Interstitial lung disease in an adult patient with dermatomyositis and anti-NXP2 autoantibody

To the Editor:

Idiopathic inflammatory myopathies (IIMs) are characterised by inflammatory involvement of skeletal muscles causing weakness and pain, with possible associated systemic manifestations including frequent interstitial lung disease (ILD), and significant morbidity and mortality. Accumulating evidence suggests an important contribution of autoimmune responses to the pathogenesis of these diseases. Autoantibodies are present in at least half of patients with IIMs [1]. Some of these autoantibodies are frequently detected in patients with other connective diseases associated with myositis (especially systematic sclerosis) and are referred to as myositis-associated autoantibodies, whereas others are considered specific to IIMs and are referred to as myositis-specific antibodies (MSAs), including antibodies against aminoacyl transfer RNA (tRNA) synthetases, Mi-2 (a nuclear helicase) and the signal recognition particle [1, 2]. MSAs, when present, contribute to the diagnosis of IIM, especially in patients with mild muscle involvement or with ILD pre-existing to the myositis, although other, nonspecific antibodies are associated with various frequencies of manifestations and distinct clinical phenotypes within the spectrum of IIM [1, 2]. Novel targets of autoantibodies have recently been described in IIM patients without "classical" MSAs, including p155/140 (transcriptional intermediary factor (TIF)-1-γ), CADM-140 (melanoma differentiation-associated gene 5), small ubiquitin-like modifier activating enzyme (SAE)1 and SAE2, and nuclear matrix protein 2/MJ (NXP2) [3].

Here, we report clinically relevant ILD in a patient with dermatomyositis associated with anti-NXP2 antibodies. A 41-year-old female never-smoker was referred for cervicalgia, myalgia without muscle weakness and rash. She had a history of type-1 diabetes since childhood, partial thyroidectomy for a benign nodule and suspected untreated cutaneous sarcoidosis 4 years previously. There was no fever and no Raynaud phenomenon. Cardiac and pulmonary auscultations were normal. Clinical examination demonstrated bilateral contracture of the trapezius muscles, lilaceous and erythematous rashes on the eyelids and the forehead, periungual erythema, and shawl sign, without Gottron's papules. Serum creatine kinase level was elevated to 1690 $IU{\cdot}L^{-1}$ (normal range 15–200 $IU{\cdot}L^{-1}$) and aldolase level was 27.2 $IU{\cdot}L^{-1}$ (normal range 4–8.5 $IU{\cdot}L^{-1}$). The C-reactive protein level was 7 $mg{\cdot}L^{-1}$. Immunological analysis showed elevated antinuclear antibodies at 1:1600 with a speckled pattern and few dots. Extractable nuclear antibodies, double-stranded DNA antibodies and anti-neutrophil cytoplasmic antibodies were negative. Complement testing was normal. An electromyogram showed typical myositis features predominating on the deltoids. A biopsy obtained from the right deltoid muscle showed evidence of myositis and fasciitis with infiltration by $CD4^+$ lymphocytes, plasma cells and macrophages. No granuloma was found. Positron emission computed tomography ruled out an occult solid tumour. A diagnosis of dermatomyositis was made, and the patient was discharged with prednisone 40 mg per day and methotrexate 15 mg per week. Initiation of treatment was followed by rapid resolution of skin and muscle manifestations.

3 months later, while the patient was receiving 20 mg per day of prednisone, she was readmitted for acute dyspnoea and productive cough resistant to two courses of oral antibiotics. She was tachypnoeic, febrile at 38° C, with crackles at the lung bases. Her arterial oxygen tension was 31 mmHg on room air and oxygen saturation was 92% with oxygen 5 $L{\cdot}min^{-1}$. White blood cell count was $13{\times}10^6$ L^{-1} with 93% neutrophils. Creatine kinase and aldolase levels were elevated to 17 and 9.8 $IU{\cdot}L^{-1}$, respectively. High-resolution computed tomography of the chest showed bilateral consolidation predominating in the right lower lobe (fig. 1). Cultures of endobronchial aspirates were not contributive. The patient was empirically started on intravenous amoxicillin/clavulanate, without improvement. A presumptive diagnosis of organising pneumonia associated with dermatomyositis was then made, and corticosteroids were increased to 1 $mg{\cdot}kg^{-1}$ per day of intravenous methylprednisolone, followed by complete clinical and radiological recovery within 1 week. Based on imaging, methotrexate toxicity was deemed very unlikely; however, it was discontinued, mycophenolate mofetil was initiated, and corticosteroids were continued orally and progressively tapered. After 33 months of follow-up, the patient is free of pulmonary, muscular and cutaneous symptoms of dermatomyositis.

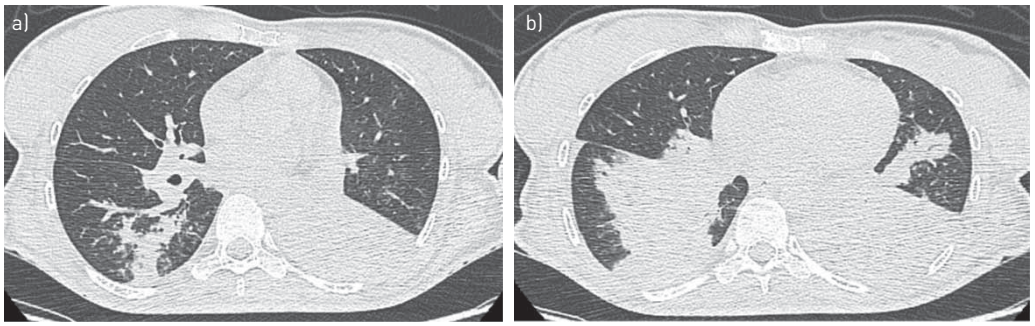

FIGURE 1 High-resolution computed tomography showed bilateral consolidation in the lower lung zones a) at the level of the right lower bronchus and b) at a level above the diaphragm.

Subsequently, further immunological testing was performed. Antinuclear antibodies were still elevated to 1:800, with a speckled pattern, but all MSAs were negative, including anti-aminoacyl tRNA synthetase and anti-Mi-2 antibodies. Additional analysis was negative for anti-p155, CADM-140, small ubiquitin-like modifier (SUMO)-1 and SUMO-2; however, anti-NXP2 autoantibodies were identified using two different techniques of qualitative line immunoassay (Euroimmun/Bioadvance (Bussy-Saint-Martin, France) and D-Tek/InGen (Mons, Belgium)).

This case illustrates that anti-NXP2 antibodies can be associated with ILD and further demonstrates how the identification of one of the newly described MSAs may contribute to the diagnosis of dermatomyositis. The patient suffered from cervicalgia from 2011 and was initially spuriously diagnosed with cervical osteoarthrosis. Despite the presence of nonspecific antinuclear antibodies, the diagnosis of dermatomyositis was only considered when skin and muscle manifestations later developed, triggering an electromyogram and a muscle biopsy, which confirmed dermatomyositis with no signs of sarcoidosis. Identification of anti-NXP2 antibodies eventually confirmed the diagnosis of autoimmune dermatomyositis and immunosuppressive therapy was initiated.

The NXP2 protein, also termed MORC3, is a 140-kDa protein that comprises RNA- and nuclear matrix-binding domains. NXP2 plays a role in RNA metabolism, maintenance of nuclear architecture and induction of cellular senescence [4]. NXP2 is also a target of SUMO and may have a role in SUMO-mediated transcriptional repression. Notably, antibodies to SAE have been reported in dermatomyositis [5]. However, the pathogenic relevance of anti-NXP2 antibodies in dermatomyositis has not been elucidated.

In recent years, MSAs have been associated to clinical phenotypes of IIMs. Autoantibodies against Jo-1, PL-7 (threonyl tRNA synthetase) and PL-12 (alanyl tRNA synthetase) are highly associated with ILD, and occasionally with subacute onset of disease and rapidly progressive hypoxaemia [2, 6]. Anti-NXP2 autoantibodies were first reported in juvenile dermatomyositis [7, 8], in which they are associated with calcinosis, severe muscle weakness, polyarthritis, joint contractures and intestinal vasculitis [9]. They are less frequently found in adult patients with dermatomyositis, with a wide range of prevalence estimates of 1.6–30% [10–12], averaging 17% of dermatomyositis patients [12]. In a cohort of adult patients with IIM [13], anti-NXP2 autoantibodies were the most prevalent antibodies, followed by anti-Jo-1 antibodies, and were mutually exclusive to other MSAs. In adult patients, anti-NXP2 antibodies are not clearly associated with a distinct phenotype, but calcinosis may be frequent [13]. Although ILD is a frequent complication of both dermatomyositis and polymyositis, it has not yet been reported in patients with dermatomyositis associated with anti-NXP2 autoantibodies. The present case therefore suggests that ILD should be considered as part of the clinical spectrum of manifestations associated with this recently described autoantibody.

Manifestations in the present patient were typical of ILD associated with dermatomyositis, with subacute onset of dyspnoea and patchy alveolar consolidation suggestive of organising pneumonia [14]. Lung biopsy was not obtained due to the expected limited added value and impact on patient management. The pattern on imaging and bronchoalveolar lavage were not consistent with methotrexate-induced lung toxicity. Making the diagnosis of dermatomyositis–ILD is particularly challenging when the lung disease precedes muscle or skin involvement, as in this case, and when serology is not contributive [15]. Infection must be ruled out systematically in patients with IIM and lung abnormalities, as well as cancer. Indeed, adult patients with dermatomyositis have a higher risk of malignancies than control subjects, with results varying according to autoantibodies. Either anti-NXP2 or anti-TIF-1γ antibodies were present in more

than 80% of patients with cancer-associated dermatomyositis in two series [11, 12]. Anti-NXP2 antibodies were especially associated with cancer in male patients with dermatomyositis and were more frequent in older patients [12]. No cancer was observed in our patient.

In conclusion, the recently described anti-NXP2 antibodies can contribute to the diagnosis of dermatomyositis and should be included in the list of diagnostic tests in patients with ILD and suspected IIM. When present, anti-NXP2 antibodies are associated with a higher risk of cancer. Large prospective cohorts of patients with myositis may further characterise the clinical phenotype associated with anti-NXP2 autoantibodies.

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Anti-NXP2 antibodies should be tested in patients with dermatomyositis, ILD and idiopathic inflammatory myopathies http://ow.ly/KiEMe

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