A new case of idiopathic recurrent acute pericarditis due to R104Q mutation in *TNFRSF1A* successfully treated with anakinra: expanding the questions

Sirs,

We read with great interest the paper by Nieto González and colleagues (1) recently published in this Journal in which the Authors report three idiopathic recurrent acute pericarditis (IRAP) paedriatic patients, non-responders to standard therapy, who were successfully treated with anti-TNF-α agents. A few months ago at our Institution, a tumour necrosis factor receptor associated periodic syndrome (TRAPS) due to the same R104Q mutation recently described by Cantarini (2) was diagnosed in a woman with IRAP.

In September 2012 we evaluated a 54-year-old female with a history of several admissions to Emergency Department since July 2011 for recurrent acute pericarditis. IRAP was only partially responsive to ibuprofen (1200-1800 mg/day) and colchicine (1 mg/day), whereas it promptly responded to corticosteroid therapy (prednisone 25 mg/day), however relapsing in every attempt to taper steroid dosage below 12.5 mg/day. Elevated levels of C-reactive protein – CRP – (20 mg/dL, n.v <0.5) and serum amyloid A (170.7 mg/L, n.v <20) where found during pericarditis flare. No signs of autoimmune, infectious disease or malignancies were present. After obtaining informed consent, the patient's DNA was analysed for mutations in *TNFRSF1A* and an heterozygous R104Q mutation in exon 4 was found. In October 2012 the patient started treatment with anakinra (IL-1 receptor antagonist), 100 mg/day, with rapid regression of symptoms and normalisation of inflammatory markers. After 8 months the patient has no longer experienced recurrence of pericarditis after withdrawal of corticosteroid therapy.

This case report, together with those in the literature, supports some considerations:

Is IRAP really idiopathic?

IRAP represent the most challenging complications of acute pericarditis occurring in up to 20–50% of patients.

Is IRAP an autoimmune disease?

An autoimmune process is suggested by the detection of serum anti-heart and anti-intercalated disk antibodies in about 67.5% of patients and by the good response to immunosuppressive drugs. Anti-nuclear antibodies have been detected in 43% of IRAP patients and pericarditis is common in autoimmune diseases (3, 4).

Is IRAP an autoinflammatory disease?

Cantarini *et al*. recently found that 6% of IRAP patients carry a mutation in the *TNFRSF1A* gene. Furthermore, recurrent pericarditis is a common feature of Familial Mediterranean Fever and TRAPS (5).

Which therapy and when to stop it?

Treatment guidelines for pericarditis were released by the European Society of Cardiology almost ten years ago. Effective agents usually include non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine, whereas glucocorticoids should be prescribed only to patients with idiopathic pericarditis who are refractory/intolerant to NSAIDs plus colchicine (6); recently growing evidence, together with our report, suggest that anakinra could be a solution for resistant cases (7-10). At the moment no clear indications on the duration of treatment exist, but CRP might be useful to monitor the disease activity and guide the appropriate length of therapy (7).

Which patients should be screened for autoinflammatory diseases?

In agreement with Cantarini we suggest that all patients with IRAP and family history of pericarditis and/or recurrent fever or personal history of colchicine failure or need for immunosuppressive therapy should be screened for autoinflammatory syndromes (5).

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References

1. NIETO GONZÁLEZ JC, MONTEAGUDO SAEZ I, LÓPEZ-LONGO F *et al*.: Idiopathic recurrent pericarditis treated successfully with tumour necrosis factor alpha blocking agents (anti-TNF-α). *Clin Exp Rheumatol* 2013; 31: 776-8.
2. CANTARINI L, LUCHERINI OM, VITALE A *et al*.: Expanding spectrum of TNFRSF1A gene mutations among patients with idiopathic recurrent acute pericarditis. *Intern Med J* 2013; 43: 725-7.
3. CAFORIO AL, BRUCATO A, DORIA A *et al*.: Anti-heart and anti-intercalated disk autoantibodies. Evidence for autoimmunity in idiopathic recurrent acute pericarditis. *Heart* 2010; 96: 779-84.
4. IMAZIO M, BRUCATO A, DORIA A *et al*.: Antinuclear antibodies in recurrent idiopathic pericarditis: prevalence and clinical significant. *Int J Cardiol* 2009; 16: 289-93
5. CANTARINI L, LUCHERINI OM, BRUCATO A *et al*.: Clues to detect tumor necrosis factor receptor-associated periodic syndrome (TRAPS) among patients with idiopathic recurrent acute pericarditis: results of a multicentre study. *Clin Res Cardiol* 2012; 101: 525-31.
6. LILLY LS: Treatment of acute and recurrent idiopathic pericarditis. *Circulation* 2013; 127: 1723-6.
7. MAESTRONI S, DI CORATO PR, CUMETTI D *et al*.: Recurrent pericarditis: autoimmune or autoinflammatory? *Autoimmun Rev* 2012; 12: 60-5.
8. CANTARINI L, LUCHERINI OM, CIMAZ R *et al*.: Recurrent pericarditis caused by a rare mutation in the TNFRSF1A gene and with excellent response to anakinra treatment. *Clin Exp Rheumatol* 2010; 28: 802.
9. VASSILOPOULOS D, LAZAROS G, TSIOUFIS *et al*.: Successful treatment of adult patients with idiopathic recurrent pericarditis with an interleukin-1 receptor antagonist (anakinra). *Int J Cardiol* 2012; 160: 66-8.
10. SCARDAPANE A, BRUCATO A, CHIARELLI F *et al*.: Efficacy of an interleukin-1β receptor antagonist (Anakinra) in idiopathic recurrent pericarditis. *Pediatr Cardiol* 2012.