

Brief Report

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Anaphylactic reaction to anakinra in a child with steroid-dependent idiopathic recurrent pericarditis and successful management with canakinumab

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Abstract

Conventional algorithm for treatment of pericarditis and prevention of recurrences consists of non-steroid anti-inflammatory drugs and/or colchicine, followed by corticosteroids in resistant patients. Anakinra has emerged as a promising and safe treatment modality for steroid-dependent idiopathic recurrent pericarditis. However, the efficacy and safety of canakinumab, another anti-interleukin-1 agent, has not been assessed up to date. Herein, we present development of an anaphylactic reaction due to anakinra and a successful subsequent treatment with canakinumab for the first time in the literature.

Recurrent pericarditis is a rare but troublesome disease. After an acute pericarditis, 30% of the patients develop a second attack without an identifiable cause, and this entity is referred as idiopathic recurrent pericarditis thereafter.^{1,2}

Non-steroidal anti-inflammatory drugs and colchicine are widely accepted as first-line therapies in management of acute pericarditis and prevention of recurrences.^{2–4} Corticosteroid is the second-line therapy for resistant and remitting cases. However, systemic side effects associated with long-lasting therapy limit its use.^{1,2,5}

In recent years, there is a tendency of experts to classify idiopathic recurrent pericarditis in auto-inflammatory diseases after exploring the pivotal role of interleukin-1 cytokine in pathogenesis and significant clinical improvement with the anti-interleukin-1 agents.¹ There have been increasing number of case reports and series, which describe the favourable efficacy of anakinra in idiopathic recurrent pericarditis.^{3,5,6} Anakinra is a competitive inhibitor of interleukin-1 receptor and has a short half-life of 4–6 hours. Canakinumab is a monoclonal antibody, which directly and selectively blocks the cytokine interleukin-1 β and has a longer half-life (21–28 days).

Herein, we present a 6.5-year-old boy with steroid-dependent idiopathic recurrent pericarditis who showed a complete response to canakinumab after an anaphylaxis with anakinra. We demonstrated the effectiveness and safety of canakinumab for the first time in a child with idiopathic recurrent pericarditis.

Case report

A 6.5-year-old boy referred to paediatric cardiology outpatient clinic with the symptoms of fever, dyspnoea, and chest pain. His past medical history in the last 6 months included two similar manifestations, which has been found to be associated with pericardial effusions. Both of the flares have been subsided with ibuprofen treatment.

Physical examination revealed fever, tachypnoea, muffled heart sounds, normal blood pressure, and normal heart rate. There were no other remarkable pathological findings in examination related to the other organ systems.

Enlarged cardiac silhouette and generalised QRS voltage suppression were detected on chest X-ray and electrocardiography, respectively. At transthoracic echocardiography, a circumferential pericardial effusion (25 mm in diameter) without evidence of tamponade was noted (Fig 1).

Laboratory tests showed an increased white blood cell count of 19,000/mm³, elevated C-reactive protein (24 mg/dl), and an erythrocyte sedimentation rate of 70 mm/hour. Anti-nuclear antibodies, anti-double-stranded DNA antibodies, and rheumatoid factor were negative. Complement levels (C3 and C4) were normal. Infectious aetiologies were ruled out by means

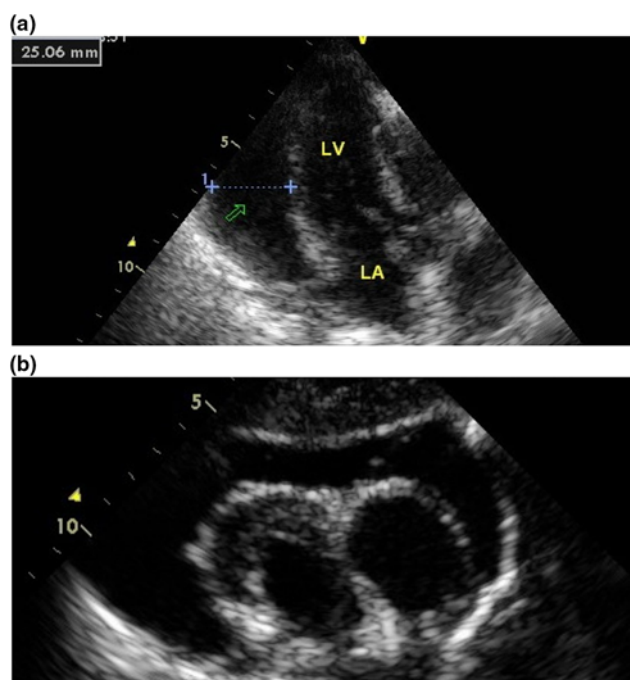


Figure 1. Echocardiographic images in parasternal long-axis (a) and subcostal transverse axis (b) view, demonstrating the diffuse pericardial effusion.

of normal intradermal skin test (Mantoux method) and negative serologic tests for other bacterial and viral agents. Heterozygous R202Q variant was detected in *MEFV* gene analysis.

The diagnosis of idiopathic recurrent pericarditis was established. Pericardial effusion regressed within 1 week after ibuprofen (40 mg/kg/day) and colchicine (1 mg/day) treatment. Ibuprofen was discontinued and the patient was discharged with colchicine therapy at the end of the second week. At the end of third month, another pericarditis episode with the same manifestations was observed while he was on colchicine therapy. Corticosteroid treatment (2 mg/kg/day) for 7 days along with colchicine resulted in complete remission of effusion and good clinical response. Two another relapses with pericarditis again developed 1 week after cessation of corticosteroid therapy. The patient exhibited favourable response to corticosteroid therapy in both of these episodes. This entity was considered as steroid-dependent idiopathic recurrent pericarditis.

Daily subcutaneous anakinra treatment (5 mg/kg/day) was initiated. Pericarditis completely resolved within 72 hours and corticosteroid therapy was terminated at the end of the first month by a slowly tapering regimen. After 1 month of daily administration, the interval between injections was gradually prolonged. Injection-site skin reactions occurred during daily anakinra injections (Fig 2) and disappeared during the alternate-day dosing regimen.

One year later, while the patient was on a biweekly anakinra treatment regime, a new pericarditis flare developed that promptly improved within 48 hours by daily anakinra doses.

Six months later, a severe anaphylactic reaction developed immediately after anakinra injection and he was hospitalised. Another anti-interleukin-1 agent, canakinumab (5 mg/kg monthly subcutaneous injections), was started after the anaphylaxis.

Monthly subcutaneous canakinumab (5 mg/kg/dose) injections were administered for 1 year, followed by alternate months dosing



Figure 2. Local skin reactions on the arm at the injection sites of anakinra therapy.

for another 1 year. The patient has never experienced a pericarditis flare or adverse event for 2 years under canakinumab and colchicine treatment.

Discussion

The recurrence rate of acute pericarditis is about 30% in patients who experienced the disease for the first time.^{1,2} Investigating the aetiology and management of recurrent pericarditis represents one of the most frustrating challenges in cardiology and rheumatology practice. Pericarditis appears to be idiopathic in 80% of the patients in developed countries.^{1,2,7}

Results of various studies regarding the efficacy of colchicine in treatment and prevention of flares are contradictory.^{3,4,8} A recent randomised-controlled multi-centre study did not find any difference in the rate of recurrence or time to first recurrence between patients using only non-steroidal anti-inflammatory drugs and patients using colchicine along with non-steroidal anti-inflammatory drugs.⁸

Corticosteroids are widely used in patients unresponsive or resistant to conventional therapy. However, in addition to the significant side effects, corticosteroid treatment has been reported to be associated with an increased risk of recurrence.³

Treatment of idiopathic recurrent pericarditis with anakinra, namely with an anti-interleukin-1 agent, for the first time described in 2009 was successful.⁷ In addition, in this study, suggestion of the auto-inflammatory mechanisms in pathogenesis of the disease was first provided in the literature.⁷ Anakinra has been found to decrease the risk of pericarditis flares.^{3,5,6} Moreover, anakinra provided withdrawal of concomitant therapies.⁹ However, the protocol for tapering or cessation of anti-interleukin-1 therapy is still a matter of

controversy.¹⁰ Previous reports consistently showed that more than half of the patients developed a flare during tapering process or after cessation, as in our case.^{5,10}

The most frequently reported minor and severe adverse events of anakinra are local skin reactions and anaphylactic reactions, respectively.^{6,9} Both of these adverse events developed in our case. In AIRTRIP trial, local skin reactions were observed in 95% of the patients after anakinra administration.⁶

Anti-interleukin-1 agents, either anakinra or canakinumab, should be considered in patients who are unresponsive to non-steroidal anti-inflammatory drugs and/or colchicine or dependent to corticosteroid. The efficacy and safety of anakinra in treatment of idiopathic recurrent pericarditis have been well established,^{2,5,6} whereas there has been no data so far regarding the usage of canakinumab which is the other anti-interleukin-1 biologic agent. This case report, for the first time, depicts the successful treatment of idiopathic recurrent pericarditis with canakinumab without any adverse event.

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Conflicts of Interest. None.

Ethical Standards. All procedures and medications performed were in accordance with the ethical standards, with the 1964 Helsinki Declaration and its later amendments. Informed written consent from parents of the patient was obtained for treatment with anakinra and canakinumab and also publishing this experience.

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