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Hypereosinophilia and Löffler's Endocarditis: A Systematic Review

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Abstract Löffler endocarditis is an uncommon, but known complication of hypereosinophilic syndrome (HES). It is a relatively rare entity, and remains poorly understood. To this point in time, the compendium of knowledge about this disease consists of various case reports, prospective studies and review articles. We aim to present a scoping study about this disease. Our goals are to identify the characteristic features found in case reports to identify characteristic features found in patients with Löffler endocarditis as a result of hypereosinophilic syndrome. An analysis of the 26 case reports showed a mean age of 41.6 years with a standard deviation of 17.1 years. Dyspnea was the most common presenting complaint (64%) followed by fatigue (23%), cough (19%), fever (19%), orthopnea/paroxysmal nocturnal dyspnea (19%), stroke related symptoms (15%), chest pain (15%) and lower extremity edema (15%). The most common cardiac structure affected was the mitral valve (65%), followed by the tricuspid valve (42%), left ventricle (23%), with 35% of cases having involvement of two valves. The most common therapeutic modality was immunosuppression (85%), followed by anticoagulation (73%) and mitral valve replacement (23%). Death was reported in 19% of the cases. Löffler's endocarditis continues to be associated with high morbidity and mortality. Further research must aim to develop guidelines for management of this uncommon manifestation of hypereosinophilic syndrome.

Keywords: *hypereosinophilia, hypereosinophilic endocarditis, heart valves involvement, tissue diagnosis of hypereosinophilic endocarditis, associated comorbitities, prognosis*

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1. Introduction

Hypereosinophilic syndrome is a group of rare disorders which are characterized by the presence of increased amounts of serum and tissue eosinophils. It was defined in 1975 by Chusid et al. [1] with the following criteria: (1) Sustained serum eosinophilia (>1.5 $^{9}/_{L}$ X10 for >6 months (2) No identifiable cause, including blood and parasitic disorders (3) signs and symptoms of organ involvement. Hypereosinophilic syndromes are varied in their clinical presentation and severity and are associated with the level of organ involvement. [2] Löffler endocarditis was first described in 1936, as an acute form of fibrinous restrictive pericarditis. [3] Histologically, it is described as the migration of eosinophils into the myocardium with, tissue damage and fibrosis resulting from eosinophil degranulation. [4] Löffler endocarditis is a rare manifestation of hypereosinophilic syndrome. Clinical signs and symptoms include fever, weight loss, rash, symptoms of heart failure and arrhythmias. [5,6]

2. Methods

On April 1st 2019, a literature search of Pubmed, Google Scholar, CINAHL, Cochrane CENTRAL and Web of Science databases was conducted using the search phrases "Löffler's endocarditis" and "hypereosinophilic syndrome" to identify cases of Löffler endocarditis related to hypereosinophilic syndrome. A total of 26 cases were

identified (Table 1). References in the aforementioned cases were reviewed to identify additional cases. Demographic date, vitals, complete blood counts (CBC), echocardiograms, computed tomography imaging, magnetic resonance imaging and management protocols were reviewed.

3. Results

A total of 26 cases (Table 1, Table 2) of Löffler endocarditis associated with hypereosinophilic syndrome were found. The mean age at presentation was 41.6 years with a standard deviation of 17.1 years. The median age was 41.5 years. 58% of the cases were found in females and 42% were found in males. Dyspnea was the most common presenting complaint (64%) followed by fatigue (23%), cough (19%), fever (19%), orthopnea/paroxysmal nocturnal dyspnea (19%), stroke related symptoms (15%), chest pain (15%), lower extremity edema (15%), palpitations (8%), left femoral artery occlusion (4%), weight loss (4%), abdominal distention (4%) and dizziness (4%). The cases had no prevalent cardiovascular risk factors. The prevalence of heart failure was 31%. Other prevalent conditions were asthma (19%), eosinophilic pneumonia (4%), systemic lupus erythematosus (4%), eosinophilic myocarditis (4%) and ulcerative colitis (4%). In the 26 cases, the most common cardiac structure affected was the mitral valve (65%), followed by the tricuspid valve (42%), left ventricle (23%), right ventricle (8%), right atrium (4%) and interventricular septum (4%). 35% had involvement of two valves (Table 3). White blood cell count was reported in 16 cases, the median WBC count was 17,550 ± 14,667. Eosinophil count was reported in 21 cases, the median eosinophil count was 6120 ± 8424. Eosinophil percentage was reported in 13 cases, the eosinophil percentage was 46% ± 25%. In terms of management, the most common therapeutic modality was immunosuppression (85%), followed by anticoagulation (73%), mitral valve replacement (23%), inotropic support (8%), tricuspid valve replacement (8%), mitral and tricuspid valve annuloplasty (4%) and right ventricle endocardial stripping (4%) (Table 4). Death was reported in 5 cases (19%).

Table 1. Patient demographics

Total cases	26
Age	Mean 41.6 years Median 41.5 years Standard deviation 17.1 years
Sex	Males 11 (42%) Female 15 (58%)
Prevalence of heart failure	8 (31%)
Prevalence of cardiovascular risk factors	DM 0% HTN 0% HLD 0% CAD 0%
Prevalence of other related conditions	Asthma 5 (19%) Eosinophilic pneumonia 1 (4%) SLE 1 (4%) Eosinophilic myocarditis 1 (4%) Ulcerative colitis 1 (4%)
Presenting complaint	Dyspnea 16 (64%) Fatigue 6 (23%) Cough 5 (19%) fever 5 (19%) Orthopnea/Paroxysmal nocturnal dyspnea 5 (19%) Stroke related symptoms 4 (15%) Chest pain 4 (15%) Lower limb edema 4 (15%) Palpitations 2 (8%) Left femoral artery occlusion 1 (4%) weight loss 1 (4%) Abdominal distension 1 (4%) Dizziness 1 (4%)
Affected structure	Mitral valve 17 (65%) Tricuspid valve 11 (42%) 2 valve involvement 9 (35%) Left ventricle 6 (23%) Right ventricle 2 (8%) Right atrium 1 (4%) Interventricular septum 1 (4%)
Investigations	Median WBC (reported in 16 cases): 17,550 ± 14,667 Median eosinophil count (seen in 21cases) = 6,120 ± 8,424 Median eosinophil % (seen in 13 cases): 46 ± 25
Management	Immunosuppressive therapy 22 (85%) Anticoagulation 19 (73%) Mitral valve replacement 6 (23%) Inotropic support 2 (8%) Tricuspid valve replacement 2 (8%) MV and TV annuloplasty 1 (4%) RV endocardial stripping 1 (4%)
Death	5 (19%)

Table 2. Cases of Löffler's endocarditis secondary to hypereosinophilic syndrome

Case number	Paper	Structure affected	Valvuloplathy
1	1977, Weyman [7]	MV , TV	MS, TS
2	1991, Boustany [8]	MV	MR
3	2004, Cunningham [9]	MV	MR
4	2007, Chao [10]	MV	MR
5	2008,Sen [11]	TV	TR
6	2008,Yoon [12]	MV	
7	2009, Lin [13]	LV, RV, RA	
8	2010, Hilty [14]	LV	
9	2010, Aydogdu [15]	MV, TV	MR, TR
10	2011, Kleinfelt [16]	MV	MR
11	2013, Aggarwal [17]	LV	
12	2013, Koneru [18]	MV, TV	MR, TR
13	2014, Dongen [19]	LV	
14	2015, Naik [20]	MV	MR
15	2015, Al-Kaisey [21]		MR, TR
16	2016, Baltasares-Lipp [22]		MR, TR
17	2017, Alam [23]		MR, TR
18	2017, Gastl [24]	MV	-
19	2017, Casavecchia [25]	IVS, LV posterior wall	
20	2017, Jin [26]	MV, TV	
21	2017, Breskvar Kac	TV	TR
22	2017, Datta	LV APEX	
23	2017, Massin [27]	MV	MR
24	2018, Gao [28]	MV, TV	MR, TR
25	2018, Kim [29]	LV, RV	
26	2018, Berto [30]	MV	MR

MV: mitral valve TV: tricuspid valve RA: right atrium RV: right ventricle LV: left ventricle IVS: interventricular septum MR: mitral regurgitation TR: tricuspid regurgitation MS: mitral stenosis TS: tricuspid stenosis.

Table 3. Summary of diagnostic imaging

Case number	Structure affected	Valvulopathy	LV thrombus	Transthoracic echo	Computer tomography of chest	Cardiac magnetic resonance imaging	Imaging suggestive of CVA
1	MV, TV	MS, TS	-	-	-	-	
2	MV	MR	-	-	-	-	
3	MV	MR	-	-	-	-	
4	MV	MR	-	Large right ventricular mass confirmed	Heterogenicity of liver, mild ascites, moderate pleural effusion, atelectasis, multiple small pulmonary emboli, large RV mass	extensive endomyocardial fibrosis, with superimposed thrombus formation which nearly obliterated the right ventricular cavity and extended into the right ventricular outflow tract. Extensive TR noted.	
5	TV	TR	-	-	-	-	
6	MV		-	-	Apical obliteration of both RV and LV by non-enhanced homogenous materials and presence of same material in RA.	-	
7	LV, RV, RA		Yes	Thickening of the LV endocardium, reduction of LV cavity, and a ~7.8- cm2 , flat, immobile thrombus extending from the apical to the posterobasal portion	-	high signal intensity on T2 weighted image and low intensity on T1 consistent with a thrombus.	CT: Focal encephalomalacia corresponding to the territory of left middle cerebral artery. Occlusion of the left internal carotid artery (ICA) and consequent hydranencephaly.

Case number	Structure affected	Valvulopathy	LV thrombus	Transthoracic echo	Computer tomography of chest	Cardiac magnetic resonance imaging	Imaging suggestive of CVA
8	LV		Yes	Preserved LV systolic function with right atrial and right ventricular dilation and hypokinesis, a dilated coronary sinus, elevated right ventricular systolic pressure	Trace pleural effusions and predominant lower lobe alveolar infiltrates	-	
9	MV, TV	MR, TR	Yes	LV myocardial thickening and infiltration	Thrombus in the right lower lobe pulmonary artery and a large consolidation area in the lower lobe of the right lung consistent with pulmonary embolism. Right hepatic lobe enlarged with splenic infarcts	-	
10	MV	MR	Yes	-	-	left ventricular intracavitary thrombus extending to the apex	MRI, Multiple fresh embolic microinfarctions in both hemispheres without manifestation of edema or any severe neurological sequelae
11	LV		-	-	-	-	
12	MV, TV	MR, TR	Yes	Apical thrombus	-	endomyocardial fibrosis with left ventricular apical thrombus	MRI: revealed old infarcts.
13	LV		Yes		-	two thrombi situated at the apex and basal laterally	
14	MV	MR	-	Dilation of RA and LA ,thickening of ventricles bilaterally at the apex at 2.1 cm.55% contractility with decreased movement at the apex. Limited atrial annulus movement indicative of restrictive pattern. Moderate to severe MR, moderate TR. Endocardial hypertrophy confirmed	-	ruled out presence of thrombus	
15		MR, TR	-	-	-	-	
16		MR, TR	-	Moderate MR,TR ,reduced LV filling because of endocardium thickening with large homogenous mass at the ventricular apex that occupied 50-65% of the cavity	Bilateral pleural effusion, large left ventricular mass	-	
17		MR, TR	-	Thickened MV leaflets, severe RA enlargement	-	Endocardial late gadolinium enhancement consistent with fibrosis, obliteration of the RV apex, bowing of the interventricular septum toward the left in diastole compatible with increased right-heart filling pressure pressures, severe RA enlargement with thrombus, and MV leaflet obliteration.	

Case number	Structure affected	Valvulopathy	LV thrombus	Transthoracic echo	Computer tomography of chest	Cardiac magnetic resonance imaging	Imaging suggestive of CVA
18	MV	-	-	Slight hypertrophy of the interventricular septum and the left ventricular posterior wall	-	-	
19	IVS, LV posterior wall		Yes	Large areas with different echogenicity in the LV and RV apex, involvement of mitral and tricuspid sub-valvular apparatus and moderate secondary insufficiency, apical hypokinesis, preserved LVSF, impaired diastolic function, RA and LA dilation, and increased RV systolic pressure	Ground glass appearance in the posterior segments of the upper lobes and other small pseudo-nodular areas in the remaining segments, moderate bilateral pleural effusion, and minimal pericardial effusion	mildly reduced volume index, diffuse thickening of the left and right ventricular apex with obliteration, apical hypokinesis with preserved left and right ventricular systolic function. Characteristics. Theuse of different sequences T1-T2 weighted as well as delayed enhanced imaging allows a precise definition of thrombotic endoluminal masses.	
20	MV, TV		-	Preserved LV ejection fraction and bi-atrium enlargements with moderate TR	-	-	
21	TV	TR	Yes	Echo dense structure that obliterated the left ventricular apex was detected, consistent with thrombus	-	-	MRI: Multiple ischemic regions in the brain
22	LV APEX		Yes	-	-	endomyocardial fibrosis with mural thrombus in LV. Sessile lesion (about 1.3 cm x 2.3 cm) projected with irregular margins from the posterior wall of LV and also was extended upto the posterior MV leaflet.LA and LV enlargement	
23	MV	MR	Yes-	moderate MR due to thickening of the posterior MV leaflet and embedding of the valvar apparatus to a thick plaque adhering to the ventricular wall	-	Confirmed early necrotic stage endomyocardial involvement associated with mural thrombi	
24	MV, TV	MR, TR	-	-	-	Intense,linear, Delayed gadolinium enhancement of the endocardium of the lateral LV wall and obliteration of LV apex	
25	LV, RV		Yes	Endocardial thickening and thrombus in both ventricular apices	-	-	MRI: Acute infarction in the left posterior middle cerebral artery territory
26	MV	MR	-	Severe MR	-	-	

MV: mitral valve TV: tricuspid valve RA: right atrium RV: right ventricle LV: left ventricle IVS: interventricular septum
MR: mitral regurgitation TR: tricuspid regurgitation MS: mitral stenosis TS: tricuspid stenosis CVA: cerebrovascular accident.

Table 4. Summary of Management

Case number	Affected Structures	Valvulopathy	Immuno-suppression	Anticoagulation	Inotropes	Surgical management	Death
1	MV, TV	MS, TS	-	Warfarin	-	MV replacement (porcine), TV commissurotomy	
2	MV	MR	Hydroxyurea Prednisone	Warfarin	-	MV replacement (St.Jude)	
3	MV	MR	Prednisone	-	Inotropes		

Case number	Affected Structures	Valvulopathy	Immuno-suppression	Anticoagulation	Inotropes	Surgical management	Death
4	MV	MR	Methylprednisolone Hydroxyurea	Unfractionated heparin	-		Yes, VF
5	TV	TR	Prednisone	Warfarin	-		
6	MV		Prednisone	Unfractionated heparin followed by warfarin	-		
7	LV, RV, RA		Hydrocortisone	Heparin followed by warfarin	-		
8	LV		Prednisolone		-		Yes
9	MV, TV	MR, TR	Methylprednisolone Chloroquine	Warfarin	-		
10	MV	MR	Corticosteroids	Anticoagulation	-		
11	LV		Corticosteroids	Anticoagulation	-		
12	MV, TV	MR, TR	Prednisolone 6- mercaptopurine	Warfarin	-		
13	LV		Prednisone Imatinib	Anticoagulation	-		
14	MV	MR	Prednisone	-	-	MV replacement (mechanical), TV replacement (Bioprosthetic)	
15		MR, TR	-	-	-	MV and TV annuloplasty	
16		MR, TR	-	-	-		Yes, heart failure
17		MR, TR	-	-	-	MV replacement TV replacement RV endarterectomy	
18	MV	-	Dexamethasone Everolimus	-	-		
19	IVS, LV posterior wall		Prednisolone Methotrexate	Warfarin	-		
20	MV, TV		Corticosteroids Imatinib	Warfarin	-		
21	TV	TR	Prednisolone Cyclophosphamide	Warfarin	-		
22	LV APEX		Methylprednisolone Prednisone	Anticoagulants	Inotropes		Yes, cardiogenic shock
23	MV	MR	Hydroxyurea Vincristine Methylprednisolone Interferon a-2b Nilotinib Mepolizumab Lenalidomide	Warfarin	-	MV replacement (Bioprosthetic)	Yes, septic shock
24	MV, TV	MR, TR	Prednisone	Warfarin	-		
25	LV, RV		Imatinib	Enoxaparin	-		
26	MV	MR	Imatinib Hydroxyurea	-	-	MV replacement	

VF ventricular fibrillation.

4. Discussion

As described by Chusid et al in 1975, hypereosinophilic syndromes are described as persistent marked elevations in blood eosinophil counts (>1.5 $\times 10^9$/L) with no discernable primary cause, and the presence of end organ involvement. [1] It is a relatively rare entity, with an age adjusted incidence rate of 0.036 cases per 100,000 person years. [31] Cardiovascular involvement in hypereosinophilic disorders were initially thought to be as prevalent as 84%, however recent studies have shown the frequency to be around 40-50%. [32,33] Cardiovascular involvement in HES is most commonly associated with Löffler endocarditis, a form of restrictive cardiomyopathy associated with the degranulation of eosinophils in the myocardium, resulting in tissue damage and fibrosis. [23] The progression of cardiac involvement in HES follows a stepwise pattern that can be described in three stages: acute necrosis, thrombosis and fibrosis. The necrotic stage describes the infiltration of the myocardium by the eosinophils. The eosinophils undergo degranulation and release toxic cationic proteins, which cause myocardial necrosis. This acute phase is usually subclinical, with minimal electrocardiographic or echocardiographic changes. [34] It

is followed by the thrombotic phase, which is a result of damage to the endomyocardial surface. It is also believed that eosinophils also contribute to thrombus formation by binding to thrombomodulin and impairing the inherent anticoagulant properties of the endothelial membrane. [35] Fibrosis follows after the thrombotic phase which has been described to occur after 24.5 months of hypereosinophilia. [36] Most of the patients with this condition tend to present with scarring of the chordae tendinae and endocardium. It leads to a restrictive or dilated cardiomyopathy with progressive valvulopathy. [37]

Cardiac manifestations of HES have been described as signs and symptoms of heart failure, ventricular thrombus formation, myocardial ischemia, arrhythmias and pericarditis. A prospective study of 25 patients done in 1979 by Parrillo JE et al. [33] showed the most common presenting symptom was dyspnea (42%), chest pain (27%), heart failure symptoms (38%), cough (12%), palpitations (8%) and embolic events (4%). Echocardiography is the mainstay of diagnostic imaging and surveillance for Löffler endocarditis caused by HES. Classic findings in HES are myocardial thickening, apical thrombus formation, and valvulopathy. An NIH study of 22 HES patients who had echocardiographs showed that 68% had left ventricular wall thickening, 37% had increased left atrial transverse dimension and 27% had in increase in right ventricular transverse dimension. [33] A Mayo clinic study consisting of 55 patients with hypereosinophilic syndromes and echocardiograms showed that 12% had endocardial thickening, 24% had left ventricular apical thrombus, 20% had right ventricular apical thrombus, 20% had posterior mitral leaflet involvement, 10% had tricuspid involvement, 16% had hyperdynamic LV, 10% had LV hypertrophy, 14% had LV dilation and 18% had pericardial effusion. [38] The mean age in this study was 45 ± 17 years; mean eosinophil count × 10^9/L was 18.6 ± 29.7 with a p value of 0.05. Seventy eight percent of the patients in the study were males, and 33% of the patients died.

Management of hypereosinophilic syndrome consists of heart failure management using established guidelines, immunosuppression with the aim of decreasing eosinophil counts and anticoagulation if there is the presence of thrombus. Routine anticoagulation is not recommended, unless there is the presence of an intracardiac thrombus or valve replacement. Most of the literature shows that warfarin is the predominant anticoagulation regimen and the direct acting anticoagulants have not been significantly used in these patients. Due to the complications associated with anticoagulation, the use of anticoagulation must be correlated to the presence of endomyocardial disease. [34] Valvulopathy as a result of Löffler endocarditis is common and bio-prosthetic valve replacement is preferred, as mechanical valves are associated with thrombus formation. [39,40,41] Current immunosuppressive regimens for Löffler endocarditis are dictated by the level of disease present. It consists of the use of corticosteroids, interferon, hydroxyurea, tyrosine kinase inhibitors and other cytotoxic medication. [23] Consensus guidelines have not been established for the management of Löffler endocarditis.

5. Conclusion

Based on our review, the majority of the primary eosinophilic syndrome patients who presented with Löffler endocarditis were young adult females and most of them presented with heart failure symptoms such as shortness of breath. These patients had a low prevalence of cardiovascular risk factors among them and nearly 1/3 were diagnosed with heart failure. Mitral valve was the most common valve affected followed by the tricuspid valve and one third of the patient's had two valve endocarditis. These patients had elevated WBC count and high eosinophil count. Medical management strategies included immunosuppression and anticoagulation. Nearly 30% of the patient's had valvular replacement. A high mortality rate was noted in these patients.

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