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CASE REPORT

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Use of Anakinra in steroid dependent recurrent pericarditis: a case report and review of literature

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ABSTRACT

Non-steroidal anti-inflammatory drugs and colchicine are the cornerstone treatment for recurrent pericarditis. Corticosteroids are frequently used in patients with recurrent episodes of pericarditis. In patients with corticosteroid dependent and corticosteroid-resistant pericarditis, several steroid-sparing options like azathioprine, intravenous immunoglobulin (IVIG), and anakinra are being recently tried. In this article, we present the case of a 44-year-old male with recurrent pericarditis, who was successfully treated with anakinra.

Abbreviations: Non-steroidal anti-inflammatory drugs, NSAIDS; Aspirin, ASA; Erythrocyte sedimentation rate, ESR; Serum Protein Electrophoresis, SPEP; Magnetic Resonance Imaging, MRI; C-Reactive Protein, CRP; Aspartate Aminotransferase, AST; Alanine Aminotransferase, ALT; Idiopathic recurrent pericarditis, IRP; Intravenous Immunoglobulin, IVIG.

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KEYWORDS
Anakinra; recurrent pericarditis; interleukin-1 inhibitor

1. Introduction

Acute pericarditis accounts for about five percent of all presentations for acute chest pain [1]. About 30% of all the cases of acute pericarditis progress to recurrent pericarditis [2]. In developed countries, most of the cases of acute pericarditis are of idiopathic or viral origin [3] while tuberculosis accounts for most of the cases in the developing countries with high prevalence [4]. NSAIDs/Aspirin (ASA) remains the cornerstone of treatment. The adjuvant use of colchicine with NSAIDs more than halves the risk of recurrence of pericarditis [5–7]. Corticosteroids are used in patients who fail initial therapy with ASA/NSAIDs/Colchicine. Third-line options include intravenous immunoglobulin, and steroid-sparing immunosuppressants like azathioprine, methotrexate, and cyclosporine [2]. IL-1 inhibitors like anakinra have been proposed in patients with recurrent pericarditis. In this article, we will discuss a case of successful treatment of recurrent constrictive pericarditis with anakinra and review the current evidence regarding the safety and efficacy of anakinra in patients with refractory recurrent pericarditis.

2. Case discussion

A 44-year-old male with a past medical history significant for gout initially presented to the primary care clinic with complaints of persistent shortness of breath with mild chest tightness after recovering from a recent upper respiratory tract infection. Physical examination revealed lungs clear to auscultation bilaterally, normal s1, s2 heart sounds with no abnormal rubs, murmurs or gallops. ECG showed normal sinus rhythm with no ST or Q wave changes. CT scan of the chest followed by an echocardiogram was done which showed a small posterior pericardial effusion. He was diagnosed with idiopathic pericarditis presenting as pericardial effusion and was started on naproxen 500 mg twice daily and colchicine 0.6 mg daily. However, he continued to have progressively worsening shortness of breath over the next two weeks and presented to the emergency department with the same. He received high-dose methylprednisolone 125 mg in the Emergency Department with rapid improvement in the symptoms. Laboratory workup revealed elevated ESR at 74 mm/hour (normal range 0–25 mm/hour) and CRP at 181 mg//L (normal range ≤9.00 mg/L). Other workup includes normal ferritin, α1-antitrypsin, IgG subclasses I, II, III, and IV. Angiotensin-converting enzyme, SPEP, antinuclear antibody, rheumatoid factor, hepatitis panel, Lyme serology, and tuberculosis screen were unremarkable. A repeat echocardiogram showed a moderate increase in the size of pericardial effusion with some evidence of thickened pericardium.

Cardiac MRI done showed diffuse pericardial thickening and an abnormal septal bounce suggestive of constrictive pericarditis as shown in Figure 1 and 2. He was diagnosed with idiopathic recurrent pericarditis (IRP) presenting as constrictive pericarditis

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The patient gave informed consent prior to the inclusion in the report.

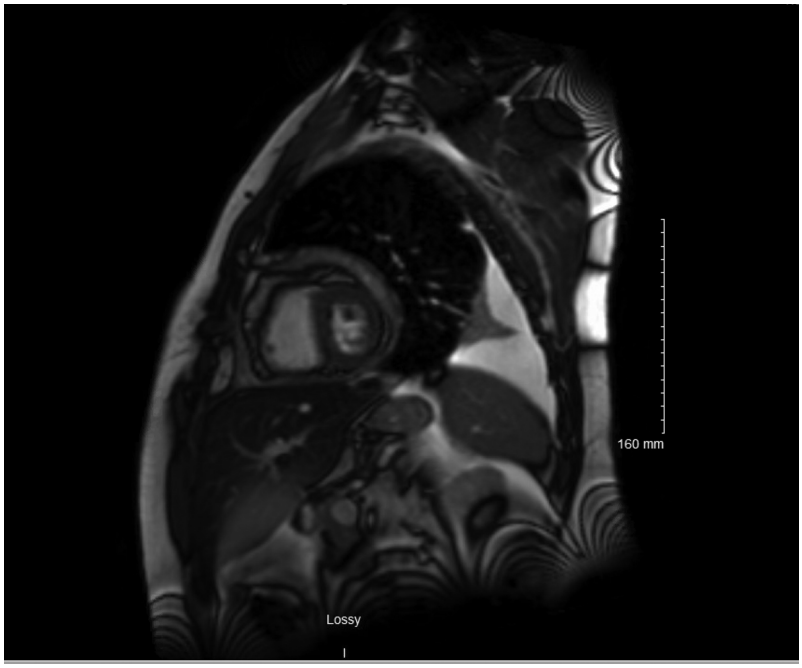

Figure 1. Diffuse thickening of the pericardium with the maximal pericardial thickness. Adjacent to the right ventricular free wall measuring approximately 1.2 cm.

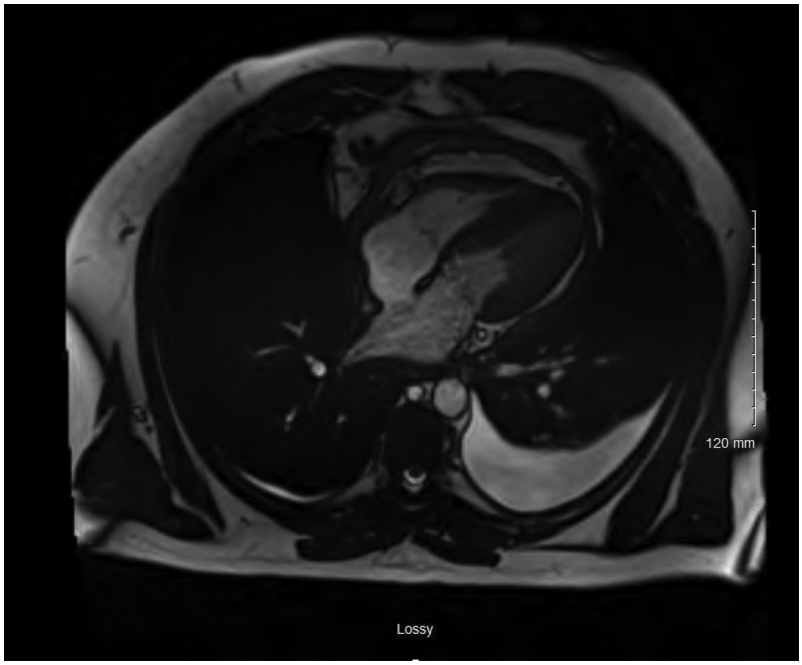

Figure 2. Abnormal septal bounce consistent with constrictive pericarditis physiology.

and was started on ibuprofen 600 mg three times daily, colchicine 0.6 mg twice daily and prednisone 40 mg daily. He was discharged on the same regimen with plans of outpatient steroid and NSAID taper. Over the next six months, he was successfully able to taper off and discontinue the ibuprofen. He was successfully able to taper down the prednisone to 10 mg/day but reported severe uncontrolled flares if he tapered below a dose of 10 mg/day. He also reported steroid-related side effects like blurry vision, headaches, facial pressure, and weight gain. In an attempt to taper him off the steroid, he was started on naproxen 500 mg twice daily and he was advised to taper the steroid by 2.5 mg every two weeks with the goal of discontinuing prednisone. On presentation to the clinic four months later, he reported that he was unable to taper the steroid to less than 5 mg/day as any such attempt led to a recurrence of fever and chest pain. He reported worsening vision, headaches, facial pain, and weight gain. Due to his

recurrent episodes of pericarditis on the current regimen and steroid-related side effects, we decided to start the patient on an alternate regimen.

Upon review of the literature, a decision was made to start the patient on anakinra on the basis of side effect profile and the promising results seen in various case series and observational studies. After informed consent, the patient was started on anakinra at a dose of 100 mg/day. He was screened negative for human immunodeficiency virus, tuberculosis, and hepatitis prior to therapy. ESR and CRP levels prior to treatment initiation were 35 mm/hour and 116 mg/L, respectively. He experienced a significant resolution of symptoms along with marked improvement in ESR 3 mm/hour and CRP <2.90 mg/L levels within two weeks. He was able to successfully taper off Prednisone within the next two weeks. He was also successfully able to taper off the colchicine and naproxen over the next month. He was continued on nightly anakinra for four months but a repeat liver function test in-clinic follow-up showed mildly elevated AST and ALT at 54 U/L (normal range 10–40 U/L) and 159 (normal range 12–78 U/L), respectively. Patient-reported that he was consuming excessive amounts of alcohol over the past few weeks. Although the risk of anakinra-induced transaminitis is rare (<1%), a decision has been made to stop Anakinra. He continued to be in remission nine months after the medication had been stopped and his liver function tests normalized. We opted to continue to hold further anakinra therapy as the evidence suggests that many patients will go into long-term remission after three months of anakinra therapy and even in patients who experience recurrence, remission can be achieved promptly by re-initiation of anakinra therapy.

3. Discussion

Recurrent pericarditis is the most common complication of acute pericarditis. Many hypotheses have been postulated like reinfections, augmented viral replication secondary to steroid therapy, inadequate treatment of the first episode, and autoimmune reaction following the initial episode of pericarditis [8,9]. However, many rheumatologists agree that there is an inflammatory component behind most of the cases of idiopathic recurrent pericarditis which involves increased production of interleukin 1 beta due to dysregulated activation of the immune system [10,11]. The initial evidence of the use of anakinra comes from a case series in 2009 by Picco et al. in which he described three children aged 14, 12, and 13 who were treated with anakinra for IRP. However, in all the reported cases, therapy was discontinued within three months followed by subsequent relapse. He reported all the patients achieved remission quickly after re-initiation. Later in 2014, Martina Finetti et al [12] published a 15-patient multicenter retrospective study in which corticosteroid dependent and colchicine-resistant patients were selected and given anakinra at a dose of one to two mg/kg/day. This study has shown more than a 95% reduction of flares after anakinra treatment compared to prior management with NSAIDs, steroids, and colchicine.

Case series reported by Jain et al. [13] in 2015 followed 13 cases who were resistant to or have failed therapy with NSAIDs, colchicine, prednisone, and other immunosuppressive therapy (methotrexate, mycophenolate mofetil, azathioprine, and hydrochlorothiazide); who were given anakinra for a median duration of 24.15 months. The case series has shown more than 90% improvement in symptoms or has become completely asymptomatic with few side effects. Amir Dagan et al. [14] in 2019 reported a case series of seven patients with a median age of 41 who were either resistant or intolerant to steroids, NSAIDs, colchicine and had failed at least one immunosuppressive drug (azathioprine, methotrexate, plaquenil, or intravenous immunoglobulin) with median disease duration of four years and a median number of six recurrences before anakinra use. After the initiation of anakinra, none of the patients had an IRP relapse and all the patients were able to successfully taper the prednisone down to 5 mg/day or less.

AIR TRIP [15] study is the first randomized control trial done to study the efficacy of anakinra compared to placebo. It is a double-blinded study done in a small patient population of 21 patients that observed that anakinra allowed successful corticosteroid withdrawal in most of the patients and a significant reduction in pericarditis flares compared to placebo. They also found no significant difference between the recurrence rate of pericarditis in patients treated with anakinra monotherapy vs anakinra plus colchicine combination therapy. However, the study did not have significant power to establish those findings.

IRAP [16] study published in 2020 is a large multicenter observational cohort study done with a study population of 224 patients with a mean patient age of 46 years. They reported an 83% reduction in pericarditis recurrence rate and a 91% reduction in emergency department admissions with anakinra. They also reported that patients who received a full dose treatment for more than three months followed by tapering for three months had a greater chance of being in remission for a longer duration.

4. Pros and Cons of anakinra use in recurrent pericarditis

The safety profile of anakinra is very reassuring with the most common side effect being a local reaction at

the injected site. Life-threatening adverse effects have not been reported so far. Arthralgias, myalgias, neutropenia, and transaminase elevations are rarely seen. Significant infections do occur but are rare in occurrence. It has a rapid onset of effect and has a quick response in the most susceptible patients.

The high cost of management, availability, and prolonged duration of therapy are the main drawbacks of its use in general practice.

5. Conclusion

From the limited data available for now, Anakinra shows promising results in patients with recurrent idiopathic pericarditis who have failed or are dependent on corticosteroid and colchicine. Data so far show only good results in patients with elevated ESR and CRP. However, limited data are available comparing it with other potential medications like intravenous immunoglobulin. There are also limited data available at this time comparing the efficacy of monotherapy vs combination therapy.

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Ethical approval

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