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Successful benralizumab for eosinophilic myocarditis in eosinophilic granulomatosis with polyangiitis

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ABSTRACT

Eosinophilic granulomatosis with polyangiitis (EGPA) is characterised by many features, including asthma, allergic rhinitis, peripheral and tissue eosinophilia, and vasculitis. Its pathophysiology is still unclear and we suggest that there are different phenotypes of EGPA, which may respond differently to available treatments. Within the most promising targeting biotherapy, benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, has proved both highly effective and safe. We report herewith a case of EGPA presenting a myocarditis relapse successfully treated with benralizumab.

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is an antineutrophil cytoplasmic antibody (ANCA)-associated autoimmune vasculitis involving small-to-medium-sized vessels and characterised by asthma, eosinophilia, and eosinophil infiltration of various organs (1). It is the least frequent vasculitis with an incidence estimated at 1.3/100,000 in the United States (2). Hence, EGPA is underdiagnosed and little is known of its pathophysiology. Thus, there is room to optimise current therapy or even discover new treatment strategies (3). Cardiac involvement is not rare and is associated with poor prognosis, and relapse after remission remains frequent, despite taking immunosuppressants. We report herewith a case of EGPA presenting a myocarditis relapse successfully treated with benralizumab, anti-interleukin-5 receptor alpha (anti-IL-5Ralpha) monoclonal antibody (Ab).

Clinical presentation

A 66-year-old male patient presented to our hospital for weakness and pain in both lower extremities. He had a recent medical history of eosinophilic asthma. The patient provided written informed consent for the publication of this case report. This study was approved by our hospital ethics review board and was conducted according to the principles of the Declaration of Helsinki.

On physical examination, his vital signs were as follows: pulse 98 beats per minute, afebrile, blood pressure 120/76 mmHg and SpO2 97% on ambient air. He had muscle weakness and mild oedema in lower extremities. Routine laboratory investigations showed elevated eosinophil counts (3000 /μL; normal range <500 cells /μL), mild elevation of C reactive protein (40 mg/L; normal range <5mg/L), stage 3b kidney disease: according to Global Outcomes (KDIGO) acute kidney injury (GFR 35 ml/mn/1.73m^2; normal range >90 ml/mn/1.73m^2). Liver (aspartate aminotransferase and alanine aminotrasnferase), myogenic (creatine kinase) and cardiac enzymes (creatinine kinase and cardiac troponin) were normal. Serum electrophoresis showed a normal plot. Urine analysis showed aseptic leukocyturia, microscopic haematuria and mild 24-hour-protéinuria of 1 gr. Electrocardiography (ECG) showed regular sinusal rhythm, normal axis, and no ST segment modifications. Transthoracic Echocardiography (TTE) was normal as well as thoraco-abdominal computed tomography. The sensory nerve action potential of bilateral sural nerves and the compound muscle action potential of the right tibial and peroneal nerves were not detected. These results indicated the existence of multiplex mononeuritis. Immunological investigations showed negative antinuclear antibodies (1/80; normal range <1/80), and an enzyme-linked immunosorbent assay demonstrated elevated ANCA specific for myeloperoxidase (MPO) (42 IU/ml; normal range <20 IU/ml). Kidney biopsy showed 9 glomeruli, 4 of which had active necrotising glomerulonephritis. According to the 1990 American College of Rheumatology (ACR) criteria, the patient fulfilled the diagnostic criteria of EGPA (4). The modified Five Factor Score (m-FFS) showed 2 points with renal involvement and the age over 65 years old (5). First line treatment consisted of high doses of oral prednisone (1 mg/kg/d) with progressive tapering associated with intravenous (IV) rituximab. To induce remission for active and severe disease, we administered 1 gramme of rituximab at day 1 and day 15 relayed with 6 month-gap IV rituximab (500 mg). The patient did not develop any

opportunist infection during the treatment course with rituximab infusions and steroids. At the third maintenance rituximab infusion, the patient developed shortness of breath. Cell blood count showed increased rate of eosinophils (2500 cells/μL), and elevated cardiac enzymes as follows: high-sensitivity cardiac troponin (hs-cTn) at 250 ng/L (normal range <14 ng/L), creatine kinase (CK) at 300 U/L (normal range <198 U/L) and N-terminal brain-type natriuretic peptide (NT-proBNP) at 1000 pg/ml (normal range <450 pg/ml). Electrocardiogram showed sinusal tachycardia and TTE was normal. We performed 3-day parasitological stool examination with a specific screening for *Cryptosporidium*, microsporidia and *Isospora* species, which was negative. Serologic test for parasites (*Toxocara canis, Schistosoma, Echinococcus, Cysticercus* and *Trichinella* species) were also negative. Cardiac magnetic resonance imaging (MRI) at short axis view revealed patchy areas at the delayed contrast gadolinium myocardial enhancement within the left ventricular myocardium (Fig. 1-a). Likewise, long axis view showed subepicardial enhancement areas on the delayed gadolinium enhancement (Fig. 1-b). Thus, we concluded to EGPA relapse with myocarditis and added 30 mg benralizumab at 1 injection every 4 weeks for 3 months, then 30 mg every 2 months. Three months after starting benralizumab injections, the patient reported an improvement of his respiratory symptoms. The cardiac enzymes normalized (hs-cTn at 11 ng/L, CK at 134 U/L and NT-proBNP at 251 pg/ml) and cell blood count showed a rapid normalization of eosinophil rate (<500 cells/μL). Repeated ECG and TTE were normal at 3, 6 and 12 months follow-up. The cardiac MRI showed normalised myocardial signal in the basal and mid thirds of the heart with mild enhancement in apical segment (Figure 2). The patient did not develop any infection after initiating benralizumab injections. We carried on rituximab infusion according to a maintenance regimen (500 mg every 6 months) for a total period of 18 months with progressive tapering of oral corticosteroids.

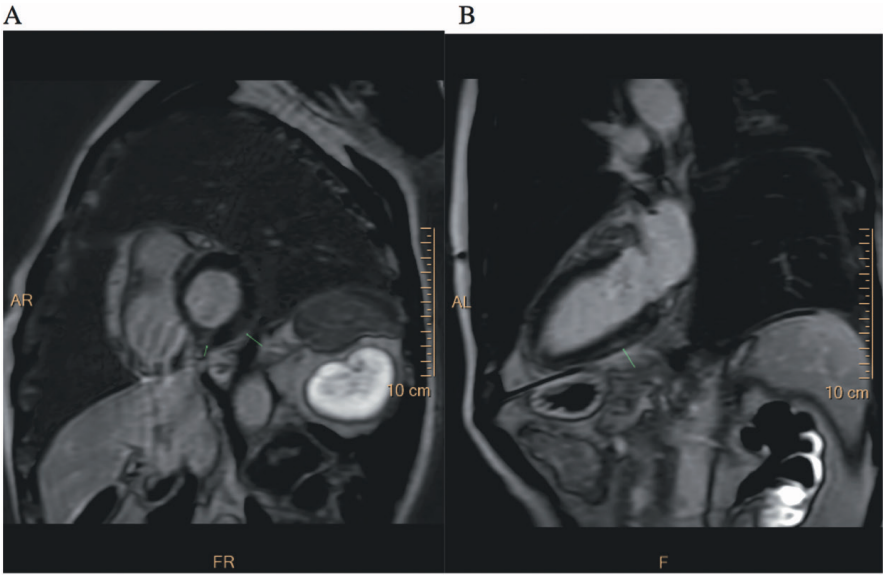

Fig. 1. A. Cardiac magnetic resonance imaging short axis view showing patchy areas of the delayed myocardial enhancement of the gadolinium within the left ventricular myocardium.
B. Long axis view showing areas of the delayed myocardial enhancement of the gadolinium within subepicardial delayed gadolinium enhancement.

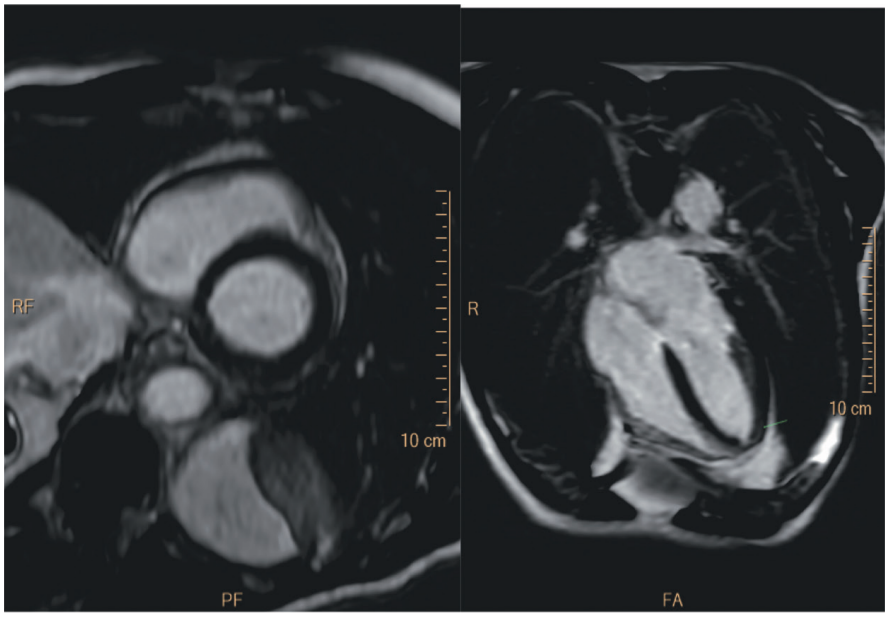

Fig. 2. Control cardiac magnetic resonance imaging (at 3 months follow-up) showing normalised myocardial signal in basal and mid thirds of the heart, persistent delayed myocardial enhancement of the gadolinium in apical lateral segment.

The current decline is 30 months and the patient is free of symptoms.

Discussion

EGPA is an ANCA-associated autoimmune vasculitis, involving small and medium-sized arteries, which could involve several organs. Typically, it is characterised by extravascular granulomas, eosinophilia, and tissue infiltration by eosinophils (6). Cardiac involvement is associated with poor prognosis, accounting for one third to half of deaths in EGPA patients (7). Eosinophilic myocarditis is associated to in-hospital death rate about 20% (8). The current presentation illustrates the case of a male patient with EGPA treated with steroids and rituximab infusions. The initial assessment did not show any cardiac involvement. Six months after diagnosis, while he was

on maintenance treatment, he developed shortness of breath not related to asthma and elevation of eosinophilia. Standard cardiac evaluation by electrocardiography and cardiac echography were normal while cardiac enzymes showed elevated troponins and NT-proBNP. Thereby, cardiac MRI led to the diagnosis of myocarditis. MRI may detect cardiac involvement through detection of myocardial late gadolinium enhancement which could reflect both chronic fibrotic and acute inflammatory lesions, and T2-weighted signalling anomalies as a marker of oedema and active inflammation (9). A recent meta-analysis of EGPA patients with cardiac involvement identified 62 cases (10). ECG was normal in 32.5%, echocardiography normal in 2 cases, and cardiac enzymes elevated in all cases. Interestingly, Cardiac MRI was abnormal in all cases (10).

Our case highlights the place of MRI in the assessment of cardiac involvement in symptomatic patients with EGPA despite normal first line classical evaluation. Thus, we suggest performing cardiac MRI in symptomatic EGPA patients with elevated cardiac markers despite normal cardiac echography.

Cardiac involvement is included as one of the five factors indicating a poor prognosis (five factor score; FFS) (5). Therefore, treatment with a combination of immunosuppressive agents and glucocorticoids are highly recommended for remission induction. The recent American College of Rheumatology (ACR) recommendations stipulate that either cyclophosphamide or rituximab may be prescribed for remission induction (11).

In our case, rituximab was considered because of positive ANCA results and active glomerulonephritis instead of cyclophosphamide treatment. At the third maintenance rituximab infusion, the patient showed a severe, active relapse with an eosinophilic myocarditis despite well-conducted treatment.

Generally, recommendations suggest re-induction of remission with rituximab over cyclophosphamide. However, cyclophosphamide should be considered in case of cardiac involvement. In fact, EGPA is the rarest ANCA mediated vasculitis and its recommendations are mainly based on experience in other ANCA mediated vasculitis and cases series (12). EGPA is an uncommon vasculitis the pathophysiology of which includes both vasculitis and eosinophilic inflammation. Consequently, we consider that targeting either vasculitis or eosinophilic inflammation in isolation would lead to adequate therapeutic effects. Our case report illustrates perfectly this postulate. Rituximab regimen could manage the EGPA vasculitic phenotype but was insufficient to control eosinophilic inflammation. Benralizumab, an anti-IL-5Ralpha Ab that depletes eosinophils mainly *via* Ab-dependent cell-mediated cytotoxicity and through blockage of IL-5 function on eosinophils, has been clinically approved for patients with severe eosinophilic asthma (13). The effectiveness of anti-IL-5Ralpha Ab in severe EGPA has not been established because patients with active, severe disease were excluded from the randomized trial (14). Until the present time, indication in EGPA was useful for reducing the steroid dose, increasing the time in remissions and lowering the frequency of relapse. In our case, we have chosen to add benralizumab and continue rituximab according to the remission maintenance scheme. Due to the fact that little is known about the place of anti-IL-5Ralpha Ab in eosinophilic myocarditis in EGPA, we undertook a literature screening which showed previous case reports illustrating the effectiveness of combination of rituximab and mepolizumab in severe EGPA; diffuse alveolar haemorrhage (15), pauci immune necrotising (16), and eosinophilic myocarditis (17,18). Our case endorses the effectiveness of anti-IL-5Ralpha (benralizumab) monoclonal Ab as first line treatment for eosinophilic myocarditis related to EGPA. We stipulate that rituximab alone is limited to manage eosinophilic inflammation in EGPA and its main target would be ANCA positive mediated vasculitis. Moreover, in the current case benralizumab showed highly effective and safe therapy in life-threatening eosinophilic myocarditis and thus, would be interesting to be evaluated as first line therapy as an alternative to standard therapy.

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