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IM - COMMENTARY

Acute pericarditis or a systemic disease with pleuropulmonary involvement?

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Pericardial diseases may be considered either as isolated diseases (more often managed by cardiologists) or as part of a systemic disease, often managed by Internists or other specialists. The main pericardial syndromes are formally distinguished in pericarditis (acute, subacute, chronic and recurrent), pericardial effusion, cardiac tamponade, constrictive pericarditis, and pericardial masses [1].

Clinical syndromes in practice range from completely asymptomatic pericardial effusions, even large [2] to very severe inflammatory conditions such as adult Still's disease [3, 4].

The pathophysiology of these systemic diseases is of undoubted complexity and may involve both the innate immune system (autoinflammatory mechanisms) and the adaptive immunity (autoimmune conditions), sometimes with a co-activation and an interplay between the two systems and a crosstalk with environmental factors [5]. Notably, investigation of the mechanisms underlying the abovementioned wide spectrum of pericardial disorders has led to deeper understanding of the activity of therapeutic milestones such as colchicine (able to modulate neutrophil chemotaxis and IL-1 release), as well as providing the rational for new treatment strategies (e.g., IL-1 receptor antagonist).

Even if it is logical to formally classify clinical presentation according to strict diagnostic criteria [1], in the modern era of personalized medicine it is also important to recognize some clinicopathological phenotypes that are probably sustained by pathogenetic pathways that may be target of specific therapies [6].

The presence of dullness at the base of the left hemithorax in patients with acute pericarditis has been recognized many years ago as the Ewart's sign [7], but the clinical significance of pleural effusions in the setting of acute pericarditis remained poorly investigated, till the present paper by Lazaros et al. [8].

This paper is important because it underlines the fact that a concomitant pleural effusion was present in more than 50% of 177 patients hospitalized with a first episode of acute pericarditis in a cardiology unit that is a referral center for pericardial diseases: when present, pleural effusion was bilateral in 53.2% of the cases, left-sided in 28.7% and right-sided in 18.1%. For the requirements of this study, chest computed tomography (CT) imaging, comprehensive echocardiography (including posterior views obtained bilaterally from the patients' back to unveil pleural effusions), and chest X-ray were performed in all patients. Pleural effusions were detected in 94/177 patients (53.1%) by CT, 89/177 (50.3%) by ultrasounds, and 42/177 (23.7%) by X-ray.

Notably, the authors observed that the presence of pleural effusion was strongly associated with C-reactive protein (CRP) levels at admission.

Lazaros et al. concluded that pleural effusions are common in patients hospitalized with a first episode of acute pericarditis that they are related to the intensity of the inflammatory reaction and should not be considered necessarily as a marker of secondary etiology. The authors also observed that bilateral pleural effusions are associated with increased risk of in-hospital cardiac tamponade, but do not affect the long-term risk of pericarditis recurrence.

This paper is relevant for Internists and Emergency Medicine physicians because it discloses the existence of an inflammatory systemic condition, involving at least the heart, lungs and pleura, but in which also other sites may be affected: e.g., liver involvement (8% of cases) [9], peritoneal involvement and anemia (personal observations).

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A not rare clinical phenotype is in fact a syndrome characterized by abrupt onset of pleuro-pericardial pain, typically sharp, exacerbated by laying and breathing (a sort of "antalgic" dyspnoea) and improved by sitting up and leaning forward, together with high fever, strikingly elevated CRP. In this condition pleuropulmonary involvement is almost a rule, even because the severity of the presentation often induces the physicians on duty to prescribe a CT scan, to exclude aortic disease or pulmonary embolism; these conditions are easily ruled out, but almost invariably pleural effusions, often bilateral, are detected, with concomitant underlying areas of pulmonary atelectasis. As a consequence, the patient is admitted with a working diagnosis of pneumonia with pleuritis (even in complete absence of cough) and antibiotic therapy is invariably started, intravenously, with only some analgesics on demand for pain, such as paracetamol 1000 mg. Pericardial involvement may be evident from the beginning, clinically when the correct questions are asked to the patient, or as a pericardial effusion visible on the CT scan or on echography. However, sometimes the diagnosis is more difficult since the pericardial effusion may be almost absent in the first hours, becoming more evident in the following days.

Sore throat may be one of the heralding symptoms, a symptom also seen in Still's disease in which pericarditis can be usually detected [10]. Diarrhea is not so rare in this condition, also because several drugs usually employed in these patients may induce it (not only colchicine but also proton pump inhibitors and antibiotics) [11].

Since the condition is not sustained by bacteria, antibiotic therapy is not able to control the syndrome, high fever persists, and second and even third-line antibiotics are started (this is a typical condition in which antibiotics are incorrectly overused), while the patient continues to complain of severe pain. Several diagnostic tests are done, including a wide battery of tests to exclude infections and hematological or solid neoplasms, but they are generally inconclusive and finally corticosteroids are started after several days to control the severe systemic syndrome, after exclusion of infections and after failure of antibiotic therapies. The patient is generally prostrated and suffering, after a long course of the disease.

The initial diagnosis of pneumonia with pleuritis, treated with repeated courses of antibiotics is finally changed into pleuropericarditis, sometimes polyserositis, for a possible concomitant presence of some peritoneal effusion. Corticosteroids solve the conditions very quickly, but as soon as they are rapidly tapered or discontinued the condition recurs, and a vicious circle starts, with a possible long history of recurrences at each attempt to taper corticosteroids. Non-steroidal anti-inflammatory drugs (NSAIDs) are sometimes prescribed, but if used at low or moderate doses and only orally they are usually ineffective in controlling this true "explosion" of the inflammasome, and the road that will lead to starting corticosteroids is easily undertaken. NSAIDs may be useful to control the condition, but only when used at high dosages (e.g., ibuprofen 800 mg three times daily or indomethacin 50 mg three times daily, well distributed every 8 h) and preferably intravenously (e.g., acetylsalicylic acid 3000 mg/daily, or indomethacin 100 mg/daily), since the suffering patient is often complaining of nausea and vomiting. According to current guidelines [1], Lazaros et al. added colchicine to the anti-inflammatory therapy as first line treatment and usually observed also regression of pleural effusions within a month [8], thus confirming that, as above mentioned, the condition resembles autoinflammatory syndromes sustained by unprovoked activation of the innate immune system, with release of IL-1. The pivotal role of IL-1 (previously known by old Internists as "endogenous pyrogen") in these conditions is also demonstrated by the quick response to the administration of anti-IL1 agents, usually anakinra, with effects on symptoms and CRP that may become evident in a couple of days [3, 12].

There are other completely different syndromes encountered in clinical practice in which a pericardial effusion coexists with a pleural effusion, and sometimes the term pericarditis is used incorrectly; they are characterized by water and sodium retention caused by heart failure or renal failure or pulmonary hypertension in which a pleural effusion coexists with a pericardial effusion. Both effusions are probably due to the same hemodynamic forces that are well accepted causes of pleural effusions, but are less well known as possible causes of pericardial effusions [2]. Whatever is the true pathogenetic mechanism of these entities, it is completely different from the "autoinflammatory" condition described above; it is not dominated by inflammation, but by water and sodium retention.

The paper by Lazaros et al. will help Internists and other specialists to better manage systemic conditions in which pericardial and pleural involvement coexist in a context of a strong activation of the inflammatory cascade.

Compliance with ethical standards

Conflict of Interest Maddalena Alessandra Wu, Nathalie Costedoat-Chalumeau and Silvia Maestroni declare no conflict of interest that could influence the present work. Antonio Brucato has received unrestricted research grants from ACARPIA and SOBI and acknowledges being part of SOBI Advisory Board.

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