

Loeffler's Endocarditis- A cause of endomyocardial fibrosis in a patient of juvenile idiopathic arthritis: A Case Report

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Abstract

Endomyocardial fibrosis secondary to hyper-eosinophilic syndrome also known as Loeffler's Endocarditis is a rare cause of restrictive cardiomyopathy. If left untreated, it carries a very high morbidity and mortality rate. The case of a 20 years old girl, a known case of polyarticular juvenile idiopathic arthritis since the age of 13 years was reported at Federal Government Polyclinic Hospital, Islamabad on 14th May 2022. She presented with an acute history of shortness of breath and cough for two weeks. Her initial echocardiogram showed suspicion of Loeffler's Endocarditis, which is attributed to be an adverse effect of etanercept- a tumour necrosis factor (TNF) inhibitor, which she had been prescribed for her arthritis. The patient is currently being managed with high doses of steroids, therapeutic anticoagulation with rivaroxaban, carvedilol for tachycardia and mycophenolate mofetil as an immunosuppressant.

Keywords: Endomyocardial fibrosis, Juvenile Idiopathic Arthritis (JIA), TNF alpha inhibitors, Hyper-eosinophilic syndrome (HES).

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Introduction

Loeffler's Endocarditis is a rare syndrome of eosinophilia associated with endomyocardial fibrosis leading to restrictive cardiomyopathy which causes impaired ventricular filling and diastolic dysfunction. The first case was documented by Loeffler in 1936, when he described eosinophilic infiltration of the endomyocardium causing tissue damage and fibrosis in a patient of Hyper-eosinophilic syndrome (HES). The common age group affected is between 20 to 50 years with an annual incidence of 0.036 per 100,000 patients particularly in the tropical rainforest regions.¹ Hyper-eosinophilic syndrome can be primary (chronic eosinophilic leukaemias and lymphomas) or secondary to the risk causing drugs,

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parasitic infections, other solid tumours and connective tissue disorders like Eosinophilic Granulomatosis with polyangiitis.² Loeffler's Endocarditis has three stages; an acute necrotic stage, thrombotic stage and the fibrotic stage. It has a poor prognosis unless picked up early with prompt initiation of treatment.³ A case of endomyocardial fibrosis in a patient of polyarticular Juvenile Idiopathic Arthritis (JIA) is reported with an underlying hyper-eosinophilic state likely to be precipitated by Etanercept.

Case Report

A 20 years old female patient, a known case of polyarticular JIA since September 2015 was being treated at Federal Government Polyclinic Hospital, Islamabad. She was prescribed Leflunomide and Methotrexate along with low dose steroids. Due to inadequate relief, Etanercept (a TNF alpha inhibitor) was started in October 2021. Her arthritis responded adequately to etanercept but five months later she presented on 14th May, 2022 with the history of acute shortness of breath associated with orthopnoea and paroxysmal nocturnal dyspnoea, palpitations and predominantly dry cough. There was no complaint of chest pain, fever, haemoptysis or pedal oedema. Her last dose of etanercept was one week prior to the onset of symptoms. On examination, she had a heart rate of 130 beats per minute, blood pressure of 110/70mmHg and oxygen saturations of 96% at room air. Cardiovascular examination revealed normal first and second heart sounds with no added sounds. The respiratory system examination showed occasional fine crepitations bilaterally on auscultation. Her electrocardiogram (ECG) displayed sinus tachycardia and chest x-ray revealed enlarged cardiac shadow with bilateral infiltrates. An echocardiogram was requested immediately which displayed small sized left ventricle (LV) with sparkling appearance of the LV myocardium and a large laminar echogenic mass attached to the LV. Right ventricular (RV) wall also had a thickened sparkling appearance and there was moderate mitral and tricuspid regurgitation with mild regurgitation across the aortic valve as shown in the Fig 1A and B. The pulmonary artery pressure was raised at 45mm of Hg. A strong suspicion of endomyocardial fibrosis secondary to Loeffler's syndrome was made and patient was admitted in the CCU. Her blood picture showed a haemoglobin of 10.7g/dl (normal

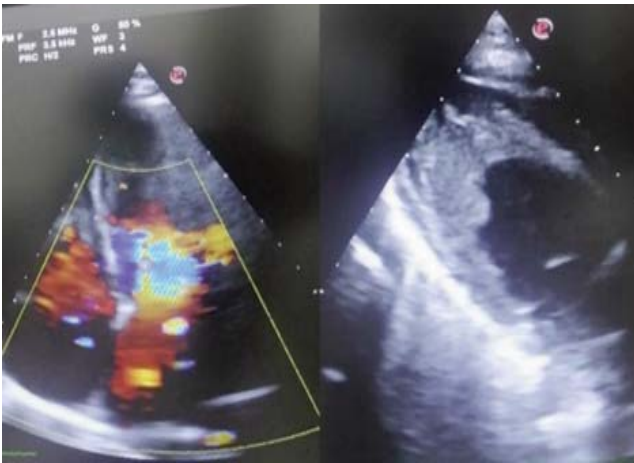


Figure-1: A. showing Mitral regurgitation on colour doppler. B Transthoracic echocardiographic findings of endomyocardial fibrosis. (arrow showing thickening and sparkling appearance.)



Figure-2: Classical Double V sign of endomyocardial fibrosis. Arrows depicting the characteristic layers as described in the MR report in text.

12-15g/dl), WBC 8900/mm³ (normal 4000-10000/mm³) out of which mixed cells were found to be 17.24% which were predominantly eosinophils with an absolute count of 1534/mm³. C-reactive protein was 54.1mg/L (normal 0-5mg/L) and rest of biochemical profile including liver and kidney function tests and cardiac enzymes were normal. The first and foremost step was to withdraw the offending agent which in this case was thought to be etanercept. She was empirically started on treatment for the acute phase of the Loeffler syndrome with steroids at 1 mg/kg, Anticoagulation was initiated with Heparin 5000 IU subcutaneously twice a day along with beta blocker carvedilol 3.125mg twice a day for the heart rate control. A cardiac MRI was done the next day which also demonstrated similar findings such as, fair biventricular function with ejection fraction of 52%. Apical and distal LV and RV obliteration and biatrial enlargement. Evidence of an active myocardial inflammation was noted. A typical double V sign on late gadolinium enhancement with

three layers of normal myocardium followed by sub-endocardial fibrosis layer and thrombus lining the fibrotic area was seen. Biventricular clots were noted along with the moderate to severe mitral and tricuspid regurgitation as shown in Fig 2.

After confirmation of diagnosis by cardiac MRI and considering the expected high morbidity and mortality risk, she was switched to pulse steroids with methylprednisolone 500mg once a day for 3 days and anticoagulation was changed to therapeutic dose of rivaroxaban. She was also started on mycophenolate mofetil as an immunosuppressive agent with a view to further halt the process of fibrosis. She is currently under close follow up of both rheumatology and cardiology departments. Her repeat echocardiography has shown slight regression of the clot size and improvement in her cardiac ejection fraction to 60%. Repeat cardiac MRI is planned.

Discussion

Loeffler's Endocarditis is a hyper-eosinophilia mediated damage to the endomyocardial tissue because of the immune dysregulation, leading to the production of certain proteins like major basic protein and eosinophilic cationic protein which are the main culprits for endothelial damage, thromboembolic state and the cytotoxic damage.⁴ The patient can initially present as an acute necrotic stage with the symptoms of fever, sweating, palpitations and chest pain which are the features of acute myocarditis but they can remain unnoticed. The second stage is the thrombotic stage which is precipitated by the damaged endocardium providing a surface for thrombus formation and can be very dangerous due to the chances of dislodging of the thrombus leading to thromboembolic phenomenon elsewhere in the body. It is the third stage when the fibrosis sets in and the patient can present with dyspnoea and signs and symptoms of heart failure.⁵ The gold standard for diagnosis is endomyocardial biopsy but other investigations like transthoracic echocardiography and the cardiac magnetic resonance imaging can also diagnose the condition with good accuracy. The findings on echocardiography are the sparkling appearance of the biventricular myocardium along with thrombus formation, however, the cardiac MRI is a more useful tool because it can help both in diagnosis and monitoring of the disease at each stage and can be a useful guide for the treatment. In the initial phase of the disease there is evidence of active inflammation on the T2 weighted images. In the second phase it can show the endocardial thrombus formation and later on typical endomyocardial fibrosis. The "double V sign" on late gadolinium

enhancement is a pathognomonic finding with three layers representing normal myocardium followed by sub-endocardial fibrosis layering and thrombus lining the fibrotic area.⁶ This 20 years old patient had all three of these classic findings.

The treatment options are treating the cause of hyper-eosinophilia, giving steroids at a dose of 0.5 to 1mg/kg body weight, anticoagulation and heart rate control to prevent thromboembolic phenomenon. Immunomodulatory agents like hydroxyurea, methotrexate, azathioprine, interferons, cyclophosphamide, mycophenolate mofetil and imatinib have been used⁷, however, there is no clear consensus on the drug of choice.

Surgical treatment options include endomyocardial resection and repair of the mitral and tricuspid valves. Although, surgery does improve the overall survival and functional capacity of the patient but an early postoperative mortality is quite high.⁸

There are very few case reports of Loeffler's syndrome leading to endomyocardial fibrosis in patients with rheumatological disorders. Two such cases have been reported with adalimumab and infliximab; both of which are anti-TNF inhibitors but none has been reported with the use of etanercept so far.^{9,10}

The presented case is very important in this regard as, this is the first case reported on etanercept being the underlying cause of Loeffler's Endocarditis in a patient of JIA. She had the classical findings of Loeffler's Endocarditis on echocardiogram and cardiac MRI. Treatment was initiated immediately on the lines and offending drug was stopped. It is a potentially fatal disease which requires prompt diagnosis and an early initiation of treatment under a multidisciplinary team. It also emphasizes on the fact that the presence of hyper-eosinophilia on blood complete picture should prompt clinicians to think about the possibility of hyper-eosinophilic syndrome.

Conclusion

In conclusion, this was a case of Hyper-eosinophilic syndrome leading to Loeffler's endocarditis in a patient with JIA. This is a rare complication of anti-TNF alpha blocker drugs and hence, every patient receiving this class

of drugs be closely monitored for the development of eosinophilia on complete blood picture.

Consent: Written consent from the patient was taken for the publication of this case report.

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Conflict of Interest: None.

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References

1. Dregoes MI, Iancu AC, Lazar AA, Balanescu S. Hypereosinophilic syndrome with cardiac involvement in a patient with multiple malignancies. *Med Ultrason* 2018;20:399-400. Doi: 10.11152/med-1574.
2. Walker S, Wang C, Walradt T, Hong BS, Tanner JR, Levinsohn JL, et al. Identification of a gain-of-function STAT3 mutation (p.Y640F) in lymphocytic variant hypereosinophilic syndrome. *Blood* 2016;127:948-51. Doi: 10.1182/blood-2015-06-654277.
3. Koyama T, Yamamoto H, Matsumoto M, Isogai J, Isomura T, Tanaka S, et al. Late-Stage Loeffler's Endocarditis Mimicking Cardiac Tumor: A Case Report. *Front Cardiovasc Med* 2020;7:589212. Doi: 10.3389/fcvm.2020.589212.
4. Madhwal S, Goldberg J, Barcena J, Guha A, Gogate P, Cmolik B, et al. Unusual cause of acute mitral regurgitation: idiopathic hypereosinophilic syndrome. *Ann Thorac Surg* 2012;93:974-7. Doi: 10.1016/j.athoracsur.2011.08.062.
5. Çetin S, Heper G, Gökhan Vural M, Hazirolan T. Loeffler endocarditis: silent right ventricular myocardium. *Wien Klin Wochenschr* 2016;128:e513-5. Doi: 10.1007/s00508-016-0981-1.
6. Kleinfeldt T, Ince H, Nienaber CA. Hypereosinophilic Syndrome: a rare case of Loeffler's endocarditis documented in cardiac MRI. *Int J Cardiol* 2011;149:e30-2. Doi: 10.1016/j.ijcard.2009.03.059.
7. Gao M, Zhang W, Zhao W, Qin L, Pei F, Zheng Y, et al. Loeffler endocarditis as a rare cause of heart failure with preserved ejection fraction: A case report and review of literature. *Medicine (Baltimore)* 2018;97:e0079. Doi: 10.1097/MD.00000000000010079.
8. Grimaldi A, Mocumbi AO, Freers J, Lachaud M, Mirabel M, Ferreira B, et al. Tropical Endomyocardial Fibrosis: Natural History, Challenges, and Perspectives. *Circulation* 2016;133:2503-15. Doi: 10.1161/CIRCULATIONAHA.115.021178.
9. Hussain N, Patel P, Yin J, Davis R, Ikladios O. A case of Loeffler's endocarditis after initiation of adalimumab. *J Community Hosp Intern Med Perspect* 2019;9:29-32. Doi: 10.1080/20009666.2018.1562852.
10. Alam A, Thampi S, Saba SG, Jermyn R. Loeffler Endocarditis: A Unique Presentation of Right-Sided Heart Failure Due to Eosinophil-Induced Endomyocardial Fibrosis. *Clin Med Insights Case Rep* 2017;10:1179547617723643. Doi: 10.1177/1179547617723643.

Authors' Contributions

TK: Involved in treatment, Literature search, proof reading.

SAS: Involved in treatment, Write up of case report.

SS: Involved in treatment, Referencing, write up.

SHQ: Involved in treatment, Proof reading.

HI: Involved in treatment, helped in making the diagnosis.

FK: Involved in treatment, diagnostic aid, Proof reading.