Hypereosinophilic syndrome with Löffler endocarditis in a patient with Rhupus syndrome

Sirs,

Eosinophilia is an uncommon event in the context of rheumatic diseases, but in certain conditions as eosinophilic granulomatosis with polyangiitis (EGPA) or IgG4-related disease can exhibit clinical relevance (1, 2). It has been described in rheumatoid arthritis, linked primarily to parasitic infections or allergic diseases (3), and in SLE (4-6), probably associated to a more active disease. However, secondary causes of eosinophilia need to be discarded (2, 7), including haematological diseases, infections, allergic reactions or drug-related eosinophilia.

High risk of evolving to hypereosinophilic syndrome (HES) is also present in these diseases (7). HES is defined by the presence of >1500 eosinophils/mm^3 in blood count, and tissue damage secondary to eosinophil activity, potentially leading to multi-organ involvement and fatal prognosis without early treatment.

We present a 51-year-old Pakistani woman diagnosed of Rhupus syndrome coursing with polyarthritis, positive rheumatoid factor, Anti-CCP antibodies and ANA at 1/640 dilution with homogeneous pattern, and low C3 and high levels of anti-dsDNA antibodies (confirmed by CLIF-test) with every flare. She was treated since 2021 with low-dose prednisone (PDN) and Rituximab (RTX) after previous failure to methotrexate and leflunomide, with poor adherence to treatment. She also presented a chronic fluctuant hypereosinophilia exacerbating with every Rhupus flare, with any secondary causes discarded, including eosinophil alterations in blood smear. Circulating ECP was not available to measure at our centre.

In 2023, she presented with chest pain, nausea and diaphoresis, without any other symptoms. Clinical exploration, chest imaging and ECG were normal. However, blood tests showed elevation of acute phase reactants, cardiac troponins and NT-proBNP together with hypereosinophilia (12500 eosinophils/mm^3), high levels of anti-dsDNA and CD19 reconstitution. During admission, echocardiogram demonstrated a left ventricle ejection fraction (LVEF) of 33% and apical hypokinesis, along with the presence of a right intraventricular mass, highly suspicious of thrombotic origin (Fig. 1A). Anticoagulation with heparin was started. Cardiac MRI confirmed the presence of a right intraventricular thrombus and demonstrated late gadolinium subendocardial enhancement (Fig. 1B-D). ANCA and thrombophilia tests (including antiphospholipid antibodies) were negative, and embolism was discarded. With all that, HES with Löffler endocarditis (LE) was highly suspected. Induction treatment with high-dose corticosteroids and cyclophosphamide (CYC) was started, and a new cycle of RTX was added. Blood test parameters normalised. After her discharge, oral anticoagulation was introduced, heart failure (HF) treatment was initiated, and once CYC treatment was completed, sodium mycophenolate was started as maintenance therapy. Consequently, low-dose PDN were accomplished, maintaining normal eosinophil count. Control echocardiogram showed improvement of LVEF (45%) but intraventricular thrombus persisted. Therefore, 100 mg subcutaneous mepolizumab every 4 weeks was initiated. To this date, the patient maintained without eosinophilic relapses, and thrombus size reduced on subsequent echocardiography evaluations.

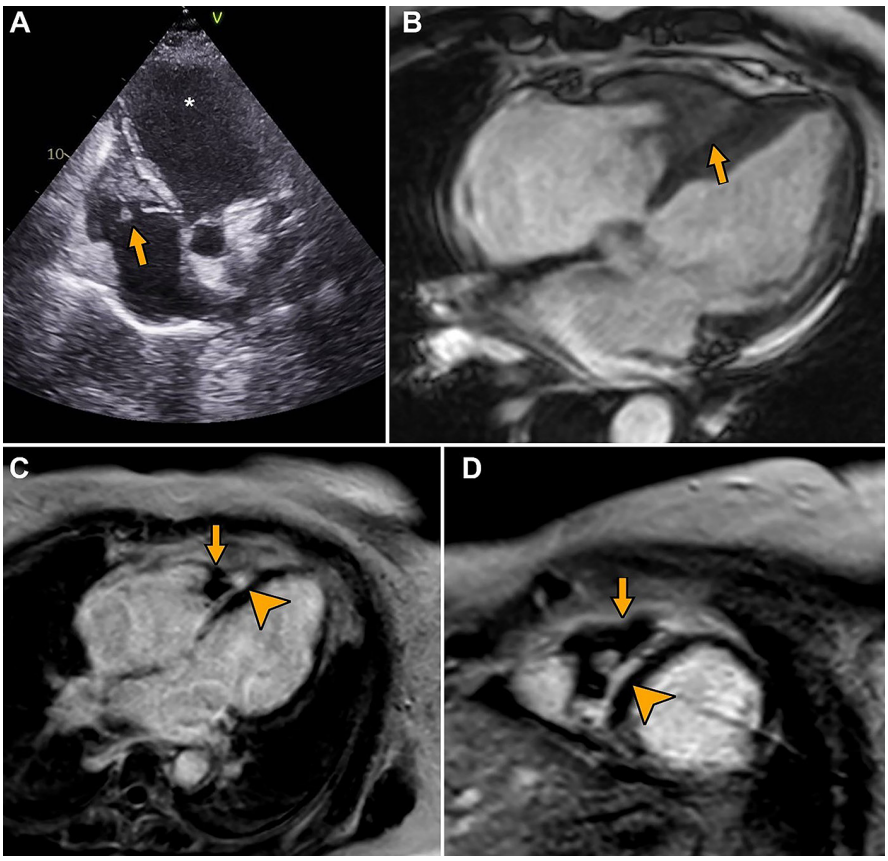

Fig. 1. Composition of echocardiography and cardiac MRI images from our patient.
A: Standard two-dimensional transthoracic echocardiogram image in four-chamber view, showing apical hypokinesis (*) and a right intraventricular mass highly suspicious of thrombotic origin (arrow).
B: Cardiac MRI image in white-blood sequence, four-chamber view, showing a right ventricle obliteration secondary to the presence of an intraventricular thrombus. In late phase gadolinium sequences, in four-chamber (**C**) and short-axis view (**D**), images show an extensive thrombus in the right ventricular apex (arrow), and subendocardial enhancement in the right ventricular apical septum and also in the left ventricular apex (arrowhead) due to fibrosis associated with Löffler endocarditis.

LE is a restrictive cardiomyopathy secondary to eosinophilic endomyocardial fibrosis. Little number of cases have been reported, appearing predominantly in women and affecting left ventricle apex (unlike our patient, who presented right ventricle involvement), potentially associating thromboembolism or HF, and having a high mortality rate (8). LE is most frequently related to HES, but it can also appear in adverse drug reactions, parasitosis or EGPA, among others. As in our patient, it can course with dyspnoea, chest pain, fever or diaphoresis. Cardiac MRI is fundamental to its diagnosis (9), identifying 3 evolutive simultaneous phases: an asymptomatic necrotic phase, a thrombotic phase and a fibrotic phase with high risk of HF and visualisation of subendocardial enhancement on MRI. Both findings were present in our patient, as described in Figure 1. Histopathology is the mainstay to LE diagnosis (8), but biopsy was not performed in our patient due to her high intraoperative risk and unavailability of cardiovascular surgeon at our centre.

Early treatment of LE is vital, and must be focused on lowering eosinophil count and preventing thromboembolic events (7, 8, 10). High-dose corticosteroids and immunosuppressants like mycophenolate or CYC can be used to control inflammation, leaving surgical management for severe cases. Anticoagulation or HF treatment must be established if indicated. In refractory cases, hydroxyurea or mepolizumab may be associated (7, 10).

To our knowledge, association of Rhupus syndrome with HES and LE has not been previously documented, making this case

significant in highlighting the need for early recognition and treatment of eosinophilic complications to avoid potentially fatal outcomes.

Acknowledgement
We acknowledge Dr Laura Piles-Roger, from the Department of Internal Medicine of our centre, for her help in discarding secondary causes of eosinophilia in our patient.

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Competing interests: none declared.

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