Recurrent Pericarditis: An Autoinflammatory Disease?

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KEY WORDS: recurrent pericarditis, autoinflammation, interleukin-1β, autoimmunity

IMAJ 2015; 17: 783–784

Recurrent pericarditis occurs in 10–30% of patients following the first episode of acute pericarditis, and frequently lasts for years. These patients suffer from recurrent episodes of chest pain accompanied by pericardial friction rub, electrocardiographic (ECG) abnormalities, and pericardial effusion. Markers of inflammation, namely elevated C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR), are present in most attacks. The incidence rate of recurrence increases further to 50% after the first recurrence, especially when patients are treated early with corticosteroids. The criteria for a definite diagnosis of recurrent pericarditis include the appearance of pleuritic pain together with at least one of the following: fever, pericardial friction rub or evidence for mild pericardial effusion, and elevated ESR, CRP and white blood cells [1]. Most patients have transient ECG abnormalities in the absence of increased serum troponin.

When evaluating recurrent pericarditis, one should consider the possibility of infectious diseases, inflammatory/autoreactive and neoplastic pericardial disease. Importantly, viral infections should be sought. This involves examining the pericardial effusion using polymerase chain reaction (PCR) assays to detect viruses such as adenovirus, cytomegalovirus and parvoviruses. Less common but reported in many studies are influenza virus, Epstein-Barr virus, varicella, rubella, mumps, hepatitis B and C viruses, and human immunodeficiency virus. *Mycobacterium tuberculosis* and *Coxiella burnetii* are the most common bacterial infections in the etiology of recurrent pericarditis.

Autoimmunity should always be considered a player (at least partly) in the pathogenesis of recurrent pericarditis. This is based on the fact that recurrent pericarditis is reported to be a factor in many autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. In some patients it was even shown to be a presenting symptom of exacerbation. However, even when recurrent pericarditis was identified as "idiopathic" it was still associated with increased prevalence of autoantibodies. In this respect, antinuclear antibodies were found in 43.4% of such patients as compared to only 9.8% in normal individuals.

Autoinflammatory diseases are increasingly recognized to be a large family of diseases some of which are genetically well defined: i.e., cryopyrin-associated periodic syndromes (CAPS), TNF receptor-associated periodic syndrome (TRAPS) and familial Mediterranean fever (FMF). Genetic disorders are characterized by dysfunction of the innate immune system and mutations in specific genes responsible for regulation or activation of inflammatory processes and characterized by recurrent episodes of fever and inflammation involving the skin, joints, gut and eyes. Thus, recurrent pericarditis has been reported to be of autoinflammatory origin in some cases [2].

The initial treatment for recurrent pericarditis is high dose non-steroidal anti-inflammatory drugs (NSAIDs), aimed to relieve both pain and inflammation. NSAIDs are rarely used alone and mostly are given in combination with colchicine. Colchicine interferes with chemotaxis, degranulation and phagocytosis in cells involved in inflammation. The combination of NSAIDs and colchicine can reduce the need for glucocorticoids in patients with recurrent pericarditis. Corticosteroids should be avoided due to their adverse effects and the fact that they facilitate the recurrence of pericarditis. Corticosteroids are usually used in refractory cases when relapses occur despite the combination therapy of colchicine and NSAIDs. When patients do not tolerate NSAIDs or colchicine, and/or frequently relapse, necessitating repeated doses of corticosteroids, one should consider initiating steroid-sparing medications such as azathioprine, methotrexate or cyclophosphamide. Of these, azathioprine is the safest and has few side effects. Thus, anti-TNFα therapy is considered a successful means of treating TRAPS, but patients become less responsive over time and have to switch to anti-interleukin (IL-1β) therapy [2,3]. High doses of intravenous human immunoglobulins were also reported to be beneficial and to act as a steroid-sparing therapy in a wide spectrum of immune mediated inflammatory diseases, including refractory recurrent pericarditis. Based on the fact that IL-1 (both IL-α and IL-β) mediated inflammation is the main pathogenic factor in the process of autoinflammatory disorders, anti-IL-1 therapy became recognized as the most feasible approach to treat resistant/severe cases. Anakinra, a recombinant human IL-1β receptor antagonist, was considered by many to be useful in recurrent pericarditis, namely, when all the above therapies fail to achieve long-lasting remission. We present the case of a man with acute relapsing recurrent pericarditis relieved only by

high dose corticosteroids, who received anakinra, a recombinant human IL-1β receptor antagonist.

PATIENT DESCRIPTION

This patient was a 33 year old man, healthy until his first hospitalization due to acute chest pain radiating to his left shoulder, and high fever of 38ºC. ECG was abnormal, documenting ST depressions. Echocardiography and computed chest tomography revealed moderate pericardial effusion. All this was in association with ESR and increased CRP. Infectious diseases, namely viral and tuberculosis, malignancy and autoimmune diseases were excluded by relevant clinical and laboratory analyses. After taking NSAIDs for a few weeks he felt much better. Two months later (while on continuous NSAIDs) he was admitted again for severe exacerbation of chest pain and a systemic fever of 38ºC. Here again, ESR was increased and pericardial effusion was found in moderate amounts. This time he was treated with oral corticosteroids to which he rapidly responded, and was discharged on continuous colchicine therapy and gradual tapering down of the corticosteroids. Since then, and almost every 2 months, while on a tapered dose of prednisone (10–15 mg/day) he suffered another recurrence of pericarditis, requiring the increase of prednisone to 40 mg/day. Aiming to reduce the rate of relapses and to spare steroids, he was started on azathioprine; however, this did not change the recurrence rate of pericarditis. At this stage the suspicion of an autoinflammatory disease raised the possibility of treatment with anti-IL-1 antibodies (anakinra). The only family history that was relevant was that his nephew suffered from FMF. The patient himself was found to be heterozygous to the M6941 mutation. No family history of TRAPS could be found. After one week of therapy with anakinra 100 mg daily he felt significantly better. During the following 2 months he was able, for the first time, to taper down steroids to a dose of 1 mg/day. He felt well, and even when pericarditis did recur it was milder and shorter, and 2–3 days of add-on NSAIDs was sufficient to maintain remission. After another 2 months on maintenance with anakinra, he was able to discontinue prednisone and later even colchicine. Today, after a year of maintenance therapy with anakinra 100 mg/day he is doing well, and even when he suffers mild attacks of chest pain, add-on therapy is not required.

COMMENT

Autoinflammatory diseases are the result of increased activation of the inflammasome, leading to enhanced IL-1 secretion. Understanding the molecular pathways involved in this type of inflammation is crucial for correctly defining these disorders and choosing the appropriate therapy. Recurrent pericarditis is highly responsive to steroids, supporting the notion that pericarditis is autoimmune or autoinflammatory in origin. However, when recurrent pericarditis is steroid resistant and improvement is closely associated with IL-1 antagonists, a pathogenic role for the inflammasome hyperactivation is suggested [4].

As we observed in our patient, the administration of anakinra was followed by an immediate clinical response and reduction in inflammatory markers, namely CRP and ESR. However, in some cases recurrence of pericarditis is observed when anakinra is stopped. Scardapane and co-authors [5] report that after renewing treatment with anakinra, remission was again achieved and patients were able to discontinue corticosteroids slowly, remaining on continuous anakinra treatment and, most importantly, with almost no side effects [5]. The recommended duration of treatment is at least 12 months during which it is advised to continue treatment with NSAIDs or colchicine until full remission is achieved. Administering anakinra to patients with refractory recurrent pericarditis is therefore highly recommended – namely, for patients in whom high doses of steroids are required, or who might be suspected of having a hidden undiagnosed genetic mutation involving the inflammasome.

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"There is only one day left, always starting over: it is given to us at dawn and taken away from us at dusk"

Jean-Paul Sartre (1905-1980), French philosopher, playwright, novelist, political activist, biographer and literary critic. His work on the philosophy of existentialism influenced sociology, critical theory, post-colonial theory, and literary studies and continues to influence these disciplines

"There are only two lasting bequests we can hope to give our children. One of these is roots, the other, wings"

Johann Wolfgang von Goethe (1749-1832), German writer and statesman