Miopericarditis autoinflamatoria aguda recurrente: de la fisiopatología a la clínica

Acute recurrent autoinflammatory myopericarditis: from pathophysiology to practice

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ABSTRACT

Recurrent myopericarditis is the acute inflammation of the pericardium and myocardium that relapses after a symptom-free interval of 4 to 6 weeks. A thorough differential diagnosis is necessary to identify uncommon causes that may have therapeutic and prognostic importance. These include autoinflammatory diseases, which can present as recurrent myopericarditis in genetically predisposed or impaired-immunity individuals.

We present a 33-year-old male with polyclonal hypogammaglobulinemia and six episodes of myopericarditis, in which the diagnosis of a probable autoinflammatory syndrome was established. Targeted treatment based on the pathophysiological mechanisms was started with immunoglobulins and anakinra, with favourable clinical and serological outcome with no relapses.

Organ-specific autoinflammatory diseases with myocardial involvement may be associated with life-threatening complications. The role of multidisciplinary care and a diagnostic approach focused on the pathophysiology of the disease could be the most important thing for early treatment to improve the prognosis and quality of life of our patients.

Keywords: Myocarditis; pericarditis; Autoinflammatory Diseases; anakinra; inflammasome.

RESUMEN

La miopericarditis recurrente es la inflamación aguda del pericardio y el miocardio que recidiva tras un periodo libre de síntomas de 4 a 6 semanas. Es necesario realizar un diagnóstico diferencial exhaustivo para identificar causas poco comunes que puedan tener importancia terapéutica y pronóstica. Entre ellas se encuentran las enfermedades autoinflamatorias, que pueden presentarse como miopericarditis recurrente en individuos genéticamente predispuestos o una inmunidad alterada.

Presentamos el caso de un varón de 33 años con hipogammaglobulinemia policlonal y seis episodios de miopericarditis, en el que se estableció el diagnóstico de un probable síndrome autoinflamatorio. Se inició un tratamiento dirigido con inmunoglobulinas y anakinra basado en los mecanismos fisiopatológicos de la enfermedad, con un resultado clínico y serológico favorable en ausencia de recaídas.

Las enfermedades autoinflamatorias con afectación cardíaca órgano-específica pueden asociarse a complicaciones potencialmente mortales. El papel de la atención multidisciplinar y un enfoque diagnóstico centrado en la fisiopatología de la enfermedad, resultan de vital importancia para instaurar un tratamiento precoz que mejore el pronóstico y la calidad de vida de nuestros pacientes.

Palabras clave: Miocarditis; pericarditis; Enfermedades autoinflamatorias; anakinra; inflamasoma.

INTRODUCTION

Recurrent myopericarditis (RMP) is an acute inflammation of the pericardium and myocardium that recurs after a symptom-free period of four to six weeks[1]. Risk factors for recurrence include female sex, glucocorticosteroids treatment and previous recurrences.In Western countries most cases are idiopathic, however, it may be the first manifestation of an underlying systemic disease and the diagnosis can become a challenge[2,3]. Among their aetiologies are autoinflammatory diseases (AID), infrequent conditions to be considered in the differential diagnosis[4]. Knowledge of the pathophysiological substrate of autoinflammation seems to be key to an approach to the diagnosis and treatment of these diseases, which in turn will condition the prognosis. Several studies suggest the pivotal role of interleukin-1 (IL-1) in the development of RMP and support the use of anti-IL1 molecules as treatment[5].

CLINICAL CASE

A 33-year-old male, smoker, with a history of polyclonal hypogammaglobulinemia and five episodes of myopericarditis, three of which were preceded by viral symptoms (Table 1), presented with three-weeks evening fever, inflammatory polyarthralgias, diffuse myalgias and odynophagia. Two days before admission to the emergency department, he had developed oppressive central chest pain.

The physical examination was normal. Routine laboratory test showed: leukocytes 3.000/mm3, platelets 110.000/mm3, C-reactive protein 28.6 mg/L, ferritin 944 ng/ml, cardiac troponin I 908 pg/ml, GOT 92 U/L, GPT 192 U/L and polyclonal hypogammaglobulinemia. The EKG showed sinus rhythm at 61 bpm with J-point elevation in V3. Transthoracic echocardiogram and chest X-ray were normal.

He was admitted to the cardiology department with a diagnosis of PMR and started treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine. Electrocardiographic monitoring showed no events. A cardiac MRI showed minimal mesocardial enhancement points. A consultation with Internal Medicine was made for collaborative follow-up.

The study was completed with an autoimmunity panel, serologies (HIV, Brucella, HCV, HBV, Toxoplasma, Rubella and Mumps) and HLA-B5, all were negative. Genetic test for monogenic AID was performed (ADA-2, ELANE, HTR1A, LPIN2, MEFV, MVK, NLRC4, NLRP12, NLRP3, NOD2, OTULIN, PLCG2, POMP, PSMB8, PSTPIP1, RELA, TN-

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FAIP3, TNFRSF1A, TRNT1) without finding any pathogenic, probably pathogenic variants or variants of uncertain significance.

Finally, the diagnosis of polygenic AID was established, as a possible atypicaladult-onset Still's disease (AOSD). The patient was treated with immunoglobulins and anakinra with a favourable evolution, in the absence of recurrences throughout the twoyears of follow-up. He only reported erythema and local pain at the anakinra injection site, which self-limited after 3 weeks.

DISCUSSION

Recurrent pericarditis and myocarditis may be the first manifestation of an AID; however, an idiopathic aetiology is often accepted without further diagnosis, despite its prognostic and therapeutic implications. In recent years, the research into the inflammatory mechanisms underlying the diagnosis and treatment of RMP has led to an increase in the scientific literature on the matter. We show a case of a not-so-uncommon cardiac disorder, that is RMP, within an uncommon disease such as AID, and highlights the importance of applying a treatment based on the pathophysiology of the underlying disease.

Our patient developed six episodes of RMP with different clinical manifestations and complications. When making the differential diagnosis, the main question is whether the aetiology is idiopathic or there is an underlying autoinflammatory mechanism. PMR is considered a multifactorial condition involving several immunological mechanisms and is usually the result of an interaction between environmental triggers and the immune system of a genetically predisposed subject[6]. Although, traditionally associated with impaired acquired immunity, recent research suggests that innate immunity may be at the epicentre of its pathogenesis[6]. When apparently unprovoked flares of inflammation occur due to activation of innate immunity, that is in the absence of specific antigens and autoantibodies, we describe an AID.

RMP can be mediated by an autoinflammatory mechanism resulting from inflammasome activation by cardiotropic viruses or by non-specific antigens in patients with impaired immunity. The final target of their activation is IL-1 production1. In our patient, this seems to be the most likely mechanism, both due to the clinical presentation and to the fact that he presented with immunodeficiency (which could facilitate repeated infections)[3]. There is increased evidence of the emergence of autoinflammatory disorders as a complication of primary immunodeficiencies, often overlapping with persistent immune dysregulation[7].

Polygenic AID include AOSD[7]. Although generally uncommon, serositis and myocarditis may develop in atypical forms of the disease, in which usual clinical manifestations may be absent[4]. In cardiac involvement, pericarditis is the most typical manifestation. Myocarditis is rare, more prevalent in younger men[4], characteristically associated with pericarditis at the onset of the disease[8] and has a favourable response to early immunosuppressive therapy. Our patient does not fulfil the criteria, but has developed 4 of the cardinal symptoms: fever (above 39°C, sudden onset, during activity periods longer than a week), prolonged inflammatory arthralgias, odynophagia and altered liver tests. In addition, he develops leukopenia and thrombopenia, which may appear in atypical Still's presentations[4], and always elevation of acute phase reactants and ferritin.

In the case of AID, regardless of the classificatory diagnosis *per se*, understanding the pathophysiology is essential to provide specific treatment[3]. In RMP, the first line-treatment for acute phase are NSAIDs plus colchicine for at least 3-6 months. The second line are colchicine plus low-dose steroids for 3 months. Recently, IL-1 receptor antagonists (anakinra and canakinumab) have been proposed as a third line, displacing classical immunosuppressants and immunoglobulins to the fourth line. Restriction of physical activity is indicated in all cases[3]. In our patient, anakinra and immunoglobulins (because of their immunomodulatory effect, the concomitant presence of an immunodeficiency and their proven efficacy in cases of RMP in AOSD)[9] were started to avoid recurrences with a good response so far. Similar clinical cases have been published[9,10].

This case highlights the relevance of finding out the aetiological diagnosis through collaborative efforts and multidisciplinary follow-up. In many cases, it is not so important the diagnostic classification itself, especially in life-threatening RMP, as it is the development of a treatment focused on the pathophysiology, which can halt the progression of the disease and improve the quality of life of our patients.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Informed consent was obtained from all individual participants included in the study.

CONSENT FOR PUBLICATION

All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

AVAILABILITY OF DATA AND MATERIALS

This material is the authors' own original work, which has not been previously published elsewhere. The paper is not currently being considered for publication elsewhere. The paper reflects the authors' own research and analysis in a truthful and complete manner. The results are appropriately placed in the context of prior and existing research. All sources used are properly disclosed (correct citation).

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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AUTHORS' CONTRIBUTIONS

The paper properly credits the meaningful contributions of co-authors and co-researchers.

Table 1. Characteristics of previous episodes of recurrent myopericarditis.

Date	Symptoms	Analysis	EKG	Imagine test	Specific treatment	Adverse outcomes
May 2005 (18 years)	Diarrhoea and diffuse myalgias for two weeks. Oppressive central chest and left upper limb pain.	TpI (21.3 ng/ml) and CPK (583 mg/dl). CRP 40 mg/l. Elevated LDH (297 U/L) and AST(97U/L)	ST-segment elevation in inferior and anterior leads.	TTE: pEF. No cardiac tamponade.	Indomethacin and colchicine for 4 weeks.	No
December 2007 (20 years)	Fever, cough and odynophagia 2-3 days. Central oppressive chest pain and left upper limb pain.	TpI (14.4 ng/ml) and CPK (569). CRP 34 mg/l.	ST-segment elevation in inferior and anterior leads.	TTE: pFE. No cardiac tamponade.	Dexibuprofenfor 4 weeks.	No
March 2008 (21 years)	Cervical pain and fever >39º 10 days. Oppressiveleftchestpain.	TpI (19 ng/ml) and CPK (591). CRP 26 mg/l LDH 469 U/L, AST 72 U/L.	ST-segment elevation in inferior and anterior leads.	TTE: pFE. No cardiac tamponade.	Ibuprofen for 4 weeks and colchicine 1 year.	No
December 2009 (22 years)	Cervical pain and headache 3-4 days. Central chest pain and in the left shoulder.	TpI (29.9 ng/ml), CPK 748 U/l. CRP 20.1 mg/l. LDH 470 u/L. AST 108 U/L.	ST-segment elevation in lateral lead.T wave inversion in III.	TTE: moderate left ventricle dysfunction; hypokinesia middle apical anterior segment and anterior septum. MRI: Myocardial uptake at basal and middle level of anterior LV wall.	Indomethacin 4 weeks and colchicine 1 year.	Admission to intensive care unit for persistent pain and left ventricle dysfunction.
November 2016 (29 years)	Central chestpain	TpI 2417 ng/m. CRP 28.6 mg/l and normal ESR.	ST-segment elevation in all leads. T wave inversion in III and aVF.	TTE: pFE. No cardiac tamponade MRI: Intense uptake in anterior and anteroseptal segment at baseline and middle level.	Acetylsalicylic acid500 mg for 4 weeks.	Paroxysmal atrial fibrillation Sinusbradycardia.

Abbreviations:
AST= aspartate aminotransferase. CPK =Creatine phosphokinase. CRP = C-reactive protein. ESR = erythrocyte sedimentation rate. LDH = lactate dehydrogenase.
LV = left ventricle. MRI: magnetic resonance imaging. pEF = preserved ejection fraction. TpI = cardiac troponin I. TTE = transthoracic echocardiogram.

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