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Kasuistika | Case report

Recurrent infective endocarditis as a manifestation of Loeffler's endocarditis: The diagnostic importance of cardiac magnetic resonance imaging

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SOUHRN

Hypereosinofilní syndrom (HES) postihuje řadu orgánových systémů. U pacientů s HES se lze často setkat s postižením srdce, které je hlavní příčinou jejich morbidity a mortality.
Popisujeme případ 60letého pacienta s anamnézou recidivující infekční endokarditidy vyvolávané různými bakteriemi rodu *Streptococcus*. Transthorakální echokardiografie (TTE) odhalila v blízkosti hrotu levé komory ohraničenou echodenzní strukturu připomínající vegetaci. Pozitronová emisní tomografie prokázala na stejném místě levé komory zvýšenou aktivitu, žádné jiné abnormality však nebyly zjištěny. Při každé epizodě infekční endokarditidy (celkem třikrát) byly pacientovi aplikovány i.v. antimikrobiální přípravky. Při kontrolní TTE byla vegetace v blízkosti hrotu stále ještě zřetelná. Diagnostické vyšetření srdce magnetickou rezonancí (CMR) prokázalo ztluštění stěny komor a difuzní pozdní sycení subendokardiálně v nepravidelných okrscích. Tyto nálezy silně připomínají Löfflerovu endokarditidu. Biopsie kostní dřeně prokázala zvýšené procento eosinofilních granulocytů, a potvrdila tak diagnózu HES.
Výskyt infekční endokarditidy současně s Löfflerovou endokarditidou již dříve jednou popsali Menz a spol. v článku publikovaném v roce 1994 v časopise Hertz. Tento případ zdůrazňuje význam CMR jako metody pro stanovení diagnózy Löfflerovy endokarditidy. Zmnožení eosinofilů v periferní krvi nebylo u našeho pacienta nalezeno. Biopsie myokardu je spojena se zvýšeným rizikem tromboembolických příhod a s možností falešně negativního výsledku. Výsledek vyšetření CMR však vyvolal podezření na Löfflerovu endokarditidu, tedy diagnózu následně potvrzenou biopsií kostní dřeně. Pacient byl léčen acenokumarolem a perorálním prednisonem, jehož dávky byly po přidání mykofenolát mofetilu postupně snižovány.

ABSTRACT

Hypereosinophilic syndrome (HES) affects many organ systems. Cardiac involvement is common and a major cause of morbidity and mortality in patients with HES.
We present a 60-year-old patient with a history of recurrent infective endocarditis due to different *Streptococcus* species. Transthoracic echocardiography (TTE) revealed a circumscript echodense structure near the apex of the left ventricle, suggestive of a vegetation. Positron emission tomography revealed increased activity at the same site of the left ventricle and showed no other abnormalities. The patient was treated with intra-

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venous antimicrobial therapy for each episode of infective endocarditis (3×). The vegetation near the apex remained visible on follow-up TTE. Diagnostic cardiac magnetic resonance imaging (CMR) was performed and showed left ventricular wall thickness, and diffuse subendocardial delayed enhancement in a patchy pattern. These findings are strongly suggestive of Loeffler's endocarditis. Bone marrow biopsy showed increased percentage of eosinophilic granulocytes, confirming the diagnosis of hypereosinophilic syndrome (HES).
The presence of infective endocarditis and simultaneous Loeffler's endocarditis has been reported once before by Menz et al. in 1994 published in Hertz. This case emphasizes the role of CMR as a diagnostic modality for Loeffler's endocarditis. Our patient had no peripheral hypereosinophilia. Myocardial biopsy conveys an increased risk for thromboembolic events and the possibility of a false negative result. CMR however, raised the suspicion of Loeffler's endocarditis, a diagnosis that was subsequently confirmed by bone marrow biopsy. The patient was treated with acenocoumarol and oral prednisone, which was gradually tapered after addition of mycophenolate mofetil.

Introduction

Hypereosinophilic syndrome (HES) was first described in 1936 by William Löffler, a professor of medicine at the University of Zürich, Switzerland. The term HES itself was not introduced until 1968 by Hardy and Anderson, who recognized Loeffler's endocarditis as one of the organ manifestations [1,2].

HES is a heterogeneous group of rare conditions characterized by hypereosinophilia and eosinophil-mediated organ damage. Hypereosinophilia is defined as an elevated peripheral blood eosinophil count of > 1500/μL on two occasions greater than a month apart or the pathologic finding of tissue hypereosinophilia (which includes >20% eosinophils on bone marrow section, tissue eosinophil infiltration considered as extensive by a pathologist or marked deposition of eosinophil granule proteins in tissue) [3].

HES is further categorized into idiopathic, primary (neoplastic) or secondary (reactive) according to the cause. Primary or neoplastic HES indicates an underlying stem cell, myeloid or eosinophilic neoplasm and is considered clonal. Secondary or reactive HES is a polyclonal condition caused by an overproduction of eosinophilopoietic cytokines, e.g. in parasitic infections, certain solid tumors, and T-cell dyscrasias. In idiopathic HES the underlying cause remains unknown [3,4].

Although in HES many organ systems can be affected, cardiac involvement, called Loeffler's endocarditis, is common, occurring in up to 60% of patients with HES and is a major cause of morbidity and mortality.

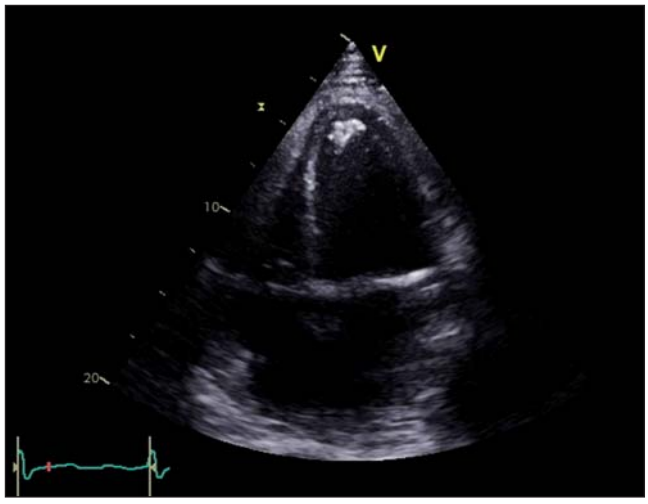
We present a case of recurrent infective endocarditis, in which cardiac magnetic resonance imaging (CMR) provided the clue to underlying HES, demonstrating the utility of CMR for the diagnosis of Loeffler's endocarditis.

Case report

A 60-year-old male patient was admitted in March 2015 in a local hospital with malaise, fever and bacteremia. His past medical history was remarkable for juvenile rheumatoid arthritis**,** coronary artery bypass grafting in 2010, hypertension, gout and type 2 diabetes. He gave up smoking and drinking alcohol 20 years ago, and has no known family history for cardiovascular disease. On physical examination endocarditis stigmata and heart murmur were not found. Laboratory studies were significant for erythrocyte sedimentation rate (ESR) of 104 mm/h, and C-reactive protein (CRP) of 120 mg/l, next to chronic pre-existent kidney and liver dysfunction. Blood cultures were positive for *Streptococcus salivarius*, a gram positive coccus found in the upper respiratory tract. Poor dental hygiene was assumed to be the primary focus and tooth extraction was performed. Transthoracic and transesophageal echocardiography (TTE and TEE) did not reveal vegetations during this first presentation. The patient was treated with intravenous (iv) antibiotics for four weeks.

A few weeks later he developed severe pitting edema of the legs. He reported no fever, chest pain or dyspnea. Again no stigmata of endocarditis were found on physical examination, but auscultation revealed a murmur suggestive of tricuspid valve insufficiency. CRP was 16 mg/l. Blood cultures tested positive again for *S. salivarius*. TTE now revealed an echodense structure near the left ventricular apex, suggestive of a vegetation (Figs. 1 and 2), and the patient was treated with iv antibiotics for infective endocarditis and diuretics for heart failure. After four weeks he showed no signs of improvement and was referred to our hospital. Echocardiography showed left ventricular ejection fraction (LVEF) of 61%, severe tricuspid insufficiency (TI) caused by right ventricular dilatation, and confirmed a left ventricular echodense structure on the distal septum near the apex suggestive of a vegetation due to infective endocarditis. The apex was not akinetic nor dyskinetic. Positron emission tomography (PET) confirmed this finding and revealed no other infective foci. Cardiac catheterization with coronary angiography showed pulmonary hypertension and partial occlusion of one of the grafts. Eventually the patient recovered with high doses of diuretics and inotropics iv and received 12 weeks of iv antibiotic treatment.

Unfortunately three months after discharge he suffered again from fever and malaise. Laboratory tests revealed raised CRP of 49 mg/l, white blood cell count of 11 cells × 10^9 L with normal eosinophil count. Blood cultures tested positive for *Streptococcus mitis*, a gram positive coccus, known as an important cause of infective endocarditis in adults. Intravenous antibiotic treatment was reinstalled. Because colonic neoplasms are associated with infective endocarditis, colonoscopy was performed revealing no portal of entry. TTE and PET-scan showed an unchanged left ventricular apical vegetation. Endomyocardial biopsy from the left ventricular vegetation was considered to be contra-indicated because of the high risk of cerebral thromboemboli and a possible false negative biopsy. Eventually the patient was discharged from hospital with long-term iv antimicrobial treatment.



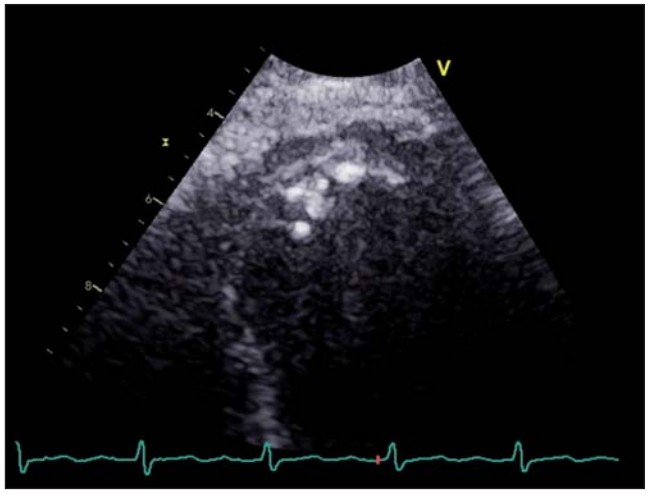


Fig. 1 and 2 – Transthoracic echocardiogram (TTE) revealing a circumscript echodense structure near the apex of the left ventricle.

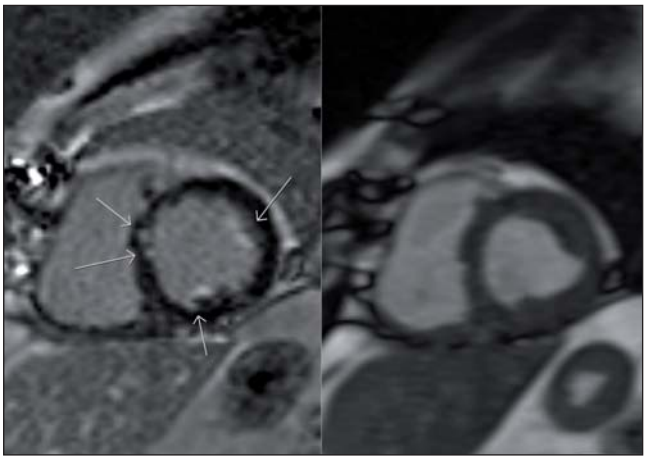


Fig. 3 – Cardiac magnetic resonance imaging (CMR) showing left ventricular wall thickness and diffuse subendocardial delayed enhancement in a patchy pattern.

During follow-up the patient continued to do well and experienced no more fever episodes, no adverse events from the antibiotics, and CRP normalized. Cardiothoracic surgery to remove the apical vegetation was discussed, however ventriculotomy involves potential serious complications, including left ventricular dysfunction afterwards, arrhythmias and risks related to reoperation. Due to severe claustrophobia of the patient, CMR was eventually performed under general anesthesia to obtain further characterization of the left ventricular apical structure. It showed left ventricular wall thickness, compatible with inflammation or fibrosis, and diffuse subendocardial delayed enhancement in a patchy pattern, no intracavitary thrombus was seen Fig. 3). These findings strongly suggest eosinophilic Loeffler's endocarditis, possibly as a manifestation of HES. Further evaluation by bone marrow biopsy showed increased percentage of eosinophilic granulocytes, confirming the diagnosis of HES. Immunophenotypic evaluation and bone marrow cytogenetic analysis showed no indications for myeloproliferative or T lymphocytic variants of HES (respectively M-HES and L-HES). Intravenous antibiotics were discontinued after 8 weeks and corticosteroid therapy was started; also oral anticoagulants were given to prevent cardiac embolism. Gradually the Prednisone was tapered off and Mycophenolate mofetil (MMF) was started as a steroid-sparing regimen based on expert-opinion. Under this regimen the patient felt well and regained his normal daily activities.

Our patient had no increase in blood eosinophil count, but HES can occur in the absence of peripheral eosinophilia [5]. Endomyocardial biopsy is the gold standard for the diagnosis of cardiac involvement in HES, but it is an invasive procedure with potential risk of cerebral embolism, especially if biopsy from a left ventricular lesion is performed. The final diagnosis of endomyocardial damage related to HES in our patient was based on clinical presentation, CMR, and bone marrow biopsy.

Noteworthy, 10 months after starting the above mentioned therapy, while developing a mild peripheral eosinophilia (800/μL), the patient again developed an infective endocarditis. This time the causative microorganism appeared to be *Enterococcus faecium*, a gram positive coccus, commensal of the human intestine. TTE revealed no valve vegetations, however the echodense structure at the apex was still present, unchanged in diameter. PET showed no infective foci elsewhere or a portal of entry. The patient was treated with Vancomycin iv for 8 weeks. Since this is the fourth episode of infective endocarditis in a period just under 2 years, ventriculotomy by thoracic surgery is reconsidered. In the near future, our patient has a high risk of recurrent infective endocarditis, which may lead to serious (cardiac) complications and/or antibiotic resistance due to frequent use of antibiotics.

Discussion

Eosinophil-mediated endomyocardial damage in HES follows three stages. An acute necrotic stage due to endomyocardial eosinophilic infiltration, during which the disease is usually clinically silent. The second intermediate phase is characterized by thrombus formation along the damaged endocardium. The final phase is the fibrotic stage which results in endomyocardial fibrosis and restrictive cardiomyopathy.

Patients with Loeffler's endocarditis may show symptoms and signs of congestive heart failure; dyspnea,

cough and chest pain are frequently mentioned. Physical examination may reveal cutaneous splinter hemorrhages (small emboli from the endocardial surface). Electrocardiography is typically non-specific, arrhythmias can occur and troponin might be raised. Neurological complications as severe as cerebrovascular accidents (due to intracardiac thrombus) are described [4,6–8].

Cardiac symptoms typically take weeks to months to evolve and when cardiac involvement in HES is suspected, different diagnostic modalities are available. The gold standard for the diagnosis of cardiac involvement in HES is endomyocardial biopsy, but is typically reserved for patients with uncertain diagnosis. Noninvasive imaging techniques are preferred to diagnose cardiac manifestations in HES. TTE usually shows no abnormalities during the initial stage. Cardiac mural thrombus and endomyocardial thickening can be identified in the following stages. Progression of the thrombus to fibrosis may lead to restrictive diastolic dysfunction and valvular regurgitation. Ultimately, TTE reveals findings characteristic for restrictive cardiomyopathy [4,9,10].

The past few years, CMR imaging has emerged as a newer modality to reliably detect eosinophil-mediated heart damage. It can differentiate between endocardium, myocardium and thrombus in suspected cardiac manifestations of HES and provides assessment of tissue characterization, including necrosis, inflammation, and fibrosis. CMR imaging is more sensitive and specific for the detection of ventricular thrombi than TTE [11–13]. Thus, CMR can distinguish among the three different stages of Loeffler's endocarditis. Besides confirming the diagnosis of HES, CMR can be used as a noninvasive method for treatment monitoring.

Though endomyocardial biopsy is the gold standard, it is an invasive procedure with risk of complications. Furthermore, due to the patchy pattern of the Loeffler's endocarditis biopsy material might not reveal abnormalities. Tissue HES can occur in the absence of peripheral eosinophilia and diagnosis might be delayed. In our patient CMR proved to be diagnostic of Loeffler's endocarditis as the underlying cause of the recurrent infective endocarditis. The presence of infective endocarditis and simultaneous Loeffler's endocarditis has been reported once before [14].

Our case demonstrates the utility of CMR for the diagnosis of cardiac involvement in HES and highlights its importance for clinical decision making. Findings were consistent with Loeffler's endocarditis showing left ventricular wall thickness and diffuse subendocardial delayed enhancement in a patchy pattern. Bone marrow biopsy confirmed the diagnosis and endomyocardial biopsy could be avoided. CMR is a powerful diagnostic tool and may obviate the need for cardiac biopsy in the future.

Conclusion

Our case demonstrates the utility and clinical importance of CMR for the diagnosis of cardiac involvement in HES. It provides a noninvasive method to diagnose all three stages of eosinophil-mediated endomyocardial damage, and avoids the complication risk of endomyocardial biopsy. Typical CMR findings along with clinical presentation may obviate the need for cardiac biopsy in the future.

Conflicts of interest
None of the authors have any conflict of interest to disclose.

Funding body
None.

Ethical statement
Authors state that the research was conducted according to ethical standards.

Informed consent
The authors declare that informed consent was obtained from the patient participating in this study.

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References

[1] W. Löffler, Endocarditis parietalis fibroplastica mit Bluteosinophilie, Schweizerische Medizinische Wochenschrift. Journal Suisse de Medecine 65 (1936) 817–820.
[2] W.R. Hardy, R.E. Anderson, The hypereosinophilic syndromes, Annals of Internal Medicine 68 (1968) 1220–1229.
[3] P. Valent, A.D. Klion, H.-P. Horny, et al., Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes, Journal of Allergy and Clinical Immunology 130 (2012) 607–612.e9.
[4] R. Mankad, C. Bonnichsen, S. Mankad, Hypereosinophilic syndrome: cardiac diagnosis and management, Heart 102 (2016) 100–106.
[5] T. Fozing, N. Zouri, A. Tost, et al., Management of a patient with eosinophilic myocarditis and normal eosinophil count. Case report and literature review, Circulation: Heart Failure 7 (2014) 992–994.
[6] J. Ten Oever, L.J.H.J. Theunissen, L.W. Tick, et al., Cardiac involvement in hypereosinophilic syndrome, Netherlands Journal of Medicine 69 (2011) 240–243.
[7] E.P. Corssmit, M.D. Trip, J.D. Durrer, Loffler's endomyocarditis in idiopathic hypereosinophilic syndrome, Cardiology 91 (1999) 272–276.
[8] J.E. Parrillo, J.S. Borer, W.L. Henry, et al., The cardiovascular manifestations of the hypereosinophilic syndrome. Prospective study of 26 patients, with review of the literature, American Journal of Medicine 67 (1979) 572–582.
[9] R. Shah, K. Ananthasubramaniam, Evaluation of cardiac involvement in hypereosinophilic syndrome: complementary roles of transthoracic, transesophageal, and contrast echocardiography, Echocardiography 23 (2006) 689–691.
[10] P. Ogbogu, D.R. Rosing, M.K. Horne, Cardiovascular manifestations of hypereosinophilic syndromes, Immunology and Allergy Clinics of North America 27 (2007) 457–475.
[11] T. Kleinfeldt, C.A. Nienaber, S. Kische, et al., Cardiac manifestation of the hypereosinophilic syndrome: new insights, Clinical Research in Cardiology 99 (2010) 419–427.
[12] T. Kleinfeldt, H. Ince, C.A. Nienaber, Hypereosinophilic syndrome: a rare case of Loeffler's endocarditis documented in cardiac MRI, International Journal of Cardiology 149 (2011) e30–e32.
[13] I.S. Syed, M.W. Martinez, D.-L. Feng, et al., Cardiac magnetic resonance imaging of eosinophilic endomyocardial disease, International Journal of Cardiology 126 (2008) e50–e52.
[14] V. Menz, L. Drude, U. Schönian, et al., Löffler endocarditis fibroplastica with simultaneous infectious endocarditis, Herz 19 (1994) 138–143.