A Case Report on Eosinophilic Hepatitis with Hypereosinophilic Syndrome

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Abstract:

Eosinophilic hepatitis could be labelled as one of the rarest cause of acute hepatitis. It is itself a part of another rare disorder called hypereosinophilic syndrome (HES), which constitute a hetergenous group of disorders, defined as persistent and marked blood eosinophilia (>1.5x10^9/L) associated with proof of eosinophil mediated end organ damage and exclusion of other cause of eosinophilia. Although the condition itself is rare but it is not rare to have hepatic involvement in HES as it can happen upto one-third of patients with HES. Excessive aggregation of eosinophils in the liver leading to inflammation and damage is regarded as eosinophilic hepatitis. Here we present a case of HES with eosinophilic hepatitis in a patient, who presented with pyrexia of unknown origin and abdominal pain.

Key Words: Eosinophilic Hepatitis, Hypereosinophilic syndrome

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Introduction:

High eosinophil count in a patient is not uncommon. It occurs frequently in parasitic infections. HES should not come in 'first consideration when we find raised eosinophil count. Three criteria have been used to define HES: (1) blood eosinophilia e" 1500/mm^3 for longer than 6 months (or death before 6 months associated with signs and symptoms of hypereosinophilic disease), (2) lack of evidence for parasitic, allergic or other known causes of eosinophilia and (3) presumptive signs of organ involvement, such as heart failure, gastrointestinal dysfunction, central nervous system abnormalities, fever or weight loss.[1] But this definition is not universal as it is showing some problem to diagnose the disease as it is highly unlikely that patient with underlying HES will be unnoticed in a patient.[1] Threshold for blood eosinophila can also be misleading in case of eosinophilic granulomatosis with polyangiitis (EGPA), eosinophilic pneumonia, and bronchial asthma as they may exhibit all the other parameters of HES except for blood eosinophil levels, yet are not classified as HES. In contrary, some patients with blood eosinophilia e" 1500/ mm^3 do not exhibit signs of eosinophil-mediated organ damage and/or dysfunction at the time of presentation.[2] Hepatitis associated with hypereosinophilia has been scarcely reported worldwide. However, one case was reported in Bangladesh.[3] It is usually seen in young middle-age (40–50 years) women.[4] The signs and symptoms are also variable, predominantly presenting as malaise, fatigue, anorexia, jaundice, and hepatosplenomegaly.[4]

There are some key secondary causes of hypereosinophillia such as allergies, atopy and helminthic infections. In case of secondary hypereosinophilia, production of interleukin (IL)-3 and IL-5 promote eosinophil proliferation. Lympho- reticular malignancy, some solid tumours and some autoimmune diseases are less common causes. In case of primary eosinophilia it is a bit different as the origins are clonal and are derived from myeloid lineage and the key causes are myelogenous leukaemia or myelodysplastic syndromes.[5,6] It is a spectrum of disease with variable organ involvement, clinical manifestations, and treatment response as well as prognosis. Here we report a case of idiopathic HES with eosinophilic hepatits in a 25-year-old man.

Case Report

A 25-year-old, non-diabetic, normotensive businessman, admitted with the complaints of fever for 3 months. Fever was initially low grade, intermittent in nature but later became high grade with highest recorded temperature of

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104°F. It was not associated with chills & rigor and subsided by taking paracetamol. There was no evening rise of temperature or night sweats. He also complained of dry cough for same duration. There was no aggravating factor including dust, relieving factor and diurnal variation. He gave no history of allergy, asthma, chest pain, sputum production and shortness of breath. On query he stated about 5 kg unintentional weight loss in last 3 months with loss of appetite. He gave no history of headache, abdominal pain, jaundice, vomiting, alteration of bowel habits, dysuria, joint pain, skin rash, itching, tremor or palpitation. There was no relevant drug history. He appeared ill looking. His pulse was 102 beats/min, blood pressure was 110/70 mmHg, SpO2 98%, temperature was 100°F and respiratory rate was 16 breaths/min. No abnormality detected in systemic examination.

Our first impression was that it could be a case of pulmonary tuberculosis, also keeping in mind that sarcoidosis could be another differential. Considering the age malignancy was not kept in the differential diagnosis, however, imaging of the chest would exclude it anyway.

His investigation reports during hospital stay are shown in Table I.

On review of the patient's previous blood reports, we found persistently elevated eosinophil count as shown in Table II.

Table-I

Investigation reports

Investigation	Report
Blood	
Haemoglobin	12.9 g/dl
Red blood cell	4.5 million/μL
White blood cell	18,780/mm^3
Neutrophil	35%
Lymphocyte	17%
Eosinophil	45%
Basophil	03%
Platelet	3,50,000/mm^3
Peripheral blood film	Eosinophilic leucocytosis
S. bilirubin	1.1 mg/dl
ALT	25U/L
Serum albumin	4.2 mg/dl
Total IgE	>2500 IU/ml
ICT for filaria	Negative
Rk 39 for Kala-azar	Negative
Urine	
Routine microscopic examination	Normal
Stool	
Routine microscopic examination	Normal, no eggs of parasites
Imaging	
Chest X ray	Normal
Ultrasonogram of abdomen	Fatty liver with mild splenomegaly
Bone marrow examination	
Morphology	Hypercellular marrow with increased myeloid/erythroid ratio Erythropoiesis was relatively depressed and normoblastic Granulopoiesis was hyperactive and majority of the cells were eosinophilic myelocytesMegakaryocytes were normal in number and morphologyLymphocytes, plasma cells and histiocytes were within normal range No evidence of malignancy or parasitic infestation was foundFeatures are consistent with marked eosinophilia
BCR/ABL1 mRNA transcripts	Not detected

Table-II

Differential leucocyte count

Investigation	16/07/23	28/05/23	29/04/23	Normal range
White Blood Cell	18,780/mm^3	13,8000/mm^3	12,5000/mm^3	(4,000-10,000)/mm^3
Neutrophils	35%	49%	63%	(40.00-80.00)%
Lymphocyte	17%	16%	22%	(20.00-40.00)%
Eosinophil	45%	30%	12%	(2.00-10.00)%

The patient was labelled as a case of hypereosinophilia. We did exlude vasculitis clinically but investigation were not done. Unfortunately due to unavoidable circumstances, he had to take discharge from hospital so he was put on prednisolone 1 mg/kg body weight and was asked to come back for follow up. He came back after 2 weeks with dull aching abdominal pain in right hypochondriac region. His eosinophil count became normal but SGPT raised to 101 U/ml and serum albumin decreased to 2.97 g/dl. His viral markers (HBsAg, Anti HCV) were negative. Computed tomography (CT) scan of abdomen revealed multiple space occupying lesions (SOL) in the liver (Figure 1).

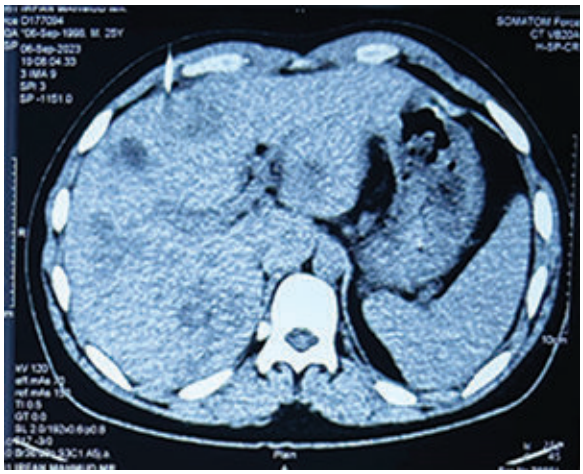

Figure 1: *CT scan of abdomen showing multiple hepatic space occupying lesions*

CT-guided fine needle aspiration cytology from the liver SOL revealed many hepatocytes arranged in clusters and sheets with bile duct epithelial cells, macrophages, red blood cells and significant number of eosinophils. No anaplastic cells were seen. The features were consistent with eosinophilic hepatitis. The patient was diagnosed as hypereosinophilic syndrome with eosinophilic hepatitis. Hydroxyurea was added to his prednisolone prescription. His condition dramatically improved within 2 weeks with eosinophil count in normal range.

Discussion

HES definition has evolved over time and the updated consensus definition has already been mentioned in the introduction.[7] According to the same consensus group, the HES can be classified into primary (neoplastic), secondary (reactive) or idiopathic.[7] Here we present a case of idiopathic HES. Our patient fits the criteria of HES. The patient had persistently raised eosinophil count and organ damage in the form of hepatitis. HES was not due to primary cause as symptoms and signs were not suggestive and the bone marrow aspiration examination did not reveal any features of myeloproliferative or lymphoproliferative disorder. Secondary causes of hypereosinophilia were also excluded by history and investigation such as allergic conditions, parasitic infection, malignancies, Loffler syndrome, EGPA, connective tissue disorders, inflammatory bowel disease and sarcoidosis. Parasitic infection like visceral larva migrans could cause hepatitis with eosinophilia but the characteristic histological finding were reported usually as eosiniphilic granuloma.[8] The possibility of parasitic infection in our patient could be excluded by the absence of contact history with pets, no granulomatous lesion in histology and rapid improvement of eosinophilia with steroids. Our patient also had liver masses on imaging and histological findings were consistent with eosinophilic hepatitis. Similar findings were also found in other case reports.[8,9] However, a range of hepatic histological findings were reported in patients with HES such as eosinophilic cholangitis, chronic active hepatitis with eosinophilic infiltration, nodular regenerative hyperplasia with portal eosinophilic infiltration and

obstructive thrombophlebitis with eosinophilic infiltration.[8]

HES can affect any organs but frequently reported manifestations are dermatological (69%), pulmonary (44%), gastrointestinal (38%), cardiac (20%) and neurological (20%).[10] The liver was effected in our patient and different studies show that hepatic involvement ranges from 30% to 43%.[8,11] Commonly reported symptoms are fatigue, cough, breathlessness, rhinitis, fever, rash, itching, myalgia and angioedema.[5,12] Variety of skin lesions are described including erythematous pruritic papules, nodules, angioedematous, vasculitic, urticarial and blistering lesions.[13] Pulmonary features include bronchial asthma, pleural effusion, pulmonary infiltrates and fibrosis.[14] Gastrointestinal involvement includes gastroenteritis, oesophagitis, ascites, hepatitis and splenomegaly.[14] Cardiac manifestations include myocardial fibrosis, restrictive cardiomyopathy, Loffler's endocarditis, thromboembolic complications, pericarditis, myocarditis, pericardial effusion and heart failure.[5,14] Neurological features that are reported are transient ischaemic attacks, embolic strokes, encephalopathy, seizures, intracranial haemorrhage, dementia and peripheral neuropathies.[15]

The algorithm for diagnosis of HES is provided in figure 2. The first step is to establish the presence of blood hypereosinophilia, which is defined by the presence of eosinophil count > 1500/mm^3 in at least two occasions measured > 1 month apart and/ or by the presence of tissue hypereosinophilia.[7] Tissue hypereosinophilia is applicable when one or more of the following criteria are present:[7]

- Percentage of eosinophils in bone marrow examination exceeds 20% of all nucleated cells
- Extensive infiltration of tissue by eosinophils as described by a pathologist
- Marked deposition of eosinophil granule proteins

The second step is to ascertain the organ damage is attributable to tissue hypereosinophilia. The organ dysfunction should be associated with marked infiltration of eosinophils and/or extensive deposition of eosinophil derived protein and 1 or more of the following:[7]

- Fibrosis of lung, heart, gastrointestinal tract, skin, and others
- Thrombosis with or without thromboembolism
- Cutaneous (including mucosal) erythema, edema/ angioedema, ulceration, pruritus, and eczema
- Peripheral or central neuropathy with chronic or recurrent neurologic deficit
- Less commonly, involvement of liver, pancreas, kidney, and other organs and the resulting organ damage should be related to hypereosinophilia

The next step would be to exclude other causes of organ dysfunction. After establishment of HES, the next step would be to ascertain secondary or reactive cases of HES (Table III).[5]

Table-III

Common causes of secondary or reactive HES

Category	Conditions
Infection	Parasitic
Allergy	Asthma, allergic rhinitis, atopic dermatitis, allergic bronchopulmonary aspergillosis
Autoimmune	Eosinophilic granulomatosis with polyangiitis, rheumatoid arthritis, systemic sclerosis, Sjogren's syndrome, sarcoidosis, inflammatory bowel disease
Malignancy	Lung, renal, colon, lymphoma
Medication	Aspirin, nonsteroidal anti-inflammatory drug (NSAID), antimicrobials
Immune deficiency	Hyper IgE syndromes, Wiskott-Aldrich syndrome
Other	Graft versus host disease, solid organ rejection, cholesterol emboli

If there is no secondary cause then the work up would focus on detection of primary or neoplastic HES, which could be bone marrow disorders such as myeloproliferative disorder, lymphoproliferative disorder, myelodysplastic syndrome, acute myeloid leukaemia or systemic mastocytosis.[5] Further investigations would include peripheral blood film, serum B12 level, serum typtase level, bone marrow morphological, cytogenetic & molecular analysis, reverse transcriptase-polymerase chain reaction (RT-PCR), fluorescence in situ hybridization (FISH) and next generation sequencing of myeloid gene panel.[5] Rearrangements of PDGFRA, PDGFRB, FGFR1 or PCM-JAK2 are usually detected in primary HES.[16] A diagnosis of idiopathic HES is established when no primary and secondary causes of HES could be identified.[5,16]

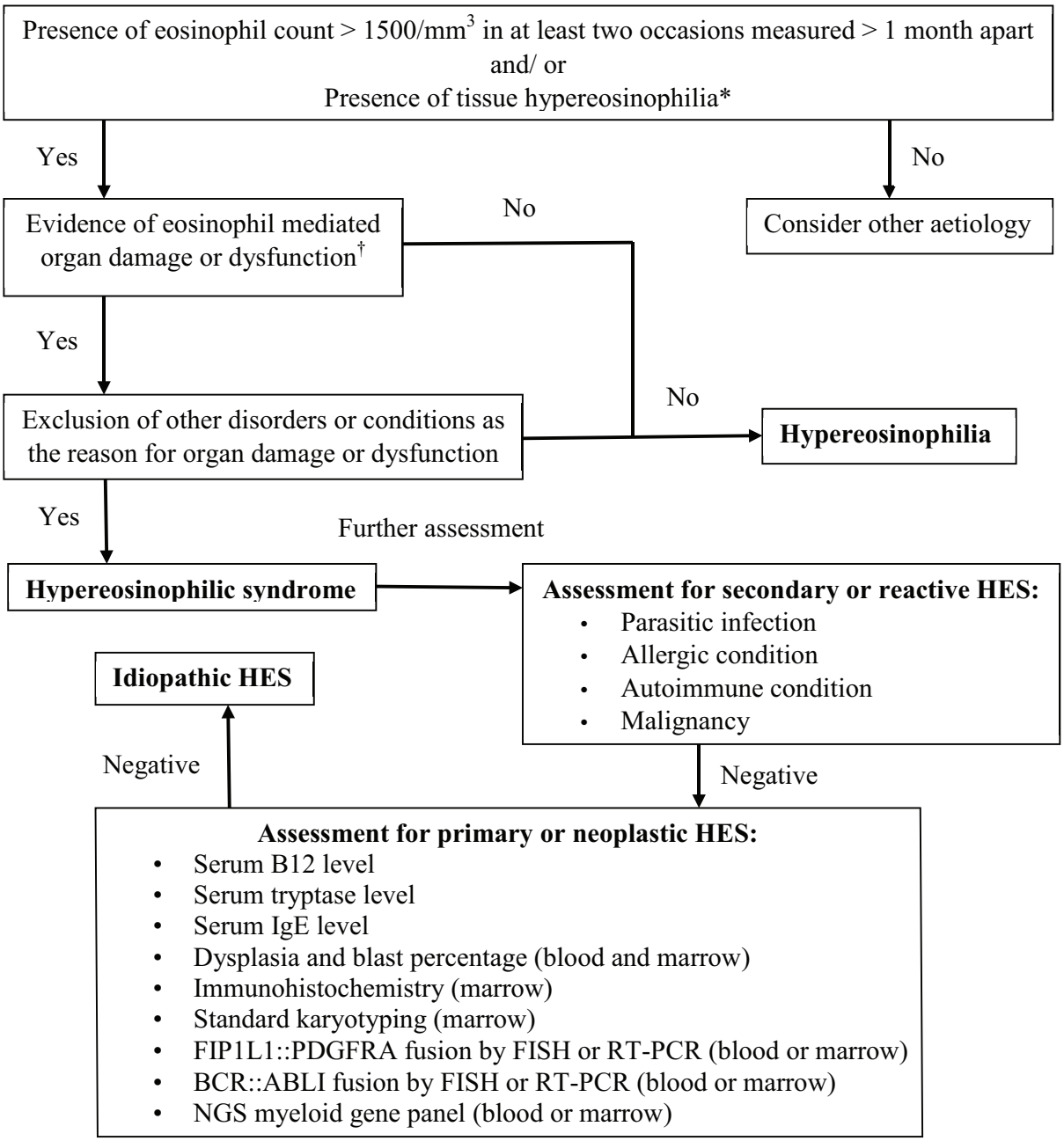

Figure 2: *Algorithm for diagnosis of HES*

*Tissue hypereosinophilia is present when one or more of the following criteria are present: (1) Percentage of eosinophils in bone marrow examination exceeds 20% of all nucleated cells (2) Extensive infiltration of tissue by eosinophils as described by a pathologist (3) Marked deposition of eosinophil granule proteins

†Organ damage or dysfunction with marked infiltration of eosinophils and/or extensive deposition of eosinophil derived protein and 1 or more of the following: (1) Fibrosis of lung, heart, gastrointestinal tract, skin, and others (2) Thrombosis with or without thromboembolism (3) Cutaneous (including mucosal) erythema, edema/angioedema, ulceration, pruritus, and eczema (4) Peripheral or central neuropathy with chronic or recurrent neurologic deficit (5) Less commonly, involvement of liver, pancreas, kidney, and other organs and the resulting organ damage should be related to hypereosinophilia

The treatment of HES will depend upon the underlying pathophysiology of the condition. Since the treatment of secondary or reactive causes of HES requires a different approach so they should be considered and ruled out early in the diagnosis.[17] Corticosteroids are usually the mainstay of treatment in acute setting or life threatening HES but before that secondary causes such as parasitic infections should be excluded as steroid can induce fatal strongyloidiasis infection.[18] If eosinophilia does not dramatically respond to steroids in 1 to 2 days then additional therapy needs to be added depending on the cause such as imatinib if myeloproliferative disease is suspected, specially FIP1L1::PDGFRA positive myeloid neoplasms, or cyclophosphamide in case of EGPA.[5,17] Other second line treatments include hyroxyurea, interferon alpha and mepolizumab.[2,16,17] Hydroxyurea is effective in combination with steroid or interferon alpha and is usually used in case of corticosteroid refractory cases.[2,15,17] Our patient initially responded to steroid but then presented with eosinophilic hepatitis, which responded well to steroid and hydroxyurea combination. Allogenic haemapoietic stem cell transplantation may be considered when standard therapy fails in selected cases although the role of transplantation is not yet well established in HES.[2,5]

Conclusion

History and examination sometimes do not yield the diagnosis and thorough investigations is needed. The presence of persistent eosinophilia should always be evaluated and HES should be kept in mind. Idiopathic HES should only be diagnosed when primary and secondary causes are excluded. Liver involvement in HES is not uncommon and may present as space occupying lesion on imaging. Steroids are usually the first line treatment but additional therapies may be needed such as imatinib, cyclophosphamide, hyroxyurea, interferon alpha or mepolizumab.

Conflict of interest: None

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