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CASE REPORT

Cardiac involvement in hypereosinophilic syndrome

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ABSTRACT

Hypereosinophilic syndrome is a heterogeneous group of disorders characterised by hypereosinophilia and organ involvement of varying intensity. We describe involvement of the heart in patients with hypereosinophilic syndrome, and the diagnostic and therapeutic clinical management of these patients.

KEYWORDS

Hypereosinophilic syndrome, chronic eosinophilic leukaemia, cardiac magnetic resonance imaging, troponin

What was known on this topic?
In the last decade, molecular biology studies elucidated the aetiology of some variants of hypereosinophilic syndrome (HES), therefore reducing the group of patients with idiopathic HES and making targeted treatment possible. Cardiac involvement is common and may lead to restrictive cardiomyopathy.

What does this add?
Cardiac MRI has recently emerged as a non-invasive imaging modality and can be used for tissue characterisation and may obviate biopsy. Increased concentrations of troponin in HES is suggestive of acute inflammation of the endomyocardium.

INTRODUCTION

In 1968 the term hypereosinophilic syndrome (HES) was introduced to describe a heterogeneous group of diseases characterised by unexplained hypereosinophilia and organ involvement in varying degrees.[1] In 1975 Chusid was the first to establish three diagnostic criteria for HES: a persistent eosinophilia of 1500 eosinophils/mm^3 for longer than six months (1) with lack of evidence for allergic, parasitic or other known causes of eosinophilia (2) and symptoms and signs of organ involvement (3).[2] Nowadays this definition is still valid.[3] Many organ systems are affected in HES, but cardiovascular complications are most prevalent and are responsible for the observed high mortality.[4]
On the basis of a case report we discuss the nomenclature, the cardiac involvement in HES, the (new) diagnostic modalities and its treatment.

CASE REPORT

A 52-year-old male without previous medical history presented to the emergency department because of acute confusion. He was found in the shower, did not know how to shave and felt slightly dizzy. In the previous weeks he had been paranoid, tired and walked slowly with a forward-flexed posture. During the last year he had experienced a blurred vision hampering driving and using his mobile phone. For two months he had been taking acetaminophen because of bitemporal headache. He did not have any fever, chest pain, palpitations, dyspnoea or oedema. On physical examination he was not acutely ill, was haemodynamically stable, had no fever and lacked disease awareness. He undressed clumsily and slowly and complete examination only revealed a rigid gait with decreased arm swing and a slight apraxia of his left hand. Laboratory examination showed a haemoglobin of 7.2 mmol/l, leukocytes 21*10^9/l with 63% esosinophils in the differentiation (on several occasions), and a thrombocyte count of 198*10^9/l. C-reactive protein was 89 mg/l, creatinine 113 µmol/l (MDRD 59 ml/min/1.73 m^2), troponin T 0.91 µg/l, creatine kinase (CK) 100 U/l, CK-MB mass 8.2 µg/l, lactate dehydrogenase 420 U/l, aspartate

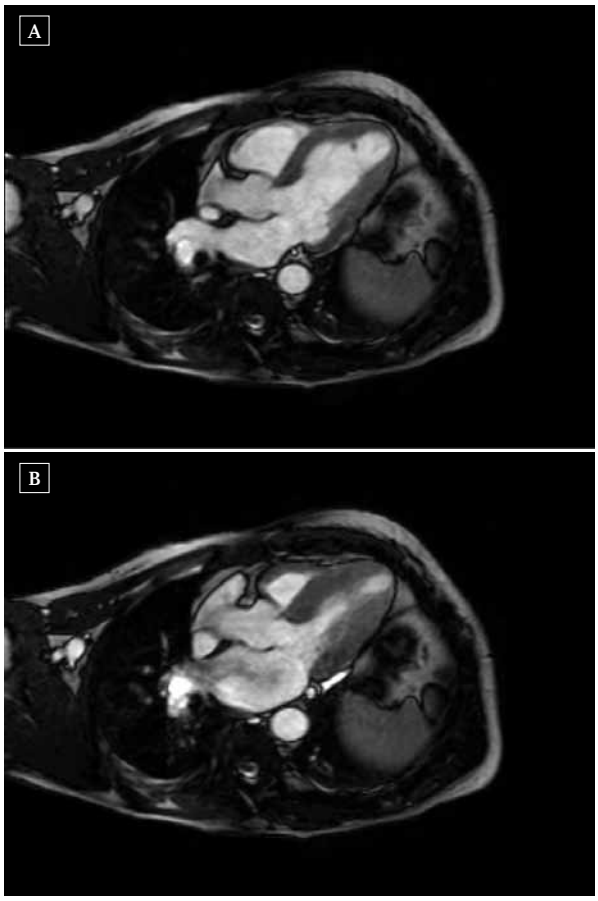
aminotransferase 37 U/l, and alanine transaminase 16 U/l. Vitamin B12 and tryptase were not elevated.

No parasitic infection, allergic or pulmonary disease were found as aetiology for the eosinophilia. Bone marrow aspirate showed 34% eosinophils, a normal percentage of blasts and many megakaryocytes in different developmental stages. No dysplastic features were present. Bone marrow biopsy was in part rich in cells with increased myelopoiesis and eosinophilia and in part hypoplastic accompanied by reticulin fibrosis. No infiltration of mast cells was visualised. To find chromosomal abnormalities associated with chronic eosinophilic leukaemia (CEL), fluorescent in situ hybridisation (FISH) examination of bone marrow cells was performed. However, a fusion of the Fip1-like 1 (FIP1L1) gene to the PDGFRα (PDGFRA) gene generated by an interstitial deletion on chromosome 4q12 was absent. On brain MRI extensive white matter lesions were present in the occipital lobes and periventricularly near the vertex of both areas vascularised by both medial cerebral arteries and in the right cerebellar hemisphere. Examination revealed decreased visual acuity but a normal ocular system. A CT scan was negative for lymphomas; only a mild splenomegaly was seen.

His ECG showed sinus rhythm, normal PQ time, normal heart axis and a QRS width of 0.09 seconds with a QS complex in V1 and V2, slight ST elevation in V2 and minimal ST depression in V4 to V6 with T-wave inversions in III, aVF, and V3 to V6. Cardiac ultrasonography showed slight left atrial dilatation and minimal mitral regurgitation. Systolic function was preserved. Diastolic dysfunction could not be excluded nor identified. Normal coronary arteries were visualised on a coronary artery angiography.

Because of the suspicion of a hypereosinophilic syndrome (HES) with neurological and cardiac involvement 60 mg prednisone was started three days after admission, even before all the tests had been performed. The concentration of troponin T rapidly decreased and was no longer detectable after ten days. Because of the persistent eosinophilia three weeks after the introduction of prednisone the tyrosine kinase inhibitor imatinib 400 mg per day was initiated. Simultaneously the prednisone was tapered to 2.5 mg during two and a half months. Within several weeks the hypereosinophilia had decreased significantly. A few days after imatinib was started (three and a half weeks after initiation of the prednisone) a cardiac MRI (CMR) was performed. On T2 weighed images apical subendocardial intensity was seen. On delayed enhancement images subendocardial enhancement of the apex was present. Hypokinesia of the apex of the left ventricle was visible. There were no signs of intracardial thrombus formation *(figure 1)*. Four months later the CMR was repeated and depicted the same subendocardial delayed enhancement following gadolinium. The apical T2 signal had disappeared. Troponin T remained within normal limits during follow-up. During follow-up of 12 months, no symptoms or signs of heart failure developed and his cognitive function and vision improved.

Figure 1. *Panel A shows the left ventricle during diastole. During ventricular contraction apical hypokinesia is seen (panel B)*



DISCUSSION

Nomenclature

Developed in 1975, Chusid's criteria are still suitable for diagnosing HES nowadays. Hasn't anything changed in 30 years? On the contrary. The heterogeneous group of disorders constituting HES is decreasing as separate disease entities are recognised. A lymphocytic variant is distinguished by the presence of clonal populations of abnormal T cells producing interleukin-5 with subsequent production of eosinophils, making it a peripheral T-cell lymphoma.[5] Increased blast cells (but less than in acute leukaemia), evidence of clonality or the presence of a fusion gene, particularly the fusion of FIP1L1 and PDGRFA caused by a deletion on chromosome 4q12, are diagnostic of CEL.[3,6] This fusion gene encodes for a protein with substantial tyrosine kinase activity which has important implications for therapy. Rearrangements of other genes (PDGRFB and

FGFR1) may also be responsible for myeloid or lymphoid neoplasms with eosinophilia.[3] If a patient fulfils Chusid's criteria and no cause is found for the eosinophilia after thorough investigation, the WHO classifies this patient as having *idiopathic* HES even if there are features suggestive, but not diagnostic, of a myeloproliferative/leukaemic disorder (dysplastic eosinophils on peripheral smear, serum vitamin B12 >000 pg/ml, serum tryptase ≥2 ng/ml, anaemia and/or thrombocytopenia, hepatosplenomegaly, bone marrow cellularity >80%, spindle shaped mast cells, myelofibrosis).[3] It is said that the term 'hypereosinophilic syndrome' should be discouraged as a diagnostic term since this term indicates either an imprecise use of language or that the patient has not been adequately investigated.[7] However, when using the (older) literature and during the diagnostic process it is inevitable to use the term hypereosinophilic syndrome. According to WHO classification our patient should be classified as having idiopathic HES.

Cardiac involvement

Pathogenesis of cardiac disease

Cardiac involvement in HES is rare in the lymphocytic variant of HES but often occurs in the myeloproliferative forms.[8,9] The overall prevalence of cardiovascular involvement is over 50%.[10] Cardiac disease follows three stages.

The first is an acute necrotic stage due to infiltration of eosinophils in the myocardium. The contents of the eosinophilic granules (eosinophilic major basic protein, eosinophilic cationic protein and eosinophil protein-X) are present within the endocardium and myocardium and are held responsible for the initiating the damage.[11] Little information is available about the duration of this stage, but a mean of 5.5 weeks with a range of one day to three months has been reported based on the duration of cardiac symptoms.[12] However, this stage is thought to be asymptomatic in many cases, which hampers the determination of the actual course of this stage.[9]

The intermediate phase is characterised by mural thrombi and thrombus formation along the damaged endocardium (thrombotic stage).[11,12] The left ventricle is more often affected and thrombi tend to be located in the apices where stasis is more of a factor.[2,9] Patients with thrombotic lesions have an average duration of symptoms of ten months.[12] This is followed by organisation of the thrombus into a thick layer of granulation tissue which replaces the normal endocardium. The third stage is the later fibrotic stage in which the granulation tissue is changed into hyaline fibrosis, sometimes still with a small inflammatory zone in deeper layers.[11,12] In comparison with the acute stage, there are no or minimal deposits of eosinophil granule proteins, suggesting that the fibrotic stage represents the final stage of a pathogenetic sequence initiated by myocardial eosinophilic infiltration.[11]

Löffler called the combination of this peculiar cardiac disease and eosinophilia 'fibroplastic parietal endocarditis with blood eosinophilia'.[13] Nowadays Löffler's endo(myo)carditis is used to describe the involvement of the heart in HES, especially in the thrombotic and fibrotic stage.[14] This end stage is similar to that in other hypereosinophilic diseases affecting the heart (such as tropical endomyocardial fibrosis in tropical parasitic infections), proving the eosinophilia itself rather than the underlying condition is responsible for the damage.[12]

Symptoms and signs

By definition HES affects multiple organ systems. Cardiovascular manifestations are the most prevalent in HES with a prevalence of 50 to 60%.[4,10] As mural fibrosis develops the left ventricular compliance decreases resulting in a restrictive cardiomyopathy. Fibrosis affecting the papillary muscle and chordae tendinae may produce papillary dysfunction and mitral regurgitation.[15] As a consequence, in such patients symptoms and signs of heart failure can be present. The structural changes of the myocardium can provoke arrhythmias. Embolic events originating from the intracardiac thrombus are seen in up to 25%.[2,9,15]

Diagnostic modalities

Electrocardiographic alterations are common in HES. T-wave inversions are most frequently observed followed by premature ventricular beats and positive criteria for left ventricular hypertrophy. The T-wave inversion is thought to represent subendocardial injury due to endocardial fibrosis and inflammation.[15] Sporadically cardiac abnormalities in HES mimic acute myocardial infarction on the ECG.[14]

Endomyocardial thickening is seen in 68% of patients on echocardiography and is progressive. Apical obliteration due to thrombus formation and posterior mitral leaflet involvement are classical findings as well.[15] Evaluation by Doppler echocardiography can show a restrictive left ventricular filling pattern.[9] Pericardial effusion can be present.[2,15]

Coronary angiogram has no role in the diagnosis and shows no specific signs, but is occasionally used to exclude coronary artery disease.[14] Rarely, coronary artery spasms have been described.[16]

CMR is a useful technique with myocardial disease. Hyperintense myocardial area on T2-weighted images is suggestive of increased free-water content due to myocardial oedema and/or necrosis.[17] In HES this is particularly seen in ventricular apices. With the advent of the contrast-enhanced inversion-recovery MRI with late imaging superior contrast can be achieved between normal and abnormal myocardium.[18] Hyperenhancement of the non-ischaemic type in delayed enhancement cardiovascular magnetic assessment is both characteristic of fibrosis and an inflammatory exudate, and cannot be distinguished from each other without follow-up imaging. CMR has a high

sensitivity and specificity for detecting (apical) thrombi.[9] Overlying thrombus is identifiable as a low signal mass on the delayed enhancement images, which does not deform on tagged images. A characteristic three-layered image can be seen: a hypointense inner rim of thrombus adjacent to an hyperenhancement of the endocardium compared with the rest of the myocardium. Cardiac function is another important pillar of the assessment of myocardial disease. Regional areas of hypokinesia or akinesia and findings of restrictive cardiomyopathy (diastolic dysfunction with atrial enlargement and valvular regurgitation) can be visualised. The diagnostic yield of endomyocardial biopsy, the golden standard for establishing cardiac involvement, can be increased using CMR-guided biopsy.[17] Moreover, the high resolution of CMR makes tissue characterisation possible and the increasing experience makes CMR promising for diagnosis and follow-up.[19] Our patient had an increased subendocardial T2 signal in the left ventricular apex. Delayed enhancement following gadolinium also showed diffuse subendocardial enhancement. During follow-up apical T2 signals disappeared and delayed enhancement images were irreversible and subsequently proved to be fibrosis. If the imaging had been performed earlier, the abnormalities would probably have been more extensive and would have represented a combination of fibrosis and an inflammatory exudate.

Little is known about the use of troponin in HES. It seems to be more sensitive than CK-MB for inflammation in HES.[20] This is in line with a previous study concerning the sensitivity of CK-MB and troponin I in humans with myocarditis.[21] In three patients with biopsy-proven eosinophilic endomyocardial infiltration and normal echocardiography troponin T was initially elevated. It normalised after treatment with steroids, suggesting troponin T can be a sensitive marker for early cardiac damage and can gauge treatment.[20] In another study troponin T predicted acute myocardial decompensation before or soon after starting imatinib.[22] Prompt initiation of corticosteroids in these circumstances resulted in a rapid amelioration. It is advised to start adjunctive corticosteroids in patients with evidence of eosinophilic myocarditis who will start with imatinib.[22,23]
The initial rise in troponin T in our case was a marker of the necrotic stage of HES. It is likely the high dose of prednisone reduced the inflammation resulting in normalisation of the troponin T, even before the first CMR was performed.

Treatment

Corticosteroids have always been the cornerstone of the treatment of the different types of HES. A dramatic change has occurred since the discovery of the fusion protein with tyrosine kinase activity encoded by the FIP1L1-PDGRFA-fusion gene.[6] This fusion protein is very sensitive for the tyrosine kinase inhibitor imatinib. As demonstrated by our case some patients without the FIP1L1-PDGRFA genotype seem to benefit from imatinib, however usually with a slower response, indicating that an as yet unidentified mechanism of receptor tyrosine kinase is responsible for HES in these cases.[3,24] Other treatment options are hydroxyurea and interferon-α. The interleukin-5 antagonist mepolizumab has shown to be corticosteroid-sparing for patients negative for FIP1L1–PDGFRA, however its Marketing Authorisation Application in the European Union for the treatment of HES was withdrawn in 2009.[25] Novel therapies including alemtuzumab, a human monoclonal antibody directed against CD52 on eosinophils, have been reviewed recently.[26] The role of allogeneic stem cell transplantation is not well established, although some patients successfully underwent this treatment.[23] Response to treatment is normally fast. However, in cardiac disease the damage can only be reverted in stages with active inflammation and without anatomic alterations due to fibrosis.[23] Furthermore, treatment should be directed to heart failure and the presence of intracardial thrombus.
Absolute eosinophil count does not correlate in a consistent fashion with eosinophil-mediated tissue damage.[23] Unfortunately no validated markers of disease progression are available and therapy is monitored on the basis of a combination of clinical manifestations and absolute eosinophil count. Concerning cardiac disease endomyocardial biopsy is the gold standard, however sequential CMR may obviate the need for cardiac biopsy. In addition, troponin T seems promising in guiding treatment during the acute phase. However, more studies are needed to evaluate the diagnostic value of troponin T and more knowledge about troponin T in later stages of cardiac involvement is necessary.

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