Eosinophilic granulomatosis with polyangiitis-related myocarditis during mepolizumab therapy reveals a Th1/Th17-mediated vasculitic response

Sirs,

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare small-vessel ANCA-associated vasculitis, considered a type 2 T helper (Th2)-mediated disease (1). Based on the pivotal role of eosinophils in EGPA pathogenesis, the anti-IL5 agent mepolizumab was approved for EGPA, resulting superior to placebo in inducing disease remission at a dosage of 300 mg/month (2, 3). Recent data suggest the efficacy of mepolizumab 100 mg/month on EGPA respiratory symptoms (4) while, its efficacy on EGPA major clinical features is uncertain.

We describe the case of a 38-year-old female patient, who developed an acute myocarditis during mepolizumab therapy. The patient was diagnosed with EGPA for the presence of blood eosinophilia, non-allergic asthma, recurrent sinusitis, nasal polyposis, migrating lung infiltrates and histologically proven eosinophilic colitis. ANCA at diagnosis tested negative. She had been initially treated with glucocorticoids and azathioprine. In October 2018 she was started on mepolizumab 100 mg/month due to refractory asthma, with a positive clinical response. From the third month after mepolizumab initiation the patient complained recurrent short episodes of chest discomfort, low-grade fever, and weight loss. Eosinophil count resulted within normal range.

In July 2019, the patient was admitted to our Vasculitis Unit for acute retrosternal chest pain at rest, worsened by deep breathing. Therapy at admission included prednisone 7.5 mg/day and mepolizumab 100 mg/month. On physical examination no abnormalities were found. Eosinophilic count and inflammatory markers tested normal; troponin T and NT-proBNP were slightly elevated. A 12-lead electrocardiogram showed diffuse S-T segment depression and negative T waves. A normal coronary angiogram excluded coronary artery disease, while imaging by cardiac magnetic resonance (CMR) was suggestive for EGPA-related acute myocarditis (Fig. 1A).

The patient received intravenous pulsed 6-methylprednisolone, followed by oral treatment, obtaining the recovery of cardiac symptoms and the resolution of CMR findings. Due to EGPA relapse during IL-5 blockage therapy, mepolizumab was discontinued.

In order to monitor treatment-induced immunological changes, we performed a functional characterisation of peripheral T lymphocytes by intracellular cytokine staining, before mepolizumab initiation, after three and nine months from therapy initiation and after three months from the acute event.

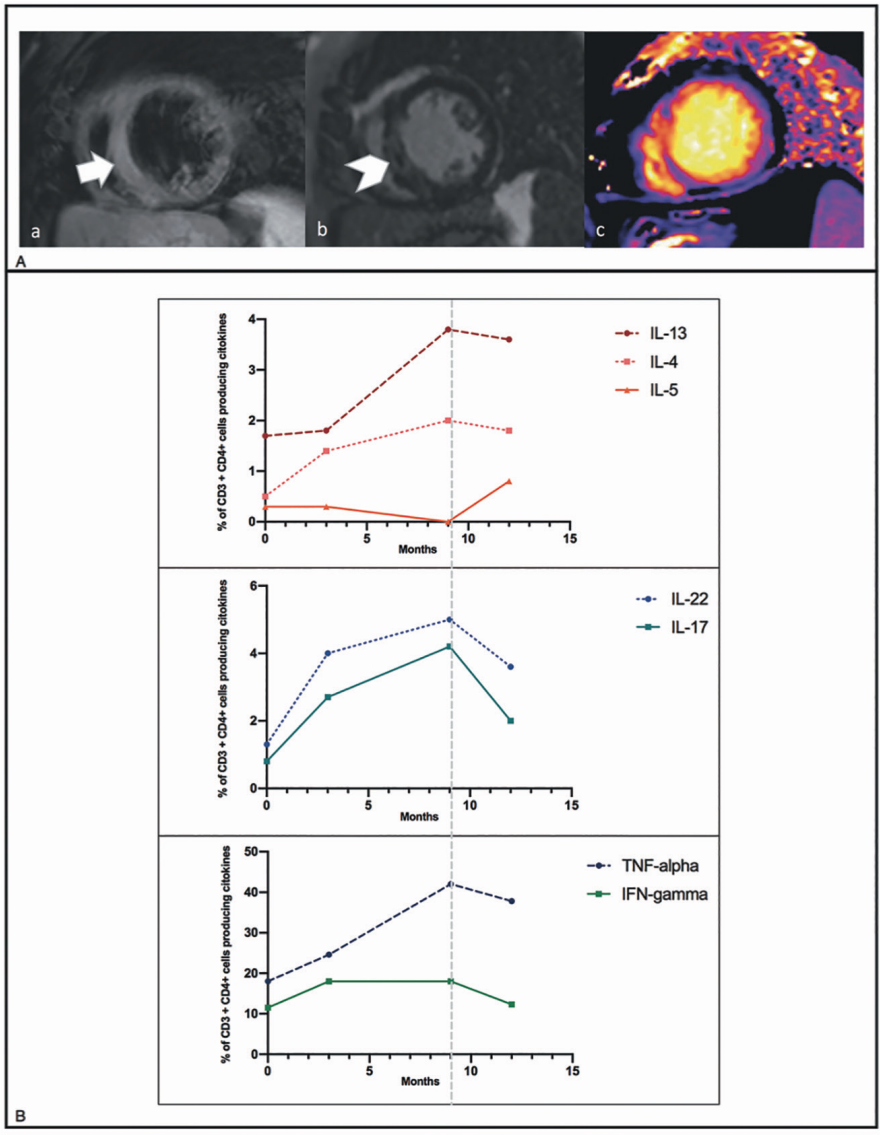

Fig. 1. A: Cardiac magnetic resonance findings. Cine-images (not shown) showed a preserved ejection-fraction (54%); T2 weighted turbo spin echo dark-blood (a) showed diffuse myocardial oedema, particularly involving the medial septum (white arrow); turbo-flash phase-sensitive inversion recovery (LGE-tFLASH-PSIR), (b) detected intramural enhancement (white arrowhead) in the mediobasal section of the septum, inferior wall, and anterolateral wall, with a non-ischaemic pattern. T1 map values post contrast (c) were increased (991 ms), particularly in the septum (1060 ms).

B: Intracellular cytokine staining results. Peripheral blood mononuclear cells at each time point were polyclonally stimulated with PMA plus ionomycin for 6 hours, the last 4 in presence of Brefeldin A, and then analysed by flow cytometry for intracellular cytokines production: IL-13, IL-4 and IL-5 defined Th2 cells (upper panel), IL-22 and IL-17 defined Th17 cells (middle panel), IFN-γ defined Th1 cells (lower panel) subsets.

The different time points are named as follows: T0: before mepolizumab initiation; T3: third month after mepolizumab introduction, concomitantly to asthma relapse; T9: nine months from therapy initiation, during acute myocarditis; T12: three months from the acute event, after induction remission treatment with high dose corticosteroids.

While detecting no significant changes in IL-5 production, a trend to increase in the proportion of CD4+ lymphocytes producing IL-4 and IL-13 was detected (Fig. 1B, upper panel). Moreover, the frequencies of Th-17 (IL-17 and IL-22) (Fig. 1B, middle panel), and Th-1 (IFN-γ)-related cytokines and of tumour necrosis factor (TNF)-α (Fig. 1B, lower panel) displayed a trend to increase in parallel with the progressive worsening of patient's cardiac symptoms. The post-therapy analysis showed a marked reduction in the frequencies of IL-17 and IL-22-producing T lymphocytes and a moderate reduction of IFN-γ-producing ones (Fig. 1B, middle and lower panel). No significant changes in the Th-2 response were recorded after corticosteroid treatment (Fig. 1B, upper panel).

Cardiac manifestations, traditionally considered eosinophil-mediated, deeply influence the prognosis of EGPA (5). Few reports suggest a possible beneficial role of anti-IL5/IL5R therapy, also at the dosage

used for asthma control (6-8). Recently, active vasculitis was recognised as an additional event for cardiac damage in EGPA patients, implying a more complex pathogenesis in myocardial injury (9).

In the case reported, myocarditis may have been the result of a vasculitic activity, as suggested by the worsening of patient's cardiac symptoms in parallel with the rise in peripheral Th1/Th17-related cytokines. Indeed, anti-IL5 therapy may not be fully effective on EGPA vasculitic manifestations, by leaving uncovered the Th1 and Th17 arms of the immune system (10). Finally, the marked decrease in IL-17 and IL-22 after high-dose steroid therapy, associated with clinical and instrumental improvement, again supports the evidence of a Th1/Th17-mediated injury.

Despite the limitation of being a single case description, our data suggest that the anti-IL-5 mepolizumab might not confer a full protection from severe EGPA manifestations. Alternatively, the dosage of 100 mg/month could be insufficient to control such manifestations. If a dose-escalation at 300 mg/month or a more effective immunosuppressive treatment is required to prevent cardiac involvement requires further investigations.

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