CLINICAL VIGNETTE

Lungs on Fire

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Case Presentation

A 42-year old woman presented to pulmonary with shortness of breath on exertion. She explained that over the past year she went from working out daily to now getting tired walking short distances. She also complained of a burning, fiery sensation in her lungs. A year ago, she started prednisone and methotrexate for diffuse muscle and joint pain. She was recently hospitalized for pneumonia, but despite antibiotic therapy she was unable to complete routine activities like bathing and cooking without rest. Her chest x-ray showed bilateral lung infiltrates consistent with ongoing pneumonia. Her oxygen saturation dropped to 93% with walking. Follow up chest computer tomography (CT) identified lower lobe predominant, diffuse bilateral fibrosis with significant ground glass opacities (GGO) and sparing of the subpleural spaces suggesting nonspecific interstitial pneumonia (NSIP, Figure 1A). Pulmonary function test (PFT) showed low forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) (both less than 80%) with a severe deficit (less than 40%) in the diffusion of carbon monoxide (DLCO). She was unable to perform total lung capacity testing, but the low FVC and FEV1 suggested restrictive lung disease and reduced DLCO is a marker of poor alveolocapillary gas exchange (Table 1).

Previous rheumatology evaluation reported proximal muscle weakness, skin discoloration over the metacarpophalangeal joints and thickened skin over the finger tips. Discoloration of the fingers was also noted with temperature changes. Initial laboratory results showed a normal complete blood count, basic metabolic panel with elevated aldolase (Ald 35, normal range 1-7.5 U/l) and creatinine kinase (CK, 3254, normal range 22-199 U/L). Lactate dehydrogenase (LDH), thyroid stimulating hormone (TSH) and liver transaminases were normal. Serum autoantibody testing was positive for aminoacyl-transfer RNA synthetase (Jo-1) antibody. Additional comprehensive testing for autoantibodies was negative. These included antinuclear anti-body (ANA), anti-double stranded DNA (DsDNA), rheumatoid factor (RF), cyclic cytrullinated peptide (CCP), anti-Smith (SM), anti-Sjogren Syndrome A/B (SSA(Ro)/ SSB(La), anti-U1 ribonucleoprotein (RNP), anti-topoisomerase Scleroderma-70 (Scl-70), anti- polymyositis-scleroderma (PM-Scl) and Anti-Ku were negative. A diagnosis of dermatomyositis was made based on clinical picture and autoantibody profile. Skin and muscle biopsies were not performed. Age appropriate cancer screening including mammogram, colonoscopy, gynecological exam, screening abdomen-pelvis CT was normal.

The case was presented at multidisciplinary interstitial lung disease (ILD) conference, which recommended substituting the methotrexate with mycophenolate and the addition of intravenous immunoglobulin (IVIG). The combination treatment resulted in significant improvement in laboratory results Ald=10, CK=69, but no change in her shortness of breath. Repeat multidisciplinary discussion recommended the addition of rituximab (RTX) to the treatment regimen. She received 2 cycles of RTX with 2 concomitant doses 4 months apart. Following RTX treatment she enrolled in pulmonary rehabilitation. Her lung function significantly improved and she was able to complete 1 hour exercises. PFT results before and after RTX are shown in Table 1. Follow up CT imaging showed pulmonary fibrosis with reduction in GGO (Figure 1B). An incidental 21 mm left thyroid nodule was also discovered on follow up CT. The original chest CT did not include the thyroid tissue and the onset of the nodule remains unclear. Fine needle biopsy identified chronic lymphocytic thyroiditis combined with papillary thyroid carcinoma (Figure 2A and 2B). The patient underwent total thyroidectomy. Post thyroidectomy there was further improvement in physical functioning and she remains in a stable condition on medication.

Discussion

Dermatomyositis is a rare autoimmune disease with an estimated prevalance of 13:100,000.[1] It is a form of idiopathic inflammatory myopathies characterized by a skin rash (Table 2) and progressive proximal symmetrical muscle weakness.[2] Dermatomyositis is often described in conjunction with polymyositis and they represent separate, but often overlapping subtypes of idiopathic inflammatory myopathies. The diagnosis is usually based on clinical exam findings, elevated CK, LDH, liver transaminases levels and a positive Jo-1 antibody. Muscle biopsy usually aids the diagnosis but in the presence of a typical rash, DM can be diagnosed without histology.[2] With the routine testing of circulating blood autoantibodies new subtypes of DM were discovered including: A. Amyotrophic DM, characterized by skin changes without muscle involvement and with the

presence specific autoantibodies, B. Overlap syndromes, a combination of DM with other collagen vascular diseases and C. Antisynthetase syndrome, which is a clinical and serological constellation of a positive anti-t-RNA synthetase antibody, myositis, mechanics' hands, Raynaud phenomenon, ILD, fever and non-erosive arthritis. The diagnosis of DM subtypes relies on the autoantibody profile of the individual patient which can also determine the prognosis. In general, with a clinical suspicion for DM, a complete blood laboratory workup for ANA, SSA/B, DsDNA, RF, CCP, SM, RNP, SCL-70, PM-Scl, Ku antibodies and an extended myositis panel is recommended. Myositis laboratory panels contain an extensive list of autoantibodies, which have been associated with a variety of IIM. From the pulmonary perspective the anti t-RNA synthetases Jo-1, PL7, PL12 and antimelanoma-associated gene (MDA)-5 are the most important. It is estimated 68% of patients with Jo-1 and 90 % of patients with PL antibodies develop ILD.[3] MDA-5 antibodies are almost always associated with rapidly progressive lung disease.[3,4] Unfortunately, there is a paucity of data on the prognosis of DM but it is generally considered poor. The mortality of IIP is estimated to be 3-fold of the general population.[5] The one-year mortality of DM is 9-10% and most people who survive 5 years, have a significant residual disability.[6,7] Observational studies suggest that respiratory complications are the leading cause of morbidity and mortality during the first year followed by cardiac and oncological problems later in the course of the disease.[5,8,9] ILD is the most common respiratory complication in DM, but pneumonias, dysphagia, aspiration, drug toxicities, pulmonary hypertension, pneumothoraces and respiratory muscle weakness also occur. A list of ILD associated with DM is shown in Table 3. Because the high risk for ILD in DM, high resolution chest CT scan and PFT are recommended at the time of diagnosis. PFT results usually show low lung volumes with decreased DLCO out of proportion to the extent of the lung disease on imaging. We usually follow the patients with PFT every 6 months because the FVC and DLCO tracks with the extent of lung pathology. Generally a 10 % change in forced FVC and 15% change in DLCO over 6 months is considered significant.[10] Invasive lung diagnostic is rarely needed in DM and usually discouraged due to the fear of ILD progression post biopsy.

The principle of treatment in DM-associated ILD is immunosuppression, guided by rheumatology. High dose oral steroids (0.5mg to 2mg/kg) followed by long-term antimetabolites e.g., azathioprine, methotrexate or mycophenolate are usually the first choice of therapy. IVIG is often added to reduce the circulating autoantibody burden. More recently, RTX, a monoclonal antibody to B-cell marker CD22, have been used for relapsed cases resulting in improved lung function.[11] However, its effect on the long-term outcome is unknown.[11,12] Malignancies have been associated with DM and population-based studies show that the risk of cancer is 6 to 8 times higher in IIM than in the general population.[13] The most common tumors in DM are nasopharyngeal, lung and breast cancers.[7] While the relationship between DM and malignancies is not well understood, cancers are the leading long-term cause of death in DM.[5] It is speculated that the abnormal immune response seen in DM is generated by tumor surface markers detected as myositis specific circulating antigens. In about 60% of patients the malignancy is discovered at the same time as DM, suggesting DM could be a paraneoplastic syndrome.[14] Ongoing immunosuppression may also be a contributing factor, but the risk of malignancy decreases with time in IIM, suggesting that immunosuppressive medications are not the major reason for the high incidence cancers in DM.[15] Thyroid papillary tumors, described in our patient are rare in DM, likely due to the low detection rate.[16]

Conclusion

Our case illustrates the close relationship of DM, ILD and malignancy. Given the poor outcomes of ILD in DM, a multidisciplinary plan should be formatted which includes active cancer surveillance for at least five-year post diagnosis.[7]

Figures

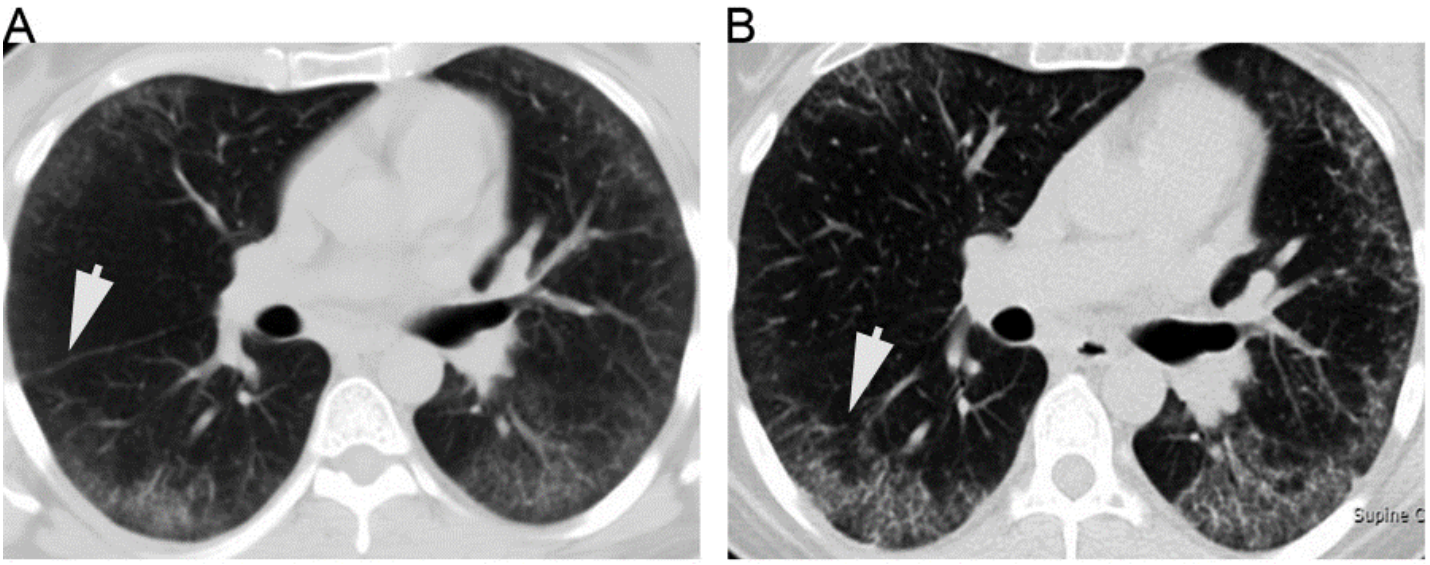

Figure 1. CT image of nonspecific interstitial pneumonia (NSIP) in our patient with dermatomyositis. A. In early, cellular NSIP, diffuse bilateral ground glass opacities (GGO) are indicators of ongoing lung inflammation. The arrow points at clear demarcation between normal and diseased lung (straight edge sign). B. CT scan two years later with fibrotic NSIP and resolution of GGO. The arrow points at fibrosing lung tissue.

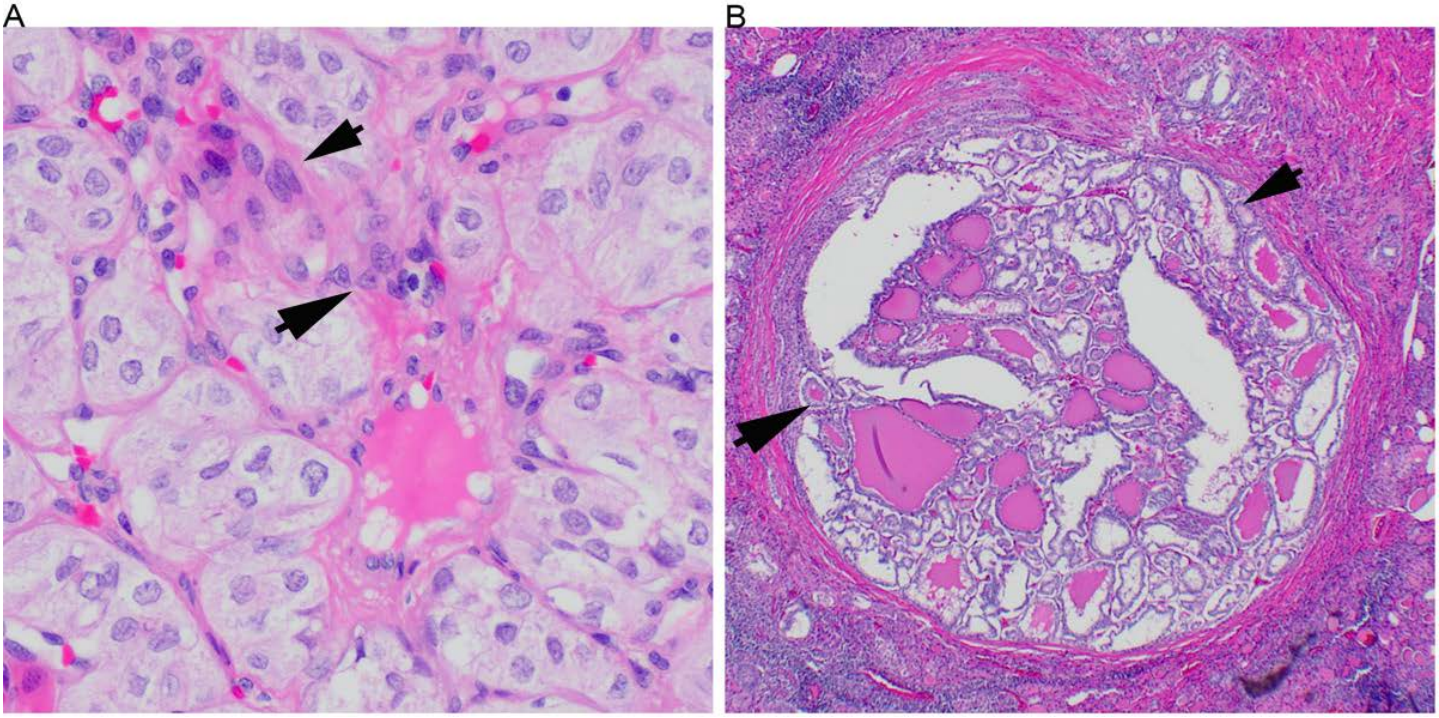

Figure 2. Papillary thyroid cancer histology post thyroidectomy in our patient. A. Low magnification image of hyalinizing trabecular tumor, which is fairly well-circumscribed arranged in wide trabeculae and small nests. Arrows are pointing at medium to large-sized and polygonal to elongated tumor cells, oriented perpendicular to the trabeculae. The cytoplasm is variably eosinophilic to clear. The background thyroid has features of chronic lymphocytic thyroiditis. Hematoxylin-eosin staining. B. High magnification image of the papillary thyroid carcinoma focus. Arrows are pointing at tumor cells with characterized by large nuclei, elongated shape, which are convoluted with prominent grooves, vacuoles and membrane irregularities.

Tables

Table 1. Pulmonary function testing results before and after rituximab treatment

	FVC	FEV1	FEV1/FVC	DLCO
Baseline PFT	2.63 (70)	2.34 (75)	89	8.85 (39)
Post RTX PFT	3.03 (82)	2.7 (88)	89	10.51 (47)

PFT=pulmonary function test, RTX= rituximab, FVC=Forced vital capacity, FEV1=forced expiratory volume in the first second, FEV1/FVC= ratio of FEV1/FVC, DLCO=diffusion capacity of carbon monoxide

Table 2. Typical skin manifestations in Dermatomyositis

Pathognomic rashes in dermatomyositis	
heliotrop rash	purple erythematous patches over the eyes with surrounding edema
Grotton's papules	erythematous papules over the extensor surfaces of fingers, elbows, knees and toes
Grotton's sign	erythematous non-palpable macules at the extensor surfaces
Skin findings commonly seen in dermatomyositis, but not specific to the disease	
facial erythema	erythema over the cheeks and nasal bridge involving the nasolabial fold
V-sign	erythematous macules on the anterior chest and neck
shawl sign	erythema of the posterior neck, shoulder and upper back
mechanics' hands	hyperkeratotic, cracked, horizontal lines of volar and lateral side of the fingers
periungual telangiectasia	dilated vessels around the fingernails
polikiloderma	atrophic skin with pigmentation of the scalp and non-light exposed areas e.g., thighs (Holster sign)
calcinosis cutis	calcium salt deposition in cutaneous and subcutaneous tissue
Raynaud phenomenon	temperature sensitive discoloration of the fingers and toes

Table 3. Common forms of interstitial lung disease in dermatomyositis

interstitial lung disease	radiographic presentation
nonspecific interstitial pneumonia (most frequent)	diffuse bilateral ground glass opacities without lobar predominance (early cellular stage) diffuse bilateral fibrosis with sharp distinction between fibrotic and normal lung (straight edge sign) extensive honeycombing (advanced, fibrotic stage)
usual interstitial pneumonia	bilateral lower lobe predominant fibrosis with traction bronchiectasis and honeycombing
organizing pneumonia	bilateral, patchy consolidative opacities without lobar predominance
acute interstitial pneumonia (Hammond-Rich syndrome)	acute, progressive, bilateral extensive infiltrates without history of lung disease It is the radiological representation of diffuse alveolar damage.

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