A 62-Year-Old Woman With Lung Cancer, Ulcerating Rash, and Rapidly Progressive Hypoxemia

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CASE PRESENTATION: A 62-year-old nonsmoking woman with no medical history initially presented with a 3-month history of rash. A painful, erythematous exanthem had progressed from her forehead, cheeks, and upper chest to her eyes (heliotrope rash) and hands, primarily involving the extensor surface finger joints with prominent digital ulceration.

Skin biopsy demonstrated a lymphocytic infiltrate with interface dermatitis, which is consistent with dermatomyositis (Fig 1). The absence of weakness, myalgias, and muscle tenderness, along with normal creatinine kinase and aldolase, confirmed a diagnosis of clinically amyopathic dermatomyositis (CADM). The remaining autoimmune workup revealed elevated inflammatory markers (erythrocyte sedimentation rate of 97 mm/h and C-reactive protein of 58 mg/L), normal antinuclear antibody titers, and the presence of antibodies against melanoma differentiation-associated protein 5 (MDA5). The remaining myositis serologies were negative. The patient was prescribed glucocorticoids with marked improvement in skin lesions. Malignancy evaluation included CT scan of the chest, which revealed a 5-cm lingular mass and mediastinal lymphadenopathy without other lung parenchymal abnormalities (Fig 2A). Subsequent mediastinal lymph node biopsy confirmed lung adenocarcinoma. The patient was staged as IIIA (T2a, N2, M0) based

on an otherwise negative PET scan. The tumor was negative for targetable mutations and programmed death-1 ligand 1 staining. She had no respiratory symptoms at that time.
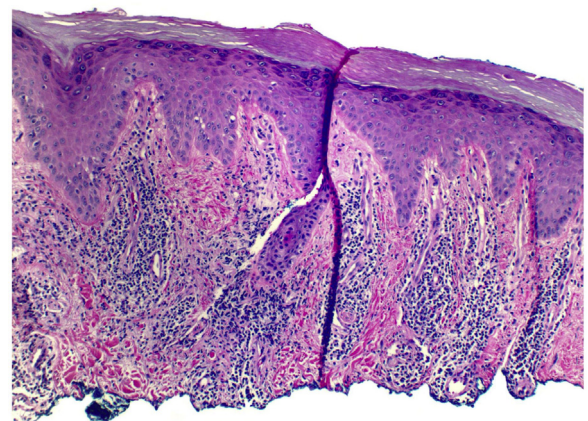

Figure 1 – *Histopathologic skin findings. Biopsy of the dorsum of the right third digit shows a lymphocytic infiltrate with interface change and slight spongiosis, which is consistent with dermatomyositis.*

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Figure 2 – *A-C, CT chest scans. A, Initial study shows a 5-cm lingular mass, two months prior to admission. B, The study performed 1 week prior to admission shows the onset of lung parenchymal abnormalities. C, The study on hospital day 1 shows evolution of infiltrates.*

Approximately one month later, the patient experienced cough and dyspnea. Her symptoms progressed, despite two outpatient courses of empiric antibiotics (cefpodoxime and doxycycline), and ultimately necessitated hospitalization. On admission, she had hypoxemia that required 3 L/min oxygen via nasal cannula. A chest CT scan with angiogram was negative for pulmonary embolism but showed new diffuse patchy opacifications in addition to the known lingular mass (Fig 2B). IV antibiotics (vancomycin and piperacillin-tazobactam) and oral prednisone produced no improvement. Given the patient's progressive hypoxemia and anticipated need for advanced immunosuppressive therapy, she was transferred to our hospital.

Physical Examination Findings

The patient was afebrile with BP of 116/71 mm Hg and heart rate of 110 beats/min. She appeared to be in moderate distress with a respiratory rate of 26 breaths/min and oxygen saturation of 94% on supplemental oxygen at 5 L/min via nasal cannula. Examination was notable for bilateral wheezing, worse on the left than the right. Skin examination revealed resolving erythematous macules and patches overlying the finger joints bilaterally, but no heliotrope rash. The rest of the examination was unremarkable.

Diagnostic Studies

Leukocyte count was 12.9 thousand/µL; hemoglobin level was 10.2 g/dL, and platelets concentration was 438 thousand/µL. Serum electrolytes and creatinine level were normal. Transaminitis was present with alanine transaminase of 94 units/L and aspartate transaminase 63 units/L. Procalcitonin level was 0.56 ng/mL, and ferritin level was 540 ng/mL. Arterial blood gas demonstrated pH 7.46; $Paco_2$ was 36 mm Hg, Pao_2 93 was mm Hg, and oxygen saturation was 97% at 5 L/min via nasal cannula . Respiratory virus and serum cytomegalovirus testing were negative. CT chest scan showed progression of multifocal airspace opacities and increasing left pleural effusion (Fig 2C).

What is the diagnosis?

Diagnosis: MDA5 disease-associated rapidly progressive interstitial lung disease (MDA5-RPILD) in the setting of lung adenocarcinoma.

Discussion

Autoimmune myositis traditionally is divided into four subtypes: polymyositis, dermatomyositis, inclusion-body myositis, and necrotizing autoimmune myositis. CADM represents a subtype of dermatomyositis that is characterized by the absence of myositis. The total incidence of autoimmune myositis is estimated at two per 100,000 annually; CADM represents roughly 10% of these cases. Given the challenge of defining autoimmune myositis subtypes clinically, serologic markers are now used to organize the myositides into distinct pathologic syndromes. Two such syndromes are linked to interstitial lung disease (ILD): MDA5 disease and anti-synthetase syndrome. MDA5 disease primarily is associated with the CADM clinical subtype and has characteristic pulmonary and dermatologic manifestations, including digital ulceration (Table 1). Anti-MDA5 antibodies are detectable in 3% to 12% of patients with autoimmune myositis and indicate a high risk of life-threatening ILD (6-month mortality rate, approximately 40%).

The pathogenesis of lung injury in MDA5-RPILD is poorly understood. One proposed mechanism involves direct antibody-mediated cytotoxicity. Indeed, immunofluorescence staining of skin biopsy specimens demonstrates the deposition of immune complexes, and lung biopsy specimens have shown small vessel vasculitis. Another line of evidence for pathogenic antibodies comes from case studies that show correlations between anti-MDA5 titers and (1) severity of ILD, (2) treatment response, (3) disease relapse, and (4) remission. Furthermore, as described later, antibody-depleting therapies appear to have efficacy in treating MDA5 disease. A second proposed mechanism involves the induction of acute lung injury secondary to macrophage activation syndrome. Consistent with this hypothesis, markers of macrophage activation including ferritin, CD163, and IL-6 rise significantly during MDA5-RPILD and correlate with severity. Regarding the association between autoimmune myositis and cancer, it has been hypothesized that tolerance to autoantigens (eg, MDA5) may be broken in the context of malignancy, initiating a paraneoplastic process that injures host tissue. However, this theory remains unproved.

The clinical course of MDA5 disease-associated ILD is characterized by rapid progression. A review of reported cases further indicates two distinguishable trajectories:

TABLE 1] Laboratory and Clinical Manifestations of Myositis-Associated Syndromes With ILD: Anti-MDA5 Disease vs Anti-Synthetase Syndrome

Variable	Melanoma Differentiation-Associated Protein 5 Disease	Anti-Synthetase Syndrome
Autoantibodies	Anti-melanoma differentiation-associated protein 5	Anti-Aminoacyl transfer RNA synthetases (Jo-1 = histidyl; PL-7 = threonyl; PL-12 = alanyl, EJ = glycyl; OJ = isoleucyl; KS = asparaginyl; ZO = phenylalanyl)
Target molecule	Melanoma differentiation-associated gene 5	Aminoacyl transfer RNA synthetase
Function of target molecules	Cytoplasmic double-stranded RNA receptor involved in innate immune recognition of viruses	Cytoplasmic amino acid-charging enzymes
Disease association	Clinically amyopathic dermatomyositis (some patients with anti-melanoma differentiation-associated protein 5 disease have classic dermatomyositis)	Polymyositis or dermatomyositis (myositis may be absent in some patients)
Dermatologic manifestations	Skin ulceration[a]	Mechanic's hands
	Gottron's papules	
	Heliotrope rash	
Pulmonary manifestations	Rapidly progressive interstitial lung disease	Chronically progressive fibrotic interstitial lung disease
Other clinical associations	Arthritis	Arthritis
	Alopecia	Raynaud's phenomenon

[a]Cutaneous phenotype unique to anti-melanoma differentiation-associated protein 5 disease.

TABLE 2] Recommended Microbiologic Testing Prior to Initiation of Immunosuppression[a]

Host	Pathogen	Diagnostic Testing
Routine testing for all patients	Typical pyogenic bacteria	Sputum or BAL culture
	Streptococcus pneumoniae	Streptococcal urine antigen
	Actinomyces species	BAL culture
	Nocardia species	BAL culture
	Non-TB mycobacteria	BAL Gram stain and culture (AFB)
	Mycoplasma pneumoniae	Serology (IgM, IgG)
	Chlamydia pneumophila	Serology (IgM, IgG)
	Legionella pneumophila	Legionella urine antigen
	Influenza and other upper respiratory viruses[b]	BAL or nasopharyngeal PCR
	Hepatitis A	Serology (IgG)
	Hepatitis B[c]	Serology (hepatitis B core antibody, surface antigen, surface antibody)
	Hepatitis C	Serology (IgG)
	MRSA colonization	Nasal swab (PCR)
	VRE colonization	Rectal swab (PCR)
Select testing for patients with baseline immunocompromise	HIV	Serum antigen/antibody (4th generation)
	Cytomegalovirus	BAL PCR
	Epstein Barr virus	Serology (IgG, IgM)
	Herpes simplex virus	BAL PCR
	Varicella zoster virus	BAL PCR, serology (IgG)
	Pneumocystis jirovecii	BAL PCR, β-D-glucan
	Cryptococcus neoformans	Serology (IgM, IgG)
	Coccidioides immitis	Serology (IgM, IgG)
	Toxoplasma gondii	Serology (IgM, IgG)
	Aspergillus species	BAL culture, galactomannan
	Mucorales	BAL culture
	Candida galabrata/kruseii	Rectal swab
	Treponema pallidum	Treponema pallidum particle agglutination assay, rapid plasma reagin test
Select testing to be considered based on patient exposures	Blastomyces species	Urine antigen testing
	Histoplasma capsulatum	Urine antigen testing
	Mycobacterium tuberculosis[c]	Sputum or BAL culture, interferon gamma release assay, AFB stain and culture, PCR
	Strongyloides stercoralis[c]	Serology (IgG), stool examination

AFB = acid-fast bacilli; MRSA = methicillin-resistant *staphylococcus aureus*; PCR = polymerase chain reaction; VRE = vancomycin-resistant enterococcus.
[a]Requires a thorough history of relevant epidemiologic risk factors (country of origin, travel history, military service, prior incarceration, animal exposures, water sources) and immunizations (influenza, measles/mumps/rubella, hepatitis A/B, varicella, Shingrix, meningococcal, Haemophilus B, Prevnar, Pneumovax).
[b]Adenovirus, rhinovirus, respiratory syncytial virus, coronavirus, human metapneumovirus, enterovirus.
[c]Perform testing prior to immunosuppression to prevent reactivation.

subacute (months) and hyperacute (weeks). Hyperacute disease usually progresses from diagnosis to death within 90 days from respiratory failure, as in the patient. The subacute form typically shows better response to immunosuppressive therapy but carries a higher risk of recurrence.

MDA5-RPILD is diagnosed based on positive anti-MDA5 serologic findings, clinical signs of CADM, and respiratory disease that is not attributable to infection or other causes. Thus, an expedient and thorough infectious workup that uses both noninvasive testing and bronchoscopic evaluation must be conducted to prevent delays in treatment (Table 2).
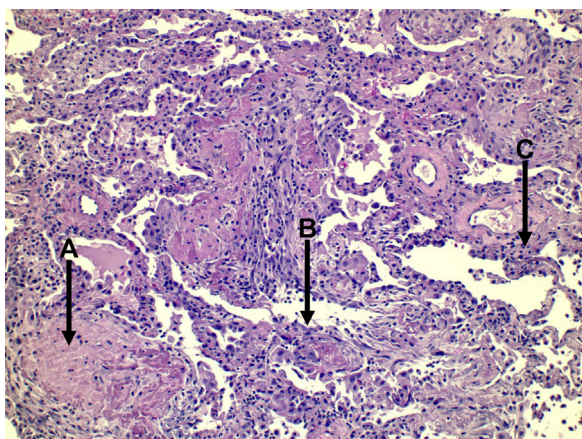
Figure 3 – *Histopathologic lung findings. Transbronchial biopsy of the right upper lobe shows proteinaceous exudates (arrow A), intraalveolar granulation tissue consistent with organizing pneumonia (arrow B), and mild interstitial inflammation with a lymphocytic infiltrate (arrow C). Alveolar macrophages were abundant within alveoli, while neutrophils were notably absent. Hyaline membranes were not observed.*

MDA5-RPILD is a rare disease. As such, there are no established guidelines for management. First-line therapy based on expert opinion is a combination immunosuppressive regimen with high-dose corticosteroids, cyclophosphamide, and a calcineurin inhibitor. Steroid monotherapy has demonstrated minimal efficacy. Because delays in treatment are associated with worse prognosis, severe cases may warrant the initiation of therapy based on clinical presentation alone, prior to serologic confirmation. Dermatology and rheumatology consultations are recommended in such cases.

In MDA5-RPILD, immunosuppressive therapy alone is often inadequate. Several advanced treatment methods have been reported that include IV immunoglobulin, plasmapheresis, and polymyxin-B direct hemoperfusion. These therapies are thought to deplete serum antibodies and cytokines and therefore address the putative pathophysiologic mechanisms described earlier. The optimal modality remains unknown, but a recent report suggests promise for plasmapheresis. Of note, rituximab has demonstrated little efficacy, perhaps due to the delayed effects of eliminating antibody producing B-cells as opposed to direct depletion of pathologic antibodies.

Clinical Course

The differential diagnosis at the time of transfer included infection, progression of primary lung cancer, MDA5-RPILD, and other forms of ILD. Bronchoscopy performed on hospital day 2 demonstrated negative microbiologic testing and absent eosinophilia.

Transbronchial biopsy revealed organizing pneumonia and a mild interstitial pneumonitis without hyaline membranes (Fig 3). The patient's hypoxemia subsequently worsened, and required oxygenation via high flow nasal cannula and transfer to the medical ICU. She was given pulse-dose methylprednisolone (1000 mg daily) on hospital days 3 to 5. On day 5, carboplatin and paclitaxel (175 mg/m^2) were administered to treat the underlying adenocarcinoma. The ensuing neutropenia was treated with granulocyte-colony stimulating factor. Her respiratory failure continued to worsen, however, necessitating invasive ventilation on day 9. At this time, she received further immunosuppression with cyclophosphamide (day 9; 500 mg/m^2) and a second round of pulse dose methylprednisolone (days 8-10), followed by 60 mg daily. She received plasmapheresis on days 17 and 18. Prophylactic acyclovir and trimethoprim-sulfamethoxazole were maintained throughout, and broad-spectrum antibiotics (piperacillin-tazobactam) were given intermittently. Her ferritin level rose steadily to a maximum level of 1200 ng/mL, but the procalcitonin level did not increase. Lung compliance was unexpectedly high, even at the late stages of disease, so modest positive end-expiratory pressures were used (approximately 10 cm water). Unfortunately, despite all interventions, the patient's respiratory status continued to deteriorate. Based on discussions with the patient's family, she was transitioned to hospice care and died on hospital day 24.

The literature contains very few published reports of MDA5-RPILD that occurred in the setting of malignancy; to our knowledge, this is the first case associated with lung cancer. This aspect of the case presented unique management questions, particularly whether to treat the underlying cancer. Ultimately, we did administer chemotherapy to reduce tumor burden and thereby control a suspected paraneoplastic pulmonary process. Such an approach is usual practice for other paraneoplastic diseases, such as Lambert-Eaton syndrome, but certain subtleties of this case require mention. Although cytoreduction with depletion of autoantigen may have blunted further antibody production, it was unlikely to affect the existing burden of antibodies given the three-week serum half-life of IgG. In fact, sudden release of autoantigen after tumor cell death potentially could have increased that generation of antibody, although the patient was likely immunosuppressed adequately to prevent such a phenomenon. Additionally, the administration of cytotoxic chemotherapy along with cyclophosphamide

rendered the patient neutropenic, which necessitated the use of granulocyte-colony stimulating factor. The subsequent rebound neutrophilia may have contributed to accelerated lung injury in light of the established role of neutrophils in ARDS pathogenesis. Therefore, the decision to treat cancer during MDA5 disease, and the potential immunopathologic sequalae, should be considered carefully.

Clinical Pearls

1. *In autoimmune myositis, severe ILD is observed in two serologically defined conditions: MDA5 disease and anti-synthetase syndrome. Careful physical examination is crucial for diagnosis and must include assessment for skin ulceration, which is a characteristic feature of MDA5 disease.*

2. *New diagnoses of MDA5 disease should prompt evaluation for malignancy and immediate pulmonary evaluation, given the high frequency of RPILD.*

3. *The current standard of care for severe MDA5-RPILD includes aggressive immunosuppression with high-dose corticosteroids, calcineurin inhibitors, and cyclophosphamide. In refractory cases, plasmapheresis should be considered.*

4. *Efficient exclusion of infectious lung disease is essential to expedite the initiation of immunosuppressive therapy.*

5. *Further understanding of MDA5 disease pathogenesis, particularly the role of autoantibodies, will help to inform therapeutic strategies.*

Acknowledgments

Suggested Readings

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