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CASE REPORT

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Hypereosinophilic syndrome associated with acute necrotizing myocarditis and cardiomyopathy

Hypereosinophiles Syndrom mit akut nekrotisierender Myokarditis und Kardiomyopathie

Zusammenfassung Wir berichten über eine 55-jährige Patientin mit einer ausgeprägten eosinophilen Myokarditis und hochgradig eingeschränkter linksventrikulärer Pumpfunktion. Klinisch manifestierte sich die Erkrankung mit reduziertem Allgemeinzustand, zunehmender Belastungsdyspnoe und peripheren Ödemen. Im Blutbild fand sich eine Leukozytose mit ausgeprägter peripherer Eosinophilie (48,8%). Eine endomyokardiale Biopsie zeigte eine massive Infiltration des Myokards mit eosinophilen Granulozyten und Nekrosen. Die Symptome und Laborparameter sprechen am ehesten für ein hypereosinophiles Syndrom. Die Differentialdiagnose eines Churg-Strauss-Syndroms wird diskutiert. Es wurde eine leitliniengerechte medikamentöse Herzinsuffizienztherapie sowie immunsuppressive Therapie mit Prednisolon (Decortin H®, 1,5 mg/kgKG) eingeleitet. Darunter lies sich eine rasche Reduktion der eosinophilen Granulozyten mit Normalisierung des peripheren Blutbildes beobachten, was mit einer deutlichen Verbesserung der klinischen Symptomatik korrelierte. Insbesondere war eine signifikante Zunahme der linksventrikulären Pumpfunktion zu beobachten. Nach langsamer Dosisreduktion auf eine Erhaltungsdosis von 10 mg Prednisolon blieben das klinische Beschwerdebild und Blutbild im Verlauf stabil.

Schlüsselwörter Eosinophilie – idiopathisches hypereosinophiles Syndrom – Myokarditis – Kardiomyopathie – Endomyokardiale Biopsie – Steroide

Summary We report the rare case of a 55-year-old female with massive eosinophilic myocarditis and severe, however reversible, impairment of left ventricular function. The patient presented with reduced physical condition, progressive dyspnea on exertion and peripheral edema. The white blood count revealed a leukocytosis and markedly elevated peripheral blood eosinophilics (48.8%). An endomyocardial biopsy demonstrated massive myocardial infiltration with eosinophilic granulocytes and necrosis. The symptoms and laboratory parameters indicate the presence of a hypereosinophilic syndrome. The differential diagnosis of a Churg-Strauss syndrome is discussed. Medical heart failure treatment according to international guidelines and an immunosuppressive treatment with prednisolone (Decortin H® 1.5 mg/kgBW) were initiated. This therapy led to a dramatic reduction of the eosinophilic granulocyte count and normalization of the peripheral blood count, which correlated with a significant improvement of clinical symptoms. Consistently, an increase of left-ventricular function was observed. Upon successive dose reduction to a maintenance dosage of 10 mg prednisolone, the patient's clinical status and peripheral blood count remained stable.

Key words Eosinophilia – idiopathic hypereosinophilic syndrome – myocarditis – cardiomyopathy – endomyocardial biopsy – steroids

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Introduction

The clinical syndrome of heart failure is the final pathway for diverse diseases that affect the heart. An initial cardiac insult results in the activation of the sympathetic nervous system, a release of renin and other vasoactive substances that trigger vasoconstriction, tachycardia and changes in myocytes which lead to disadvantageous ventricular dilatation [17]. In western countries the major causes for heart failure are coronary artery disease and hypertension. Despite considerable advancement of our understanding of the pathophysiological mechanisms and improvements of therapies, in most patients heart failure perpetuates to a progressive functional deterioration of the heart with a poor prognosis. Therefore, substantial effort should be made to identify the few patients with potentially reversible forms of heart failure and direct them to appropriate causal treatment.

We report the case of a 55-year-old women who presented with an increased eosinophil count and severe, however reversible, impairment of the left ventricular function. Endomyocardial biopsy revealed a massive accumulation of eosinophil granules with necrosis, in the absence of coronary heart disease.

Case report

A 55-year-old woman was repeatedly admitted to a general hospital with abdominal pain, cramps, nausea, vomiting and persistent diarrhea. Laboratory testing revealed severe leukocytosis and eosinophilia. Abdominal sonography showed chronic cholecystitis and gastroscopy revealed mild antrum gastritis and duodenitis. The patient was treated with proton pump inhibitors and an antibiotic regimen with amoxicillin. In addition to the abdominal symptoms, the patient presented with dyspnea on exertion. Chest X-ray revealed pleural effusions without pulmonary infiltrates. Echocardiography demonstrated a severely reduced left ventricular function. The patient was transferred to our cardiology department for further diagnosis and therapy.

Her past medical history was positive for bronchial asthma and hysterectomy. Her family history was unremarkable. Medication taken on a regular basis consisted of ipatropium bromide, symbicort and montelukast. A previous long-term medication with orally administered steroids was discontinued about one month prior to the onset of above mentioned symptoms.

The physical examination revealed a reduced general condition, with a body weight of 50 kg and height of 162 cm. Heart rate was 122 bpm, blood pressure was 120 mmHg over 85 mmHg. Temperature was normal. Respiratory rate was 16 breaths per minute and auscultation of both lungs revealed crackles in both lower lungs with reduced breathing and percussion sounds in both lower lung fields. The heart sounds were normal without S3 or S4. No murmur or pericardial friction rub were detected. Peripheral pulses were palpable. Pitting peripheral edema was present on both lower legs. On abdominal examination the patient complained of pain upon palpation in the right middle quadrant. Lymphatic node status was regular. Neurological examination revealed no pathologic findings.

An electrocardiogram showed sinus tachycardia (heart rate 110 bpm), normal AV-conduction time, indifferential axis and lateral ST segment inversion. The white blood count revealed a leukocytosis and an increased eosinophilic count. Further pathological laboratory values were present for gamma GT 326 U/l, AP 540 U/l, GOT/AST 94 U/l, and GPT/ALT 164 U/l. All other parameters were within normal ranges. Microscopical examination of the bone marrow showed massive granulocytopoetic eosinophilic hyperplasia of the hematopoetic bone marrow with reticulumcellsiderosis. Acute leukemia was excluded. Genetic testing for chromosomal translocation 8 (p11) was negative. Echocardiography revealed severe depression of left ventricular function with an ejection fraction (EF) of 19%, mild global heart dilation (LVESD 48 mm, LVEDD 58 mm, IVS 8 mm, PWT 8 mm) and consecutive mitral valve regurgitation II°, tricuspid regurgitation I° and pericardial effusion of 1.1 cm (diastolic). Repeated chest X-ray confirmed pleural effusions on both sides of about 6 cm without 6 evidence of pulmonary infiltrates. Cytological examination of the pleural punctuate showed no evidence of malignancy. Coronary heart disease was excluded by cardiac catheterization. Laevocardiography confirmed the severely impaired left ventricular function with an EF of 19% (EDV 203 ml, ESV 164 ml, SV 39 ml). End diastolic left ventricular pressure (26 mmHg) and mean pulmonary capillary wedge pressure (24 mmHg) were increased. Microscopy of three endomyocardial biopsy probes from the right ventricle revealed interstitiare edema and massive eosinophilic granules in all portions of the myocardium with aggregated eosinophils and necrosis. Fibrinoid wall necrosis of arteriolar vessels was not present. Only minimal subendocardial fibrosis was detected, without evidence of mural thrombi (Fig. 1). Virological and bacteriological tests from peripheral blood cultures and stool probes gave no evidence for any florid infection. Repeated testing of stool probes for the presence of parasites was consistently negative. Autoimmune diagnostic tests were

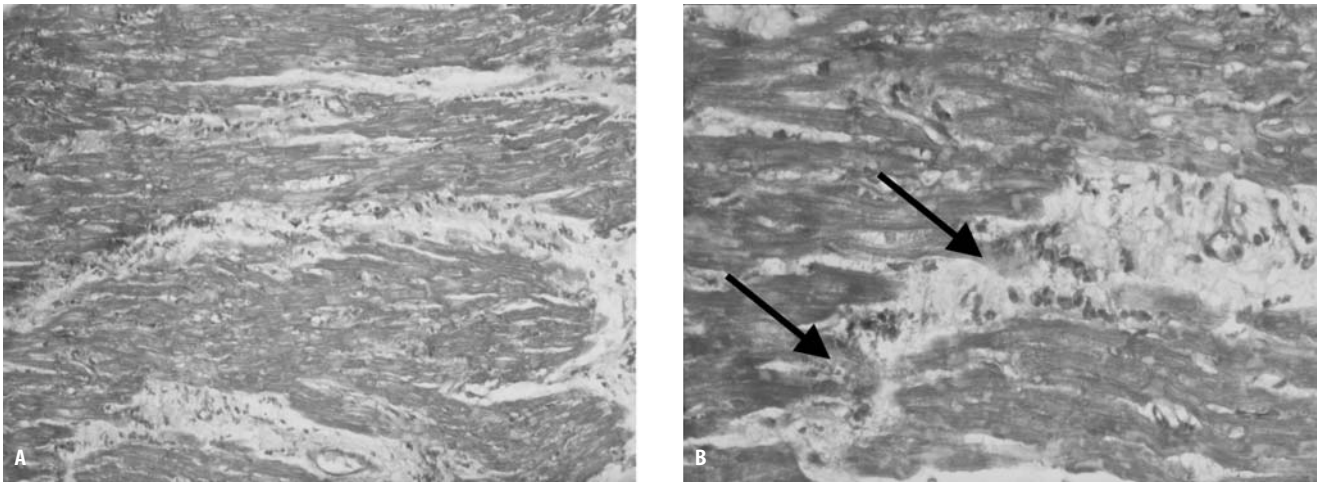

Fig. 1 **A** Eosinophilic myocarditis: microfocally accentuated, loose aggregates of eosinophilic granulocytes in the intersitium of cardiac muscle syncytium. Masson trichrome stain. Magnification 250×. **B** Insert: myocardial necrosis (arrows). Masson trichrome stain, magnification 500×

positive for ANA (1:100; reference interval <1:100) and negative for ANCA, dsDNA, IgE-RAST (wheat, nuts, fruits and herbs). As a possible inductor of the increased eosinophilic count and consecutive impaired left ventricular function, the leukotriene receptor antagonist montelukast (Singulair®), which had been given for the treatment of allergic bronchial asthma, was discontinued.

Standard heart failure therapy with ACE inhibitor (ramipril), β-blocker (bisoprolol), diuretics (thiazid, torasemid) and digitoxin was initiated according to the standard guidelines [15, 16, 25]. In addition, corticosteroid therapy was started at a dosage of 75 mg prednisolone/day for 5 days (1.5 mg/kg body weight, Decortin H®). Within 3 days after the onset of medication the patient's clinical status and symptoms improved dramatically. Within 5 days the leukocyte count decreased markedly from 22 300/µl to 12 300/µl (reference interval 4 400–11 300/µl), and the eosinophilic count from 48.8% to 7.7% (reference interval 2–4%). Prednisolone was gradually reduced to a maintenance dosage of 10 mg per day. After 4 months control echocardiography revealed an increase of the ejection fraction from 19% to 43%, leukocyte and eosinophilic counts were normal; the patient was asymptomatic (Fig. 2).

In summary, we present a case of necrotizing myocarditis due to an idiopathic hypereosinophilic syndrome with cardiomyopathy and severe impaired left ventricular function, which was reversible under heart failure medication and prednisolone therapy. The differential diagnosis of an early stage Churg-Strauss syndrome (CSS) or the induction of a CSS due to tapered or discontinued treatment with steroids (termed "forme frustes") is discussed.

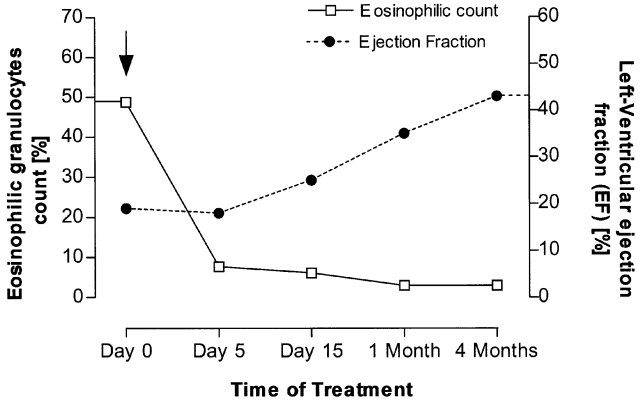

Fig. 2 Changes in eosinophilic count (left Y-axis) and echocardiographic ejection fraction (right Y-axis) in the time course of treatment (X-axis) (↓, marks the onset of prednisolone treatment)

Discussion

An increased eosinophilic count in the peripheral blood (eosinophilia) is diagnostically nonspecific and can be caused by various medical disorders [3]. Eosinophilia is a relatively rare condition which is usually caused by parasitic infection, allergic disease, lymphoma, carcinoma, and drug-induced allergy, and is then considered reactive [1, 20]. Recently, several cases of eosinophilic conditions including Churg-Strauss syndrome (CSS) have been reported in asthmatic patients being treated with leukotriene receptor antagonists such as montelukast, zafirlukast or pranlukast [26]. However, in most of these patients CSS developed when oral corticosteroids were withdrawn

suggesting that steroid discontinuation might have unmasked CSS. Therefore, it remains controversial whether systemic symptoms in affected patients occurred as part of the natural course of the disease or were directly related to leukotriene antagonist therapy. Our patient had received montelukast as therapy of allergic bronchial asthma already for several years. Though a direct relation of hypereosinophilia and montelukast was thus considered unlikely in our patient leukotriene antagonist therapy was discontinued as a precaution. Since our patient presented with a combination of asthma, gastrointestinal symptoms, blood eosinophilia and eosinophilic infiltrates of the heart, the differential diagnosis of a hypereosinophilic syndrome versus a CSS possibly unmasked by the discontinuation of steroids (so called "forme frustes") has to be considered [4, 5]. The CSS is defined as a constellation of clinical symptoms and pathological findings which slightly vary according to the classification applied (Churg and Strauss, Lanham and colleagues, American College of Rheumatology and the Chapel Hill Consensus Conference, for review see Noth et al., 2003 [21, 27]). Briefly, the most important criteria are a history of asthma, eosinophilia, (necrotizing) pulmonary infiltrates and potentially life-threatening vasculitis involving multiple organs such as heart, lung, gastrointestinal tract and the nervous system [18, 21, 27]. While symptoms and pathologic findings of our patient seem to be typical for CSS, they do no completely fulfill any of the above mentioned, currently established definitions. Therefore, it remains speculative whether our patient exhibited an early "prodromal" phase of CSS.

For further differential diagnosis as well as in unclear cases of hypereosinophilia other causes have to be ruled out. The 'non-reactive' eosinophilia is considered of clonal origin in conditions like acute or chronic myeloid leukemia, myelodysplastic syndrome, and other carcinogenic disorders. Recently, a myoproliferative disorder due to a mutation in a tyrosine kinase has been identified. This FIP1L1-PDGF-receptor alpha mutation results in an insertional deletion 4q12 with concomitant fusion of the FIP1L1 to the platelet-derived growth factor receptor α (PDGFRA) locus [7]. However, this condition was not present in our patient. Cases in which reactive and 'non-reactive' causes are excluded can be classified as idiopathic hypereosinophilic syndrome (idiopathic HES). Idiopathic HES is defined as peripheral blood eosinophilia persisting for at least 6 months, which is associated with eosinophil-mediated end-organ damage in various organs including the lungs, heart, or the nervous system [6]. Since no clear cause for the hypereosinophilia could be determined and the criteria for CSS were not fulfilled in our patient, idiopathic HES was diagnosed.

Pathophysiology of hypereosinophilia and cardiac involvement

Eosinophilic endomyocardial disease can be classified into three groups: The acute necrotizing stage, the thrombotic phase and the late fibrotic phase, corresponding clinically to eosinophilic myocarditis, Löffler's endocarditis and endomyocardial fibrosis, respectively [22]. In our patient microscopy demonstrated acute necrotizing eosinophilic myocarditis which typically presents with an elevated peripheral blood eosinophil count and acute congestive heart failure that has previously been uniformly fatal [9]. Pathologically it is characterized by an active infiltration of the myocardium by eosinophils, lymphocytes and histiocytes [11]. Reparatory interstitial fibrosis with collagen deposition in damaged myocardial areas, induced by necrosis, can lead to cardiac arrhythmias resulting in sudden cardiac death [8].

The causes and pathomechanisms leading to myocardial eosinophile infiltration remain unknown. Interleukin-5 (IL) is being postulated to trigger liberation of chemotactic signals by CD4-positive lymphocytes, which leads to adhesion and infiltration of eosinophils. The myocardium is being damaged by proteins derived from eosinophilic granules, such as eosinophilic cationic protein (ECP), major basic proteins and eosinophilic protein X, which results to necrosis. ECP is an unspecific mediator that correlates with the grade of activity of eosinopils as well as clinical symptoms [14, 19].

Diagnostic process for hypereosinophilia and myocarditis

Research and recent advances on this topic permit a more reasonable approach to detect a definite diagnosis of patients with hypereosinophilia. The systematic evaluation should begin with a detailed history, including a drug and travel history, physical examination and a blood count, followed by specific testing for the above mentioned common causes for hypereosinophilia and myocarditis (e.g., tests for parasites, cardiotropic viruses, bacteria, etc.). Laboratory testing should include a differential white blood count, liver function tests, immunglobulines, ANCA (ELISA) and urine analysis. Special focus should lie on changes in previous asthma treatment, especially tapered or discontinued steroids and/or the initiation of treatment with leukotriene receptor antagonists. In any affected organ, biopsies can be a diagnostic tool to identify eosinophil infiltrates and evidence for vasculitis. In our patient a myocardial biopsy was taken, while a gastrointestinal biopsy during gastro-duodenoscopy was not. Gastrointesti-

nal biopsy could have shown eosinophil infiltation, but caution has to be taken in the interpretation since small numbers of eosinophils are commonly found in healthy individuals [4]. In any event in our patient, gastrointestinal biopsy findings would not have established the diagnosis of CSS.

Any abnormalities in blood testing such as lymphocytosis or cytological abnormal lymphocytes are an indication for immunophenotyping of peripheral blood lymphocytes and gene rearrangement analysis. Bone marrow aspirate and trephine biopsy with cytogenetic analysis and molecular analysis (e.g., for FIP1L1-PDGFRA) should be considered in the presence of monocytosis, basophilia, immature granulocytes in the peripheral blood or hepatosplenomegaly. Diagnosis of impaired left-ventricular function of unknown origin requires cardiac catheterization with angiography as well as endomyocardial biopsy with further histopathological examination.

Therapy

Therapy of an eosinophilic syndrome with cardiac involvement consists of standard heart failure medication [15, 16, 25] and early treatment with high dosages of cortisone, which represents the therapy of first choice after diagnosis of eosinophilic myocarditis. In our patient, we initiated treatment with oraly prednisolone at 1.5 mg/kg body weight on a daily basis (Decortin H® 75 mg) for 3 days with gradual reduction to a maintenance dosage of 10 mg per day. In patients not responding to steroids further therapeutic options include cyclophosphamid or hydroxyurea (0.5–1.5 g/day) [10]. Plasmapheresis was not superior compared to sole steroid therapy in CSS [13]. In patients with diagnosed CSS and insufficient treatment with steroids, administration of immunglobuline or interferon alfa are further therapeutic options [21]. In addition, imatinib mesylate (Gleevec™), which may be superior to hydroxyurea [2], can be considered in patients with therapy-resistant HES [12, 23, 24].

Conclusion

Acute necrotizing eosinophilic myocarditis is a rare cause of congestive heart failure. Every effort for establishing the diagnosis should be performed since even severe cardiac dysfunction may be reversible upon appropriate therapy including corticosteroids and possibly cyclophosphamid, hydroxyurea and imatinib mesylate.

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