Clinical Research in Cardiology (2019) 108:963–966
https://doi.org/10.1007/s00392-019-01434-w

LETTER TO THE EDITORS

Severe eosinophilic myocarditis associated with modafinil in a patient with normal peripheral eosinophil count

Marina Bäuml[1,2] · Josefina Udi[1,2] · Karin Klingel[3] · Christoph Bode[1,2] · Klaus Warnatz[4] · Andreas Zirlik[1,2] · Daniel Duerschmied[1,2] · Paul Biever[1,2]

Received: 3 September 2018 / Accepted: 5 February 2019 / Published online: 12 February 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Sirs:

Eosinophilic myocarditis (EM) is a rare form of myocardial inflammation characterized by myocardial eosinophilic infiltration [1]. It can lead to a broad spectrum of clinical symptoms, ranging from asymptomatic cases to dramatic and life-threatening progression with rapid myocardial damage and acute heart failure [1–4]. The etiology is heterogeneous and hypersensitivity or allergic reactions as well as hematological diseases or neoplastic disorders can lead to EM [2]. Eosinophilia in peripheral blood is present in the majority of patients and often suggestive for the diagnosis [1, 5]. EM in the absence of hypereosinophilia, however, is a diagnostic challenge and can lead to a potentially fatal delay in suitable treatment [6]. We present the second description of modafinil-associated acute necrotizing myocarditis after a fatal case, which was published in 2006 [7]. In our case, timely diagnosis by histology and administration of corticosteroid therapy enabled full recovery.

A 40-year old previously healthy male patient developed flu-like symptoms and fever up to 40.4 °C, only partially responsive to ibuprofen and acetaminophen. Thus, he presented himself to the emergency department 3 days after the onset of symptoms. The only abnormalities found in blood chemistry were an elevated leukocyte count (11.4×10^9/L, reference range $4.0–10.4 \times 10^9$/L) and an elevated CRP level (283 mg/L, reference range < 5 mg/L). Electrocardiography, chest X-ray, urine chemistry and a test for viral respiratory agents were unremarkable. Empiric antibiotic therapy (sultamicillin) was prescribed for suspected bacterial infection of the lower respiratory tract and the patient was discharged.

The following day, the patient was admitted again to the emergency department with dyspnea, persistent fever and angina pectoris and then transferred to the intensive care unit due to progressive cardiogenic shock. The laboratory findings now showed increased leukocyte count (12.9×10^9/L) and further elevated inflammatory markers compared to the day before (CRP 377 mg/L). Interestingly, a normal peripheral eosinophil count was observed (0.03 Tsd/µL, reference range 0.03–0.44 Tsd/µL; 0.2% of leukocytes, reference range 0–7% of leukocytes). Total IgE levels were, however, elevated (211 IE/mL, reference range 10–100 IE/mL).

Troponin T level was also elevated with a further increase after 3 h (177.4 ng/L and 303.5 ng/L, respectively; reference range < 14 ng/L). Electrocardiography remained unremarkable, but echocardiography revealed rapid deterioration of left ventricular systolic function with an ejection fraction (LVEF) of 50% at admission, which decreased to 35% after 24 h, with hypokinesia of the inferior wall in the absence of pericardial effusion. Computed tomography showed left lower lobe pneumonia with small pleural effusion. Type-1-myocardial infarction due to coronary artery disease was excluded via coronary angiography.

Empiric antibiotic therapy was escalated to piperacillin/tazobactam, clarithromycin, and clindamycin. The clinical situation of the patient worsened with a peak in CRP (541 mg/L), persisting fever and progressive hypoxic respiratory failure. Echocardiography showed continued depression of cardiac function (LVEF 26% on day 3 after admission, Fig. 1). Attempted cardiac magnetic resonance tomography [8] had to be interrupted because of respiratory insufficiency. Low-dose norepinephrin was temporarily administered and

✉ Marina Bäuml
marina.baeuml@universitaets-herzzentrum.de

1 Department of Medicine III (Interdisciplinary Medical Intensive Care), Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

2 Department of Cardiology and Angiology I, University Heart Center Freiburg University, Freiburg, Germany

3 Cardiopathology, Institute for Pathology, University Hospital Tübingen, Tübingen, Germany

4 Center for Chronic Immunodeficiency, Faculty of Medicine, Medical Center - University of Freiburg, Freiburg, Germany

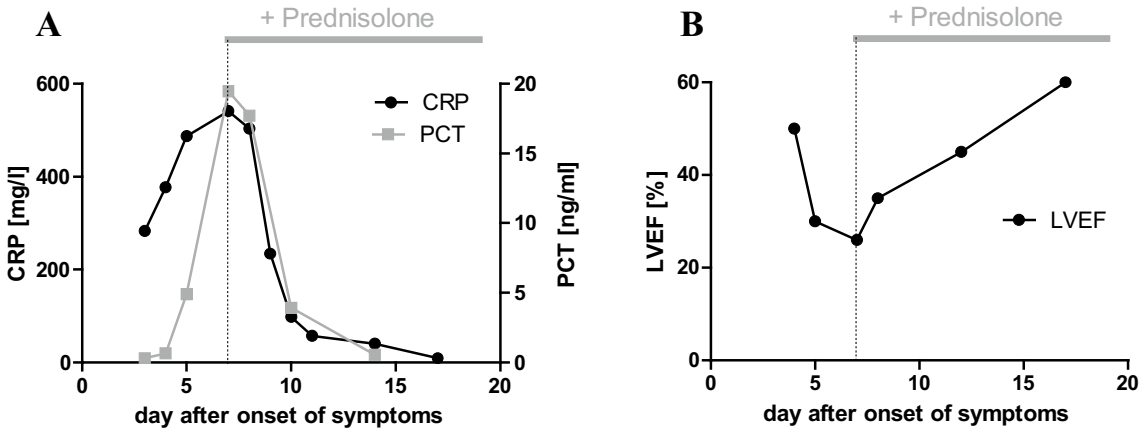

Fig. 1 Profile of (**a**) inflammatory parameters [C-reactive protein (CRP), procalcitonin (PCT)] and (**b**) left ventricular ejection fraction (LVEF) before and during the course of corticosteroid treatment

levosimendan was initiated [9, 10]. Non-invasive ventilation was temporarily necessary.

A thoracentesis allowed the exclusion of an empyema and revealed an eosinophilic pleural effusion (i.e., eosinophilic pleuritis).

Due to the rapid deterioration, the decision to obtain endomyocardial biopsy (EMB) samples was made. Histological and immunohistological evaluation of the EMB revealed myocyte necrosis and the infiltration of the myocardium with large amounts of CD3+ T cells, CD68+ macrophages expressing MHC class II and less frequent with eosinophilic granulocytes (Fig. 2). Infectious causes for acute myocarditis were excluded by nested RT-PCR and quantitative PCR. Notably, throughout the entire hospitalization period, the peripheral eosinophilic blood count remained normal.

The definitive diagnosis of acute necrotizing eosinophilic myocarditis confirmed by EMB histology/immunohistology now allowed the administration of high-dose corticosteroid (prednisolone 250 mg for 3 days, then 1 mg/kg/BW for 1 week, followed by a stepwise reduction of 20 mg/week up to a dosage of 40 mg/day, then a stepwise reduction of 10 mg/week up to a dosage of 10 mg/day, then 5 mg/day for another 7 days with a complete tapering during the next 4 weeks). The used schema had been proven successful in our clinic to treat systemic autoimmune disorders with organ-threatening course.

Twenty-four hours after starting corticosteroid therapy, LVEF improved to 35%. Within a few days, further increase could be noted, CRP had almost normalized and antibiotics were discontinued. Ten days after starting prednisolone, echocardiography showed a complete recovery of the left ventricular function (LVEF 60%) and absence of pleural effusion. A follow-up cardiac magnetic resonance tomography 1 month after the end of corticosteroid therapy confirmed stable normal bi-ventricular function.

The search for possible triggers of eosinophilic inflammation revealed intake of modafinil the week before the onset of symptoms (three single doses of 200 mg). Modafinil promotes wakefulness by an unknown mechanism and is used to treat sleepiness caused by narcolepsy or abnormal sleep disorder due to shift work.

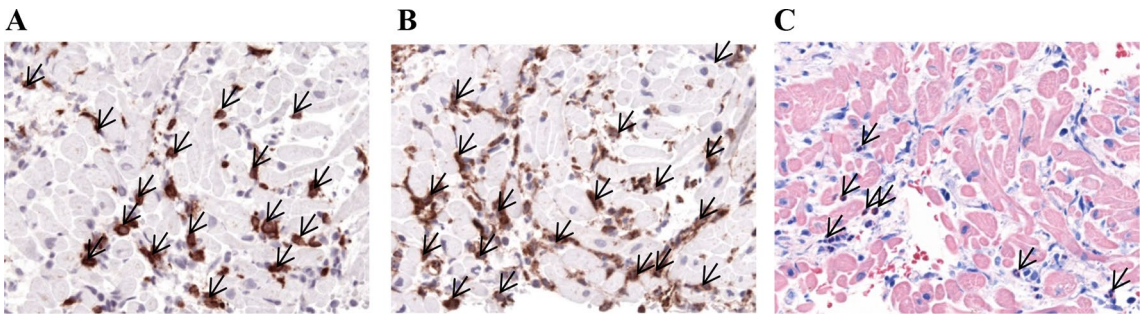

Fig. 2 Immunohistochemical stainings of endomyocardial biopsies reveal numerous CD3+ T cells (**a**) and MHCII+ macrophages (**b**). In addition, Giemsa staining illustrates the presence of eosinophilic granulocytes (**c**); all ×400

The patient had also taken ibuprofen and acetaminophen, but only after onset of symptoms. Haematological diseases or neoplastic disorders were ruled out. Therefore, hypersensitivity to modafinil was considered as the most likely cause.

EM is rare and was identified in only 0.1% of cases among a cohort of patients biopsied because of the tentative diagnosis of myocarditis [11].

A broad spectrum of clinical presentations ranging from asymptomatic forms to cardiogenic shock, ventricular arrhythmias and sudden cardiac death is possible, but as in our case most patients initially complain of chest pain, palpitations, and dyspnea and two-thirds report the symptoms of a common cold [2, 12, 13].

Pathomechanistically, a variable amount of eosinophils infiltrate the interstitial compartment and their degranulation can result in tissue damage and consecutively lead to acute heart failure [14]. This can be life-threatening and about 36% of patients with hypersensitivity-associated acute EM, the most frequent cause for EM in developed countries, die in hospital [1, 14].

NSAIDs are frequently described as capable of causing hypersensitivity reactions [14], but there is only one case report in literature linking modafinil and EM [7]. The patient described in that report died in 2006 and as a consequence, the package insert for modafinil was modified to include a warning relating to multiorgan hypersensitivity reactions.

Identifying the causative agent is often not trivial, because of the delay between the intake of medication and the clinical manifestation of EM, which may be up to 2 years [3]. In our case, the patient had been healthy before and did not consume any other drugs than modafinil.

A specific laboratory marker for EM is lacking. An elevation of CRP and cardiac markers is not necessarily present in all cases of EM and is a very unspecific marker for myocarditis. More suggestive for EM is an elevated peripheral eosinophilic blood count. Among 59 patients with eosinophilic myocarditis collected by Brambatti et al. from the literature, peripheral hypereosinophilia was lacking in approximately 25% of cases [1]. The prevalence of peripheral hypereosinophilia was lowest in the hypersensitivity group (63.5%, $p < 0.05$ compared with other etiologies). The case hereby presented did not develop hypereosinophilia during hospitalization. Nevertheless, some patients with normal eosinophil count on admission may develop hypereosinophilia during the ensuing days [1, 5]. Thus, white blood cell including eosinophil count should be repeated in the days after admission to reduce the possibility of misdiagnosis.

In cases without development of peripheral eosinophilia like the one described here, obtaining an EMB is the only way to make the definitive diagnosis of EM and initiate the correct and life-saving treatment [2].

Corticosteroid administration is the mainstay of therapy by consensus, but there are no clinical guidelines for duration and dosage of corticosteroid and supportive therapy [2, 15]. In our case, the reported schema of corticosteroid use and tapering led to complete and stable recovery of LVEF.

In patients with the tentative diagnosis of myocarditis, EMB is sometimes the only way to identify the etiology for this potentially life-threatening cardiac disease. We therefore advocate for early invasive diagnostics and close collaboration between clinicians and pathologists to prevent delays in treatment.

Compliance with ethical standards

Conflict of interest All authors agreed to submit this case report and declared no conflict of interests.

References

1. Brambatti M, Matassini MV, Adler ED, Klingel K, Camici PG, Ammirati E (2017) Eosinophilic myocarditis: characteristics, treatment, and outcomes. J Am Coll Cardiol 70(19):2363–2375
2. Kuchynka P, Palecek T, Masek M, Cerny V, Lambert L, Vitkova I (2016) Current diagnostic and therapeutic aspects of eosinophilic myocarditis. Biomed Res Int 2016:1–6
3. Al Ali AM, Straatman LP, Allard MF, Ignaszewski AP (2006) Eosinophilic myocarditis: case series and review of literature. Can J Cardiol 22(14):1233–1237
4. Yanagisawa T, Inomata T, Watanabe I, Maekawa E, Mizutani T, Shinagawa H (2011) Clinical significance of corticosteroid therapy for eosinophilic myocarditis. Int Heart J 52(2):110–113
5. Morimoto S, Kubo N, Hiramitsu S, Uemura A, Ohtsuki M, Kato S (2003) Changes in the peripheral eosinophil count in patients with acute eosinophilic myocarditis. Heart Vessels 18(4):193–196
6. Fozing T, Zouri N, Tost A, Breit R, Seeck G, Koch C (2014) Management of a patient with eosinophilic myocarditis and normal peripheral eosinophil count: case report and literature review. Circ Heart Fail 7(4):692–694
7. Sabatine MS, Poh K-K, Mega JL, Shepard J-AO, Stone JR, Frosch MP (2007) Case 36-2007. N Engl J Med 357(21):2167–2178
8. Veulemans V, Hellhammer K, Polzin A, Bönner F, Zeus T, Kelm M (2018) Current and future aspects of multimodal and fusion imaging in structural and coronary heart disease. Clin Res Cardiol Off J Ger Card Soc 107(Suppl 2):49–54
9. Bekfani T, Westphal F, Schulze PC (2018) Therapeutic options in advanced heart failure. Clin Res Cardiol Off J Ger Card Soc 107(Suppl 2):114–119
10. Luedde M, Spehlmann ME, Frey N (2018) Progress in heart failure treatment in Germany. Clin Res Cardiol Off J Ger Card Soc 107(Suppl 2):105–113
11. Maisch B, Pankuweit S (2012) Current treatment options in (peri) myocarditis and inflammatory cardiomyopathy Aktuelle Behandlungsoptionen bei (Peri-)Myokarditis und inflammatorischer Kardiomyopathie. Herz 37(6):644–656
12. Kawano S, Kato J, Kawano N, Yoshimura Y, Masuyama H, Fukunaga T (2011) Clinical features and outcomes of eosinophilic myocarditis patients treated with prednisolone at a single institution over a 27-year period. Intern Med Tokyo Jpn 50(9):975–981
13. Shoaib A, Farag M, Nolan J, Rigby A, Patwala A, Rashid M, Kwok CS, Perveen R, Clark AL, Komajda M, Cleland JGF (2018)

Mode of presentation and mortality amongst patients hospitalized with heart failure? A report from the first euro heart failure survey. Clin Res Cardiol. https://doi.org/10.1007/s00392-018-1380-6
14. Baandrup U (2012) Eosinophilic myocarditis. Herz 37(8):849–852
15. Escher F, Kühl U, Lassner D, Poller W, Westermann D, Pieske B (2016) Long-term outcome of patients with virus-negative chronic myocarditis or inflammatory cardiomyopathy after immunosuppressive therapy. Clin Res Cardiol Off J Ger Card Soc 105(12):1011–1020