Case report

Case report of an elderly patient with constipation: Hypereosinophilic Syndrome

Abstract

Hypereosinophilic Syndrome (HES) is diagnosed when there is peripheral hypereosinophilia with eosinophil count of more than >1500/uL. The duration of the illness usually lasts more than 6 months, with evidence of target organ damage, affecting mainly the skin, heart, and neurological system, without apparent aetiology. The study present a case report of an elderly patient with constipation called Hypereosinophilic Syndrome. An 80-year-old gentleman, ex-smoker, with background history of old pulmonary tuberculosis, diabetes mellitus, hypertension, dyslipidemia and history of transient ischemic attack, was recently discharged from coronary care unit where the patient underwent a successful cardioversion for undetermined cause of symptomatic slow atrial flutter. Interstitial lung changes with bronchiectasis due to old pulmonary tuberculosis, and paraseptal emphysema were also noted. Sputum acid fast bacilli direct smear, sputum culture and sensitivity, and sputum fungal culture and sensitivity were negative. it is important to consider the diagnosis of hypereosinophilic syndrome when there is an unexplained peripheral eosinophilia, and thus intervene rapidly to prevent life-threatening complications.

Keywords: Hypereosinophilic Syndrome, pulmonary tuberculosis, dyslipidemia, paraseptal emphysema

Introduction

Hypereosinophilic Syndrome (HES) is diagnosed when there is peripheral hypereosinophilia with eosinophil count of more than >1500/uL. The duration of the illness usually lasts more than 6 months, with evidence of target organ damage, affecting mainly the skin, heart, and neurological system, without apparent aetiology. In recent years, the guidelines have been revised [1, 20], as some of the cases were diagnosed and treated with eosinophilia-lowering drugs earlier than 6 months duration, in order to manage its potentially fatal complications. A normal eosinophil percentage is 1-4%, with absolute eosinophil counts of 50-400/uL. Eosinophilia is commonly seen in clinical practice, in which it is often attributed to parasitic infection, allergy, autoimmune diseases, and drug reactions. In contrast, HES is a rare disorder, with associated tissue damage. If there is no tissue damage, idiopathic hypereosinophilia is the preferred diagnosis [1]. The prevalence around the world of HES is 1-9/100,000 population. The disease commonly affects adults between 20-50 year-old [2], with a mean age of 33 year-old, predominantly affecting adult male, with no predilection for race [3]. An older review of 57 patients with advanced hypereosinophilic syndrome reported a mean survival of 9 months and a 3-year survival rate of 12% [4]. However, a recent analysis from France noted an 80% survival at 5 years and a 42% survival at 15 years [5].

Case History

An 80-year-old gentleman, ex-smoker, with background history of old pulmonary tuberculosis, diabetes mellitus, hypertension, dyslipidemia and history of transient ischemic attack, was recently discharged from coronary care unit where the patient underwent a successful cardioversion for undetermined cause of symptomatic slow atrial flutter. He was then discharged with a newer oral anticoagulant, Apixaban, whilst continue Clopidogrel. However, four days after discharge from the cardiology ward, he was admitted for passing dark tarry stool suggestive of melena. He had also complained of cough of 2 weeks duration and had few months history of skin lesions (Figure 1) affecting his upper limbs intermittently, which improved transiently with local steroid cream. He has a family history of pulmonary tuberculosis, psoriasis, and gouty arthritis. There is no known allergy. Physical examination was largely unremarkable. However, he was noted to be hypoxic with oxygen saturation of 94% under room air. Coarse crepitations were heard over the lower zones of both lungs. Otherwise, he was haemodynamically stable. The cardiac, abdominal, and neurological examinations were normal. He had no lymphadenopathy or evidence of melenic stool on per rectal examination.

He was admitted a few days earlier, when he experienced 2 days history of worsening constipation with episodic severe generalised abdominal discomfort. During investigation, plain abdominal radiograph showed faecal laden large bowel loops, Haemoglobin was 13 g/dL, white blood count was 12 x 10^9/L with 34.2 % of eosinophils. Erythrocyte sedimentation rate was 45mm/hour. Electrocardiograph detected atrial flutter and variable block, with heart rate of 42 beats per minute (Figure 2). Additional test of echocardiography showed an ejection fraction of 53%, with normal left atrium, right atrium and left ventricular size. There was trivial mitral regurgitation and mild tricuspid regurgitation. Pulmonary artery systolic pressure was elevated at 45mmHg. The creatine kinase and lactate dehydrogenase were normal. Chest radiograph revealed pulmonary fibrosis, calcified mediastinal and right hilar lymph nodes, and bronchiectatic changes consistent with old pulmonary tuberculosis change (Figure 3). He was prescribed a course of anti-parasitic medication and apixaban for thromboembolic prevention. Elective cardioversion was performed. The patient was treated as pneumonia due to his bibasal coarse crepitations and hypoxia. He improved with antibiotics.

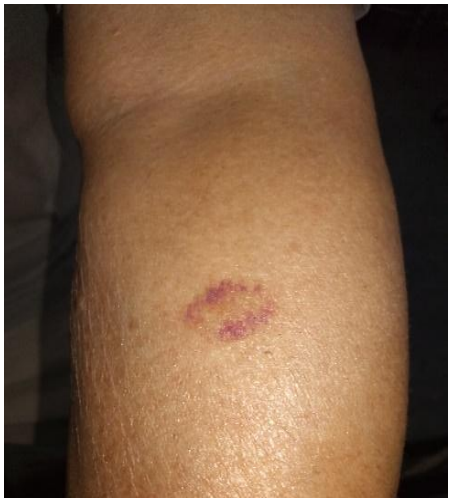

Figure 1 - An annular lesion on left forearm with erythematous-edematous margins, and a clear center.

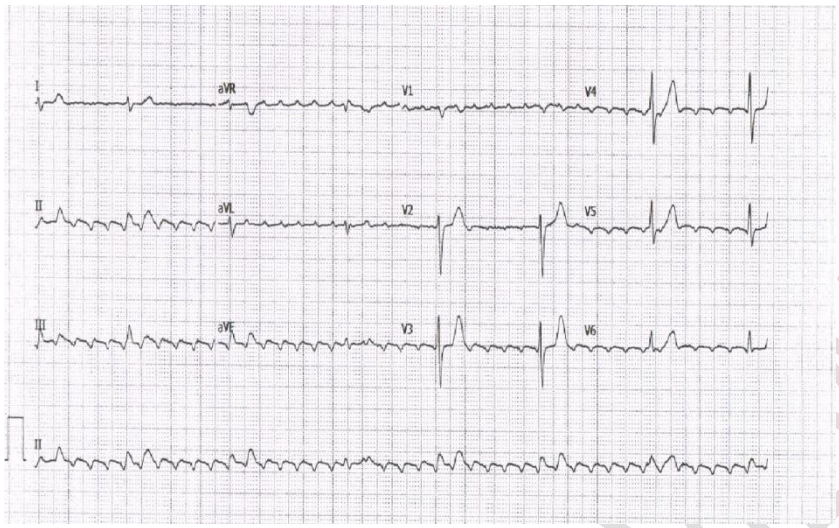

Figure 2 - Atrial flutter with variable atrio-ventricular block, heart rate of 42 beats / minute.

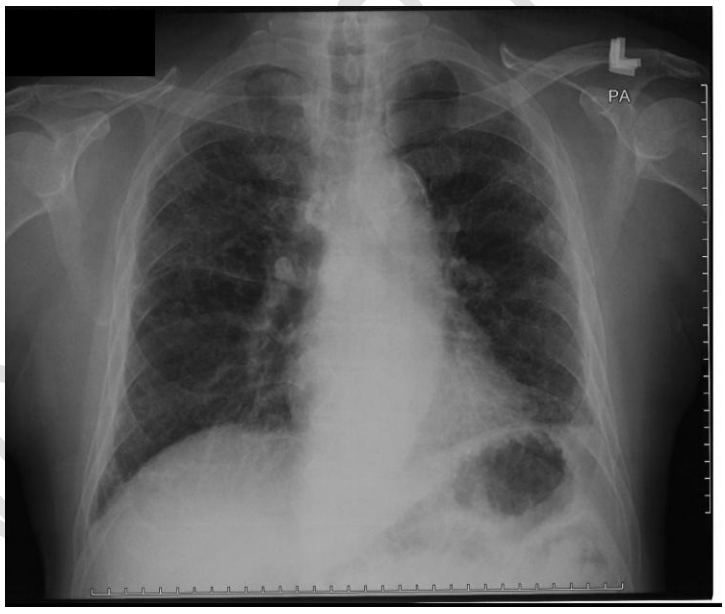

Figure 3 - Bilateral pulmonary fibrosis and bronchiectatic changes associated with calcified mediastinal and right hilar lymph nodes.

In the current admission, several investigations were repeated. Hemoglobin was 12.7 g/dL, white blood count 15.9 x 10^{9}/L, platelets of 376 x 10^{9}/L, with eosinophil counts increased to 8300/uL, and eosinophils % of 52. There was no blast cell seen on peripheral blood film. Other results include prothrombin time of 13.2s, International Normalised Ratio of 1.17 and activated partial thromboplastin time ratio of 0.9. However, repeat chest radiograph (Figure 4) showed marked upper zone consolidation and computed tomography of the thorax (Figure 5) showed bilateral upper lobe alveolitis and patchy consolidation changes which were

predominantly peripherally located, consistent with pulmonary eosinophilia. Interstitial lung changes with bronchiectasis due to old pulmonary tuberculosis, and paraseptal emphysema were also noted. Bronchoscopy was done and showed minimal thick whitish secretion at left upper lobe and lingula. Bronchoalveolar lavage done at right upper lobe and left upper lobe were negative. Spirometry was consistent with a diagnosis of restrictive lung disease.

Sputum acid fast bacilli direct smear, sputum culture and sensitivity, and sputum fungal culture and sensitivity were negative. Sputum cytology, stool ova and cyst, blood culture and sensitivity were negative. Liver function test and renal function test were normal. Fluorescent in-situ-hybridisation (FISH), platelet-derived growth factor receptor A (PDGFRA) and platelet-derived growth factor receptor B (PDGFRB) were both negative. Tumor markers showed elevated cancer antigen (CA) 19.9 of 47.6 U/ml. Other tumor markers such as alpha-feto-protein (AFP), carcinoembryonic antigen (CEA), cancer antigen (CA) 15.3, prostate specific antigen (PSA) and BCR-ABL fusion gene were negative. Connective tissue markers which included C-ANCA, p-ANCA, anti-myeloperoxidase, anti-proteinase and rheumatoid factor were negative. There was no bone marrow aspiration and trephine biopsy, and skin allergic test was not done.

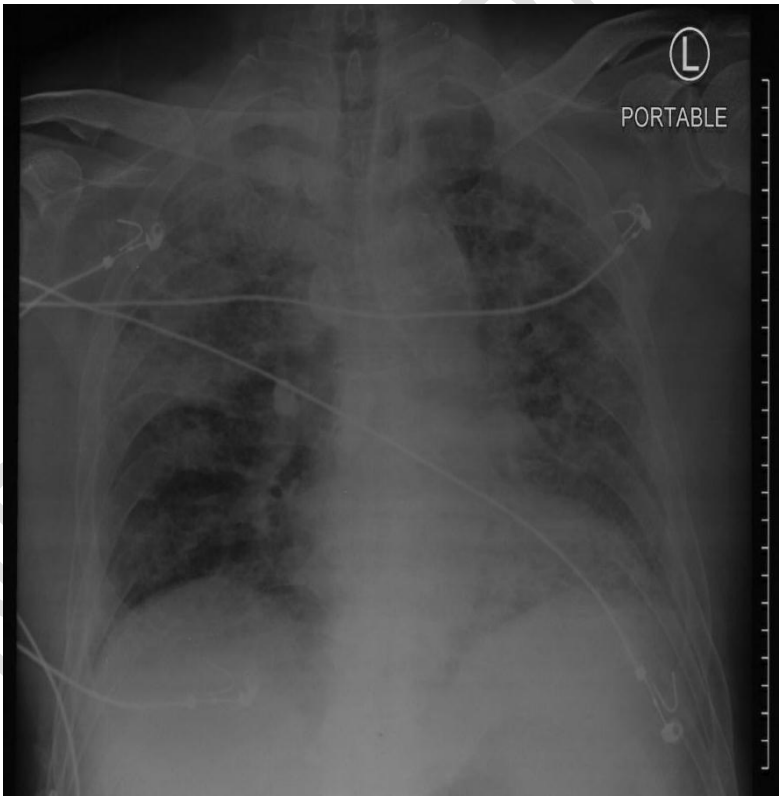

Figure 4 - Marked upper lung zone consolidation, predominantly on the right side.

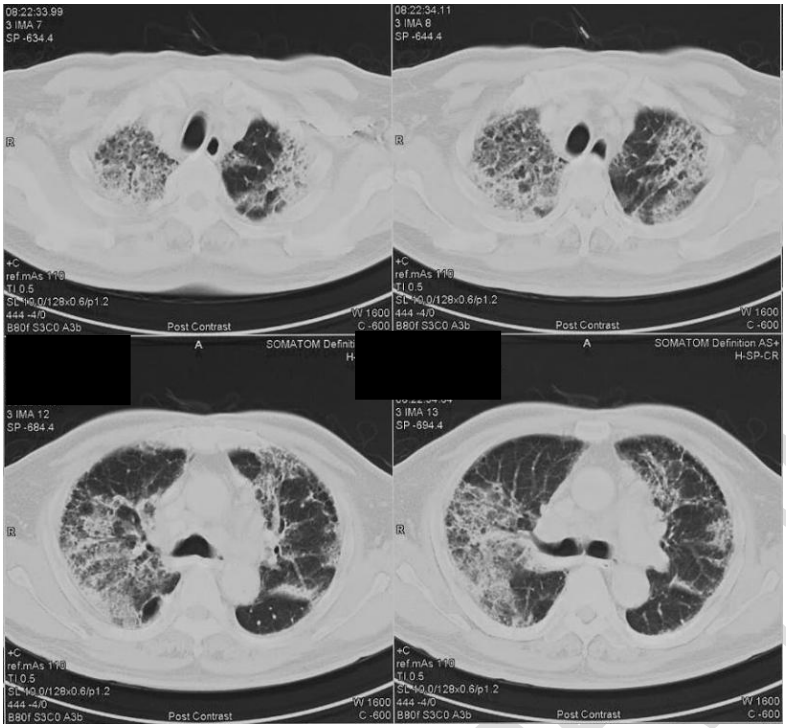

Figure 5 - CT thorax showing bilateral upper lobe alveolitis and peripherally located patchy consolidation.

The patient was treated for upper gastrointestinal bleed secondary to anticoagulant therapy, as well as eosinophilic pneumonia. The patient was treated with prednisolone of 35 mg twice a day. After 5 days, the eosinophilic count dropped markedly, from a level of 5200/uL or eosinophilic % of 37.6, to 0. A repeated chest radiograph after a few days also showed significant improvement (Figure 6). Skin rash resolved following treatment. Follow-up eosinophilic count done weeks later, on tailing down dose of prednisolone (3 weeks after initiation of prednisolone, whilst the patient was on 30 mg daily), was 300/uL, with eosinophil % of 1.9. Prednisolone was stopped 10 months after the initial presentation. He remains well and in sinus rhythm a year later.

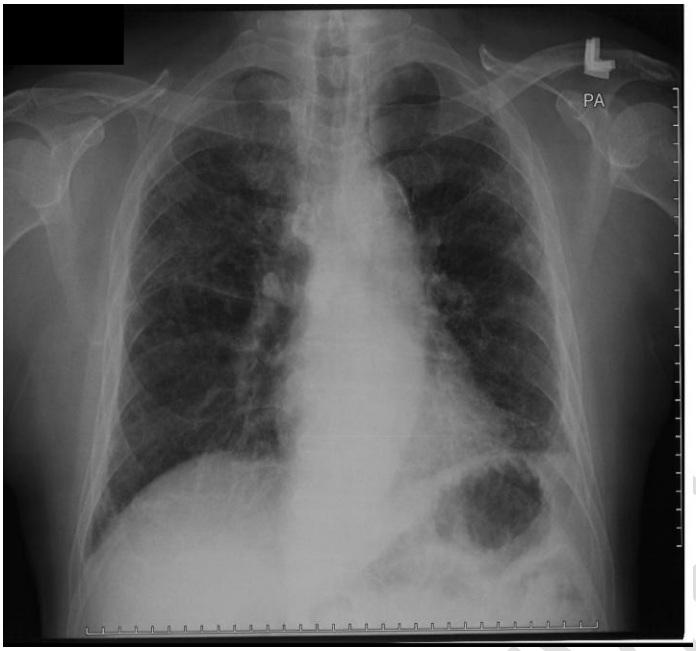

Figure 6- Improved CXR with resolved consolidation over both upper lung zones.

Discussion

This is a case of an elderly patient who initially presented with constipation and abdominal pain, and was incidentally noted to have markedly raised eosinophil count, with dermatological, gastrointestinal, cardiac, and pulmonary manifestation. There was 2 to 3 months delay in diagnosing the hypereosinophilic syndrome, from the time of initial skin presentation. World Health Organisation (WHO)endorses a semi-molecular classification scheme of hypereosinophilia subtypes as follows.

1. Myeloid/lymphoid neoplasms with eosinophilia and abnormalities of (PDGFRA), Platelet-Derived Growth Factor Receptor B (PDGFRB), or Fibroblast Growth Factor Receptor 1 (FGFR1). It is commonly associated with identifiable FIP1L1/PDGFRA (F/P positive), a fusion tyrosine kinase,

2. Chronic eosinophilic leukemia, not-otherwise-specified (CEL-NOS). CEL-NOS is defined by exclusion of the Philadelphia chromosome or a rearrangement gene involving PDGFRA/B and FGFR1, and the absence of primary neoplasms associated with eosinophilia. It has a peripheral blast cells count of more than 2% but less than 20%, and more than 5% blast cells in bone marrow. Chronic eosinophilic leukemia patients carries a rare risk of acute blast transformation.

3. Lymphocyte-variant hypereosinophilia (L-HES). The lymphoproliferative variant of HES (L-HES) represents a distinct clinical syndrome in the presence of a phenotypically distinct clonal T cell population in the peripheral blood [1, 21]. Hypereosinophilia in these patients appears to occur in response to the production of eosinophilopoietic cytokines, particularly interleukin-5, causing a reactive eosinophilia[2]. It carries a risk of malignant transformation to T cell lymphoma[1]. The confirmatory test, includes identification of phenotypically aberrant T-cell population by flow cytometry, clonal T cell rearrangement pattern via PCR, increased serum IgE, and IL-5. .

4. Idiopathic hypereosinophilic syndrome[1], by exclusion, for F/P negative patients, corticosteroids are administered initially, followed by agents such as hydroxycarbamide, interferon-alpha, and imatinib, in corticosteroid resistant cases. Recent data suggests that anti-IL 5 (Mepolizumab) is an effective steroid sparing agent for F/P negative patients[20].

This patient had markedly raised eosinophilia with multiple end organ involvement, without identifiable cause. History, physical examination, and investigation are not suggestive of secondary causes of eosinophilia. A slightly elevated CA 19.9 needs to be follow-up serially. This patient's eosinophilia reverted to normal within 5 days of treatment of high dose prednisolone. These features suggest that myeloid neoplasm with eosinophilia and rearrangement of gene are less likely[17]. L-HES is less likely, too, as he has a normal level of IgE and immunoglobulin. However, other confirmatory test for L-HES were not done in this patient. Thus, by exclusion, this patient is most likely to have idiopathic hypereosinophilic syndrome [1].

The gastrointestinal and liver involvement are seen in a third of patients with hypereosinophilic syndrome [1, 19, 20]. Splenomegaly is seen in 40 % of patients. Gastrointestinal symptoms include weight loss, abdominal pain, diarrhoea (20%), nausea, and vomiting. Eosinophilic gastritis, enterocolitis, or colitis may be present, and the latter may be associated with ascites when eosinophilic infiltrates involve deeper layers of the intestinal wall [20]. Patients with eosinophilic gastroenteritis typically presents with acute bowel obstruction with nausea, vomiting, crampy abdominal pain and bloating. Patients can either present with diarrhoea or constipation [22].This patient's acute worsening of constipation resolved with the initiation of prednisolone. No colonoscopy was done subsequently. This patient has preserved liver function.

Moreover, this patient developed significant cardiac involvement. His arrhythmia was successfully treated. The eosinophils were 34.2 % at the time of cardiac manifestations. The heart may be affected in 3 different ways in 20% of patients with hypereosinophilic syndrome [1, 20]. This includes acute necrotic stage with mean of 5.5 weeks , thrombotic stage with 10-month means of eosinophilia, and endomyocardial fibrosis after 2 years [8,9,10,11,12,20]. The cardiac involvement occurs seemingly early in his presentation. The heart may be infiltrated by eosinophils which could result in endomyocardial fibrosis, which carries a bad prognosis in the long run. The patient did not have features suggestive of restrictive cardiomyopathy, as might occur in patients affected by endomyocardial fibrosis. Follow-up needs to be vigilant in this case, as cardiac involvement is the most common cause of mortality in hypereosinophilic syndrome. It tends to occur late as the disease progresses when endomyocardial fibrosis develops, leading to congestive cardiac failure and death.

Cough is present in 24% of hypereosinophilic syndrome patients. Pulmonary manifestations present in 44% of HES patients [1]. Patients with hypereosinophilic syndrome may have respiratory symptoms due to congestive heart failure. However, this patient has a normal ejection fraction, with no evidence of heart failure. In this patient, worsening of chest radiograph in the peripheral of upper zones with negative tuberculosis work-up, is consistent with a diagnosis of pulmonary eosinophilia. Symptoms cleared rapidly soon after the initiation of prednisolone. His presentation was typical of the pulmonary involvement in which patient commonly presents with prolonged non-productive cough[20].

Dermatologic involvement is seen in 68% of HES patients [1.]. They usually present with pruritus, atypical urticaria, angioedema [20], atypical rash, or dermatographism [15, 16]. Presence of urticaria or angioedema lesion is suggestive of a better long term prognosis of hypereosinophilic syndrome.The cutaneous manifestations in this patient was retrospectively linked to hypereosinophilic syndrome. There was erythematous ring-like margin of the lesion, as shown in Figure 1. The lesion bears resemblance to eosinophilic annular erythema.

Regarding the pharmacological treatment, prednisolone produces a response in approximately 85% of patients with hypereosinophilic syndrome[1], as in this patient. The prednisolone was stopped after 9 months of treatment in this patient.

Good prognostic factors include a good response to prednisolone, urticaria or angioedema lesions as the type of skin involvement, and an absence of heart failure symptoms [1, 20]. This patient has a prompt positive response to prednisolone. With no evidence of congestive cardiac failure, the outlook of the disease is favourable.

The current challenge lies in monitoring for the recurrence of the disease. Though currently treated as idiopathic hypereosinophilic syndrome, this patient needs to be monitored long term, for recurrence of disease, development of new symptoms, or its long term complication, i.e. haematological or cardiac anomalies.

Conclusion

Patients with hypereosinophilic syndrome presents variably, from relatively indolent non-specific symptoms, like constipation in this patient, to rapidly fulminating fatal disease. Its prognosis has improved significantly, from its inception days. The mortality associated with hypereosinophilic syndrome is due to the occurrence of hypereosinophilic syndrome-related irreversible heart failure and the eventuality of malignant transformation of myeloid or lymphoid cells into a frank eosinophilic leukemia. Thus, it is important to consider the diagnosis of hypereosinophilic syndrome when there is an unexplained peripheral eosinophilia, and thus intervene rapidly to prevent life-threatening complications.

Consent:

A written informed consent was received from the patient for publication of this case report and any images provided in this article.

Conflict of interest: None

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