connective tissue diseases (polymyositis, systemic lupus erythematosus, systemic sclerosis, CADM, classical DM, cancer-associated DM) or primary ILD [5, 10, 13, 20]. In particular, anti-MDA5 was reported in 32.5% of CADM compared to 9.4% in DM in one study from China [20]

and 65 versus 3% in another from Japan [13].

Different drug regimens have been attempted to treat CADM and the associated severe, rapidly progressive ILD. Corticosteroids such as prednisone or (methyl) prednisolone are generally used as first-line drugs, with more or less satisfying responses depending on the studies. Hydroxychloroquine has been tried against DM/CADM skin lesions with responses that seem to be less satisfying than in other autoimmune conditions [21, 22]. The use of thalidomide, high-dose immunoglobulins or immunosuppressive agents such as MMF, azathioprine, methotrexate, cyclophosphamide, cyclosporine A, oral tacrolimus, or biological agents such as etanercept or infliximab have also been reported with various success. Rituximab has been used in polymyositis, DM and the antisynthetase syndrome in the attempt to control muscle and lung disease, but also predominant skin involvement [23, 24]. To the best of our knowledge, our case is the first example of response to rituximab, in MDA5-related CADM. Cao et al. [20] reported that the severity of the clinical manifestations in MDA5-related DM is in relationship with the titer of anti-MDA5 antibody, implying a direct pathogenic role of this antibody.

Thus, it could be speculated that rituximab may exert its beneficial effects by decreasing the titer of anti-MDA5 antibodies. It cannot be excluded that wider effects through antigen-presenting and cytokine-producing properties of B cells could be at play.

MDA5-associated DM has been reported in Asia and in the USA [3–5, 8–11, 13, 19, 25–31]. This is the first report of such a condition in Europe. Further studies will be needed to better understand the role of anti-MDA5 antibodies and better exploit the diagnostic value of this autoantibody exquisitely associated with a clinical picture characterized by specific mucocutaneous lesions, severe ILD and necrotic lesions due to vasculopathy.

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