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EDITORIAL COMMENT

Diversity in Acute Pericarditis

Picking the Apples From the Oranges

Danilo Malandrino, MD, PhD,[a] Brittany Weber, MD, PhD,[b] Michael S. Garshick, MD, MS,[c] Antonio Abbate, MD, PhD[d]

Pericarditis refers to inflammation of the pericardial sac; it may represent a manifestation of systemic inflammatory disease (ie, autoimmune diseases) or, if occurring in isolation, acute idiopathic pericarditis. Epidemiologic data on pericarditis are scarce and largely limited to single-center cohort studies. The available data show that systemic diseases are only identified in a minority of patients with pericarditis (3%-7%). Data from cohorts of patients with systemic inflammatory diseases, however, show that pericardial involvement is common, as high as 50% of cases, and pericarditis can be part of the initial presenting symptoms.[1] Pericarditis associated with autoimmune diseases has a worse prognosis, including a higher risk of potentially life-threatening complications such as cardiac tamponade and constrictive pericarditis.[2] It is therefore important to take a careful and complete history and perform a complete physical examination to identify autoimmune conditions in all patients with pericarditis.

In this issue of *JACC: Asia*, Aikawa et al[3] provide an overview of a nationwide Japanese registry study of acute pericarditis, identifying differences in characteristics and outcomes between patients with acute idiopathic pericarditis and patients with acute autoimmune pericarditis. Based on the International Classification of Diseases, Tenth Revision, codes, this research study included 20,469 hospitalized patients admitted from April 2016 to March 2020 in Japan with acute pericarditis. Ultimately, after applying exclusion criteria, 5,197 patients were analyzed; 5,027 (96.7%) were diagnosed as having idiopathic pericarditis and 170 (3.3%) were identified as having an autoimmune pericarditis.[3] The patients with autoimmune pericarditis had a higher frequency of cardiac tamponade than idiopathic pericarditis (8.8% vs 4.7%, respectively; $P = 0.023$), although no differences were found regarding rehospitalization or in-hospital death.

The most common autoimmune conditions associated with autoimmune pericarditis were systemic lupus erythematosus (23.5%), rheumatoid arthritis (19.4%), systemic sclerosis (8.2%), and mixed connective tissue disease (4.7%).[3] Those diagnosed with lupus were also more commonly associated with cardiac tamponade, followed by rheumatoid arthritis and systemic sclerosis. The identification of systemic lupus erythematosus as the most common cause of autoimmune pericarditis is consistent with previous data. Despite a low incidence of lupus in Japan (ranging from 0.9 per 100,000 persons per annum),[4] it is reported that up to 50% of patients with lupus had pericardial involvement, thus making it a common presentation for patients with this disease. As such, pericarditis is listed among the diagnostic criteria for lupus, and it is the only cardiac manifestation, from the first 1997 American College of Rheumatology criteria and the new 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus.[5]

In the study by Aikawa et al,[3] more than 30% with autoimmune disease, however, lacked a specific diagnosis. The patients with pericarditis who did not have a specific autoimmune disease identified had a higher rate of hospitalization due to pericarditis recurrence and a lower frequency in the prescription of steroids at discharge compared with those with a specific diagnosis. The determination of the cause of

From the [a]Department of Experimental and Clinical Medicine, Internal Interdisciplinary Medicine Unit, University of Florence, Careggi University Hospital, Florence, Italy; [b]Heart and Vascular Center, Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [c]Leon H. Charney Division of Cardiology, NYU Langone Health, New York, New York, USA; and the [d]Berne Cardiovascular Research Center and Division of Cardiology, University of Virginia, Charlottesville, Virginia, USA.

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TABLE 1 Diversity of Diagnosis in Cohorts of Adult Subjects With Acute Pericarditis

First Author	N	Years	Location	Idiopathic	Neoplastic	Tuberculosis	Other Bacterial	Autoimmune
Permanyer-Miralda et al[6]	231	1977-1983	Western Europe	199 (86.0%)	13 (5.6%)	9 (3.9%)	2 (0.9%)	4 (1.7%)
Zayas et al[7]	100	1991-1993	Western Europe	78 (78%)	7 (7.0%)	4 (4.0%)	1 (1.0%)	3 (3.0%)
Imazio et al[8]	453	1996-2004	Western Europe	377 (83.2%)	23 (5.1%)	17 (3.8%)	3 (0.7%)	33 (7.3%)
Reuter et al[9]	233	1995-2001	Africa	32 (13.7%)	22 (9.4%)	161 (69.5%)	5 (2.1%)	12 (5.2%)
Gouriet et al[10]	933	2007-2012	Western Europe	516 (55.0%)	85 (8.9%)	4 (<1%)	29 (3.0%)	1 (<1%)
Aikawa et al[3]	5,197	2016-2020	Asia	5,027 (96.7%)	(excluded)	(excluded)	(excluded)	170 (3.3%)

autoimmune disease can be complex, and reporting biases may be present that affect the accuracy of the diagnosis; however, the findings of worse outcomes in patients with pericarditis associated with undifferentiated autoimmune diseases underscore the importance of carefully evaluating for possible underlying rheumatologic disease in all patients with acute pericarditis and a medical history suggestive for autoimmune features. The goal is to provide a more rational treatment inherent to the different autoimmune backgrounds. These data are in agreement with a retrospective cohort study at the Cleveland Clinic showing a significantly higher recurrence rate of autoimmune pericarditis when compared with idiopathic and post-cardiac injury pericarditis cases, highlighting the prognostic value of etiology in subjects with recurrent pericarditis.[11]

By providing an estimate of the systemic autoimmune diseases to the clinical burden of acute pericarditis in Japan, Aikawa et al[3] confirm and expand prior findings to a different geographic region and population (**Table 1**). The use of International Classification of Diseases, Tenth Revision, codes should, however, be discussed as a potential limitation for the diagnostic accuracy and the ability to detect all cases of pericarditis and of the comorbid conditions.[12] The authors[3] also chose to exclude subjects affected by chronic, recurrent, or incessant pericarditis and patients with inflammatory bowel disease from the autoimmune pericarditis group, possibly leading to an underestimation of specific forms.[13,14]

The definition of systemic autoimmune disease also carries therapeutic implications. Colchicine is considered the mainstay of the treatment of idiopathic pericarditis or pericarditis associated with cardiac procedures or post-pericardiotomy syndrome. Corticosteroids are generally reserved for the treatment of patients with autoimmune pericarditis.[14] Aikawa et al[3] reported a greater use of corticosteroids in patients with specific autoimmune diseases. They also reported that less than one-quarter of patients in the registry were undergoing treatment with colchicine at postdischarge analysis (17.0% of patients with autoimmune disease); the lowest percentage was in the subgroup of subjects with undifferentiated autoimmune pericarditis (10.6%). The use of colchicine was, however, also low in patients with idiopathic pericarditis (23.2%). The low use of colchicine across the different groups is difficult to reconcile; although these may reflect practice patterns specific to Japan, these data may also identify a treatment gap that should be addressed.

Colchicine's mechanism of action is related to the inhibition of microtubule assembly interfering with key functions of the innate immune response such as inflammasome formation, cytokine secretion, and neutrophil migration. It is not fully understood how much innate and adaptive immunity contributes to the immunopathogenesis of pericarditis in the setting of autoimmune disease; limited research exists exploring pathophysiological mechanisms that drive the heterogeneity of outcomes observed in specific forms.[8,14]

In conclusion, pericarditis associated with systemic autoimmune disease is substantially different than idiopathic pericarditis, portending a worse prognosis. Although the correct diagnosis of the pericardial and systemic syndrome is essential for the appropriate treatment of the patient, the preferred treatment strategy for pericarditis associated with systemic autoimmune diseases remains unclear. Thus, an urgent need remains to determine the preferred treatment strategies in patients with pericarditis associated with systemic autoimmune diseases.

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ADDRESS FOR CORRESPONDENCE: Dr Danilo Malandrino, Department of Experimental and Clinical Medicine, Internal Interdisciplinary Medicine Unit, University of Florence, Careggi University Hospital, Largo Giovanni Alessandro Brambilla, 3, Florence 50134, Italy. E-mail: danilo.malandrino@unifi.it. X handle: @bweber04, @garshick, @AbbateAntonio.

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