RHEUMATOLOGY

Letter to the Editor (Case report)

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Type I interferonopathy in a young adult

Rheumatology key message

- Early onset chilblain lupus-like lesions and lung involvement should raise the suspicion of a type I interferonopathy.

SIR, An 18-year-old male has suffered since early infancy from recurrent febrile episodes, failure to thrive, RP and violaceous vasculitic-like cutaneous lesions in the genitalia and acral locations, including the dorsal aspects of the fingers, knees, toes, heels, nose, cheeks and ears, precipitated by cold. In the winter, these lesions often progress to either significant exfoliation or to deep ulcerations, leaving atrophic skin and pigmentary changes. At 8 years old, histopathology of a skin lesion revealed vasculopathic lesions predominated by neutrophilic infiltrations. Neither the patient nor his parents reported photosensitivity or arthralgias. His skin lesions improved significantly during the summer. Family history was not contributory.

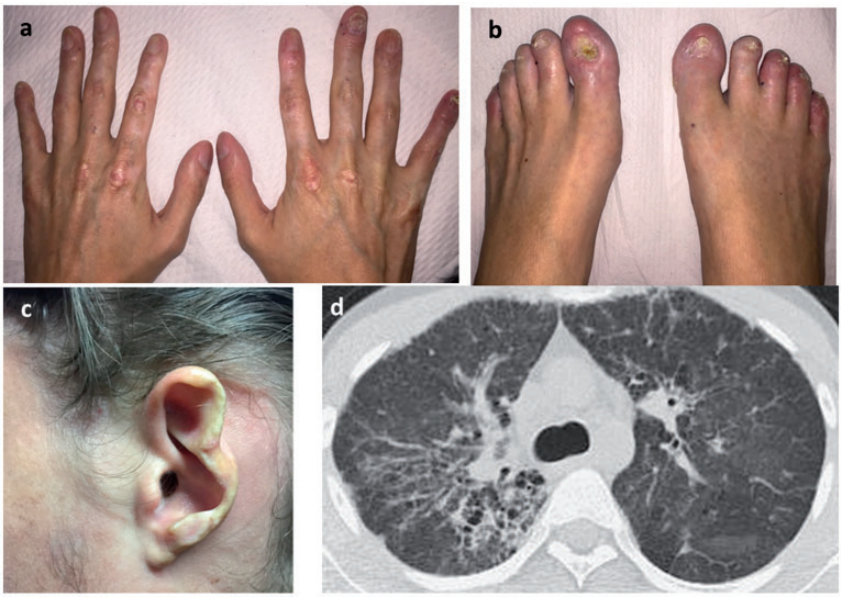
In a recent evaluation the patient complained of shortness of breath on exertion, which had developed during the last 4 years. On physical examination, psoriasiform dermatitis, diffuse livedo reticularis, telangiectasias, resorption of the distal phalanges, nail dystrophy (Figs 1A and B) and disfiguring scarring of the ears' pinnae (Fig. 1C) were evident. Lung auscultation revealed bilateral rales, most prominent on the right lower lung lobe, and wheezing. Laboratory tests had repeatedly revealed highly elevated acute phase reactants as well as high serum levels of RF and IgG antibodies to phospholipids and to β2 glycoprotein I, whereas other evaluations were unremarkable, including ANA and ANCA autoantibodies, cryoglobulins and complement. Pulmonary function tests were indicative of a restrictive pattern (total lung capacity 55% of predicted value). Chest high-resolution CT showed interstitial lung disease with areas of honeycombing, reticular opacities and patchy ground-glass that was considered suggestive of follicular bronchiolitis or lymphocytic interstitial pneumonitis (Fig. 1D). The patient suffered from recurrent febrile episodes that reportedly showed improvement following antibiotic treatment. Nevertheless, blood cultures were repeatedly negative for bacterial growth, except for the isolation of a drug-susceptible *Pseudomonas* species at 13 years old.

On the basis of chilblain lupus-like lesions and pulmonary involvement, a diagnosis of undifferentiated connective tissue disorder was made and the patient was placed on corticosteroids and various combinations of immunosuppressive agents, but with minimal response. Importantly, febrile episodes repetitively resulted in early discontinuation of regimens, including the administration of rituximab. The constellation of systemic inflammatory response, destructive vascular lesions and interstitial lung disease from early infancy were highly suggestive of a novel type I interferonopathy, termed stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) [1]. SAVI has been recently characterized as an autoinflammatory disease caused by gain-of-function mutations in the transmembrane protein 173 gene (*TMEM173*). *TMEM173* encodes the protein STING, which is a key component of cytosolic DNA sensing and whose activation is normally induced by 2′3′ cyclic guanosine monophosphate–adenosine monophosphate (cGAMP) produced in response to cytosolic foreign or self DNA [2]. STING activation leads to the induction of type I IFNs, which in turn drive the activation of Janus kinase 1 (JAK1) and tyrosine kinase 2 and the subsequent expression of IFN-stimulated genes [3].

With this in mind, the type I IFN activity score was determined in the patient's peripheral blood, as previously [4], and was found to be 302 times higher compared with age-/sex-matched controls. In addition, following written informed consent, according to the Declaration of Helsinki, DNA was isolated from the peripheral blood of the patient and genotyped by next-generation sequencing for the 25 genes included in the Infevers database for autoinflammatory syndromes. The analysis revealed a heterozygous germline mutation in exon 6 of *TMEM173/STING* (c.616T>G p.Cys206Gly), which was not detected in the parents or the brother of the patient by bidirectional Sanger sequencing of exon 6 of the *TMEM173* gene. To date, seven gain-of function mutations of the *TMEM173* gene have been described in 25 SAVI patients from 15 families (reviewed in Melki *et al.* [5]). To the best of our knowledge, the case presented herein is the second in the literature related to an amino acid substitution at position 206. SAVI-associated variants at positions 147, 154, 155 and 166 are located close to the cGAMP site of the STING molecule, whereas substitutions at positions 206, 281 and 284 were shown to lead to constitutive activation of type I IFN signalling in a cGAMP-independent manner, which is dampened by treatment with the JAK1 and JAK2 inhibitor ruxolitinib [5, 6]. Considering previously published reports supporting a beneficial role for oral selective JAK1/2 inhibitor in patients with SAVI [5–7], the patient was initiated on ruxolitinib initially at a dose of 2.5 mg twice a day, followed by an increase in 10 mg twice a day, with minimal response as far as the febrile episodes but significant improvement in cutaneous lesions following 1 month of treatment. Unfortunately his lung function was remarkably deteriorated over the last weeks and the patient died after a 2-week hospitalization in the intensive care unit.

LETTER

Fig. 1 Recurrent vasculitic-like cutaneous lesions since infancy in our patient ultimately led to resorption of distal phalanges of fingers and toes with accompanying dystrophic nail changes (**a**, **b**) and disfiguring scarring of the ears' pinnae (**c**). Chest high-resolution CT showed interstitial lung disease with areas of honeycombing, reticular opacities and patchy ground-glass (**d**).



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