Concise report

Management of MDA-5 antibody-positive dermatomyositis with interstitial lung disease—an Auckland case series

Michael Dick 1, Julia Martin2 and Nicola Tugnet2

Abstract

Objective The aim was to present our experience of managing six cases of anti-melanoma differentiation-associated gene 5 (anti-MDA-5) DM with associated interstitial lung disease (ILD), presenting between June 2017 and October 2020.

Methods The electronic notes were reviewed for six patients being followed up by the Rheumatology service at Auckland District Health Board. Three patients were initially diagnosed and treated in neighbouring Counties Manukau District Health Board and later transferred to Auckland District Health Board. All had different initial treating clinicians at a time before any predefined treatment algorithm. Emphasis was placed on initial diagnosis and treatment, subsequent disease activity and changes in management. Local management was compared retrospectively with existing evidence relating to the treatment of anti-MDA-5 DM with ILD. Ethical approval was not obtained, according to the New Zealand Health and Disability Ethics Committee exemption for audits and related activities.

Results Six patients with a variety of clinical presentations were identified appropriately as having anti-MDA-5 DM with ILD. They were commenced on different immunosuppressive regimens, with treatment adjusted according to response and on-going disease activity. Four have achieved clinical and biochemical remission, a fifth has improving active disease, and the sixth is in the early stages of their illness.

Conclusion Anti-MDA-5 DM is commonly associated with ILD. This can be rapidly progressive, with a poor prognosis in spite of treatment, particularly among Asian patients. Disease activity can seemingly be monitored with serum ferritin. The most effective management of this condition remains poorly researched; however, increasing retrospective evidence favours early aggressive multi-agent immunosuppression and a low threshold for escalation of therapy.

Key messages:
- Anti-MDA-5 DM is associated with interstitial lung disease, which can be rapidly progressive with poor prognosis.
- Early, aggressive, combined immunosuppression seems to be the most effective treatment.
- Ferritin may be a useful biomarker of disease activity.

Introduction

DM is an idiopathic inflammatory myopathy characterized by proximal weakness, associated with muscle inflammation and numerous skin manifestations. It is a multisystem disease, manifesting with interstitial lung...
disease (ILD), dysphagia, polyarthritis, malignancy and other features that may overlap with several systemic rheumatic diseases. Consistent laboratory findings include elevated muscle enzymes (creatine kinase, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase) and positive autoantibodies (ANA and myositis-specific antibodies). One autoantibody is the anti-melanoma differentiation-associated gene 5 (anti-MDA-5), which was first reported in Japanese patients in 2005 [1]. Histopathological, electrondemiographic and MRI findings also aid diagnosis.

The MDA-5 gene encodes the clinically amyopathic DM-140 protein. Generally, anti-MDA-5 DM patients have a lower incidence of myositis, although anti-MDA-5 can be detected in clinically amyopathic, hypomyopathic or classic DM [2]. It is highly specific for DM, strongly associated with rapidly progressive ILD (rp-ILD), confers poor prognosis, and is associated with the lowest survival rates for all DM patients, even when compared with those with malignancy-associated DM [1, 2]. Many recommend serum ferritin as a marker of disease activity to assess treatment response and guide treatment intensification [3].

Classical DM is treated with oral glucocorticoids, preceded by pulse i.v. methylprednisolone in severe cases, with a prolonged taper over 9–12 months according to response [4, 5]. Owing to the poor overall prognosis of anti-MDA-5 DM, additional immunosuppressive agents are commonly commenced from the time of diagnosis, even when ILD is initially mild. A recent prospective study showed efficacy of early aggressive combined immunosuppressive therapy with improved prognosis compared with step-up therapy of initial high-dose glucocorticoid and gradual intensification [6]. This involved a tapering course of oral glucocorticoid, i.v. CYC and tacrolimus, with plasmapheresis added if patients deteriorated. This study also reported improvements in anti-MDA-5 titre, serum ferritin and respiratory function after treatment [6]. Pre-treatment CRP, ferritin and the presence of skin ulcers were poor prognostic factors [6].

More recently, recommendations, largely based on poor-quality evidence and expert opinion, have been published for the treatment of rp-ILD in anti-MDA-5 DM [7]. This evidence was not available when our paper was first written in 2019. An overall recommendation is given for initial multi-agent immunosuppression combining high-dose glucocorticoids and calcineurin antagonists, with or without CYC, with scope for individualized changes to the regimen based on contraindications or treatment failure [7].

Here, we present six cases demonstrating the spectrum of clinical features associated with anti-MDA-5 DM, emphasizing the immunosuppressive agents used and the response to therapy. We highlight the association with ILD, including four cases with definite or possible rp-ILD, requiring a regimen of potent, multi-agent immunosuppression to achieve remission.

Cases

Demographic details, relevant initial investigations and a summary of the treatment agents used and current disease status is provided in Table 1. Anti-MDA-5 testing was positive in all cases. Assessment of anti-MDA-5 status was performed as part of a myositis antibody panel by an external laboratory using a multi-parameter line blot test (EUROLINE by EUROIMMUN, Lübeck, Germany). Although the manufacturer reports the ability to quantify positive signal intensity and correlate this with antibody titre, our laboratory reported only a positive or negative result, with no information on the anti-MDA-5 titre [8]. Remission was defined by improvements in clinical and functional outcomes, including ferritin level, appearance of skin lesions, diffusing capacity of the lungs for carbon monoxide (DLCO), high-resolution CT (HRCT) appearance and patient-reported modified HAQ-2 scores.

Patient A

Patient A presented with 6 weeks of itchy rash, 3 weeks of progressive exertional breathlessness and mild weakness when raising her arms. Spirometry showed restriction with reduced DLCO (50%), and HRCT showed evidence of ILD. MRI demonstrated muscle oedema. Skin and muscle biopsies were consistent with DM, confirming the diagnosis of anti-MDA-5 DM with predominant ILD, skin involvement and mild myositis.

Two days of i.v. methylprednisolone was given, followed by 80 mg prednisone. A 15 mg/kg fortnightly i.v. CYC (total 6 g) and 100 mg twice a day CSA were started, with initial clinical improvement. CSA was stopped and prednisone reduced to 40 mg within 1 month owing to worsening liver function tests, although investigations concluded that this was likely to be related to non-alcoholic fatty liver disease. Subsequently, the existing rash worsened, a new hollitrope rash developed, hyperferritinaemia persisted, and breathlessness rapidly worsened. Prednisone was increased to 80 mg. CSA re-started and MMF added (maximum dose 3 g). HRCT revealed progressive organizing pneumonia, dictating further escalation of immunosuppression. Tacrolimus replaced CSA (dose titrated to 3 milligrams (mg) twice a day, to maintain trough concentrations between 10 and 15 ng/ml). A few weeks later, characteristic new painful digital ulcerations appeared, and ferritin worsened (1030 µg/l). Given the progressive disease activity and marked disability despite CYC, tacrolimus, MMF and glucocorticoids, rituximab infusions were commenced.

Since rituximab was added, the patient’s 6 min walk test and DLCO (75%) have improved. No new digital ulcerations or rash lesions have developed, and the hollitrope rash has resolved. Ferritin has normalized (106 µg/l). She remains prednisone dependent and has developed CS-induced diabetes, but anti-MDA-5 DM is in remission.
| Parameter                  | Patient A          | Patient B          | Patient C          | Patient D          | Patient E          | Patient F          |
|----------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| Age, years                 | 36                 | 27                 | 72                 | 39                 | 47                 | 48                 |
| Sex                        | Female             | Female             | Female             | Female             | Male               | Male               |
| Ethnicity                  | Tongan             | Tongan             | Tongan             | New Zealand–European | Māori             | Filipino           |
| Phenotype                  | Breathlessness, rash, myopathy | Breathlessness, rash, myopathy | Breathlessness, rash, amyopathic | Breathlessness, rash, amyopathic | Breathlessness, rash, myopathy | Breathlessness, rash, amyopathic |
| CK, U/l (normal range 60–220 U/l) | 1010              | 910                | 75                 | 192                | 375                | 52                 |
| Peak CK, U/l (normal range 60–220 U/l) | 1010              | 910                | 75                 | 192                | 1002               | 52                 |
| Ferritin, μg/l (normal range 20–450 μg/l) | 1474              | 942                | 161                | 784                | 1553               | 607                |
| Peak ferritin, μg/l (normal range 20–450 μg/l) | 3198              | 2404               | 798                | 2283               | 4545               | 860                |
| ALT, U/l (normal range 0–45 U/l) | 100               | 47                 | 50                 | 40                 | 45                 | 55                 |
| AST, U/l (normal range 0–45 U/l) | NP                | 71                 | 33                 | NP                 | 64                 | 28                 |
| CRP, mg/l (normal range 0–5 mg/l) | 8                 | 19                 | 7                  | 33                 | 4                  | 7                  |
| ANA                        | 1:640              | Negative           | Negative           | Negative           | Negative           | Negative           |
| Anti-MDA-5                 | Positive           | Negative           | Positive           | Positive           | Positive           | Positive           |
| HRCT findings              | Scattered areas of peripheral ground-glass change | Positive Peribronchovascular and subpleural patchy ground-glass opacities and nodularities | Positive Inflammatory changes in both upper lobes, with ground-glass peripheral infiltrates and mild centrilobular emphysema bilaterally | Positive Small upper lobe foci of ground-glass change | Positive Bilateral patchy, peripheral and peribronchial areas of consolidation | Positive Subtle bibasal traction bronchiectasis, right > left; peripheral irregular densities in middle lobe and lingula |
| ILD                        | Rapidly progressive | Not rapidly progressive | Possible rapidly progressive | Possible rapidly progressive | Rapidly progressive | Not rapidly progressive |
| Initial treatment agents   | i.v. methylprednisolone; CSA; CYC | Prednisone; CSA | Prednisone; MMF | Prednisone; MMF | Prednisone | Prednisone |
| Other agents used          | Rituximab          | IVIG; CYC          | i.v. methylprednisolone; CYC | i.v. methylprednisolone; MMF; CYC | i.v. methylprednisolone | i.v. methylprednisolone |
| Current treatment agents   | Prednisone; tacrolimus; MMF | Nil              | MTX; CSA          | Prednisone; CSA    | Prednisone; CSA    | Prednisone; CSA; CYC |
| Disease status             | Remission          | Remission          | Remission          | Remission          | Remission          | Active; early disease |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; HRCT: high-resolution CT; ILD: interstitial lung disease; NP: not performed.
Patient B

Patient B presented with 2 months of exertional breathlessness and 4 weeks of progressive proximal muscle weakness, myalgias, arthralgias and rash. Spirometry showed restriction (DLCO not measured); HRCT demonstrated evidence of ILD, and muscle biopsy was consistent with DM. Diagnosis of anti-MDA-5 DM with ILD, skin involvement and myositis was made. Concern regarding cardiac function prompted cardiac MRI, suggestive of myocarditis/cardiomyopathy related to DM.

Progressive skin involvement and carpal tunnel syndrome related to left wrist swelling occurred despite commencing CSA 4 mg/kg and prednisone 80 mg. Ferritin did not improve. IVIG 1 g/kg over 2 days was added, with monthly doses given for 6 months. CS-induced psychosis prompted prednisone dose reduction and taper. Muscle strength improved, while respiratory and cardiac function stabilized. Ferritin decreased at 6 months (270 l g/l). She remained well at 12 months, returning to work part time. All medications were stopped at 14 months (ferritin 15 l g/l), mainly owing to the large size of CSA tablets and mild derangement of liver function tests (probably related to either CSA or steatosis). She became pregnant and remained well off all medications for 2 months. Subsequent worsening of cough and breathlessness was deemed inconsistent with recurrent ILD, based on normal spirometry and chest X-ray. Recurrent abdominal rash and pustular lesions on her fingers and soles were thought to be related to recurrent disease, although ferritin remained normal (50 l g/l). She was commenced on AZA (maximum dose 150 mg once a day), with improvement in the rash and cough. Respiratory opinion suggested that late-onset asthma might be contributing, with flutotide markedly improving her breathlessness.

Patient B successfully carried her pregnancy to term and remained stable on AZA, with ferritin improved (108 l g/l), before ceasing this of her own volition. Recent HRCT shows no on-going evidence of ILD; she is anti-MDA-5 antibody negative and remains asymptomatic off all treatment.

Patient C

Patient C presented with 3 months of breathlessness and typical rash, with severe digital ulceration and features of DM on skin biopsy (Fig. 1a). There was no muscle weakness. Spirometry showed no restriction but reduced DLCO (52%). HRCT revealed changes reflecting possible ILD or aspiration pneumonitis, with emphysema from previous smoking. Diagnosis of anti-MDA-5 DM sine myositis, with predominant skin involvement and evidence of ILD, was made.

HCQ 400 mg once a day, MTX 10 mg weekly and prednisone 20 mg were started without improvement. Digital ulcerations caused major disability: loss of functional grip, with inability to dress, wash or drive, necessitating hospital admission. Prednisone was increased to 60 mg and MTX to 20 mg weekly, and CSA 100 mg twice a day was added. Digital ulcerations proved refractory to treatment; therefore, HCQ was stopped, and two doses of IVIG (1 g/kg) were given. Investigation of progressive breathlessness within 2 months showed stable spirometry (DLCO 48%), but progressive ILD on HRCT. Intravenous CYC was added (15 mg/kg for six cycles), leading to complete resolution of digital ulcerations (Fig. 1b). Worsening flexor tenosynovitis improved with increased MTX (25 mg weekly).

Patient C weaned off prednisone and remains on MTX 25 mg weekly and CSA 100 mg once a day. The digital ulcerations have resolved, and ferritin has normalized (82 l g/l). Breathing has improved (DLCO 63%) such that she is independent with daily activities and exercising regularly. Recent HRCT showed non-progressive fibrosis.

Patient D

Patient D presented with 2 months of a photo-distributive, erythematous rash, with associated arthralgias and alopecia. Co-morbidities included brittle asthma, morbid
obesity, hypertension and valvular heart disease from previous rheumatic fever. She had no muscle weakness. Skin biopsy was consistent with DM or SLE. HCQ 400 mg once a day and 10 mg prednisone were initiated for possible ANA-negative SLE while awaiting myositis panel results. Progressive breathlessness and rash with Gottron’s papules developed within 2 months following patient-initiated cessation of prednisone. HRCT was suspicious for early ILD or reflux. Coronavirus disease 2019 pandemic restrictions prevented spirometric assessment. Echocardiogram revealed indirect signs of possible pulmonary hypertension. Diagnosis of anti-MDA-5 DM sine myositis with predominant skin involvement was inferred. Breathlessness was probably multifactorial.

Prednisone 40 mg and MMF 1 g twice a day were commenced, with more aggressive immunosuppression withheld, given the lack of significant ILD. Repeat HRCT 2 weeks later confirmed mild DM-related ILD. Ferritin was increasing (peak 2283 µg/l). Spirometry revealed normal lung volumes with reduced DLCO (56%). Right-heart catheter detailed normal pulmonary arterial pressures. She was admitted for 3 days of pulse i.v. methylprednisolone followed by 100 mg prednisone. One gram of i.v. CYC fortnightly (6 g total) and CSA 150 mg twice a day were commenced; MMF was stopped.

Patient D responded well to treatment and remains on prednisone 5 mg (weaning) and CSA 200 mg twice a day. Ferritin has normalized (195 µg/l). The rash improved markedly, with resolution of active erythematous areas, but with evidence of scarring present. Breathlessness still limits activity but has improved subjectively and objectively, with near resolution of HRCT findings and DLCO 72%.

Patient E

Patient E presented with 4 weeks of progressive exertional breathlessness, fatigue, weakness, myalgia and rash. Examination revealed Gottron’s papules, heliotrope rash, digital ulceration, proximal muscle weakness and bibasal crepitation. HRCT was in keeping with organizing pneumonia. Skin biopsy was consistent with DM. Coronavirus disease 2019 pandemic restrictions prevented spirometric assessment. Diagnosis of DM with ILD, skin involvement and myositis was made.

He initially improved with 60 mg prednisone, pending myositis panel results. Subsequent rapid clinical and radiological progression necessitated treatment escalation with i.v. methylprednisolone, CSA 400 mg once a day and i.v. CYC 1 g monthly, resulting in clinical stabilization. Spirometry at this time demonstrated restriction, with impaired gas transfer (DLCO 54%). Further subsequent deterioration in breathlessness was associated with fever, cough and sputum production. Repeat HRCT demonstrated progressive ILD and a new cavitating pneumonic process. Bronchoalveolar lavage and sputum PCR were positive for Mycobacterium tuberculosis, probably representing reactivation of latent infection following immunosuppression. CYC was withheld, CSA stopped and prednisone reduced to 30 mg to allow for treatment of M. tuberculosis. MMF 1 g twice a day was commenced. Increasing disease activity prompted gradual prednisone re-intensification to 80 mg once a day, cessation of MMF and re-introduction of CSA 400 mg twice a day with uptitration (higher dose owing to interaction with rifampicin). Screening also revealed re-activation of CMV with immunosuppression, prompting treatment.

His condition stabilized and subsequently continues to improve (ferritin 811 µg/l). The rash has resolved, and breathlessness no longer limits activity. He remains on outpatient treatment for his pulmonary M. tuberculosis. Immunosuppression consists of prednisone 10 mg twice a day (weaning) and CSA 400 mg twice a day, with oral CYC ceased owing to leucopenia.

Patient F

Patient F presented with 2 months of progressive malar rash, alopecia, additional rash over his hands, elbows and knees and increasingly swollen hands and wrists with arthralgia. Examination revealed the rash as above, Gottron’s papules, bibasal crepitation and evidence of symmetrical synovitis affecting multiple hand joints (Fig. 1c). There was no muscle weakness. Breathlessness on exertion developed while awaiting outpatient investigations, prompting admission to hospital. Spirometry showed mild restriction with moderately reduced DLCO (65%), and HRCT was consistent with ILD. Skin biopsy was consistent with DM. Diagnosis of anti-MDA-5 DM sine myositis with predominant skin involvement and evidence of ILD was made.

Prednisone 5 mg was commenced and rapidly escalated with pulse i.v. methylprednisolone (1000 mg/day for 3 days), fortnightly 1000 mg i.v. CYC (six doses), prednisone 60 mg (weaning), and CSA 100 mg twice a day on recognition of ILD. He remained well during a brief admission.

Currently, he is stable as an outpatient, with evidence of on-going active disease, early in his disease course, on prednisone 30 mg, CSA 100 mg twice a day and fortnightly CYC infusions. Ferritin is 740 µg/l. The rash and hand swelling are improving, while breathlessness limits his activity to climbing two flights of stairs.

Discussion

Anti-MDA-5 DM is increasingly recognized and is strongly associated with rp-ILD and non-rp-ILD [2]. rp-ILD is observed more frequently among patients of Asian/Japanese descent compared with patients from European or American populations, probably representing a combination of genetic susceptibility and environmental factors [6]. Distant Asian ancestry and the associated greater propensity for anti-MDA-5 DM might
explain the ethnicities of our patients despite the predominantly European population of New Zealand.

To identify existing evidence relating to the treatment of anti-MDA-5 DM with ILD, a literature search was performed in PubMed (MEDLINE) using a strategy to identify publications current up to August 2019 relating to any combination of ‘interstitial lung disease’ or synonyms, ‘MDA-5’ or synonyms and ‘dermatomyositis’. Two significant studies were subsequently identified and ultimately included before publication [6, 7]. Numerous case reports and case series have reported efficacy for various immunosuppressive agents; however, comparative studies have not been performed. Additionally, most reports include all DM patients with associated ILD, with little evidence specific to anti-MDA-5 DM. Recent data suggest that patients with ILD associated with anti-MDA-5 DM have lower mortality and better outcomes with aggressive early combination therapies involving CYC, calcineurin antagonists and glucocorticoids [6, 7]. This builds on previous evidence demonstrating the efficacy of early combined therapy among DM patients complicated by respiratory involvement [9].

Initial treatments varied widely among all patients in our cohort, probably reflecting the different initial treating clinicians, varying disease severity at presentation and prior lack of consensus opinion regarding the most effective treatment strategy. From our experience, we have found multi-agent immunosuppression involving glucocorticoids, a calcineurin antagonist and CYC to be effective for inducing remission in patients with both rp-ILD and non-rp-ILD, and our experience with patient A supports the notion of adjusting the treatment approach when first-line therapy is insufficient. It is often difficult to differentiate those patients who will develop rp-ILD from those who might have non-rp-ILD at initial presentation. As such, we recommend aggressive multi-agent immunosuppression in all patients with anti-MDA5-associated ILD, even when ILD is initially mild, because delayed treatment for the most severe cases can be life threatening. On this basis, we would largely support the recent consensus recommendations [7]. It is important to consider that immunosuppression, particularly when intensive, predisposes patients to various infections, as seen in patient E. Another important consideration in younger patients is the infertility that might result from CYC therapy, requiring balance against treatment efficacy. As such, judicious use of CYC is encouraged, especially if the initial disease is less severe.

Although we have no available data relating to ferritin levels in patients with other conditions, in our experience ferritin seems to be an effective biomarker for monitoring disease activity in patients with anti-MDA-5 DM. It might also be useful in identifying patients more likely to experience rp-ILD, as demonstrated by patients A and E having high initial and peak ferritin levels.

Conclusion

Myositis-specific autoantibodies are becoming increasingly important in guiding management. Here, we have presented our experience with six patients with anti-MDA-5 DM with associated ILD. Increasing poor-quality evidence suggests that the greatest likelihood of disease suppression and survival can be achieved through an early multi-agent immunosuppressive regimen. Also, ferritin appears to be a useful biomarker for monitoring disease activity and severity. Further prospective studies focused on anti-MDA-5 DM treatment regimens and monitoring of biomarkers such as ferritin are required to improve existing management algorithms based on this pattern of myositis-specific autoantibodies.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

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

References

1 Sato S, Hirakata M, Kuwana M et al. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. Arthritis Rheum 2005;52:1571–6.
2 Moghadam-Kia S, Oddis CV, Sato S, Kuwana M, Aggarwal R. Antimelanoma differentiation-associated gene 5 antibody: expanding the clinical spectrum in North American patients with dermatomyositis. J Rheumatol 2017;44:319–25.
3 Gono T, Kawaguchi Y, Ozeki E et al. Serum ferritin correlates with activity of anti-MDA5 antibody-associated acute interstitial lung disease as a complication of dermatomyositis. Mod Rheumatol 2011;21:223–7.
4 Schwarz MI, Matthay RA, Sahn SA et al. Interstitial lung disease in polymyositis and dermatomyositis: analysis of six cases and review of the literature. Medicine (Baltimore) 1976;55:89–104.
5 Marie I, Hachulla E, Chérin P et al. Interstitial lung disease in polymyositis and dermatomyositis. Arthritis Rheum 2002;47:614–22.
6 Tsuji H, Nakashima R, Hosono Y et al. Multicenter prospective study of the efficacy and safety of combined immunosuppressive therapy with high-dose glucocorticoid, tacrolimus, and cyclophosphamide in interstitial lung diseases accompanied by anti-melanoma differentiation-associated gene 5-positive dermatomyositis. Arthritis Rheumatol 2020;72:488–98.
7 Romero-Bueno F, Diaz del Campo P, Trallero-Arguás E et al.; MEDRA5 (Spanish MDA5 Register) group (listed
contributors at the end of the article). Recommendations for the treatment of anti-melanoma differentiation-associated gene 5-positive dermatomyositis-associated rapidly progressive interstitial lung disease. Semin Arthritis Rheum 2020;50:776–90.

8 EUROIMMUN. Product Catalogue 2021 [Internet]. Lübeck (Germany): EUROIMMUN; 2020. https://www.euroimmun.com/documents/Catalogue/EUROIMMUN-Product-Catalogue.pdf (22 December 2020, date last accessed).

9 Kameda H, Nagasawa H, Ogawa H et al. Combination therapy with corticosteroids, cyclosporin A, and intravenous pulse cyclophosphamide for acute/subacute interstitial pneumonia in patients with dermatomyositis. J Rheumatol 2005;32:1719–26.