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LETTERS TO THE EDITOR

Life-threatening hypereosinophilic syndrome in a patient with rheumatoid arthritis: a case report

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Dear Editor,

Hypereosinophilia is unusual in rheumatoid arthritis (RA), but can occur in severe long-lasting disease, especially in patients with extra-articular manifestations and high titers of rheumatoid factor (RF) [1,2,3,4, 5,6]. The hypereosinophilic syndrome (HES) occurs when hypereosinophilia leads to organ dysfunction[5,6,7], and can be divided into 4 major types depending on the underlying mechanism: clonal, reactive, familial and idiopathic[6]. Even though there are only a few case reports of RA associated to eosinophilic pneumonia[1,4,8] and myocarditis (Loeffler's endomyocardial fibrosis)[9], the possible association of RA and HES remains yet poorly known. Some studies mention a possible autoimmune etiology, in which an identical immune complex with RF stimulates the bone marrow to produce excessive amounts of eosinophils[5]. Here, we present a case of HES with life-threatening multiorgan involvement in a patient with known RA.

A 46-year-old female patient presented to the emergency department (ED) in March 2022 with acute oppressive chest pain. She also reported one-week of shortness of breath and inflammatory arthralgias of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of both hands. The patient has been previously diagnosed with RA by a rheumatologist when she was 33 years-old and remained in remission for several years with methotrexate and low-dose prednisolone, without known extra-articular involvement. She was lost to follow-up between 2017 and 2022 and, according to her, remained asymptomatic without medication during that period.

At the ED, the physical examination revealed both reduced respiratory murmur in pulmonary bases and also reduced heart sounds, pruritic erythematous skin papules on the forearms and legs and symmetric polyarthritis of the hand joints (2nd-5th MCP and 2nd-4th PIP bilaterally). While in the ED, she had two episodes of cardiopulmonary arrest, which were responsive to resuscitation. The urgent cardiopulmonary study revealed a constrictive pericarditis with cardiac tamponade and bilateral pleural effusion, without myocardial involvement. She was submitted to urgent pericardial drainage and partial pericardiotomy and admitted to the cardiology intensive care unit. Laboratory analyses revealed highly elevated inflammatory parameters - leukocytosis (22300/cm^3) due to hypereosinophilia (7000/cm^3, 20%), thrombocytosis (1027000/cm^3), elevated CRP (25.4 mg/dL) and ESR (46 mm/h). She also had elevated immunoglobulin E (IgE, 3740 UI/mL). The histological study of the pericardium showed thickened pericardial wall, with fibrosed areas and fibrin adherence to the pericardium with eosinophilic inflammatory infiltrate, with no granulomas (Figure 1). A diagnosis of HES was made, and the patient was started on prednisolone (0.25 mg/Kg/day), with significant clinical and analytical improvement and was discharged after 4 weeks.

At the first outpatient rheumatology visit, she presented with polyarthritis (1st right MCP, 2nd and 3th bilateral PIP) but no skin lesions, and she still had a slight elevation of the eosinophiles count (1560/cm3) and mildly elevated inflammatory parameters. No organomegaly was detected. Hands and feet radiographs revealed typical erosions of RA, and the immunological study identified high titers of Rheumatoid Factor (RF, 1130 UI/mL) and anti-citrullinated protein antibodies (ACPA, 305 UA/mL). She started treatment with methotrexate 15mg per week and maintained 20 mg per day of prednisolone, which resulted in completed clinical and analytical remission within 12 weeks. After 24 weeks, a complete tapering of glucocorticoids was possible, and at that time the patient had normal blood eosinophils count, showing no signs of pleural or pericardial effusion and no irreversible cardiac lesions, or involvement of other organs.

After an intensive diagnostic study, we could rule out other potential causes of HES (e.g., parasitic infections, solid or hematologic malignancies, clonal HES,

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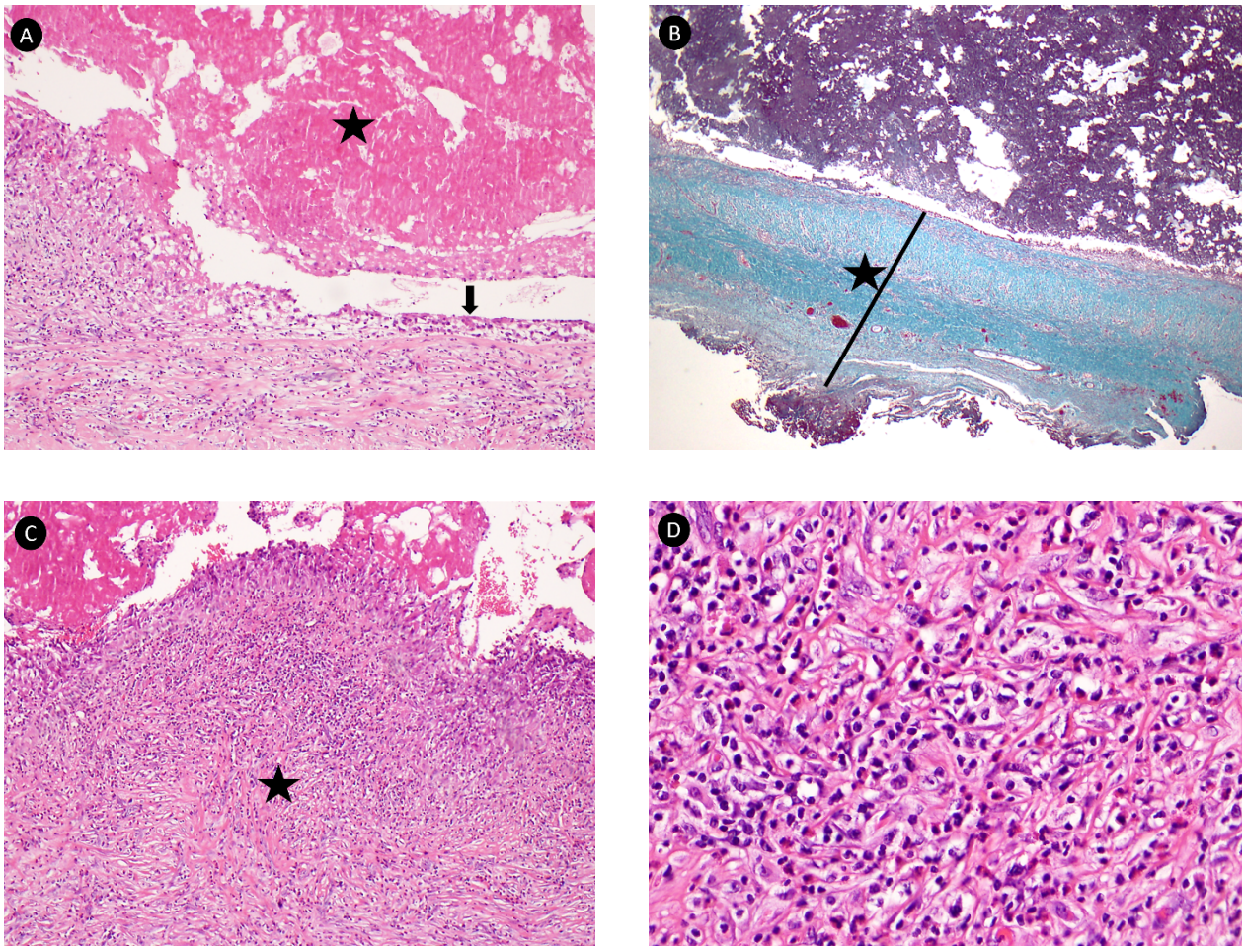

Figure 1. Pericardial biopsy with inflammatory fibrinous pericarditis: (A) Fibrine (star) and reactive pericardium (arrow) (haematoxylin and eosin); (B) Thickening fibrosis (line and star) (Masson's trichrome); (C) Inflammatory infiltrate (star) (haematoxylin and eosin); (D) Detail of Figure 1-C, with inflammatory infiltrate rich in eosinophils (haematoxylin and eosin).

drug-induced, other rheumatic diseases including IgG4-related disease). Taking into account the presence of some characteristics that are usually present in cases of reactive HES instead of idiopathic HES (e.g., elevation of inflammatory parameters and IgE)[6], the diagnosis of HES associated with RA was made.

This case illustrates that clinicians should be aware that HES (including severe life-threatening cases) can occur in patients with RA, especially in cases of long-lasting disease with high titters of RF and without treatment, even in the absence of extra-articular features.

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