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Accepted 2 March 2006

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Refractory auto-inflammatory syndrome associated with digenic transmission of low-penetrance tumour necrosis factor receptor-associated periodic syndrome and cryopyrin-associated periodic syndrome mutations

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See linked article, p 1427

Ann Rheum Dis 2006;**65**:1530–1531. doi: 10.1136/ard.2006.054312

Two dominant periodic fevers, tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) and cryopyrin-associated periodic syndrome (CAPS), are prominent auto-inflammatory disorders. Mutations in the 55 kDa TNF receptor superfamily 1A gene (*TNFRSF1A*) and in the cold-induced auto-inflammatory syndrome 1 gene (*CIAS1*) were recently associated with TRAPS[1] and CAPS,[2] respectively. Following publications describing the efficacy of etanercept (enbrel), a recombinant human TNF receptor 1B fusion protein in patients with TRAPS[3] and anakinra (kineret), a recombinant human interleukin-1 (IL1)-receptor antagonist, in patients with CAPS,[4] targeted biotherapies have been repeatedly and successfully given for these two conditions.

Our proband (fig 1) is a 36-year-old French woman who presented with rashes of urticaria and oedema precipitated by exposure to heat and water. These rashes, lasting a few hours and recurring twice a month since the patient was 6 years old, were associated with moderate fever, symmetric arthralgia of the wrists, ankles and hip, myalgia, painful cutaneous contact, bipolar aphthosis, intense fatigue and conjunctivitis. She had no uveitis, no folliculitis and no pathergy, ruling out Behçet's disease. Levels of C reactive protein were repeatedly found to be normal. Her mother, now aged 60 years, exhibited the same symptomatology, except that she had no genital aphthosis and no urticaria and her oedemas were triggered by both cold and heat. She also showed severe bilateral deformation of the distal interphalangeal joints. The proband's daughter, aged 8 years, had fever, urticaria and oral aphthosis. Because these phenotypes overlapped with symptoms reported for TRAPS and CAPS, we first sequenced *TNFRSF1A* exons 2–4 and *CIAS1* exon 3, thereby covering 98% of the known mutations in both genes. We discovered double heterozygosity for R92Q and V198M in both the proband and her mother. No mutation was found in the two other periodic fever genes: *MEFV* responsible for familial Mediterranean fever and *MVK* responsible for the hyper immunoglobulin D syndrome (not shown). Although the IL1-receptor antagonist has been consistently shown to dramatically improve CAPS, and sometimes TRAPS, in patients within hours of the first injection, the proband's symptoms did not decrease even after 1 month of daily subcutaneous injections of 100 mg anakinra. Instead, she needed to be hospitalised for severe side effects, including fatigue, erythema and anaemia. Four weeks later, she was given etanercept 25 mg subcutaneous

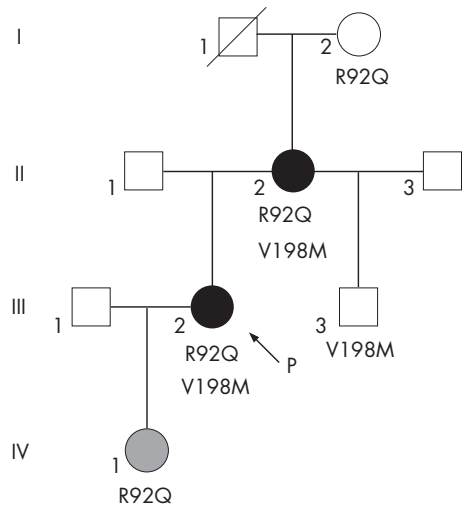

Figure 1 Digenic expression of tumour necrosis factor receptor-associated periodic syndrome and cryopyrin-associated periodic syndrome mutations. The two patients with the most severe phenotypes (black circles), including the proband (P, arrowed), who is refractory to anakinra, inherited both tumour necrosis factor receptor superfamily 1A gene (R92Q) and cold-induced auto-inflammatory syndrome 1 (V198M) mutations. By contrast, two of the three people with only one variant, the grandmother (R92Q) and the step-brother (V198M), were completely asymptomatic. The daughter (grey circle, R92Q) had a milder symptomatology.

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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Competing interests: None declared.

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Accepted 30 April 2006

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

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Ann Rheum Dis 2006;**65**:1531–1532. doi: 10.1136/ard.2005.045195

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]