CHEST

Severe Pulmonary Fibrosis as the First Manifestation of Interferonopathy (*TMEM173* Mutation)

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We report three cases of pulmonary disease suggesting fibrosis in two familial and one sporadic case. Pulmonary symptoms were associated with various clinical features of systemic inflammation and vasculitis involving the skin, and appeared at different ages. A strong interferon signature was found in all three cases. Disease was not responsive to corticosteroids, and lung transplantation was considered for all three subjects at an early age. One of them underwent double-lung transplantation, but she immediately experienced a primary graft dysfunction and died soon after. Recognized causes of familial interstitial lung disease were all excluded. All three subjects had a mutation in the previously described autoinflammatory disease called SAVI (stimulator of interferon genes [STING]-associated vasculopathy with onset in infancy). These cases emphasize the need to consider this possibility in children and young adults with lung fibrosis after common causes have been ruled out. CHEST 2016; 150(3):e65-e71

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Inherited inflammatory syndromes related to the transmembrane protein 173 (*TMEM173*) gene mutation have been recently described.[1] The main clinical features include early-onset systemic inflammation, cutaneous vasculopathy, and pulmonary inflammation. We report three cases (two familial, one sporadic) in which extrapulmonary symptoms were minimal. After unbiased genetic analysis ruled out common genetic

ABBREVIATIONS: ANA = antinuclear antibody; c-ANCA = anti-neutrophil cytoplasmic antibody; CRP = C-reactive protein; DLCO = diffusing capacity of the lung for carbon monoxide; ESR = erythrocyte sedimentation rate; GER = gastroesophageal reflux; HRCT = high-resolution CT; IFN = interferon; ILD = interstitial lung disease; NK = natural killer; SAVI = STING-associated vasculopathy with onset in infancy; STING = stimulator of interferon genes; WES = whole-exome sequencing

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causes of pulmonary fibrosis, familial cases were screened by whole-exome sequencing (WES). We identified a mutation in the *TMEM173* gene encoding for the DNA sensor STING (stimulator of interferon genes). Here, we detail the manifestations of this new genetic cause of severe lung fibrosis in one adult and two pediatric patients.

Case Reports

Cases 1 and 2

A 12-year-old boy (case 1) was referred for evaluation of lung transplantation at 11 years, 1 year after his mother died of an undifferentiated interstitial lung disease (ILD) (case 2). He was the first child of unrelated parents of Algerian origin. There was no history of neonatal respiratory distress. He was first investigated at the age of 5 years for chronic cough with digital clubbing. He was noted to have failure to thrive since the age of 1 year. At 11 years, high-resolution CT (HRCT) scanning of the chest showed pulmonary fibrosis (Fig 1A, Table 1). Bilateral basal crackles appeared with time. Telangiectasia and chilblains had been repeatedly noted since the age of 11, which worsened in cold weather (Fig 2). Febrile attacks were rare. A decrease in blood CD4+ T and natural killer (NK) lymphocytes with normal B-cell counts associated with oligoclonal hypergammaglobulinemia (IgG, IgA) and type III cryoglobulinemia were identified, in association with mild systemic inflammation (C-reactive protein level [CRP] to 50 mg/L and erythrocyte sedimentation rate [ESR] to 40 mm/h). Antinuclear antibodies (ANA) were initially slightly positive and disappeared with time. Antineutrophil cytoplasmic antibodies (c-ANCA) were negative. Surgical lung biopsy showed multiple pulmonary nodules in a central alveolar peribronchiolar location composed of a lymphocytic inflammatory infiltrate forming aggregates and associated with fibrosis, without vasculitis (Fig 3A-C). There was no response to hydroxychloroquine and pulses of corticosteroids. Serial pulmonary function tests showed a severe restrictive lung function pattern with a decreased diffusing capacity for carbon monoxide (DLCO). Evaluation for double-lung transplantation was discussed owing to the progression of lung dysfunction and poor quality of life under nocturnal oxygen therapy.

The patient's mother (case 2) had been followed since the age of 20 for ILD. She was one of 11 children and the only one with a known pulmonary disease. Acral telangiectasia, atrophic plaques on the hands, and nail dystrophy were noted as well as an erythematous rash over the extensor surface of the fingertips. She had chronic polyarthralgia, and basal fine crackles were repeatedly noted. Low CD4+ T and NK lymphocytes with a normal B-cell count, hypergammaglobulinemia

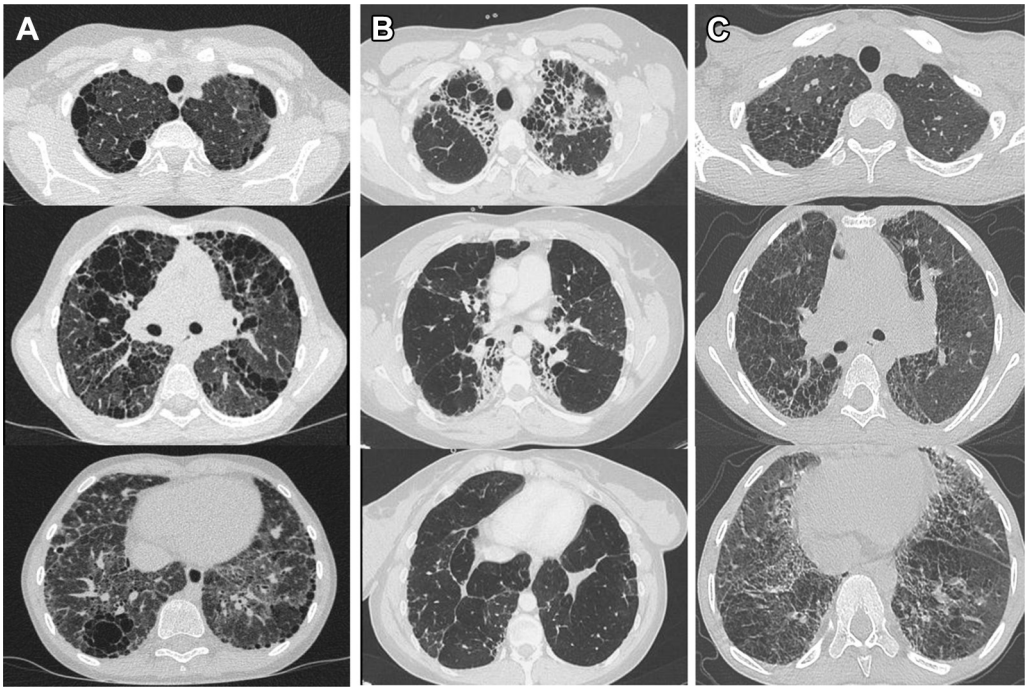

Figure 1 – *A, B, C, High resolution thoracic CT of the chest of familial (A and B) and sporadic (C) cases. Note the presence of cystic lesions (paraseptal emphysema) in upper lobes in the three cases. In case 1 (A), there is a clear subpleural distribution in the upper lobes, and a right-side predominance of the lesion in case 3 (C). Ground glass areas were mainly found in the lower lobes in case 1 (A) and case 3 (C).*