An unusual case of idiopathic hypereosinophilic syndrome presenting with myopericarditis and a polypoid cardiac mass

Miyoperikardit ve polipoid kardiyak kitle ile ortaya çıkan nadir bir idiyopatik hipereozinofilik sendromlu olgu

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Summary– Idiopathic hypereosinophilic syndrome (IHES) is a rare systemic disorder with blood eosinophilia and multiple system involvement. Commonly, there is endocardial fibrosis with overlying mural thrombus, and mitral and tricuspid valves can be involved concomitantly. Outflow tracts near the aortic and pulmonary valves are generally protected. We herein describe an atypical case of IHES with a mass on the left ventricular outflow tract (LVOT), which showed regression under steroid therapy. There are two features that make our case worthy of reporting: First, the mitral and tricuspid valves are expected to be involved in IHES, and outflow tracts near the aortic and pulmonary valves are generally protected. Second, within one month of steroid therapy, the vegetation had reduced dramatically in size and signs of myocarditis and pericarditis had also disappeared.

Özet– İdiyopatik hipereozinofilik sendrom (İHES), çoklu sistem tutulumu ve eozinofili ile seyreden nadir sistemik bir hastalıktır. Genellikle altta yatan mural trombüs ile birlikte endokartta fibröz mevcut olup mitral ve triküspit kapaklar eş zamanlı olarak etkilenebilir. Aort ve pulmoner kapak çıkış yolları genellikle korunmuştur. Biz burada steroit tedavisi ile regresyon gösteren sol ventrikül çıkış yolunda (LVOT) bir kitle ile birlikte seyreden, atipik bir idiyopatik hipereozinofilik sendromlu olguyu sunduk. Bu olgunun sunulmasını değerli kılan iki özellik vardır: Birincisi, İHES'de mitral ve triküspit kapak tutulumu beklenir ve aort ve pulmoner kapak çıkış yollarında etkilenme son derece nadirdir. İkincisi, bir aylık steroit tedavisi ile vejetasyon dramatik olarak küçülmüş olup miyokardit ve perikardit bulguları da kaybolmuştur.

Idiopathic hypereosinophilic syndrome (IHES) is a rare systemic disorder with blood eosinophilia and multiple system involvement. Commonly, there is endocardial fibrosis with overlying mural thrombus, and mitral and tricuspid valves can be involved concomitantly. Outflow tracts near the aortic and pulmonary valves are generally protected. We herein describe an atypical case of IHES with a mass on the left ventricular outflow tract (LVOT), which showed regression under steroid therapy.

Abbreviations:

CK	*Creatine kinase*
CT	*Computerized tomography*
Hb	*Hemoglobin*
Hct	*Hematocrit*
IHES	*Idiopathic hypereosinophilic syndrome*
LVOT	*Left ventricular outflow tract*
TTE	*Transthoracic echocardiography*
WBC	*White blood cell*

CASE REPORT

A 20-year-old male with symptoms of fever, nausea, vomiting, loss of appetite, and pleuritic chest pain admitted to our hospital. He had experienced these complaints for nearly one month. He gave no previous medical history. On the physical examination, he had pericardial friction rub and rapid heart sounds. His body temperature was 38.4°C. The pulmonary examination was normal. On electrocardiography, the rhythm was sinusal with 1.5 mm ST segment elevation in leads V2 and V3 and T negativity in leads V4-V6. Chest X-ray showed moderate

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cardiomegaly. Blood biochemistry was normal. On hemogram, the white blood cell (WBC) count was 11700/mm^3 (63.4% neutrophils, 11.4% lymphocytes and 21% eosinophils), hemoglobin (Hb) 13.7 g/dl, hematocrit (Hct) 40.3%, and platelet count 275000/mm^3. The number of eosinophils was 2500/mm^3. Erythrocyte sedimentation rate was 30 mm/h, and C-reactive protein was elevated at 13.3 mg/dl (N: 0-1 mg/dl). When the Waters' view X-ray revealed maxillary sinusitis, he was started on 400 mg daily moxifloxacin therapy. On the day of admission, the patient was referred to our laboratory for emergency transthoracic echocardiography (TTE) with a pre-diagnosis of myopericarditis.

On TTE, the left ventricular size was normal with generalized hypokinesis (especially in the inferoposterior walls). The myocardium seemed slightly thick and echogenic, suggesting infiltration. The ejection fraction was approximately 42%. The aortic valve was mildly thick and bicuspid with mild aortic regurgitation. There was moderate pericardial effusion surrounding the heart. The echocardiogram suggested myopericarditis, and the patient was started on nonsteroidal antiinflammatory drug therapy. Initial and repetitive creatine kinase (CK), creatine kinase-MB fraction (CK-MB) and troponin I levels were all normal. When the patient's young age with respect to coronary artery disease was considered together with the lack of other diagnostic parameters like elevation in cardiac enzymes, coronary angiography was not performed as the first step. Three sets of blood cultures and blood samples were taken for viral serology, antinuclear antibodies (ANA), anti-double-stranded (ds) DNA, anti-histone antibodies, and rheumatoid factor. In order to establish the etiology of hypereosinophilia, stool analysis for parasites, FIP1L1-PDGFRA and BCR/ABL reverse transcription-polymerase chain reaction (RT-PCR) were evaluated. The patient had no allergic disease. On the third day of hospitalization, the patient suddenly developed left hemiparesis. The cranial computerized tomography (CT) immediately after the event was normal.

A repeat TTE was performed in order to investigate the cardiac source of embolism. TTE revealed an ejection fraction of 37% and a 1.9 cm x 1.9 cm polypoid mobile mass attached to the posterior wall of the LVOT (Figure 1).

The mass had no attachment with the bicuspid aortic valve. Although an atypical location, we first considered the mass to be an infective vegetation, and gentamicin 180 mg daily in three divided doses and daptomycin 6 mg/kg were started. IHES was not considered at first because of the localization of the mass and existence of bicuspid aortic valve, and in order to not cause a delay in the treatment, we promptly started antibiotherapy upon recommendations of the Infectious Diseases Department in consideration of the poor clinical status of the patient. A cranial CT in the active phase of the stroke was normal. Paranasal CT revealed inflammatory soft tissue and polypoid masses in the sinuses. On the day of stroke, Hb was 12.9 g/dl, Hct 37.4%, WBC 11100/mm^3 (33% eosinophils, 48.1% neutrophils, 15.7% lymphocytes), and platelets 319000/mm^3. In addition, tests for hypercoagulability were performed: protein C was 54.7% (N: 7-140%), protein S 45.3% (N: 58-127%), antithrombin-III 72.5% (N: 75-125%), activated protein C resistance 0.58 (0.69-1.56), and homocysteine 20.4 Mmol/L (N: 5-12), and he was heterozygous for factor V Leiden mutation. No MTHFR A1298C mutation or prothrombin gene mutation was detected.

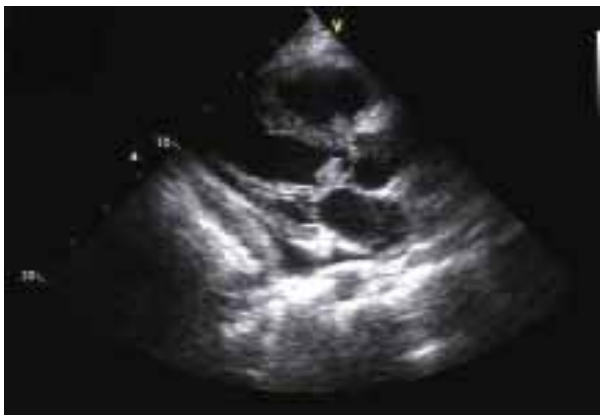

Figure 1. Polypoid mobile mass attached to the left ventricular outflow tract.

A cranial diffusion magnetic resonance imaging (MRI) revealed multiple ischemic areas. Our neurology department started acetylsalicylic acid 100 mg and clopidogrel 75 mg daily. On the 7th day of antibiotics, the patient was unresponsive, and piperacillin and tazobactam were added to gentamicin and daptomycin. Blood cultures were also repeated. After a week of triple antibiotherapy, his body temperature ranged from 37.5-38.4°C and all blood cultures were nega-

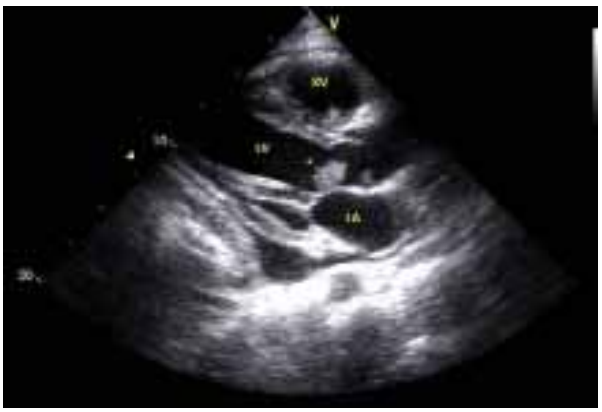

Figure 2. Regression of the aortic mass to 1.0x0.7 cm.

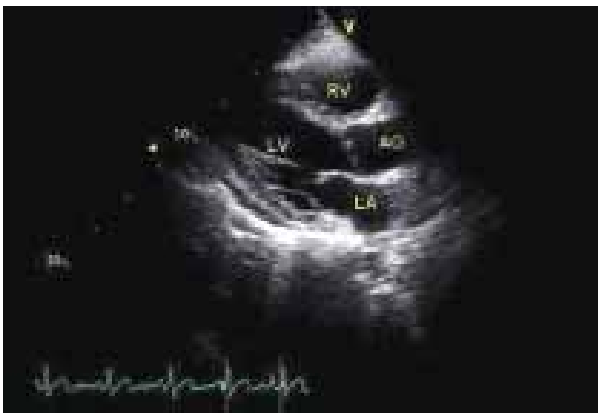

Figure 3. Disappearance of the mass and pericardial effusion.

tive. Therefore, an eosinophilic vegetation was considered, and 64 mg total (1 mg/kg) steroid was started. Under steroid therapy, the eosinophil count dropped dramatically. On the 3rd day, the fever resolved, and on the 4th day, hemogram was as follows: Hb 10.8 g/dl, Hct 32.8%, WBC 10400/mm^3 (neutrophils 77.2%, lymphocytes 13.5% and eosinophils 1.8%), and platelets 351000/mm^3. Eosinophil count was 200/mm^3. Gentamicin and daptomycin were stopped on the 21st day, and piperacillin and tazobactam on the 23rd day of antibiotherapy. On the follow-up TTE after seven days of steroid therapy, pericardial effusion had disappeared and the follow-up TTE after 14 days showed regression of the aortic mass to 1.0x0.7 cm (Figure 2).

The patient was negative for FIP1L1-PDGFRA and BCR/ABL PCR. No parasites were found in the stool examination. He was discharged after one month of steroid therapy with 16 mg oral methylprednisolone. The patient was advised to taper the dose every week and was scheduled for follow-up examinations. The mass and pericardial effusion completely disappeared and left ventricular systolic functions had improved at two months after discharge (Figure 3). The subsequent course of the patient could not be followed because there were no follow-up visits after two months.

DISCUSSION

Idiopathic HES is a rare systemic disorder with blood eosinophilia and multiple systemic involvement. It is characterized by a marked, sustained and unexplained hypereosinophilia (>1500/μL) accompanied by organ involvement. Cardiac involvement occurs in more than 60% of patients. Endomyocardial biopsy findings have shown that endothelial cells in the endocardium and microvasculature are the primary targets of the tissue damage. Generally, the involvement is endocardial fibrosis with overlying mural thrombus. Mitral and tricuspid valves can also be involved.[1]

Hypereosinophilia has three stages as: 1) Acute necrotic stage (~5.5 weeks), 2) Thrombotic stage (10 months), and 3) Fibrotic stage (~24.5 months-requires 2 years of hypereosinophilia).

Intracardiac vegetation-like masses are unexpected findings in IHES. Our patient had bicuspid aortic valve, which at first suggested an infectious vegetation. However, he was unresponsive to antibiotics, and blood cultures were all negative. In the differential diagnosis for hypereosinophilia, parasitic infections and allergic and myeloproliferative diseases had to be considered. Stool analysis for parasites was negative, the patient had no current or recent allergic disease, and he was negative for BCR/ABL RT–PCR, which presents a mutation for chronic myeloproliferative disorders. Although FIP1L1-PDGFLA mutation, which is positive in about 40-60% of IHES patients, was also negative, his clinical status and laboratory findings made IHES the most likely diagnosis. Therefore, we thought that the mass could be a vegetation with eosinophils. In a previous case report, Gudmundsson et al.[2] reported a fibrotic aortic valve with a vegetation. The pathologic specimen showed eosinophils.

In another report, a patient with an eosinophilic mitral valve vegetation was described, in which complete resolution was achieved after two months with 40 mg oral prednisolone and warfarin 5 mg.[3] Hen-

dren et al.[4] also described aortic and mitral valvular involvement in IHES. Dauphin et al.[5] described a small papilloma-type tumor in the aortic valve, which regressed with steroids.

Our patient also had eosinophilic myocarditis with moderate pericardial effusion. However, there was no echocardiographic evidence of associated endomyocardial fibrosis with typical apical obliteration. When the staging of the disease as mentioned above is considered, absence of the fibrotic stage can be attributed to steroid therapy in the second stage, which prevented progression to the third, fibrotic stage. Moreover, further evaluation of endomyocardial fibrosis via more sophisticated imaging and diagnostic modalities like cardiac MR and endomyocardial biopsy were not performed because the patient was considered to be in the second stage. The fibrotic stage would have been the next process if the patient had not been treated appropriately. After administration of steroids, all findings of myocarditis, pericardial effusion and LVOT vegetation regressed dramatically.

Symptomatic patients with IHES should first be treated medically, because the lesions can regress on a medical regimen and the postoperative course can be complicated. Patients with IHES should be treated with steroid therapy (prednisolone at a dose of 1 mg/kg/day) until clinical improvement occurs, after which the dose should be tapered gradually.[6] Symptomatic patients non-responsive to steroids should be given chemotherapeutic agents, which include hydroxyurea, vincristine, 6-mercaptopurine, busulphan, and chlorambucil. Interferon-alpha and cyclosporine have also been found to be useful in HES. Endocardial resection in endocardial fibrosis and valve replacement in severe atrioventricular valve regurgitation can be lifesaving.

There are two features that make our case worthy of reporting: First, mitral and tricuspid valves are expected to be involved in IHES, and outflow tracts near the aortic and pulmonary valves are generally protected. Second, within one month of steroid therapy, the vegetation had reduced dramatically in size, and signs of myocarditis and pericarditis had also disappeared.

In conclusion, this case report is a good illustration of many features of IHES. It shows that the toxicity of the eosinophils can involve any cardiac segment. It also shows that antiplatelet agents and normalization of the eosinophil count can result in regression of the lesions caused by toxicity if the disease is diagnosed early. These findings argue in favor of early, regular, systematic screening for cardiac involvement once HES has been diagnosed, because cardiac involvement can be rapid and dangerous, resulting in systemic embolism or heart failure. All attempts should be made to bring the hypereosinophilia under control.

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Key words: Aortic valve/ultrasonography; cardiomyopathies; heart neoplasms; hypereosinophilic syndrome; rare diseases.

Anahtar sözcükler: Aort kapağı/ultrasonografi; kardiyomiyopatiler; kalp neoplazisi; hipereozinofilik sendrom; nadir hastalık.