Autoimmunity Reviews 14 (2015) 90–97

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Autoimmunity and autoinflammation as the yin and yang of idiopathic recurrent acute pericarditis

Luca Cantarini [a,*,1], Giuseppe Lopalco [b,1], Carlo Selmi [c,d], Salvatore Napodano [e], Gabriella De Rosa [e], Francesco Caso [a,f], Luisa Costa [g], Florenzo Iannone [b], Donato Rigante [e]

[a] Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinic, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Siena, Italy
[b] Interdisciplinary Department of Medicine, Rheumatology Unit, Policlinic Hospital, University of Bari, Bari, Italy
[c] Division of Rheumatology and Clinical Immunology, Humanitas Research Hospital, Rozzano, Milan, Italy
[d] BIOMETRA Department, University of Milan, Milan, Italy
[e] Institute of Pediatrics, Università Cattolica Sacro Cuore, Rome, Italy
[f] Department of Clinical and Experimental Medicine, University of Padua, Padua, Italy
[g] Rheumatology Unit, Department of Clinical Medicine and Surgery, University Federico II, Naples, Italy

ARTICLE INFO

Article history:
Received 5 September 2014
Accepted 23 September 2014
Available online 12 October 2014

Keywords:
Pericardial effusion
Recurrence
Interleukin-1
Anakinra

ABSTRACT

Autoimmunity and autoinflammation are generally considered as mutually exclusive mechanisms of diseases but may concur to specific syndromes. Idiopathic recurrent acute pericarditis (IRAP) is defined as the recurrence of pericardial symptoms at any point following the prior cessation of acute pericarditis, and the latency is generally 6 weeks. Manifestations of pericarditis such as pericardial friction rub, electrocardiographic changes, and pericardial effusion are less frequent in the subsequent episodes compared to the index attack, and in some cases the only clinical sign is represented by a suggestive chest pain. Several autoimmune diseases may manifest with pericarditis which is often related to viral infections, while postviral pericarditis may in turn display a nonspecific autoimmune background. Similarly, autoinflammatory syndromes such as familial Mediterranean fever and tumor necrosis factor receptor-associated periodic syndrome are characterized by self-limiting pericardial symptoms. Corticosteroids are generally effective, thus supporting the autoimmune nature of IRAP, but dramatic results are obtained with interleukin-1 blocking agents in corticosteroid-dependent cases, pointing to a pathogenic role for the inflammasome. Based on these observations, we submit that IRAP represents a paradigmatic example of the putative coexistence of autoimmunity and autoinflammation: the main aim of this review is to critically discuss the hypothesis as well as the current understanding of this enigmatic clinical condition.

Contents

1. Introduction

Diagnosis of acute pericarditis can be made when chest pain is variably combined with pericardial friction rub, electrocardiographic changes, new or worsening pericardial effusion, normal creatine kinase-MB, and increased C-reactive protein, but criteria for diagnosis of IRAP include the combination of typical chest pain, electrocardiographic and/or

* Corresponding author at: Policlinico "Le Scotte", University of Siena, Viale Bracci 1, 53100 Siena, Italy. Tel.: +39 347 9385457; fax: +39 0 577 40450.
E-mail address: cantariniluca@hotmail.com (L. Cantarini).
[1] These authors equally contributed to this manuscript.

http://dx.doi.org/10.1016/j.autrev.2014.10.005
1568-9972/

echocardiographic abnormalities, and increased C-reactive protein [1]. Idiopathic recurrent acute pericarditis (IRAP) is among the most alarming and mysterious complications of acute pericarditis, which commonly represents a diagnostic and therapeutic challenge, occurring 6 weeks after an acute pericarditis presumably caused by viral agents, such as Enterovirus [2]. There are no controlled clinical trials about the optimal duration of treatment or the appropriate dosages of drugs in acute pericarditis, and recurrences are reported in up to one third of patients, while their number and the interval between the episodes might vary consistently and are not predictable [3]. In the majority of patients, recurrent attacks of chest pain are the only major disabling feature of IRAP, while other manifestations of pericarditis such as pericardial friction rub, electrocardiographic changes, and effusion are less frequent than in the index attack. The traditional diagnostic approach to pericarditis may include a pericardial biopsy or effusion analysis but not lead to an etiological definition, and most cases are thus coined idiopathic. A cardiac tamponade might rarely appear as a complication of IRAP, and failure to respond to standard treatment requires hospital admission mainly to prevent life-threatening complications and rule out primary causes such as endocrine disorders, uremia, and malignancies [4].

Inappropriate doses of nonsteroidal anti-inflammatory drugs (as aspirin, indomethacin, or ibuprofen) or suboptimal duration of treatment of the index attack might explain pericardial relapses in some cases [5]. Colchicine [6–8] was evaluated as add-on to the standard treatment of acute pericarditis in a large randomized prospective trial in acute pericarditis, producing a significant reduction of the recurrence rate [9–12]. Corticosteroids for at least 4 weeks may be required in recurrent pericarditis, but steroid therapy is also considered an independent risk factor for the disease recurrence [13]. Also, intrapericardial administration of triamcinolone has been attempted in the treatment of the most difficult forms of IRAP [14].

2. The autoimmune side of IRAP

It has been hypothesized that a significant number of IRAP is determined by misdirected immune reactions against microorganisms, frequently viruses, or microbial toxins [15], also in agreement with the privileged immunity status which is encountered in the pericardium, similar to other organs [16]. Agents involved in postviral recurrent pericarditis include Echovirus, Coxsackie B virus, Epstein–Barr virus, Cytomegalovirus, Adenovirus, and Parvovirus B19, but apparently not hepatitis C virus [17]; a bacterial etiology is on the other hand mainly related to *Mycobacterium tuberculosis*, commonly as a result of the human immunodeficiency virus infection. Many experts advocate that once collagen vascular diseases or a previous myocardial infarction have been ruled out, most cases of IRAP are caused by autoimmune mechanisms with or without an initial viral trigger [18]. However, it is misleading to consider all cases of IRAP as autoimmune per se, and definite evidence of an autoimmune basis should be indeed documented, while polymerase chain reaction for cardiotropic viruses or other infectious agents should be negative, and immunoglobulin M against these agents should be undetectable [19]. A role of autoimmunity in the pathogenesis of recurrent postviral pericarditis may ensue through the activation of both innate and adaptive immune pathways in predisposed hosts, and it is known that microbial DNA can strongly stimulate the immune system, activating both toll-like receptors (TLR) and other germline-encoded receptors [20]. Following the response of activated dendritic cells, naïve CD4 + T cells can differentiate into different Th subsets with distinct effector functions and variable cytokine release: recent data suggest that dendritic cells can break tolerance by priming autoreactive T cells, both Th1 and Th17 [21–23].

Different lines of evidence support an autoimmune basis for IRAP. First, self-antigens may be overexposed following a damage to pericardial or myocardial tissues and act as endogenous triggers interacting with TLRs and stimulating B and T cells to elicit an autoimmune process [24,25]. Sequelae of pericardiotomy, myocardial infarction (Dressler's syndrome) or pacemaker implantation can be associated with the release of cardiac autoantigens that stimulate the production of cross-reactive anti-heart antibodies [26,27]. We note that the functional relevance of autoantibodies against cardiac myosin in idiopathic dilated cardiomyopathy remains unclear [28], and no studies exist evaluating their role in IRAP. In 2010, Caforio et al. evaluated the frequency of serum anti-heart (AHA), anti-intercalated-disk (AIDA), and non-cardiac autoantibodies by indirect immunofluorescence in a series of 40 patients with IRAP [29]: three of the autoantigens recognized by AHA were identified as α and β myosin heavy chain and myosin light chain-1v isoforms, while the autoantigens responsible for AIDA were not identified [30]. AHA and/or AIDA represent autoimmune markers in patients with biopsy-proven myocarditis or dilated cardiomyopathy and have been found in 67.5% of patients with IRAP: a higher frequency of cross-reactive AHA and AIDA (respectively, 50 and 25%) has been found in IRAP, in comparison with non-inflammatory or ischaemic cardiac diseases. On the contrary, the frequency of organ-specific AHA was similar in patients with IRAP and in controls, whereas their presence was more common in biopsy-proven myocarditis and dilated cardiomyopathy than in normal subjects [31]. The discrepancy of these results could be explained by different antibody specificities, resulting in distinct clinical phenotypes in autoimmune diseases [32] and suggesting that cross-reactive AHA may be more prevalent in pericarditis, while organ-specific AHA in myocarditis. Alternatively, the appearance of autoantibodies in patients with autoimmune diseases tends to follow a predictable course, with a progressive accumulation of specific autoantibodies in a late phase of the disease [33]. Therefore, it would be conceivable to assume that organ-specific AHA are early markers, followed by AIDA and cross-reactive AHA in the long-lasting forms of IRAP.

Second, recurrent pericarditis is characteristic of vasculitides and connective tissue diseases, especially systemic lupus erythematosus but also rheumatoid arthritis, progressive systemic sclerosis, Sjögren's syndrome, polyarteritis nodosa, and other systemic vasculitides [34–37]. In many cases, pericardial involvement may be subclinical with a silent pericardial effusion or clinically overt with symptoms of marked severity.

Third, the autoimmune background of IRAP is suggested by the presence of proinflammatory cytokines, such as interleukin (IL)-6, IL-8 and interferon (INF)-γ in the pericardial fluid, but not in the plasma, to represent a local inflammatory reaction [38].

Fourth, antinuclear autoantibodies (ANA) are commonly found in patients' sera, but their relationship with IRAP is still unclear [39]: ANA have been detected in 43.4% of patients with IRAP and only in 9.8% of healthy controls [40]. However, positive ANA at low titres (1/40 to 1/80) is nonspecific, and might suggest a potential mechanistic role in IRAP if repeatedly confirmed. In addition, the clinical significance of ANA is limited, as they are equally distributed in patients with IRAP who have or not a definite rheumatologic disorder, with higher prevalence among females, older individuals, and people of African/American descent [41–43]. In one study, ANA at titres exceeding 1/160 were found in patients with IRAP (5%) and associated with the risk of recurrence [39]. Whether or not these autoantibodies may provide clinically useful biomarkers of IRAP requires future assessment. In spite of these findings, actual guidelines still suggest that the diagnosis of autoimmune pericarditis should be based upon a pericardial biopsy ruling out other etiological factors [44].

3. The autoinflammatory side of IRAP

Cases of IRAP without plausible immunological causes have been recently related to autoinflammatory disorders, a growing family of innate immunity dysfunctions mainly caused by mutations in genes involved in the inflammatory response, without any apparent involvement of antigen-specific T cells or autoantibodies [45,46]. In particular, a lack of regulation in the inflammasome, a large intracellular multiprotein