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Anti- melanoma differentiation-associated gene 5 antibody-positive dermatomyositis with rapidly progressing interstitial lung disease

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Case Report

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Abstract

Background

Anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody-positive dermatomyositis is a rare subset of idiopathic inflammatory myopathy with a distinctive skin phenotype, little or no muscle involvement and a high risk of rapidly progressive interstitial lung disease (RP-ILD). Normal muscle strength and creatine kinase often lead to misdiagnosis as infection or idiopathic ILD. We report this case because the skin findings were the only clue to a fulminant lung process, and because the adequacy of sequential step-up immunosuppression in high-risk disease remains unresolved.

Case presentation:

A 60-year-old never-smoking man presented with 3 months of progressive dyspnea, dry cough, fever, 10-kg weight loss and a photosensitive rash. He was hypoxemic (SpO2 88% on room air) with bibasal crackles, heliotrope rash, shawl sign, Gottron papules, ulcerated chest papules and mechanic's hands. Muscle power and creatine kinase were normal. C-reactive protein, D-dimer and lactate dehydrogenase were elevated; ferritin was 450 ng/mL. Computed Tomography (CT) Pulmonary Angiography showed basal-predominant ground-glass opacities with subpleural sparing and traction bronchiectasis, without thromboembolism. Extensive infectious work-up, including bronchoalveolar lavage, was negative. Antinuclear antibody was positive (1:320) and the myositis-specific antibody panel was strongly positive for anti-MDA5. He received pulse methylprednisolone, tapering oral glucocorticoids and intravenous immunoglobulin, but deteriorated rapidly, requiring non-invasive ventilation, intubation and tracheostomy; repeat CT chest showed dense consolidation. Ventilator-associated pneumonia and refractory septic shock followed, and he died on hospital day 18.

Conclusions

Myositis-specific antibodies should be tested promptly in any patient with subacute hypoxemic ILD and compatible skin findings, even when muscle strength and creatine kinase are normal, and the infectious work-up should run in parallel with treatment. Glucocorticoids with immunoglobulin alone were inadequate; early combination immunosuppression and multidisciplinary care, weighed against opportunistic infection risk, should be considered in high-risk patients.

Background

Anti-melanoma differentiation-associated gene 5 (MDA5) antibody-positive dermatomyositis is a distinct subset of idiopathic inflammatory myopathy, first described in Japanese patients with clinically amyopathic dermatomyositis (CADM) [1]. It is defined by a characteristic mucocutaneous phenotype, minimal or absent clinical muscle involvement and a high risk of interstitial lung disease (ILD), a

substantial proportion of which follows a rapidly progressive course (RP-ILD) [2, 3]. Mortality from RP-ILD exceeds 50% in many series, with most deaths occurring within the first 6 months despite treatment [2, 4, 5]. Because weakness and creatine kinase (CK) elevation are frequently absent, the presentation is commonly mistaken for infection, drug reaction or idiopathic ILD, and diagnosis is delayed.

Optimal treatment remains unsettled. No randomized trials exist, and recent cohorts report conflicting results for upfront triple therapy and for Janus kinase (JAK) inhibition [6–10]. We report a fatal case in a 60-year-old man to emphasize that skin findings may be the only visible clue to impending RP-ILD, and to discuss the limits of sequential immunosuppression when the therapeutic window is narrow.

Case presentation

A 60-year-old man, a lifelong never-smoker with no known comorbidities, presented with a three month history of gradually progressive exertional dyspnea (modified Medical Research Council grade 2) and a dry cough that had worsened over the preceding month, without diurnal or postural variation. He also reported intermittent fever for one month, a 10-kg weight loss with reduced appetite, and a pruritic rash over sun-exposed skin for 2 months. He denied chest pain, wheezing, hemoptysis, joint pain, hair loss and muscle weakness.

On examination, blood pressure was 118/76 mm Hg, heart rate 78 beats/min, and he was afebrile. Oxygen saturation was 88% on room air, requiring 4 L/min of supplemental oxygen. Skin examination showed violaceous periorbital erythema with facial edema (heliotrope rash); an extensive violaceous poikilodermatous rash over the upper back and posterior neck (shawl sign); erythematous papules over the knuckles (Gottron papules); ulcerated erythematous papules over the anterior neck and upper chest; and hyperkeratotic, fissured skin along the lateral aspects of the fingers (mechanic's hands) (Fig. 1). Bilateral fine end-inspiratory crackles were heard in the infrascapular and infra-axillary areas. Cardiac and abdominal examinations were normal. Proximal muscle power was normal, and there was no clubbing, lymphadenopathy or peripheral edema.

Leukocyte count was 5,200/mm3 with neutrophil predominance, hemoglobin 14.9 g/dL and platelet count 214,000/mm3. Serum creatinine (1.05 mg/dL) and CK were normal. C-reactive protein was 55 mg/L (normal < 5), D-dimer 1,873 ng/mL (< 500) and lactate dehydrogenase 873 IU/L (< 250). Ferritin was borderline raised at 450 ng/mL, and procalcitonin was < 0.05 ng/mL. Arterial blood gas on 3 L/min oxygen showed pH 7.46, PaCO2 27.9 mm Hg, PaO2 79.6 mm Hg and bicarbonate 20.0 mmol/L. Serology for HIV, hepatitis B surface antigen and hepatitis C antibody was negative. Echocardiography showed a left ventricular ejection fraction of 60% with no other abnormality.

Computed Tomography (CT) Pulmonary Angiography showed multifocal, symmetric ground-glass opacities with interlobular septal thickening in a basal, peripheral and posterior gradient, with relative subpleural sparing and traction bronchiectasis, consistent with a nonspecific interstitial pneumonia (NSIP) pattern (Fig. 2). There was no pulmonary thromboembolism. CT of the abdomen and pelvis showed no malignancy. Bronchoscopy showed a normal tracheobronchial tree; bronchoalveolar lavage

(BAL) cytology was paucicellular with neutrophil-predominant inflammation. BAL Gram, acid-fast and fungal stains, *Mycobacterium tuberculosis* nucleic acid amplification test, *Pneumocystis* PCR and a multiplex respiratory pathogen PCR panel detected no organisms, and blood and urine cultures were sterile. Nailfold capillaroscopy showed dilated capillary loops with hemorrhages. Antinuclear antibodies were positive at 1:320 (speckled pattern), anti-cyclic citrullinated peptide antibodies were negative, and a myositis-specific antibody panel was strongly positive for anti-MDA5 antibodies.

The unrevealing infectious work-up, typical cutaneous findings, NSIP pattern, positive antinuclear antibodies and nailfold changes prompted dermatology and rheumatology consultation. A diagnosis of anti-MDA5 antibody-positive clinically amyopathic dermatomyositis with ILD was made after multidisciplinary discussion. Treatment consisted of pulse intravenous methylprednisolone (1 g/day for 3 days), followed by tapering oral glucocorticoids and weight-based intravenous immunoglobulin (IVIG) for 5 days.

Despite this, his oxygen requirement escalated rapidly. He required intermittent noninvasive ventilation and high-flow nasal oxygen, then intubation for noninvasive ventilation failure and later tracheostomy for prolonged ventilatory dependence. Repeat chest CT after 10 days showed rapid progression of ILD with dense consolidation (Fig. 3). His course was complicated by ventilator-associated pneumonia caused by *Acinetobacter* and *Klebsiella* species, treated with culture-directed antibiotics, and he progressed to refractory septic shock with multiorgan dysfunction despite multiple vasopressors. He died on hospital day 18.

Discussion

MDA5 is a cytosolic pattern-recognition receptor that senses viral double-stranded RNA and triggers type I interferon production. Autoantibody formation is thought to follow excessive interferon signaling, and the resulting vasculopathy likely underlies both the ulcerative skin lesions and the diffuse alveolar damage of the severe phenotype [2]. Patients typically present with fever, fatigue and weight loss, followed by dry cough and exertional dyspnea, with heliotrope rash, Gottron papules, shawl sign, mechanic's hands and ulceration over the digits and upper trunk [2, 3]. Skin ulceration marks vasculopathy and is associated with worse outcomes; nailfold capillary dilation and hemorrhage are common, as in our patient. Muscle weakness is absent or mild and CK is normal or only slightly raised, so the disease is frequently mistaken for infection, drug reaction or idiopathic ILD, and in some patients ILD precedes the skin signs [3].

High-resolution CT most often shows an NSIP pattern, an organizing pneumonia pattern or a mixture, with lower-zone ground-glass opacities, septal thickening, traction bronchiectasis and relative subpleural sparing. In RP-ILD, opacities can progress to dense consolidation within days, reflecting diffuse alveolar damage [3]. Older age, fever, ferritin of 800 ng/mL or more, high lactate dehydrogenase and C-reactive protein, lymphopenia, high anti-MDA5 titers, coexisting anti-Ro52 antibodies, skin ulceration, severe hypoxemia and extensive CT involvement predict RP-ILD and death [2–5]. Our patient had most of these

features (age, fever, ulceration, severe hypoxemia, raised lactate dehydrogenase and C-reactive protein), yet his ferritin was below the usual threshold, indicating that a modestly raised ferritin does not exclude a fulminant course. Anti-Ro52 status and antibody titer are not reported here and would have refined risk stratification.

Diagnosis rests on the clinical phenotype, anti-MDA5 detection on a myositis-specific antibody panel and high-resolution CT; lung biopsy is rarely needed [3]. Because infection is the main mimic and intensive immunosuppression follows, BAL is warranted, but the infectious work-up should proceed in parallel with treatment rather than delay it [3, 6]. Malignancy screening is reasonable, although the cancer association is weaker in this subtype [3].

No randomized trial guides therapy. Early combination immunosuppression rather than sequential step-up is the prevailing approach, and expert recommendations favor glucocorticoids plus a calcineurin inhibitor, with or without cyclophosphamide [6]. A prospective study of high-dose glucocorticoid, tacrolimus and cyclophosphamide showed improved survival compared with step-up controls [7], but a larger Chinese cohort found no prognostic benefit, with higher mortality among high-risk patients [8]. JAK inhibition, which interrupts interferon signaling, is increasingly used; tofacitinib-based regimens were associated with better 1-year transplant-free survival than calcineurin inhibitor-based regimens in a multicenter cohort [9]. In severe disease with raised ferritin, intensive induction combining tofacitinib, rituximab, plasma exchange and triple therapy improved survival, at the cost of opportunistic viral and fungal infections [10]. Glucocorticoids with IVIG alone are frequently insufficient once RP-ILD is established [3, 6], as our patient's course illustrates, and similarly fulminant courses have been reported [11, 12].

Opportunistic and nosocomial infections, including *Pneumocystis* pneumonia, cytomegalovirus disease, invasive fungal infection and ventilator-associated pneumonia, are leading causes of death [3, 10]. Our patient died of ventilator-associated pneumonia with septic shock, underscoring the dilemma: undertreatment allows irreversible lung injury, whereas intensive immunosuppression raises infection risk. *Pneumocystis* prophylaxis, close surveillance and early collaboration among pulmonology, rheumatology, dermatology and critical care are essential, and early referral for lung transplant evaluation or extracorporeal support should be considered in selected refractory patients [3, 6].

Limitations

This is a single case without autopsy, and we cannot determine whether earlier combination therapy would have altered the outcome.

Conclusions

In a patient with subacute hypoxemic ILD, skin findings such as heliotrope rash, shawl sign, Gottron papules, mechanic's hands or ulcerated papules should prompt immediate suspicion of anti-MDA5 dermatomyositis, even when muscle strength and CK are normal. A myositis-specific antibody panel

should be sent promptly, with the infectious work-up run in parallel with, rather than before, treatment decisions. Features such as older age, fever, skin ulceration, severe hypoxemia and raised lactate dehydrogenase and C-reactive protein identify patients at highest risk of RP-ILD and death. In such patients, glucocorticoids with IVIG alone may be inadequate, and early combination immunosuppression, individualized to infection risk and supported by *Pneumocystis* prophylaxis and infection surveillance, should be considered together with early multidisciplinary care and, in refractory cases, early transplant referral. Further studies are needed to define the optimal induction regimen.

Abbreviations

anti-MDA5
anti-melanoma differentiation-associated gene 5
BAL
bronchoalveolar lavage
CADM
clinically amyopathic dermatomyositis
CK
creatine kinase
CT
computed tomography
ILD
interstitial lung disease
IVIG
intravenous immunoglobulin
JAK
Janus kinase
NSIP
nonspecific interstitial pneumonia
RP-ILD
rapidly progressive interstitial lung disease.

Declarations

Ethics approval and consent to participate: Not applicable for a single case report.

Consent for publication: Written informed consent for publication of clinical details and images was obtained [please confirm: from the patient before his deterioration / from his next of kin]. A copy is available for review by the Editor-in-Chief.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

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