twice a week. This treatment was rapidly withdrawn after the onset of bronchitis, then unsuccessfully re-introduced for one month 8 months later. The other symptomatic family members declined any treatment.

We describe here the first CIAS1-positive patient refractory to anakinra and provide a possible molecular basis for this. R92Q and V198M are individually recognised as mild and low-penetrance mutations.[5] The two patients with combined mutations (II2 and III2) presented with quite atypical, overlapping and severe symptoms, whereas the three people with only one variant were either totally asymptomatic (I2, III3) or had a much milder disease (IV1). Clustering of hereditary autoinflammatory mutated genes has been occasionally reported,[5] but familial molecular analysis showing a clear segregation between the phenotype and the genotype has never been carried out before. Our data strongly suggest that severe phenotypes and unresponsiveness to biotherapies may result from digenic inheritance, which is consistent with the transmission pattern observed in this family (fig 1).

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Behçet's disease with life-threatening haemoptoe and pulmonary aneurysms: complete remission after infliximab treatment

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A 25-year-old man was admitted to our hospital because of life-threatening haemoptoe and haematemesis. Recurring painful oral and genital aphtae and an episode of epididymitis led to a diagnosis of Behçet's disease 18 months earlier.[1] Treatment with colchicine (1 mg/day) and prednisone (50 mg/day) was started, with a rapid tapering of prednisone. Intermittent fever and a cardiac murmur led to the suspicion of endocarditis 6 months later. Transoesophageal echocardiography disclosed a right ventricular cardiac thrombus of 4 cm diameter. The clinical investigation did not show signs of vasculitis nor could a thrombophilia be diagnosed. Oral anticoagulation was initiated and continued until complete resolution of the cardiac thrombus. Azathioprine (75 mg/day) was prescribed in combination with prednisone (75 mg/day), with the recommendation to increase the dose of azathioprine and to taper prednisone.

On admission, the patient showed signs of a systemic inflammation; he had scrotal ulcers and acneiform eruptions on the skin and oral aphtae. A computed tomogram of the thorax showed multiple pulmonary aneurysms with signs of vasculitis, as well as thrombi in the affected vessels (fig 1A,B). Because of the life-threatening situation and the poor prognosis of patients with pulmonary artery involvement, we decided, after a thorough interdisciplinary discussion and with the informed consent of the patient, to treat him immediately with the tumour necrosis factor (TNF)-neutralising monoclonal antibody infliximab (5 mg/kg body weight) and not to choose the conventional treatment strategy of cyclophosphamide in combination with high doses of glucocorticoids.[2] The clinical and radiological response was impressive. The symptoms resolved within a few days. The C reactive protein fell from 227 to <10 mg/l and a computed tomogram of the thorax showed an important reduction of vasculitic changes and resolution of the thrombi within 2 weeks (fig 1C,D). Six months later, the size of the pulmonary aneurysms was markedly reduced (fig 1E,F). Infliximab treatment was continued over a period of 14 months, with increasing intervals. Azathioprine was added (75 mg/day). Prednisone was gradually tapered over 6 weeks to 2.5 mg/day. The patient has been in complete remission for >2 years.

DISCUSSION

Behçet's disease is a multisystemic inflammatory disorder presenting with orogenital ulcers, changes in the skin, arthritis, ocular and vascular inflammation.[3] Pulmonary artery vasculitis is rare, affects mainly young men, presents with dyspnoea, cough, chest pain and haemoptysis, and has a bad prognosis. Of 534 patients with Behçet disease presented in a recent publication, only 8 suffered from pulmonary aneurysms and 6 of these died despite immunosuppressive treatment or surgery.[4] A more recent report presents the data of 26 patients with pulmonary aneurysms, showing a survival rate of 62%.[1]

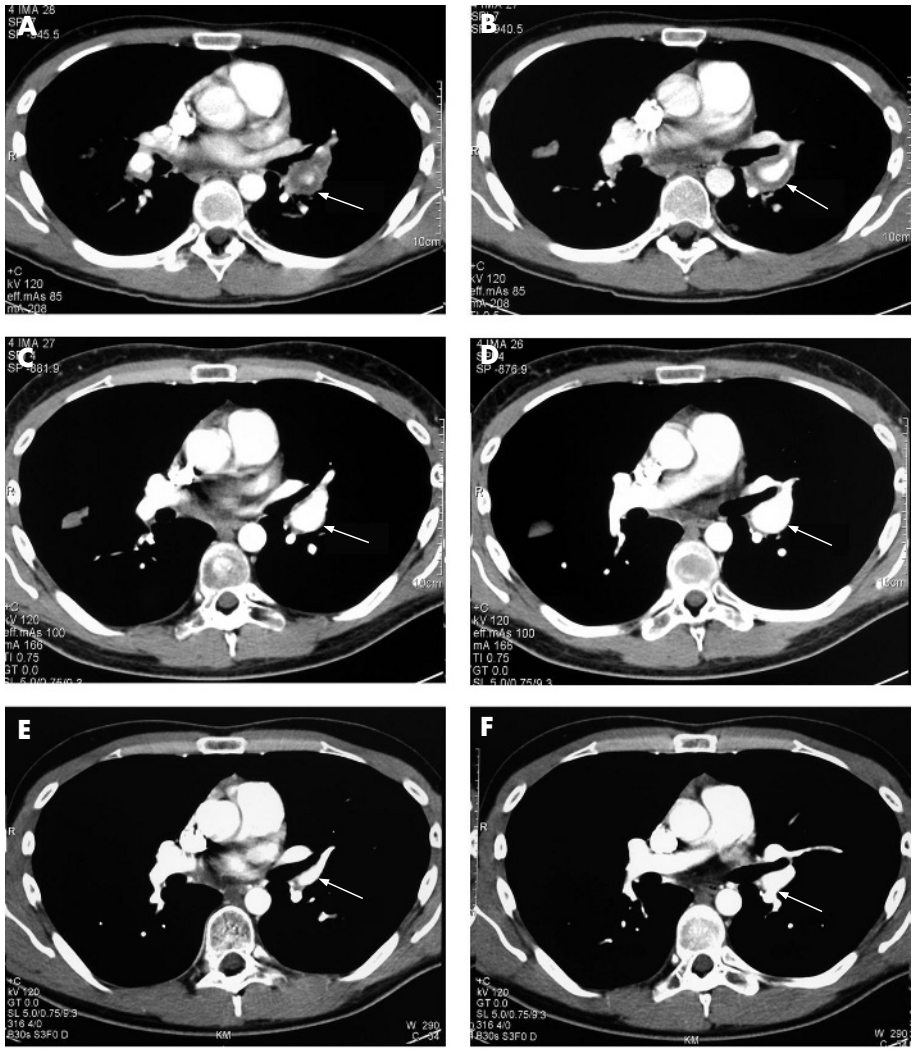

Figure 1 The same two computed tomography scan slices over a period of 6 months. (A,B) At admission, large aneurysms of the pulmonary artery, a marked vascular wall thickening (consistent with vasculitis) and thrombus formation are present (arrow). (C,D) Twelve days after the first infusion of infliximab the vascular wall has normalised but the aneurysms are still present. (E,F) After 6 months and a total of six infusions of infliximab, the diameters of the aneurysms have substantially decreased.

TNFα has a central role in the inflammatory response. It initiates an inflammatory cascade and triggers the expression of prothrombotic adhesion molecules. As documented by anecdotal reports and small case series, TNF-blocking agents such as infliximab have been successfully applied in patients with Behçet's disease.[5 6] However, its use in the treatment of pulmonary vasculitis with aneurysms has not been reported so far.

Our case shows that the inhibition of TNFα using the neutralising monoclonal antibody infliximab has the potential to induce rapid, complete and longlasting remission in a life-threatening manifestation of Behçet's disease.

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