Letters to the Editors

Recurrent pericarditis caused by a rare mutation in the *TNFRSF1A* gene and with excellent response to anakinra treatment

Sirs,

Recurrences develop in up to 20–50% of patients with acute pericarditis (1). Although several mechanisms have been hypothesised in order to explain recurrences, the etiology remains obscure in up to 85% of cases, which are therefore labelled as idiopathic (1).

Increasing interest is currently being devoted to autoinflammatory disorders, a group of diseases caused by a primary dysfunction of the innate immune system (2).

Among monogenic autoinflammatory disorders, tumour necrosis factor receptor-1 associated periodic syndrome (TRAPS) is the most common autosomal dominant one. It is caused by mutations in the *TNFRSF1A* gene (3) and is characterised by recurrent attacks of fever associated with other clinical features such as periorbital oedema, erythematous plaques, myalgia, and arthritis or arthralgia. The tumour necrosis factor (TNF)-α neutralising agent etanercept is considered to be the first-line therapy for TRAPS, but resistant cases have been reported (4). In these patients, interleukin-1 (IL-1) inhibition has proven successful (5, 6). Though promising, the results obtained with IL-1 antagonists are, to date, limited to very few cases and must undergo further evaluation.

Recurrent pericarditis (RP), usually in the form of polyserositis, is a feature of TRAPS (7). In addition, patients carrying mutations in the *TNFRSF1A* gene and presenting with RP as the sole clinical manifestation have recently been reported (7-9).

Here we report the first patient with isolated RP associated with a rare heterozygous V95M mutation in the *TNFRSF1A* gene, and also confirm anakinra as an efficacious treatment in patients with TRAPS.

In May 2009, a 26-year-old female was admitted to our Unit for RP unresponsive to a combination of colchicine (1mg/daily) and indomethacin (75-225mg/daily) over the past three years. In order to prevent recurrences, the only reasonably effective drug was prednisone (at least 25mg/daily), and every attempt to taper steroid dosage was followed by a recurrence of fever and pericarditis. Laboratory investigations upon admission showed an elevated eritrocyte sedimentation rate (ESR) (112mm/hour; n.v <35), C-reactive protein (CRP) (4.65mg/dl; n.v <0.5), serum amyloid A (308mg/L; n.v <10) (SAA) and TNF-α levels (47.5pg/mL; n.v <25pg/mL). After obtaining informed consent, the patient's DNA was analysed for mutations in *TNFRSF1A* (Exons 2-4, 6) and a heterozygous V95M mutation was found. Since her mother, father and sister, who were clinically healthy, did not carry the mutation, the mutation is likely to have occurred *de novo*. The patient was diagnosed with TRAPS and started treatment with etanercept 25mg twice weekly. Unfortunately, its administration was interrupted within a few days of the start of treatment, due to the onset of diffuse pruritic urticarial lesions distant from injection sites. Anakinra at a dose of 100mg daily was then started, and led to a remarkable improvement of symptoms and decrease of CRP, ESR and SAA concentration to normal values within a few weeks. Prednisone was gradually discontinued, and at six-month follow-up the patient was symptom-free and did not show any sign of disease relapse.

Dodè *et al*. described two adults presenting with recurrent pericarditis as the only clinical manifestation and who carried the low-penetrance TRAPS mutations R92Q and P46L (7). We have also recently studied RP patients for mutations in the *TNFRSF1A* gene (8, 9). Five patients carried the R92Q allele, whereas one carried a novel heterozygous ΔY103-R104 deletion (9). We also recently proposed criteria (positive family history and poor response to colchicine) for identifying among patients with RP those for whom testing for genetic mutations of the *TNFRSF1A* gene should be carried out (8, 9).

These findings suggest that the low-penetrance TNFRSF1A variants seem to contribute to atypical inflammatory responses, including cardiac diseases such as pericarditis (7-10). The V95M mutation, previously described only once (11), is characterised by a G/A substitution in exon 4, which results in the exchange of valine by methionine at amino acid position 95. Our report broadens the spectrum of low-penetrance mutations in the *TNFRSF1A* gene associated with isolated RP, and strengthens the hypothesis that TRAPS should be kept in mind in the differential diagnosis of RP.

Etanercept has been shown to be efficacious in most TRAPS cases as its administration may prevent disease flares and/or allow reduction of corticosteroid dosage (9, 10, 12, 13). Nevertheless, a decline in responsiveness may occur in some cases (5, 6), and resistant cases have been reported (4). Anakinra, a recombinant human interleukin-1 receptor antagonist, has been shown to be effective in etanercept-resistant patients, although to date only few cases have been described (6 patients) (5-6), including the one we describe. In conclusion, we report an additional low-penetrance mutation in the *TNFRSF1A* gene that may be associated with isolated RP presentation and we also confirm the efficacy of anakinra in the treatment of TRAPS.

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