SIR, A 15-year-old Caucasian girl with obsessive compulsive disorder (OCD) was referred to Paediatric Rheumatology in 2006, housebound with a 4-year history of exertional dyspnoea requiring home oxygen and small-volume haemoptysis. Other symptoms included episodic fever, severe oropharyngeal ulceration, diarrhoea, large joint arthritis and urticarial vasculitic rash. She was anemic. There was no relevant family history; she was a non-smoker and denied substance abuse. Examination revealed oxygen saturations of 84% with desaturation to 61% post-exercise. There was microcytic anaemia and elevated inflammatory markers on blood testing: haemoglobin 7.7 g/dl (normal range 12.0–15.0 g/dl), mean cell volume 67 fl (83–105 fl), CRP 97 mg/l (0–5 mg/l) and ESR 44 mm/h (5–15 mm/h). A severe restrictive lung deficit was evident on lung function testing [forced vital capacity (FVC) 1.2 l, 38% of predicted] and a CT chest revealed florid ground glass change with a mosaic pattern (Fig. 1A). Open lung biopsy histology demonstrated macrophage and neutrophil infiltration of a desquamating interstitial pneumonia (DIP) pattern with evidence of previous pulmonary haemorrhage suggesting a DIP-like reaction to underlying pulmonary capillaritis. An oesophago-gastro-duodenoscopy and colonoscopy demonstrated patchy erythematous change, however, mucosal biopsies were non-contributory. Skin biopsy histology showed a mild leukocytoclastic vasculitis. Pulmonary angiography was normal and HLA-B51 was negative. Genetic testing for periodic fever syndromes and hereditary surfactant dysfunction, all serological tests (including anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, electrophoresis, anti-transglutaminase antibodies and viral serology), neutrophil function tests and toxicology were negative.

She was initially managed for systemic vasculitis with deteriorating interstitial pneumonitis. She failed to improve despite high-dose oral steroids (1 mg/kg), although she responded to courses of i.v. methylprednisolone 1 g/day. Steroid-sparing agents and anti-TNF-α therapy were ineffective, sequentially and in combination, including HCQ, colchicine, AZA, mycophenolate, i.v. CYC and infliximab. She developed steroid toxicity, including a Cushingsoid appearance and osteoporotic wrist fracture.

The working diagnosis was revised to an autoinflammatory type disorder upon detailed case review after an isolated episode of genital ulceration and a further single episode of erythematous swelling of the cartilaginous pinnae associated with unilateral red eye. Anakinra 100 mg/day (IL-1R antagonist) was thus tested in trial in October 2008 and resulted in immediate resolution of rash, oral ulceration, arthritis and fatigue, with subsequent improvement in OCD symptoms and a return of menses. The CRP dropped to 35 mg/l and the anaemia resolved. However, there was no symptomatic improvement in the lung disease, supported by deteriorating appearance on CT scans. Moreover, she suffered two severe mucocutaneous and respiratory flares requiring admission. The decision was made to target downstream of IL-1 with IL-6 blockade, with a switch to tocilizumab (8 mg/kg/month) in December 2009.

Tocilizumab maintained control of the extrapulmonary disease, but additionally resulted in a striking improvement in respiratory symptoms, now sustained for over 2.5 years. The oxygen saturations returned to normal and are maintained after exertion; she engages in normal activities without oxygen supplementation. She has had only one short-lived flare of oral ulceration and dyspnoea. A repeat chest CT scan in June 2011 showed a striking reduction in parenchymal ground glass change (Fig. 1B) in the upper and mid zones.

We present a case of a refractory, undifferentiated systemic inflammatory condition that bears many of the features of an autoinflammatory disorder, such as Behcet’s disease, with recurrent episodes of fever, oral ulceration, arthralgia and rash. However, interstitial lung involvement in Behcet’s disease is very rare and often secondary to pulmonary aneurysms and haemorrhage [1, 2]. Other diagnoses were considered and excluded, including genetic surfactant dysfunction (genetic tests negative, presence of systemic symptoms), Schnitzler’s syndrome (absence of monoclonal gammopathy or bone pain), periodic fever syndromes (genetic testing normal, symptom spectrum atypical), relapsing polychondritis (serology negative, absence of laryngeal cartilage involvement, poor steroid response) and systemic vasculitis (serology negative, absence of specific vasculitis on multiple biopsies).

Due to the autoinflammatory disease-like nature of her symptoms and the partial response to anakinra, she was switched to tocilizumab, a monoclonal antibody against the IL-6 receptor. IL-6 has been implicated in the pathogenesis of many inflammatory conditions and there is growing evidence of the efficacy of tocilizumab in several of these, including systemic-onset juvenile arthritis [3].
There are also case reports of success with tocilizumab in refractory Schnitzler’s syndrome [4] and Behcet’s disease [5, 6]. It is interesting to note the differential responsiveness of the systemic and pulmonary manifestations in our patient to IL-1 blockade compared with the global improvement with IL-6-targeted treatment. The mechanism underlying this response is unclear; however, the disparity may provide an insight into the pathogenesis of autoinflammatory disorders.

To our knowledge, this is the first report of the use of IL-6 blockade for interstitial lung disease and urticarial vasculitis. Although further studies are required, tocilizumab represents a treatment option in autoinflammatory disease refractory to other medications including anakinra.

**Rheumatology key message**

- Interstitial lung disease in an autoinflammatory disorder responsive to tocilizumab.

*Disclosure statement:* The authors have declared no conflicts of interest.

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