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Case report

Asymptomatic necrotizing myositis in a young male with progressive interstitial lung disease

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ABSTRACT

Necrotizing autoimmune myopathy (NAM) is a rare inflammatory process characterized by bilateral proximal muscle weakness and elevated creatinine kinase levels. It is one of the idiopathic inflammatory myopathies. It can be associated with anti-signal recognition particle (SRP) antibody which is commonly seen in middle-aged females. Classic findings on muscle biopsy include muscle fiber necrosis without inflammation. Pulmonary manifestations associated with anti-SRP NAM is rare, and often a challenging correlation to make as our understanding of inflammatory myopathies and interstitial lung disease is still evolving. There have been some associations of Anti SRP NAM with NSIP which responds to corticosteroids. We present a 29 year old male with asymptomatic NAM who presented with a combination of NSIP and pulmonary arterial hypertension (PAH). His PAH was responsive to oral vasodilator therapy however his interstitial lung disease (ILD) rapidly progressed to usual interstitial pneumonia (UIP) requiring lung transplantation. This case highlights 1) an extremely rare presentation of rapidly progressive NAM associated ILD in a young man, in which pulmonary manifestations occurred in the absence of myopathy, 2) The importance of doing a complete work up for interstitial lung disease, including diligent examination for myopathic features and obtaining CK levels, 3) Identifying that interstitial lung diseases can progress despite control of the underlying etiology with corticosteroids and immunosuppressives, 4) Recognition of pre capillary PAH in patients with disproportionally elevated pressures relative to their pulmonary findings, 5) The first report of treatment responsive pulmonary vascular disease associated with NAM, and 6) The importance of early lung transplantation evaluation.

1. Background

Necrotizing autoimmune myopathy (NAM) is a rare inflammatory process characterized by bilateral subacute proximal muscle weakness and elevated creatinine kinase levels [1]. It is an idiopathic form of inflammatory myopathy that includes polymyositis, dermatomyositis, and inclusion body myositis. Etiologies associated with NAM include anti-signal recognition particle (SRP) antibody, malignancy, statin use, and connective tissue diseases [1]. Muscle biopsy classically reveals muscle fiber necrosis without inflammation [2]. Those with Anti-SRP are most commonly middle aged females [3,5,6]. Pulmonary manifestations are uncommon, albeit when present NSIP of mild severity is most commonly identified [4]. Pulmonary arterial hypertension has not been associated with anti-SRP NAM [7]. The clinical course of anti- SRP NAM is variable with usual treatment strategies including a combination of steroids with immunosuppressants largely based on clinical expertise [6].

We report a rare case of anti-SRP NAM causing rapidly progressive interstitial lung disease and pulmonary arterial hypertension in a young male with asymptomatic myopathy.

2. Case

A 29 year old male without significant past medical history presented with progressive exertional dyspnea and cough over the past three years. The cough started as intermittent and productive of yellow sputum. It was not associated with any exposures or eating, and he did not have chest tightness or wheezing. About one month prior to presentation, his

Abbreviations: NAM, necrotizing autoimmune myopathy; SRP, signal recognition particle; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; V/Q, perfusion/ventilation; RHC, right heart catheterization.

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cough became more frequent and he was dyspneic while walking short distances. He denied joint pain, swelling, skin changes, weakness, Raynaud's, eye pain, urinary symptoms, fevers, or changes in weight. He did not have pets at home and was without exposures to birds. He denied recent travel. He did not smoke and never vaped. He had no family history of pulmonary disease.

On exam, he had scattered crackles at the bases and was hypoxic to 86% on room air requiring 2 L supplemental oxygen. Initial chest x-ray showed bilateral hazy interstitial opacities. Blood work showed an elevated troponin of 0.35, creatine kinase (CK) of 3,610, (U/L) beta-type natriuretic peptide of 355 (pg/ml), alanine aminotransferase of 150 (U/L), aspartate aminotransferase of 131 (U/L), serum creatinine of 0.85 (mg/dL) and a white blood cell count of 8.8 (THOU/uL). An echocardiogram showed moderate right ventricular enlargement and a positive "D" sign consistent with right ventricular pressure overload. CT of the chest was without pulmonary embolism, but showed interstitial changes consistent with NSIP, ground glass opacities, and extensive hilar and mediastinal lymphadenopathy (Fig. 1).

He underwent endobronchial ultrasound fine needle aspiration and bronchoalveolar lavage (BAL). Histology from the mediastinal lymph node did not show granulomas or a monotypic B cell population. The BAL showed increased CD4:CD8 ratio of 9.6 among T-cells. He was referred for evaluation of PAH as his right ventricular dysfunction was felt to be out of proportion to the severity of interstitial lung disease. A perfusion scan excluded chronic thrombotic disease. A right heart catheterization (RHC) showed pre capillary pulmonary hypertension (Table 1). A presumptive diagnosis of undifferentiated interstitial lung disease (ILD) with PAH was made. His baseline FEV1 was 32% predicted (Table 3). He had not received any immunosuppression or corticosteroid therapy at this point, thus treatment for ILD and PAH was warranted prior to lung transplant evaluation.

He started combination vasodilator therapy with tadalafil and ambrisentan. At 3-month follow up he had significant improvement in dyspnea only requiring supplemental oxygen at night. His echocardiogram no longer showed right ventricular pressured overload. His CK remained elevated at 5349 (U/L) (Fig. 2). He continued to deny extremity pain, weakness or sensory changes. On exam, he had normal muscle tone and strength. Serologic testing for an underlying rheumatologic condition was negative (Table 2). A myositis workup was performed and positive for anti-SRP antibody (Table 2).

He was referred to a neuromuscular neurologist and did not have any weakness or sensory changes on their exam. He underwent a right quadriceps skeletal muscle biopsy that showed necrotizing myopathy without inflammatory cell infiltrates, ragged red fibers consistent with autoimmune necrotizing myositis. He was started on mycophenolate mofetil and prednisone 40 mg daily with improvement in CK (Fig. 2). Twelve months after being on immunosuppression he started to notice worsening dyspnea with activity. An echocardiogram showed a normal right ventricle without echocardiogram estimated pulmonary hypertension. Pulmonary function testing showed a rapid decrease in diffusing capacity (Table 3), which prompted a repeat CT Chest that showed the prior NSIP pattern had transformed into an usual interstitial pneumonia pattern (UIP) (Fig. 1).

Pirfenidone was added and his supplemental oxygen requirements increased to 4–6 L/min. Given the rapid progression he was urgently referred for evaluation of lung transplantation. A repeat RHC showed improved hemodynamics (Table 1). Two months after evaluation his respiratory status continued to decline and successfully underwent bilateral lung transplant. At the time of transplant, his CK remained normal (Fig. 2). Histology from the explanted lung showed chronic fibrosing interstitial pneumonia with mixed features of UIP and fibrotic NSIP, as well as identification of myointimal thickening of the pulmonary arteries (Fig. 3).

Table 1
Right heart catheterization.

	Baseline	18 months
Right atrial pressure (mmHg)	5	1
Mean pulmonary artery pressure (mmHg)	34	20
Pulmonary vascular resistance (WU)	4.95	3.81
Pulmonary capillary wedge pressure (mmHg)	15	10
Cardiac index (L/min/m^2)	2.26	2.69

Table 2
Serologic testing for interstitial lung disease.

Anti- RNP	<0.2 AI
Anti-Smith	<0.2 AI
Anti- RO/SS-A	1.1 AI
Anti- LA/SS-B	<0.2 AI
ANA Screen	Negative
ANCA Screen	Negative
Cyclic Citrullin Peptide	6 U
dsDNA Ab	1 IU/mL
PM/SCL-100 IgG	Negative
Rheumatoid Factor	<10
Scleroderma SCL-70	<0.2 AI
SM/RNP AB	<0.2 AI
SAE (SUMO activating enzyme)	Negative
NXP-2 (Nuclear matrix protein)	Negative
MSA5 (CADM-140) AB	Negative
TIF-1 gamma (155-kDa AB)	Negative
SRP AB	Positive
M1-2 (nuclear helicase protein) AB	Negative
P155/140 AB	Negative
Jo-1 IgG AB	0
KU AB	Negative
Ribonucleic Protein (U1) IgG AB	0
Fibrillarin (U3 RNP) IgG AB	Negative

Table 3
Changes in FEV1 and DLCO overtime.

	Baseline	12 Months	15 Months
FEV1 (L)	1.06 (32%)	1.01 (29%)	1.02 (27%)
DLCO (ml/min/mmHg)	20.63 (67%)	4.57 (15%)	1.43 (5%)

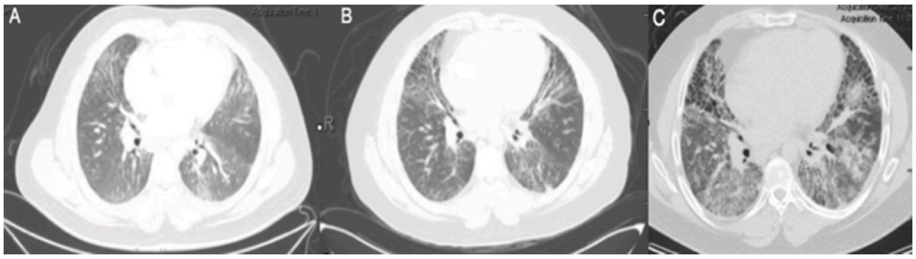

Fig. 1. CT chest coronal views showing rapidly progressive interstitial changes. On presentation there was diffuse ground glass opacities (A). Imaging three months later showed areas of ground glass opacities and early honeycomb cyst formation and traction bronchiectasis (B). CT imaging 18 months later showed progressive inflammatory and fibrotic changes suggesting previous NSIP pattern had transformed into an usual interstitial pneumonia pattern (C).

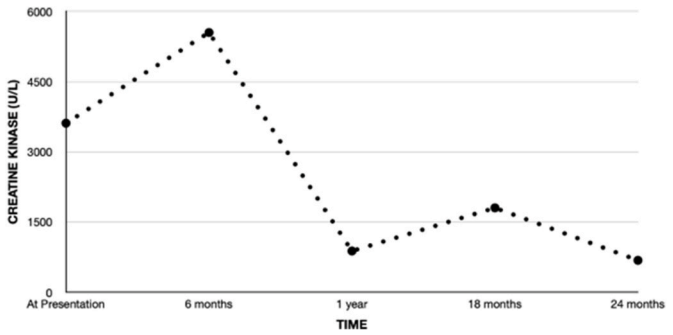

Fig. 2. Creatinine kinase levels trended over time. Immunosuppression was started after the 6-months.

3. Discussion

We present a rare case of a young man with amyopathic anti-signal recognition particle (SRP) necrotizing autoimmune myopathy (NAM) requiring bilateral lung transplantation due to rapidly progressive interstitial lung disease (ILD), despite high dose immunosuppression, and treatment responsiveness pulmonary hypertension with vasodilator therapy.

Idiopathic inflammatory myopathy are a rare group of diseases that include NAM, dermatomyositis, polymyositis, and inclusion body myositis. They typically present with proximal symmetric muscle weakness in combination with an elevated creatinine kinase [1,6]. NAM is identified on muscle biopsy by the absences of inflammation, and presence of macrophages surrounding prominent necrotic muscle fiber. The lack of MHC-I staining and inflammatory cell infiltrate suggests cytotoxic lymphocytes or cell-mediated destruction is not occurring which differentiates it from the other inflammatory myopathies [2]. Instead, this may be an antibody-dependent complement-mediated lysis. NAM can be caused by autoantibodies (anti-SRP typically), malignancies, statin use, and connective tissue diseases [1]. Anti-SRP, which is present in ~4.9–20% of cases of NAM [5], is found primarily in middle-aged females [4]. There are no randomized therapy trials, but corticosteroid therapy is the mainstay of treatment with additional immunosuppression needed based on initial response.

The lung is a common target for extra-muscular site in idiopathic inflammatory myopathies [8]. Anywhere from 20 to 86% of patients have been found to have ILD [8]. In 20% of cases ILD can precede muscle symptoms [9]. Multiple antibodies have been associated with ILD development in dermatomyositis and polymyositis [10]. For example, in dermatomyositis, anti-Mi-2 is specific for diagnosis of the disease, and presence of anti-melanoma differentiation-associated gene 5 (anti--MDA5) positivity increases the risk of development of ILD [11]. Anti-Jo-1, anti-PL-7 and anti-PL-12 antibodies have been seen in multiple case series to have a higher risk of ILD [12,13]. In amyopathic dermatomyositis, anti-melanoma differentiation-associated gene 5 (anti-MDA5) is strongly associated with a rapidly progressive ILD; polymyositis is associated with more severe ILD [14,15].

Interestingly, there may be protection in younger ages as juvenile cases are not typically associated with ILD development [16]. High resolution CT and biopsy are associated with NSIP and UIP is seen less often [8,17]. There are no randomized trials for treatment of ILD, but glucocorticoid therapy and combination immunosuppression therapy have been used successfully [10]. Morbidity and mortality is associated with ILD severity and does not correlate with myositis activity [8,10]. Pulmonary arterial hypertension can be associated with dermatomyositis and polymyositis, and in the absence of ILD, treatment with vasodilator therapy appears favorable [18].

There is less reported about pulmonary involvement and outcomes in the setting of anti-SRP associated NAM. One report evaluating all case reports and series found 17% of patients had mild ILD with NSIP being the predominant pattern seen on CT imaging [5]. Most patients appear to respond to immunosuppression therapy [5,19]. The French Pulmonary Hypertension registry found dermatomyositis was the only inflammatory myopathy associated with PAH and did not find any anti-SRP cases [7]. Our patient is much younger than what is typically associated with anti-SRP NAM lung disease, and had a much more severe and rapidly progression from NSIP to UIP. We want to highlight the importance of doing a complete ILD work up, including checking CK, on all patients regardless of age and symptoms. Despite having an elevated CK during his initial work up a myositis evaluation was not done until after PAH diagnosis was made. We also want to point out that after starting combination vasodilator therapy he had a favorable clinical response without disrupting V/Q matching, which suggests there was a pulmonary vascular component along with his ILD. Even though he did have interstitial inflammation on diagnosis, his degree of pulmonary hypertension was out of proportion to the lung disease and warranted a trial of vasodilator therapy. Had this not been done early on in his treatment his pulmonary hypertension may have precluded him from transplantation. Finally, this supports the notion that myositis activity and pulmonary disease do not follow the same trajectory and close monitoring of both systems are warranted. Especially in younger patients, early evaluation with lung transplantation is key in improving long term outcomes.

In conclusion, we present a young man with amyopathic anti-SRP associated NAM with rapidly progressive ILD requiring bilateral lung transplant and treatment responsive PAH. This case highlights the importance of doing a complete ILD evaluation including CK in order to make a proper diagnosis. Pulmonary hypertension could be a contributing factor and should not be overlooked because of interstitial lung disease. These complex patients should be managed by a multiple disciplinary team including pulmonary, rheumatology, neurology with neuromuscular specialty, and early transplant evaluation in selected patients.

Author statement

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval

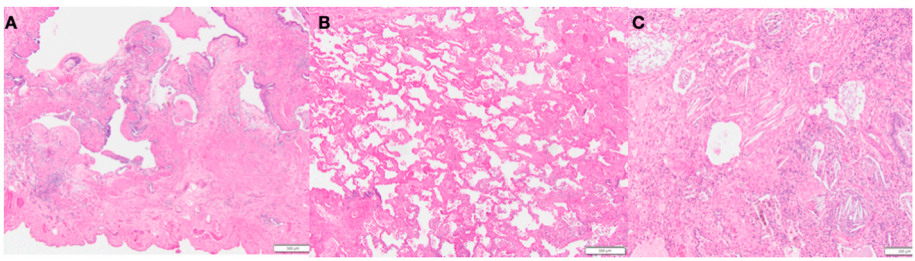

Fig. 3. Histology from the explanted lungs showed **c**hronic fibrosing interstitial pneumonia with mixed features of UIP (A), fibrotic NSIP (B), and chronic interstitial inflammation, eosinophils and airspace cholesterol granulomas (C).

of the version to be submitted.

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Declaration of competing interest

The authors declare no Conflicts of Interest (COI) in association with this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2021.101374.

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