Case report

Mycobacterium avium complex infection in a patient with systemic sclerosis-associated interstitial lung disease: A case report

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A B S T R A C T
We describe a case of a 65-year-old male with recently diagnosed diffuse cutaneous systemic sclerosis associated with usual interstitial pneumonia and pulmonary hypertension. Patient presented to the emergency department complaining of low-grade fever, increased sputum production, progressive dyspnea and weight loss. High-resolution computed tomography scan showed multifocal bronchiectasis with multiple small nodules. Bronchoalveolar lavage culture was positive for Mycobacterium intracellulare. Antimicrobial treatment was started which improved respiratory symptoms. One month after the initiation of antibiotics, cyclophosphamide therapy was started with adequate tolerance.

1. Resumen y palabras clave
Se presenta el caso de un hombre de 65 años con diagnóstico reciente de esclerosis sistémica varidad difusa asociada a neumonía intersticial usual e hipertensión pulmonar. Acudió al servicio de urgencias por fiebre, incremento en la producción de esputo, disnea progresiva y pérdida de peso. Una Tomografía de tórax de alta resolución evidenció bronquiectasias multifocales con nódulos múltiples. El cultivo de lavado bronchoalveolar fue positivo para Mycobacterium intracellulare. Se inició terapia antibiótica la cual condujo a una mejoría de los síntomas respiratorios. Después de un mes del inicio de los antibióticos, se inició manejo con Ciclofosfamida con adecuada tolerancia.

Palabras clave: mycobacterium avium complex, esclerosis sistémica, enfermedad pulmonar intersticial.

2. Introduction
Systemic sclerosis is a systemic connective tissue disease characterized by fibrosis of skin and internal organs, vasculopathy and immune dysregulation with autoantibodies production [1]. Interstitial lung disease (ILD) and Pulmonary arterial hypertension (PAH) are frequent manifestations, occurring early in the course of the disease if it is a diffuse cutaneous systemic sclerosis variety. These conditions lead to a detriment in quality of life and are currently the leading cause of death in systemic sclerosis [2].

Based on the evidence from two double-blind, randomized trials (Scleroderma Lung Studies I and II [SLS-I and SLS-II]) in patients with symptomatic systemic sclerosis-related interstitial lung disease, the immunosuppressants cyclophosphamide and mycophenolate are both beneficial in improving thickening of the skin, dyspnea, lung function and health-related quality of life [5,6]. However, these immunosuppressants should be started with caution and based on a risk-benefit analysis; clinicians should always consider the patient’s risk of developing toxicity and infection.

In the following case, patient presented several features that indicate a high risk of disease progression and severe restriction, this makes him a good candidate for immunosuppression; the elements taken into consideration were: male sex, black race, low baseline FVC and DLCO, diffuse systemic sclerosis variety, rapid insaturation of lung disease, dyspnea with minimal exertion, presence of fibrosis on CT scan and lung biopsy, and disease affecting more than 20% of the lungs [5,6].

However, during the initial evaluations, it was evident that he was currently presenting a pulmonary Mycobacterium avium complex infection. This event postponed the initiation of immunosuppressants and implicated a diagnostic and clinical challenge.
3. Case report

A 65-year old male presented at our emergency department on February 10th, 2019. He was complaining of low-grade fever, increased sputum production, progressive dyspnea, pyrosis and weight loss.

He is of Colombian origin, and used to work as a mechanical engineer producing hard metals. His past medical history included diffuse cutaneous systemic sclerosis and recurrent venous thromboembolism on 1995 and 2013 without an identifiable cause. His medication included acetylsalicylic acid (100 mg/day). He was a former smoker (from age 33 to 63; 40 pack-year). In his family history his mother had rheumatoid arthritis.

He complained of dyspnea that had worsened over the last year, occurring with minimal exertion at the time of evaluation. Chronic, persistent cough, that in the past month was associated with expectoration of mucoid sputum. He also complained of unexplained weight loss.

Physical examination showed a vitiligo lesion on the forehead region, bilateral basal Velcro crackles, Raynaud’s phenomenon, skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints and digital pitting scars.

High-resolution chest computed tomography revealed ground-glass opacities, multifocal bronchiectasis with basal predominance, multiple small nodules, reticular opacities and an obvious apicobasal gradient with no honeycombing. Distal esophageal dilation was also noted. (Fig. 1). Radiological patterns were indicative of non-specific interstitial pneumonia (NSIP), esophageal dilation seen correlated with the presence of pyrosis.

Spirometry showed FVC of 1.79 L (40% of the predicted), FEV1 of 1.72 L (50% of the predicted). DLCO: 37% of the predicted. 6-Minute walk test: 424 m (78% of the predicted) and patient develop desaturation during the study.

Peripheral blood count, renal and liver functions were normal. Indirect immunofluorescence test for antinuclear (ANA) antibodies was positive (titer ≥ 1:1280, nuclear coarse speckled pattern). Testing for rheumatoid factor, anti-cyclic citrullinated peptide, anti-extractable nuclear antigen, and anti Scl-70 was negative. Transthoracic echocardiogram was unremarkable but for a pulmonary artery pressure (PAP) of 55 mmHg. Skin biopsy confirmed scleroderma.

A thoracoscopic lung biopsy was taken. Histopathology showed representative vascular lesions suggestive of pulmonary arterial hypertension, and fibrotic lung disease with heterogeneous distribution, fibroblastic foci and honeycombing consistent with a usual interstitial pneumonia (NIU) pattern (Fig. 2) (Fig. 3) (Fig. 4).

He underwent bronchoscopy with bronchoalveolar lavage and multiple samples were gathered. Mycobacterium culture was positive for Mycobacterium intracellulare.

Four weeks after the bronchoscopy, patient presented again to the emergency department complaining of fever, dyspnea, loss of appetite, night sweats and general malaise. At the time of hospital admission, the patient was febrile (38.4 °C), his heart rate was 112 beats per minute and respiratory rate of 22 breaths per minute. Based on these clinical findings and due to the presence of multifocal bronchiectasis, pulmonary nodules an a positive bronchoalveolar lavage culture; treatment for Mycobacterium avium complex infection was started with Ethambutol 25 mg/kg three times per week, Rifampicin 600 mg three times per week and Azithromycin 500 mg three times per week. Symptoms improved during the first month of treatment and no adverse reactions has been reported. Two months after, patient was started on prednisolone 10 mg daily. And immunosuppression with cyclophosphamide was started with a dose of 500 mg/m² of surface area, administered in an ambulatory manner every month. Patient’s dyspnea and exercise capacity has remain stable.

4. Discussion

Mycobacterium avium complex (MAC) is extensively found in the environment, including natural or treated freshwater, saltwater, house dust and soil. The bacteria is manly acquired through inhalation or ingestion, but can also enter the organism through direct inoculation via an invasive procedure or trauma. Only producing infection in a minority of the exposed [7].

MAC is isolated from the sputum and bronchoalveolar lavage of healthy subjects; but it may cause infection or be associated with other lung diseases and cause their progression [8,9].

The epidemiology of pulmonary MAC disease is difficult to establish because it is a rare condition, the differentiation between colonization and disease is troublesome and it is not mandatory to report its occurrence; most countries do not require this infection to be reported because there in non-proven person-to-person transmission [10].

Host susceptibility almost always plays a key role in the development of the disease. Susceptibility can be divided in those with anatomical lung conditions either genetically determined or acquired, those with immunological abnormalities and those with no known lung condition, immunological disease or immunosuppression [11].

Lung disease seems to the be the primary risk factor; conditions that are commonly associated with the disease are cystic fibrosis, chronic obstructive pulmonary disease, prior Mycobacterium tuberculosis disease,
In this case report, despite his history of tobacco use, patient did not recall any chronic respiratory disease or previous infections prior to the onset of the respiratory symptoms that motivated his visits to the emergency department. However, he has a condition (Systemic sclerosis) in which several humoral and cellular immunological abnormalities occur, an associated pulmonary interstitial disease with bronchiectasis and an esophageal compromise [13].

Collagen vascular diseases have been identified in up to 16.9% of Japanese patients with pulmonary MAC disease [14]. However, it is unclear if the infection was related to the disease immunological abnormalities or to the use of immunosuppressive drugs such as methotrexate, corticosteroids and TNF-α antagonists [15].

Immunity to Mycobacteria relies on the (IL-12/IFN-γ) pathway, which connects the myeloid with the lymphoid cells [16]. The critical cell for controlling MAC infection is the macrophage. After engulfing the bacteria, it produces IL-12, which stimulates T lymphocytes and natural killer cells. STAT4 is then activated, which leads to IFN-γ production, this cytokine activates and differentiates macrophages, increasing expression of TNF-α and IL-12. Activated macrophages will be able to destroy intracellular organisms like MAC [17]. Understanding the immune response to this infection, enable us to understand why several immunosuppressive drugs commonly used in collagen vascular diseases and that alterations in innate and adaptive immune response, as seen in Systemic sclerosis, impairs the body’s ability to control MAC infection [18].

Patient has a history of working in milling and grinding metal components and during these procedures, metal working fluids (MWF) are used. Contaminating non-tuberculous mycobacteria has been identified in almost all metal working fluid samples; particularly in samples coming from workplaces with cases of acute and chronic hypersensitivity pneumonitis (105 out of 107 MWF samples from 10 United States workplaces) [19]. A finding that has been noted in other studies, which has led some authors to consider that this bacteria has an increased capacity to cause colonization in this setting, and this occurrence, is a risk factor for hypersensitivity pneumonitis development [20].

Pulmonary interstitial diseases (ILDs) have been identified in up to 7.3% of Japanese patients with pulmonary MAC disease [12]. There is evidence that hypersensitivity pneumonitis and idiopathic pulmonary fibrosis are high risk conditions for developing pulmonary MAC disease, however, it is unclear if this findings can be extrapolated to other ILDs [21].

It was considered relevant to exclude, based on patients past working history, the possibility of chronic hypersensitivity pneumonitis. The patient presented in this case report had an insidious onset of clinical symptoms that are present in several entities but, by taking into account, the history of Systemic sclerosis, the radiological NSIP pattern and the UIP histological pattern; idiopathic pulmonary fibrosis and hypersensitivity pneumonitis were excluded.

In addition, Nontuberculous mycobacteria (NTM) lung disease has also been related with gastroesophageal reflux and other esophageal disorders [22]. Association that may have increased the risk of MAC disease in our patient, who reported a 1-year-long history of pyrosis and had a distal esophageal dilation seen on the high-resolution chest computed tomography.

Diagnosing pulmonary MAC disease is a challenge. In order to distinguish infection from colonization or contamination, several considerations must be made [23].

According to the Infectious Disease Society of America and the American Thoracic Society, in patients with respiratory symptoms, imagenological evidence of pulmonary disease (cavitary or nodular opacities on chest radiograph or multifocal bronchiectasis on high-resolution computed tomography) and when exclusion of other diagnosis including malignancy and fungal infection is made; then the following findings will support the diagnosis of a non-tuberculous mycobacterial infection:

- Positive culture from two separate expectorated sputum samples
- Positive culture from one bronchial wash or lavage
- Transbronchial or other type of lung biopsy with histopathological features suggestive of mycobacterial infection and positive culture
- Biopsy showing histopathological features and a positive culture from one expectorated sputum sample or one bronchial washing
- Positive culture from pleural fluid of other normally sterile extrapulmonary site [24]
In this case report, diagnosis was made taking into consideration the respiratory symptoms, bronchiectasis on high-resolution computed tomography, exclusion of other diagnosis and the presence of a positive culture from a bronchial lavage.

Following the British Thoracic Society guideline for the management of Non-Tuberculous Mycobacterial pulmonary disease [23], patient was started on Ethambutol 25 mg/kg three times per week, Rifampicin 600 mg three times per week and Azithromycin 500 mg three times per week. In the meantime, patient has tolerated treatment and has not presented any adverse effects. After 1 month of treatment, patient reported an improvement in his exertional dyspnea and cough, which further supports the pertinence of the antibiotic regimen started.

Two months after the initiation of the treatment for Non-Tuberculous Mycobacterial pulmonary disease, we decided to initiate immunosuppressant treatment with prednisolone and cyclophosphamide due to the patient’s high risk for interstitial lung disease progression. In the first 5 months of treatment patients respiratory symptoms have not progressed.

5. Conclusion

Interstitial Lung Disease is one of the leading causes of death from diffuse cutaneous systemic sclerosis. This condition may require immunosuppressant treatment to improve dyspnea, lung function, lower progression rate and enhance quality of life.

Patient presented several features that suggested a high risk of interstitial Lung Disease progression and was considered a candidate for immunosuppression. However, patient also presented a pulmonary Mycobacterium avium complex infection; this is an infrequent infection, a diagnostic challenge and may be reason to postpone immunosuppression.

It was decided to treat Mycobacterium avium complex infection, which partially improved pulmonary symptoms. Two months afterwards, immunosuppressant treatment was started without complications. Patient’s dyspnea and pulmonary function has remain stable.

Declaration of competing interest

None to declare.

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