Case Report

Fatal rapidly progressive interstitial lung disease in a patient with amyopathic dermatomyositis

Abdullah Mobeireek[1], Walter Conca[1], Shamayel Mohammed[2], Fahad AlObaid[1], Mohammed AlHajji[1]

Departments of [1]Medicine and [2]Laboratory Medicine and Pathology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Address for correspondence:
Prof. Abdullah Mobeireek, King Faisal Specialist Hospital and Research Centre, Department of Medicine, PO Box 3354 (MBC 46), Riyadh 11211, Saudi Arabia.
E-mail: mobeireek@yahoo.com

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Abstract:

Interstitial lung disease (ILD) is a well-established common manifestation of idiopathic inflammatory myopathies. Yet, till now, the pathogenetic mechanisms are still poorly understood, classification is evolving and prognosis is variable. A refractory and rapidly progressive ILD (RPILD) that is associated with dermatomyositis (DM) with minimal muscle weakness and normal creatine kinase (termed clinically amyopathic DM) is increasingly being recognized, with more incidence in Asians. However, we are not aware of reports of the Arab region. Herein, we present a 38-year-old male with this condition that ended with a fatal outcome despite aggressive therapy, with a review of recent literature.

Keywords:

Amyopathic dermatomyositis, connective tissue disease, idiopathic inflammatory myopathy, interstitial lung disease

The association of interstitial lung disease (ILD) with connective tissue disease (CTD) is quite common; up to two-thirds of ILD patients may have one form of CTD if a careful assessment and follow-up are performed.[1] Furthermore, classification is evolving as more knowledge is gained about the autoimmune mechanisms of the disease. More recently, terms such as "interstitial pneumonia with autoimmune features"[2] and "autoimmune ILD"[3] have been suggested to further discern this group and distinguish them from the idiopathic type, which has a different management strategy and prognosis. Although, in general, the prognosis of ILD associated with CTD is more favorable than the idiopathic type (typically idiopathic pulmonary fibrosis),[2] certain types can be fulminant and refractory to modern therapy. We present, for the first time from the Arab region, a patient with amyopathic dermatomyositis (DM) who succumbed because of rapidly progressive interstitial lung disease (RPILD) despite aggressive management.

Case Report

A previously healthy 38-year-old male was referred for the evaluation of worsening dyspnea. Two months prior to his presentation, he started to have low-grade fever associated with dry cough, generalized fatigability, arthralgia, and documented weight loss of 12 kg. He also developed skin rash, painless, and nonitchy at both elbows, knuckles, and eyebrows. Three weeks later, he was admitted to the intensive care unit (ICU) in another hospital after developing hypoxic respiratory failure and was treated with antibiotics and corticosteroids without any improvement. He has significant smoking history of pipe smoking for the past 15 years (three times/week). He was receiving prednisone 40 mg daily.

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On examination, he was afebrile with respiratory rate of 24 breath/min, oxygen saturation was 94% on 4 L of oxygen by nasal canula. Erythematous scaly papules were noted over the elbows and knuckles as well as scattered scales over the eyebrows, nose, and beard area (xerosis). On auscultation, there were bilateral inspiratory fine crackles. Neurologically, he had no significant muscle weakness. His initial routine laboratory investigations, including autoimmune panel, are shown in Table 1. Of note, creatine kinase (CK) was within normal limits.

Initial chest radiograph and computed tomography (CT) showed bilateral patchy ground-glass opacities/consolidations with interstitial septal thickening [Figure 1]. These changes were bilateral and predominantly peribronchial, and more pronounced at the lower lobes. Microbiological screening was unremarkable. Skin biopsy showed epidermal atrophy, altered keratin and serum crust. The dermis showed mild dermal telangiectasia and mild mucin deposition. These features were consistent with interface dermatitis. DM was suspected initially. Bronchoscopy did not show any endobronchial lesion and the transbronchial biopsies are discussed below.

Histology and immunohistochemistry

Hematoxylin and eosin (H&E) staining and immunohistochemistry on sections of lung tissue were performed order to determine the phenotype of infiltrating inflammatory cells [Figures 2 and 3]. The histomorphology revealed the characteristic features of organizing pneumonia and interstitial inflammation [Figure 2a]. Differentiation of the cellular components revealed the simultaneous presence of CD3+ T lymphocytes [Figure 2b], including CD4+ [Figure 2c], and CD8+ [Figure 2d] T cells, CD20+ B cells [Figure 2e] and CD68+ macrophages [Figure 2f]. While CD3+ T cells were sparsely distributed throughout the interstitium, some CD20+ B cells accumulated at the margins and some within the T cell-rich area. In

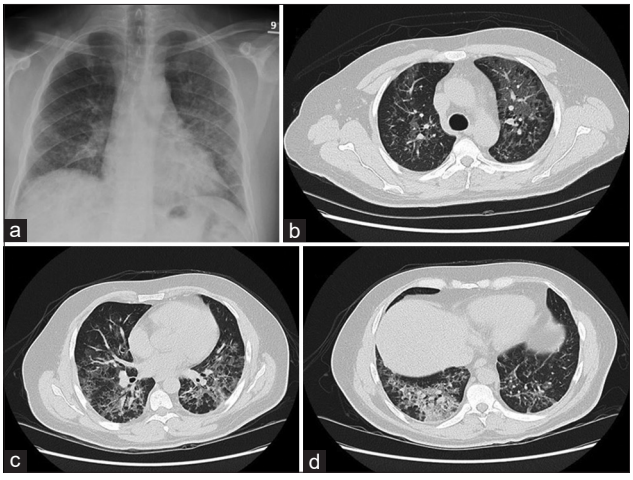

Figure 1: Initial chest radiograph and selected images of computed tomography of the chest

Table 1: Laboratory investigations

Category	Parameter	Value
Hematology	WBC (total)	4.9
	Neutrophils	87%
	Lymphocytes	4%
	Hb	115 g/L
	Platelets	219
	ESR	81 mm/h
	BAL WBC	215 (10^6/L)
	Neutrophils	24%
	Lymphocytes	12%
	Histocytes	52%
Biochemistry	Electrolytes, urea and creatinine	WNR
	CK	75 u/L
	ALT	79 u/L
	AST	56 u/L
	AP	108 u/L
	Ferritin	3387 ug/L (30-400 ug/L)
Immunologic tests	CRP	7.7 mg/L
	Complement (g/L)	
	C3	1.23
	C4	0.33
	Immunoglobulins (A, G, M, E)	WNR
	Cryoglobulin	Negative
	ANA	1: 180, speckled pattern
	RF	7.3 u (negative)
	ACCP	<15.6 u (WNR)
	C-ANCA (PR3)	4.3 u (WNR)
	P-ANCA (MPO)	2.6 u (WNR)
	ANCA (IF)	Negative
	Anti-ds-DNA	99.1 iu/mL (WNR)
	Anti SSA (Ro)	10.6 u (WNR)
	Anti SSB (La)	2.5 u (WNR)
	Anti-Smith	4.8 u (WNR)
	Anti-smooth muscle	Negative
	Anti-Scl-70	3.3 u (WNR)
	Anti-Jo	4.5 u (WNR)
	Anti-RNP	12.8 u (WNR)
	Anti-phospholipid	Negative
	PTT-LA screening	35 s
	Lupus anticoagulant	Negative
	Anti-myositis panel	N/A
	Anti-GBM	4.3 u (WNR)
Miscellaneous	HIV serology	Negative
	Hepatitis B and C serology	Nonreactive

WBC=White blood cells, Hb=Hemoglobin, ESR=Erythrocyte sedimentation rate, BAL=Bronchoalveolar lavage, CK=Creatine kinase, AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, AP=Alkaline phosphatase, CRP=C-reactive protein, ANA=Antinuclear antibody, RF=Rheumatoid factor, ACCP=Anti-cyclic citrullinated peptide, MPO=Myeloperoxidase, PR3=Proteinase 3, ANCA=Antineutrophil cytoplasmic antibodies, C-ANCA=Cytoplasmic-ANCA, P-ANCA=Perinuclear-ANCA, IF=Immunofluorescence, Anti-ds-DNA=Anti-double stranded DNA, Anti-SSA=Anti-Sjögren's-syndrome-related antigen A, Anti SSB=Anti Sjögren's syndrome related antigen B, Anti-RNP=Anti-ribonucleoprotein, PTT-LA=Partial thromboplastin time-lupus anticoagulant, Anti-GBM=Anti-glomerular basement membrane, WNR=Within normal range, N/A=Not available

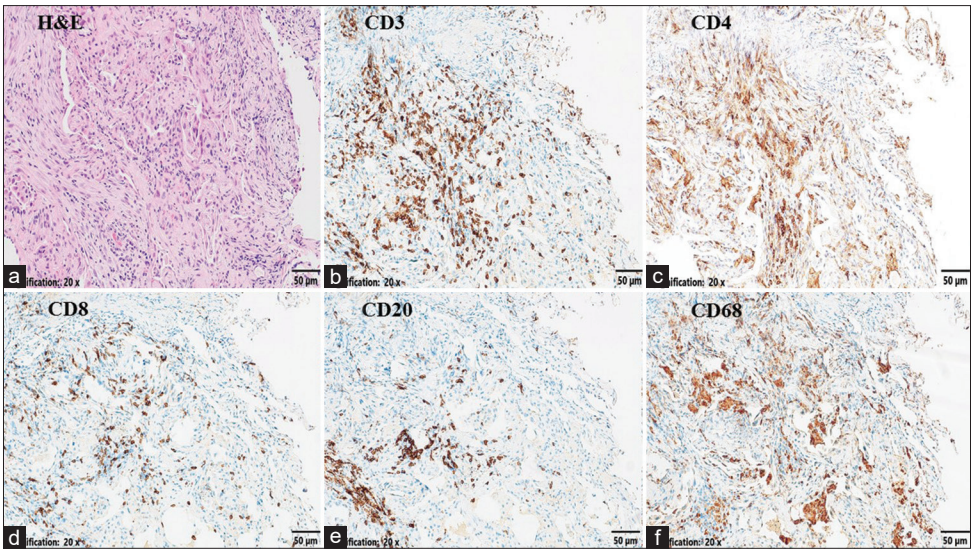

Figure 2: Histomorphology and immunohistochemical characterization of inflammatory cells in dermatomyositis-associated RPILD. Transbronchial biopsy showing organizing pneumonia with interstitial inflammation (a). CD3+ T lymphocytes sparsely distributed throughout the interstitium (b), and encompassed CD4+ (c) and CD8+ T cells (d). CD20+ B cells infiltrating the interstitium (e). The majority of CD68+ macrophages concentrated as clusters in the alveolar spaces (f). Magnification: ×20, bar length: 50 µm

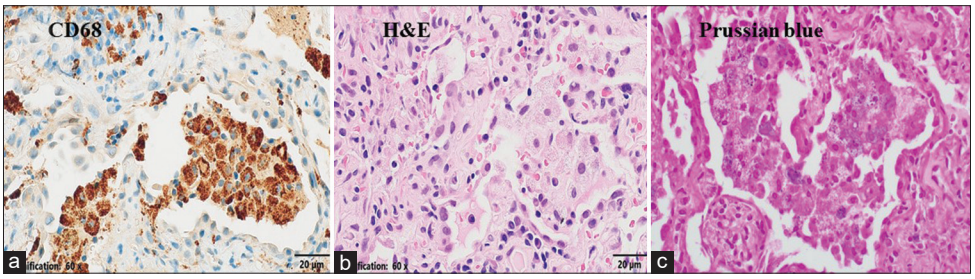

Figure 3: Histomorphology, immunohistochemistry and Prussian blue staining of macrophages in dermatomyositis-associated RPILD. CD68+ macrophages forming conspicuous clusters in alveoli (a) and displayed the characteristic morphology of "lipid-laden" macrophages (b). A faint bluish discoloration of cytoplasmic particles observed after Prussian blue staining indicated the presence of iron-binding macromolecular structures (c). Magnification x60, bar length: 20 µm

contrast, most CD68+ macrophages formed clusters predominantly in the alveolar spaces [Figure 3a]. On higher magnification, macrophages were "lipid-laden" with multilocular droplets [Figure 3b] and showed faint Prussian blue staining of iron-containing microparticles in the cytoplasm [Figure 3c], suggesting that they represent a source of ferritin, now considered as the most prominent and clinically useful biomarker in RPILD.[4]

Clinical course

Prednisone was increased to 1 mg/kg daily. Five days later, there was no clinical improvement. Pulse steroids were started in the form of methylprednisolone 1 g intravenously for 3 days. Subsequently, tacrolimus 0.5 mg orally twice daily was added to the regimen. Despite this, his condition kept worsening, and he was transferred to ICU because of worsening hypoxemic respiratory failure. He was started on intravenous immunoglobulin 40 g daily for 3 days and then given cyclophosphamide 800 mg intravenously without response. However, he continued to deteriorate and required ventilatory support for worsening respiratory failure (acute respiratory distress syndrome). He was considered for lung transplantation but found not to be a suitable candidate because of high risk being on ventilatory support and the likelihood of disease recurrence. After discussion with the family, the patient was designated not for resuscitation and the patient expired 6 weeks after admission.

Discussion

Idiopathic inflammatory myopathies (IIM), such as DM or polymyositis, are associated with a variety of respiratory manifestations including ILD, respiratory muscle weakness, pleural disease, aspiration, and infection.[5] Among those, ILD occurs in 65% of patients and is the most important complication that can cause significant morbidity and mortality.[5,6] In the Arab region, only one case series of IIM in adults was reported.[7] However, all patients had proximal muscle weakness and 90% had elevated CK. Interestingly, our patient had the DM variant without muscle involvement and normal

CK called clinically amyopathic DM (CADM), which is more common in Asians and in which ILD is also much less frequent but more severe than the classical DM.[4-6,8-11]

The exact mechanisms of RPILD are complex and yet to be elucidated. However, a recent study identified a circulating CD4+ T-cell subset characterized by the presence of CXCR4, a surface receptor for CXCL12.[12] This newly described T-cell population could play a crucial role in the florid inflammatory phase of RPILD. We hypothesize that the newly discovered pathogenic T-cells were among the CD4+ T-cell population beside other cellular components of innate and adaptive immunity such as alveolar macrophages, CD8+ T-cells, and B-cells.

Although it is generally stated that the prognosis is more favorable for ILD associate with CTD in comparison to their idiopathic counterparts,[3,9] specific groups in the former may have a catastrophic course. Among these, falls ILD associated with CADM, with a mortality exceeding 50%.[4,5,9,10] Recent research showed considerable heterogeneity within the IIM group. Specific autoantibodies were associated with phenotypes with varying degrees of pulmonary and extrapulmonary manifestations.[5,6] Of note, RPILD in association with MDA5 autoantibodies is a predictor of poor prognosis.[4-6,9,10,13] Others, such as the anti-synthetase group, have lower incidence and milder ILD and more favorable prognosis.[5,6,9] Unfortunately, these assays were not available to us, but the clinical picture and biopsy findings of our patient were highly suggestive of the MDA5 type. In this group, disease is often refractory to steroids and other immunosuppressive therapy and ends up with a fatal outcome.[5,6,9,10] Other autoantibodies may coexist, especially if there is an overlap with other CTDs such as Systemic lupus erythematosus (SLE) or systemic sclerosis.[5,6] Discovery of these autoantibodies may give insight to the pathogenesis of these diseases, which is believed to result from environmental factors (such as viruses) and genetic susceptibility, as indicated by racial variation and Human Leukocyte Antigen (HLA) predisposition.[5]

Guidelines on therapy have been published recently, but there is still lack of controlled trials on the optimal regimen.[14] Although the initial lung biopsy of our patient showed organizing pneumonia, which is associated with a favorable prognosis, his disease progressed despite high-dose corticosteroid and different immunosuppressive regimens. It is likely that the pathology evolved to diffuse alveolar damage and interstitial fibrosis. Kwan *et al*. reported a 62-year-old Vietnamese lady with a similar condition who received corticosteroids and mycophenolate who survived for nearly a year, but she was still left with considerable morbidity.[9] Novel therapies that may have a potential therapeutic role in the future include tofacitinib, a Janus kinase inhibitor.[4]

In conclusion, although ILD associated with CTD in general has a more favorable prognosis compared with the idiopathic type, certain phenotypes, can have a fulminant form (RPILD) that is refractory to modern therapy. It is prudent to be vigilant to clinical and laboratory clues to identify the high-risk groups of the "autoimmune" ILD to allow early intervention. Liaison between pulmonologists and rheumatologists and more collaborative research with basic scientists is required for newer approaches and innovative therapies to improve the outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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