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CASE REPORT



Anti-MDA5 positive dermatomyositis complicated with rapidly progressive interstitial lung disease – a case report

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ABSTRACT

Case presentation: We present a case of a 55-year-old Caucasian male with manifestations of dermatomyositis complicated with rapidly progressive interstitial lung disease (RP-ILD). Diagnosis of anti-MDA5 positive dermatomyositis was made.

Discussion: Myositis specific antibodies (MSA) can be used for diagnosis and predicting prognosis in patients with polymyositis and dermatomyositis. Anti-MDA5 positive dermatomyositis should be considered in patients presenting with dermatomyositis and a disease course resembling antisynthetase syndrome in the absence of antisynthetase autoantibodies, especially if a remarkably high ferritin is noted. Anti-MDA5 autoantibodies have been associated with RP-ILD and adverse outcome. In patients with anti-MDA5 autoantibodies, early diagnosis and aggressive immunosuppressive treatment may improve prognosis.

Conclusion: This case highlights the importance of determining MSA in patients with dermatomyositis and associated interstitial lung disease, as this has implications for diagnosis, prognosis and therapy.

KEYWORDS

Dermatomyositis; interstitial lung disease; myositis specific antibodies; anti-MDA5

1. Introduction

Dermatomyositis is an inflammatory autoimmune disorder characterized by cutaneous manifestations and weakness of the proximal musculature with variable involvement of other organs [1]. The clinical presentation and disease course is variable and myositis specific antibodies (MSA) appear to be associated with distinct clinical phenotypes [2]. Anti-MDA5 autoantibodies are found in 7–13% of dermatomyositis and are associated with an amyopathic or hypomyopathic presentation and rapidly progressive interstitial lung disease (RP-ILD) with poor prognosis, but ethnical and environmental differences in presentation and prognosis have been proposed [2–4].

2. Clinical presentation

A 55-year-old Caucasian male with a history of psoriasis was referred with progressive respiratory failure. The patient had a four-month history of systemic symptoms starting with progressive fatigue, arthralgia, and diffuse muscle weakness followed by bilateral arthritis of the metacarpal joints and arthralgia of the wrists, Gottron's

papules, mechanic's hands and an ulceration on the left ear. Approximately, one month after initiation of symptoms, the patient developed a non-productive cough and progressive dyspnea on exertion. These symptoms were accompanied by fever (39 °C) and night sweats. The past four months he lost 12 kg of weight.

Initial pulmonary function testing showed a restrictive pattern with a reduced diffusion capacity. Arterial blood gas showed hypoxemia (PaO₂ 64 mm Hg; PaCO₂ 34 mm Hg; pH 7.51; satO₂ 94%; A-a gradient 43.2 mm Hg). On lung high-resolution computed tomography (HRCT), diffuse subpleural and peribronchial inhomogeneous pulmonary infiltrates were present, together with atelectasis and honeycombing in both lower lobes (Figure 1). A bronchoscopy with broncho-alveolar lavage was performed. Cultures were negative. There was no evidence for malignancy on cytological evaluation. An increased CD4/CD8 ratio was noted. Laboratory findings showed a high sedimentation rate (35 mm/h), normal white blood cell count (3.5 10³/μl), slightly elevated C-reactive protein (CRP) (19 mg/l), high ferritin (1669 μg/l), normal creatine kinase (CK) (14 U/l) and negative autoimmune serology (rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), antineutrophil cytoplasmic antibodies

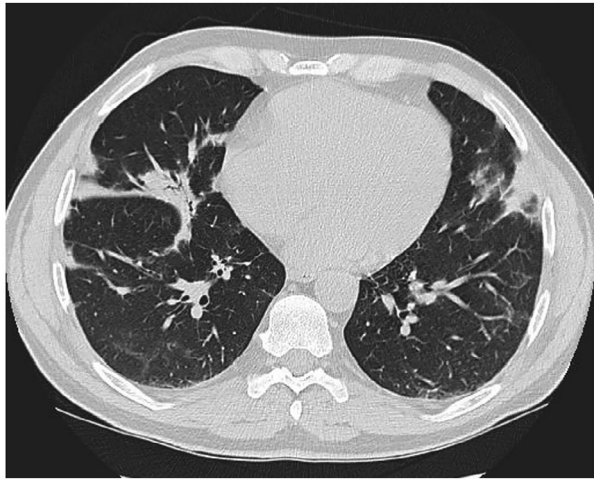


Figure 1. First HRCT showing diffuse subpleural and peribronchial infiltrates and parenchymal consolidations.

(ANCA), antinuclear antibodies (ANA)). Treatment with methylprednisolone 32 mg resulted in resolution of clinical symptoms and was then progressively reduced over a three-week period, after which relapse occurred. Methylprednisolone 2 × 40 mg was restarted, with dose reduction to methylprednisolone 32 mg after one week. A maintenance dose of methylprednisolone 32 mg was given in combination with sulfamethoxazol/trimethoprim (*Pneumocystis jirovecii* prophylaxis). A positron emission tomography/computed tomography (PET-CT) scan showed heterogenous 18F-fluorodeoxyglucose (FDG)-avid groundglass infiltrates in both lungs, reactive mediastinal lymph nodes, and a mild polyarthritis of the knees and hips. There were no findings suggestive of malignancy. Progression of parenchymal disease was confirmed on HRCT (Figure 2).

The patient was transferred to our department because of persistent respiratory failure. At that time, the systemic symptoms (arthritis, fever) had resolved under maintenance treatment with methylprednisolone 32 mg. An acute respiratory deterioration occurred with desaturation: transcutaneous saturation fell to 80% (under 5 l/



Figure 2. Second HRCT (47 days after the first HRCT) showing progression of peribronchial and parenchymal disease.

min oxygen). The patient was admitted to the intensive care unit and treatment with amoxicillin/clavulanic acid 4 × 1 g and clarithromycin 2 × 500 mg was started empirically to cover potential infection. Methylprednisolone 32 mg was continued. Thoracoscopic lung biopsy was performed. Histopathological evaluation showed marked thickening of the interalveolar septa with multiple foci of fibroblastic proliferation and extensive lymphocytic interstitial infiltration. Prominent hyperplastic type II pneumocytes were focally present. These findings were compatible with diffuse alveolar damage in the organizing (proliferative) stage (Figure 3). Screening for respiratory viruses was positive for human Metapneumovirus. Culture of broncho-alveolar lavage showed no bacteria. Extended testing for autoimmunity, with in particular testing for MSA, was performed: auto-antibodies for antisynthetase were negative, MDA5-auto-antibodies were markedly positive. Initially, the respiratory status progressively improved. The patient had normal oxygen saturation values under 1–2 l/min oxygen, but dyspnea and desaturation on exertion were still present. A treatment plan with high pulse dose corticoid (1 g for 3 days) and cyclophosphamide (10 mg/kg) was made. However, a sudden acute respiratory failure with desaturation (to 30%) and need for intubation occurred before this therapy could be administered. A new HRCT-scan showed the presence of diffuse confluent consolidations in both lungs (Figure 4). Both the possibility of progression of the ILD or an infectious cause for the acute deterioration were considered. However, as the patient had no purulent sputa, no fever, no signs of inflammation on initial laboratory evaluation and as microbiological cultures were negative, progression of the ILD was thought to be most likely. A first dose of cyclophosphamide (10 mg/kg) and methylprednisolone (1 g for 3 days) was administered, followed by a maintenance dose of methylprednisolone 80 mg. In addition, piperacillin/tazobactam was started for empirical anti-infectious coverage. On day 6 following intubation, the patient developed fever and a rising CRP (day 6: 15 mg/l; day 7: 80 mg/l) with the appearance of a new consolidation in the right lower lobe on chest radiography. Culture of aspirate showed *Escherichia coli*. Diagnosis of ventilator-associated pneumonia was made. Treatment was started with meropenem and downgraded to cefuroxime guided by antibiogram results. Repeat HRCT performed on day 11 after treatment with cyclophosphamide and high dose corticosteroid showed a reduction of the consolidations in both lungs with residual consolidations in both lower lobes. Treatment with cyclophosphamide (10 mg/kg) was repeated. Unfortunately, after stopping cefuroxime (day 14), the fever relapsed with rising CRP (141 mg/l). Meropenem was restarted, but the patient developed progressive respiratory failure with increasingly difficult mechanical ventilation and died of intractable hypoxemia and respiratory acidosis.

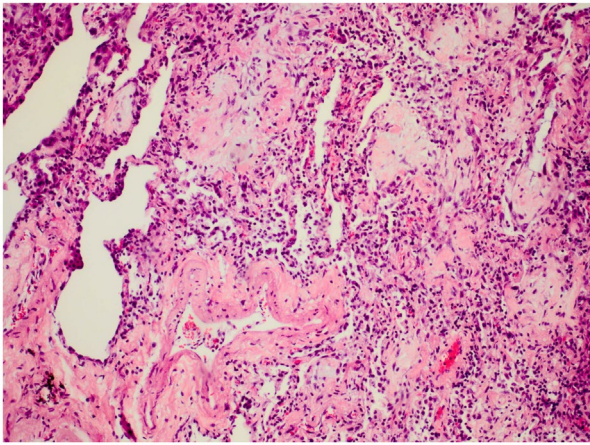


Figure 3. Thoracoscopic lung biopsy: area showing impressive thickening of interalveolar septa by a cellular fibroblastic proliferation. A mild to moderately dense lymphocytic infiltrate is also present. Hematoxylin and eosin stain, original magnification: $\times 100$.



Figure 4. Third HRCT (19 days after the second HRCT) showing diffuse confluent consolidations in both lungs.

3. Discussion

3.1. Dermatomyositis

Dermatomyositis is an autoimmune inflammatory disorder characterized by pathognomonic cutaneous manifestations such as Gottron's papules and heliotrope eruption which can be accompanied by muscle weakness [1,3,5]. Interstitial lung disease may be an important complication, and is rapidly progressive in some cases. Also, a wide variety of extrapulmonary manifestations are possible including fever, Raynaud's phenomenon, arthralgia and nonspecific cutaneous modifications. The clinical spectrum is heterogeneous and may depend on the presence of a specific type of MSA [1]. Several MSA have been described and appear to be associated with distinct clinical phenotypes. Detection of these MSA may thus be useful in establishing the diagnosis and estimating prognosis [1].

3.2. Anti-MDA5 antibodies

Anti-MDA5 autoantibodies (initially named anti-CADM-140) were at first described by Sato et al. in eight patients with clinically amyopathic dermatomyositis [6]. The target of this antibody was found to be a RNA helicase encoded by the melanoma differentiation-associated gene 5 [3,7]. Anti-MDA5 autoantibodies have been described in several east-Asian cohorts and appear to be associated with RP-ILD, more severe cutaneous vasculopathy and clinically amyopathic dermatomyositis [8,9]. Nevertheless, the presentation of anti-MDA5 positive dermatomyositis can be diverse, varying from a more benign to a very aggressive disease course with RP-ILD. In the Caucasian population, the clinical presentation of anti-MDA5-associated ILD is less well established [3,10]. Although two North American cohorts suggested a less aggressive course of ILD, RP-ILD has also been described in Caucasian cohorts and case reports [2,11]. In addition, anti-MDA5 autoantibodies have shown to be associated with clinically amyopathic dermatomyositis. However anti-MDA5 autoantibodies are also frequently found in myopathic patients, especially in the Caucasian population as shown by Hall et al. [2]. Our case patient had subjective proximal weakness at presentation, but muscle enzymes were normal on initial laboratory evaluation.

To date, there is still controversy on the differences between populations in frequency and presentation of anti-MDA5 positive dermatomyositis. It is possible that genetic differences in susceptibility contribute to these differences in frequency and presentation. However, publication bias can be another explanation as literature on anti-MDA5 positive dermatomyositis in the Caucasian population is less extensive [2,3,12–14].

3.3. Rapidly progressive interstitial lung disease (RP-ILD)

Anti-MDA5 autoantibodies are associated with ILD, which especially in Asian cohorts is rapidly progressive and has a high mortality rate despite aggressive immunosuppressive therapy [1,7,15,16]. However, a North American cohort showed a more benign course of ILD. In this cohort, ILD was present in 8 of 11 patients with anti-MDA5 autoantibodies, but only 2 patients were progressive on immunosuppressive therapy [2]. On the contrary, a Mediterranean cohort showed a more aggressive disease course with RP-ILD occurring in 8 out of 14 patients, with a 1-year mortality rate of 62,5% (5/8) [12].

A restrictive lung function pattern is expected in ILD. The main role of BAL is to rule out infection [3]. HRCT patterns of dermatomyositis-related ILD may include linear opacities, ground-glass attenuations, reticulation, peribronchovascular thickening, and consolidations. Honeycombing, traction bronchiectasis, and subpleural

bands have also been described [3]. The pattern found on HRCT may suggest a histopathologic pattern, such as organizing pneumonia, nonspecific interstitial pneumonia (NSIP), mixed NSIP-organizing pneumonia and less frequent a usual interstitial pneumonia (UIP) pattern. However, the correlation with histopathologic findings is rather limited. Histopathologic changes in dermatomyositis-related ILD include NSIP, UIP, organizing pneumonia and diffuse alveolar damage [3]. A surgical lung biopsy is not strictly indicated in dermatomyositis-associated ILD, but can be performed in aspecific cases with diagnostic uncertainty [3,17]. If a clear diagnosis can be made on clinical evaluation, MSA and imaging, a surgical lung biopsy might not alter therapeutic decisions based on this less invasive evaluation [3,17–19]. However, in our case, a lung biopsy was performed to rule out potential treatable causes of RP-ILD before diagnosis of anti-MDA5 dermatomyositis was made. A histological pattern compatible with diffuse alveolar damage in the organizing phase was noted, consistent with the rapidly progressive disease course. Previous histopathology reports of RP-ILD in anti-MDA5 positive patients also show diffuse alveolar damage in most cases, but other patterns such as NSIP have been described [17,18].

3.4. Cutaneous manifestations

Anti-MDA5 autoantibodies have been associated with a more severe cutaneous vasculopathy with skin ulcerations and tender palmar papules, next to the hallmark skin changes of dermatomyositis (e.g. Gottron's papules, heliotrope eruption photosensitivity, shawl or 'V' sign, mechanic's hands...) [11]. These skin ulcerations are mainly described on the Gottron's papules and digital pulps, but can occur in other sites such as the ears [3,11]. Our case patient presented with Gottron's papules, roughening of the skin with rhagades on the tips and sides of the fingers (mechanic's hands) and an ulcer on the left ear.

3.5. Extrapulmonary manifestations

Other extrapulmonary and extracutaneous manifestations are frequent in anti-MDA5 positive patients. Arthritis, Raynaud's phenomenon, and fever are frequently noted [3]. In the cohort of Hall et al., patients frequently presented with inflammatory arthritis similar to rheumatoid arthritis. Eight of 11 patients with anti-MDA5 autoantibodies presented with the clinical manifestations of the antisynthetase syndrome (e.g. ILD, myositis, polyarthritis, fever, weight loss, Raynaud's phenomenon and/or mechanic hands) in the absence of antisynthetase antibodies, suggesting that anti-MDA5 autoantibodies should be tested in patients with dermatomyositis and a clinical course resembling antisynthetase syndrome without typical antisynthetase

antibodies [2]. Interestingly, screening of ANA may be negative in patients with anti-MDA5 autoantibodies, as can also be the case in antisynthetase syndrome [3].

3.6. Prognostic factors

Serum ferritin is significantly higher in anti-MDA5 positive dermatomyositis compared with other MSA [15]. Therefore, if high ferritin is found in patients with dermatomyositis, anti-MDA5 positive dermatomyositis should be considered. High ferritin has been proposed as a negative prognostic factor in anti-MDA5 positive dermatomyositis [1,15,16,20]. Other negative prognostic factors proposed in literature are an alveolar–arterial oxygen gradient of ≥ 32 mmHg and high anti-MDA5 titers [15,21]. Interestingly, anti-MDA5 auto-antibody titers may decrease during treatment and may even disappear during remission. In our case, these three prognostic unfavorable factors were present [15,21].

3.7. Treatment

To date, evidence on the treatment of ILD in dermatomyositis is scarce. In general, corticosteroids remain the mainstay of treatment. In chronic ILD this might be sufficient [3]. However, the response rate in RP-ILD is much lower and additional immunosuppressive therapy added to high pulse dose corticoids is required [3,7]. In most case reports and cohorts, a combination of corticoids with cyclophosphamide and/or cyclosporin is used, although treatment with azathioprine, IV immunoglobulins and rituximab has also been described [2,3,22]. Early aggressive treatment should be started in case of RP-ILD, as it may improve prognosis. Our case patient was initially treated with methylprednisolone 32 mg until definite diagnosis of anti-MDA5 positive dermatomyositis was made. A rapid deterioration occurred and treatment with high pulse dose corticoid and cyclophosphamide was started. Unfortunately, the patient developed progressive respiratory failure and deceased.

4. Conclusion

We present a case of a patient with anti-MDA5 positive dermatomyositis complicated with RP-ILD. Testing for anti-MDA5 antibodies among other MSA should be considered in patients with dermatomyositis who develop ILD, as ILD in anti-MDA5 positive patients may be rapidly progressive and early treatment is warranted.

Informed consent

Written informed consent was obtained from the patient's legal representative before publication of this case report and accompanying images.

Disclosure statement

No potential conflict of interest was reported by the authors.

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