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Eosinophilic granulomatosis with polyangiitis (EGPA) with low activity EBV replication during the COVID 19 pandemic

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1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome) is a rare systemic necrotizing vasculitis (SNV) of medium and small arteries, which characteristically affects the upper and lower respiratory tract and may present with neuropathy and other organ manifestations [1]. Additionally, eosinophilia and perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) can be found in 30–70 % of EGPA patients. Cardiac manifestations of EGPA are estimated to be as high as 27–47% and are associated with increased mortality [2]. Cardiac involvement is considered a leading cause of death in EGPA patients [3]. This report describes a case of EGPA complicated by an Epstein-Barr virus inflammatory cardiomyopathy during the COVID-19 pandemic.

A 47-year-old woman with a 10-year history of EGPA presented with exertional burning chest pain and a gripping pain sensation around her heart [4]. In addition, the patient had been previously diagnosed with non-ischemic cardiomyopathy and asthma. The diagnosis of EGPA had been made many years ago based on perivascular infiltrates of eosinophilic granulocytes detected on a skin biopsy (Fig. 1 A and B). Additional diagnostic tests to evaluate for differential diagnoses of eosinophilia had not been performed at that time.

Physical examination revealed fever, hypesthesia of the lower extremities, sinusitis and a fulminant respiratory presentation with wheezes, consistent with an exacerbation of asthma. These findings, as well as increased inflammatory markers (C-reactive protein) and eosinophilia (1.05 eosinophils/ nl absolut, eosinophils 12%), were found to be consistent with an exacerbation of the underlying medical condition and matched the criteria for EGPA of the American College of Rheumatology [1].

Causes of eosinophilia, such as parasitic infections and drug reactions were ruled out [5]. Additionally, laboratory findings and clinical presentation indicated signs and symptoms of heart failure (NYHA II-III). Initial echocardiography revealed a moderately reduced left ventricular function (LVEF 40%). Given the severe symptoms of EGPA, which the patient was not able to tolerate, in the context of severe eosinophilia, her rheumatologist initiated prednisolone therapy with 30 mg daily for the duration of 6 weeks.

One week after initiation of immunosuppression, the patient presented to our hospital and underwent endomyocardial biopsy to evaluate for cardiac involvement by EGPA, given her reduced left ventricular function and symptoms of burning sensation in her chest. Cardiac catheterization excluded coronary artery disease and the LVEF was found to be moderately reduced, similar to prior measurements (LV-EF 40%). Endomyocardial biopsy (EMB) was performed and did not reveal any signs of eosinophilic infiltration or giant cells. However, it was consistent with inflammatory cardiomyopathy with a predominance of macrophages and T-lymphocytes (Fig. 1 C and D). Potential prior eosinophilic infiltration may have been masked given the preceding treatment with steroids prior to EMB. Nested-PCR detected low level Epstein-Barr virus (EBV) reactivation in the myocardium with low rate of replication. This finding added a layer of complexity in the treatment of this patient. The most likely explanation for this finding is that EBV reactivation was a consequence of immunosuppression, given that about 90 % of the population is infected with EBV [6]. Also, we have recently shown that in patients with advanced giant cell myocarditis, EBV DNA sequences can be found in the myocardium after long-term immunosuppression [7].

A less likely explanation for the inflammatory cardiomyopathy with absence of eosinophils and presence of EBV DNA would be a concomitant event – EBV induced lymphocytic myocarditis. However, this is very unlikely since the patient did not have systemic symptoms of EBV infection and EBV has not been shown in the literature to directly induce myocarditis as it had been for coxsackievirus B3.

To complete the screening for differential diagnoses of eosinophilia, the patient underwent bone marrow aspiration ruling out proliferation of eosinophilic precursors or other types of malignancies. During her hospital stay, the patient experienced one episode of non -sustained ventricular tachycardia (NSVT), despite treatment with beta-blocking agents.

Cardiovascular magnetic resonance imaging (CMR) was performed for risk stratification[8,9,10]. CMR revealed a dilated left ventricle with an LVEF of 47%, akinesia of the inferior wall, and hypokinesia of the basal inferior septum, as well as the lateral wall (Fig. 2). Furthermore,

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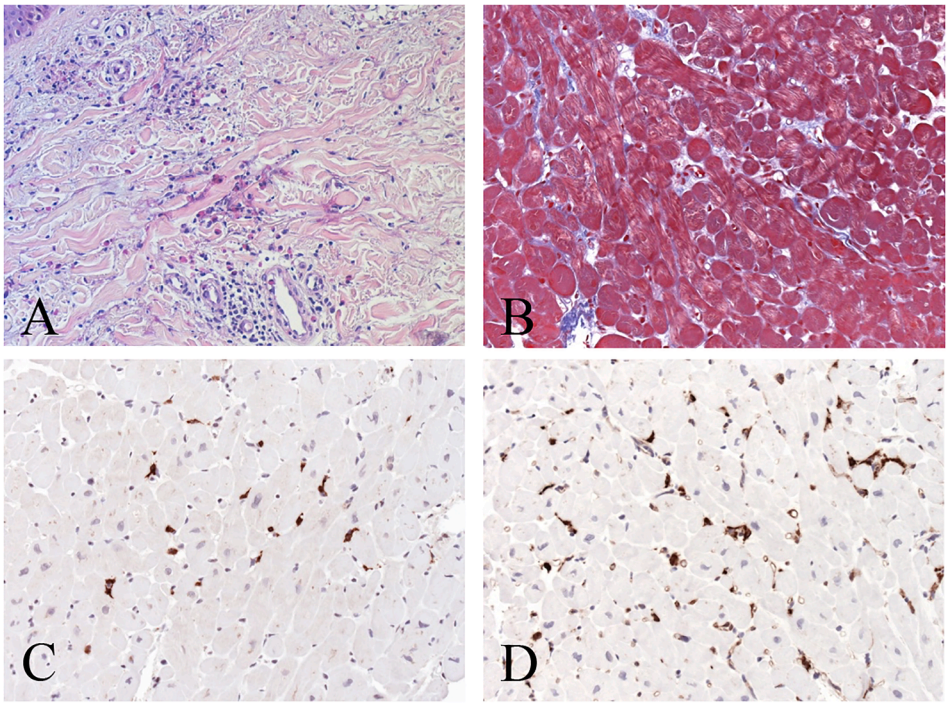

Fig. 1. Differential histological examination of the patient (200x)(A) with Masson's Trichrome stain (B) and CD3 (C) and MHCII (D) immunohistochemical stains.

fibrosis and late gadolinium enhancement (LGE) were present in the septum, the inferior and anterior wall [5].

A decision was made to provide the patient with a wearable cardioverter defibrillator (WCD) after the episode of NSVT in the context of myocardial inflammation and LGE on CMR for 3 months. Since the patient did not have any signs of active systemic EBV infection with predominant symptoms of EPGA, it was decided to increase immunosuppressive therapy, while closely monitoring EBV titers and EBV DNA through serial PCR measurements.

The patient had been on maintenance therapy with azathioprine 150 mg daily and prednisolone ranging between 6 mg and 10 mg daily since 2009. Dose adjustments had been based on the count of eosinophils. Notably, prior to presentation to our clinic, the patient's prednisolone dosage was increased to 30 mg daily over the course of 6 weeks, which reportedly had improved her overall condition. Accordingly, in the context of her symptoms, the elevated inflammatory markers in the blood and biopsy findings it was decided to further increase prednisolone to 60 mg daily (1 mg/kg bodyweight) over a course of 4 weeks, despite the low EBV concentration found in the myocardium. The patient experienced immediate improvement of symptoms and the eosinophil count almost normalized.

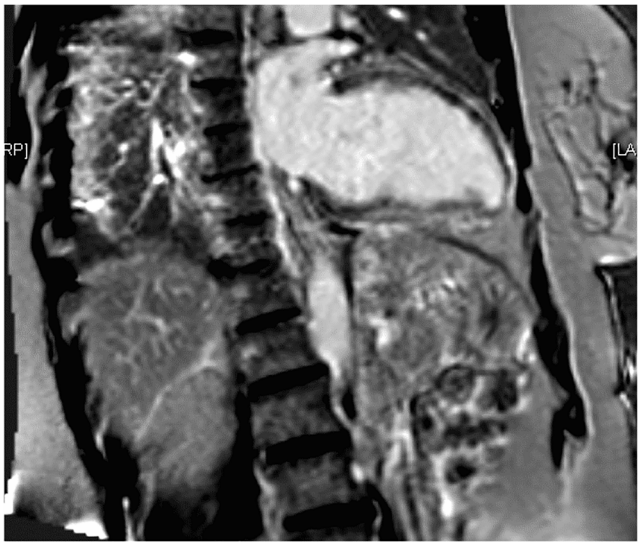

Fig. 2. Cardiac magnetic resonance imaging of the patient. Late Gadolinium enhancement visible in the inferior wall of the heart.

We continued to monitor the patient in close intervals to evaluate for symptoms of EGPA reactivation, as well as a potential increase of Epstein-Barr virus viral load. Viral DNA was not detectable by PCR during serial blood tests. Therefore, no antiviral therapy with ganciclovir was considered necessary. Also, the patient was tested for COVID-19 through PCR of a nasal swab sample, which was negative.

After an excellent response to therapy, prednisolone was gradually reduced with a maintenance therapy goal of 10 mg daily. Despite informing our patient comprehensively of the associated risks of non-adherence to a slow dose reduction, i.e. reduction of 5 mg every 2 weeks, she chose a fast prednisolone taper of 10 mg every 2 weeks, expressing concerns about the risks of immunosuppression during COVID-19 pandemic. The patient reduced the dose by 10 mg every 2 weeks and reported at her follow up visit that she noticed an initial increase in chest pressure with every dose reduction, which would subside after 2 days. Given her symptoms, the patient agreed to a slower taper of prednisolone by 5 mg every 2 weeks, which she tolerated well. WCD monitoring did not detect any further arrhythmias. Furthermore, echocardiography revealed normalization of left ventricular function to LVEF 60%.

In summary, treatment with prednisolone pulse therapy quickly reduced the severity of clinical symptoms without systemic reactivation of EBV. We recommend obtaining serial EBV testing (EBV PCR) during immunosuppressive therapy in this clinical scenario to detect systemic reactivation early.

Our patient chose a fast taper of prednisolone therapy, which led to recurrence of symptoms. Thus, a slow taper continues to be the recommended approach.

The heart biopsy revealed no signs of eosinophilic infiltrates as would be expected with EGPA, but revealed low intensity EBV

reactivation in the myocardium. If the inflammatory cardiomyopathy was caused by the underlying systemic vasculitis, the absence of eosinophils in the myocardium could be explained with preceding prednisolone therapy. Immunosuppressive therapy can lead to reactivation of latent virus infections, such as EBV.

To the best of our knowledge this is the first case report describing EGPA with concurrent EBV inflammatory cardiomyopathy.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Melina Mueller[a], Wolfgang Poller[a], Karin Klingel[b], Thomas Neumann[c], Ulf Landmesser[d], Bettina Heidecker[d,*]

[a] *Department of Cardiology, Charité Universitätsmedizin Berlin, Berlin, German*

[b] *Cardiopathology, Institute for Pathology, University Hospital Tübingen, Tübingen, Germany*

[c] *Kantonsspital St., Gallen, St. Gallen, Switzerland*

[d] *Department of Cardiology, Charité Universitätsmedizin Berlin, Berlin, Germany*

[*] Corresponding author.

E-mail address: bettina.heidecker@charite.de (B. Heidecker).