

CASE REPORT

A case of hypereosinophilic syndrome with STAT5b N642H mutation

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Abstract

Hypereosinophilia is defined as persistent eosinophilia ($>1.5 \times 10^9/L$). Hypereosinophilic syndrome (HES) is a term used to describe a group of disorders characterized by sustained hypereosinophilia associated with end-organ damage. Based on underlying molecular mechanism of eosinophilia, there are different subtypes of HES. Diagnosis of HES subtype can be challenging, especially in the absence of overt lymphoid/myeloid neoplasms or discernable secondary causes. Long-term outpatient follow-up with periodic complete blood count and repeated bone marrow biopsy may be needed to monitor disease activity. Somatic signal transducer and activation transcription 5b (STAT5b) N642H mutation was recently found to be associated with myeloid neoplasms with eosinophilia. We report a case of HES who presented with pulmonary embolism and acute eosinophilic pneumonia, found to have recurrent STAT5b N642H mutation by next-generation sequencing, suggesting possible underlying myeloid neoplasm.

INTRODUCTION

Hypereosinophilic syndrome (HES) is a group of disorders characterized by persistent eosinophilia and evidence of eosinophilia-related end-organ damage [1]. The recent application of next-generation sequencing (NGS), a high-throughput DNA sequencing technology, allows identification of additional myeloid neoplasm-related mutations in a subset of patients with idiopathic HES [2, 3]. Recurrent somatic signal transducer and activation transcription (STAT5b) N642H mutation was recently reported to be associated with myeloid neoplasms with eosinophilia, however limited cases have been reported [4]. We report a case of HES who presented with pulmonary embolism and acute eosinophilic pneumonia, and was found to have recurrent somatic STAT5b N642H mutation by NGS.

CASE REPORT

A 72-year-old Caucasian gentleman without significant past medical history was admitted to the intensive care unit (ICU) with acute hypoxic respiratory failure requiring 0.7 FiO₂ oxygen by high-flow nasal cannula. He was in his usual state of health until 2 weeks earlier when he traveled to CA, where he was briefly hospitalized twice for chest pain, fever and diarrhea. He was diagnosed with 'type B aortic dissection', pneumonia and viral gastroenteritis.

He presented to our institute with dry cough and shortness of breath. He was on beta-blocker for recent diagnosis of 'type B aortic dissection'. On physical examination, he was hypotensive (84/44 mm Hg) without tachycardia (88/min), afebrile, tachypneic (22/min) and hypoxic (SpO₂ 85% at room air). There were

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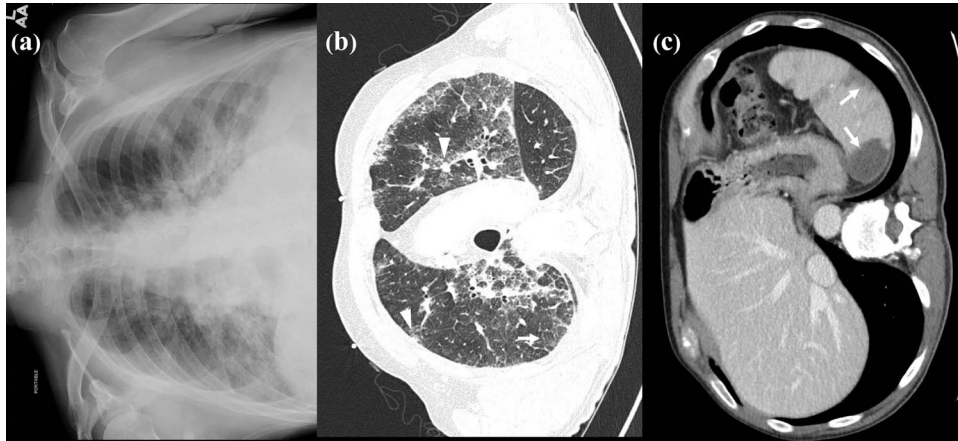


Figure 1: (a) Chest X-ray shows bilateral, perihilar mixed interstitial and alveolar infiltrates simulating pulmonary edema. (b) Chest CT shows bilateral patchy ground glass opacity, interlobular septal thickening (arrow) and several sub-6 mm lung nodules (arrowhead). (c) Abdomen and pelvis CT shows multiple peripheral low-attenuation areas in the spleen consistent with splenic infarcts (arrow).

bibasilar rales on lung auscultation. Initial differential diagnosis included aortic pathology, thromboembolism, infection and hematologic disorders. Electrocardiogram and serum troponin were normal. Complete blood count (CBC) revealed marked leukocytosis (50 k/ μ l) with eosinophilia (4.0 k/ μ l), thrombocytopenia (82 k/ μ l) and normal hemoglobin level (15.6 g/dl). Chest X-ray showed mixed interstitial and alveolar infiltrates [Fig. 1a]. Computed tomography (CT) pulmonary angiography ruled out acute aortic injury, but revealed acute pulmonary embolism in the right middle lobe, patchy peribronchial ground glass opacity, consolidation and interlobular septal thickening in bilateral lungs [Fig. 1b]. Doppler ultrasound of the lower limbs was negative for deep vein thromboses. Transthoracic echocardiogram was normal. He was given oxygen by high-flow nasal canula, heparin infusion, and broad-spectrum antibiotics, and was admitted to the ICU.

Infectious workup including blood culture, stool ova and parasites, and serologic testing for *Strongyloides* and coccidiomycosis were negative. Peripheral smear was absent for dysplastic eosinophils. Flow cytometry was negative for a B- or T-cell clonality. Cytogenetic testing of peripheral blood was negative. CT abdomen and pelvis revealed multiple new splenic infarcts without hepatosplenomegaly or lymphadenopathy [Fig. 1c]. To confirm eosinophilia-related end-organ injury and rule out infection, diagnostic bronchoscopy with bronchoalveolar lavage was performed. It revealed a total nucleated cell count of 663 with significant eosinophilia (86%). Transbronchial biopsy showed focal interstitial pneumonitis, foci of organizing pneumonia and clusters of eosinophils within alveolar spaces and interstitium [Fig. 2].

Given significant hypereosinophilia and evidence of end-organ damage, a working diagnosis of HES was made. Treatment with oral prednisone at 1 mg/kg (60 mg) was initiated. Leukocytosis and eosinophilia responded to prednisone [Fig. 3]. Dyspnea improved and the patient was discharged home at room air with prednisone 60 mg daily and rivaroxaban 20 mg daily.

At 2-month follow-up, the patient was asymptomatic with normal WBC (8.4 k/ μ l) and eosinophil count (0.4 k/ μ l) [Fig. 3]. Prednisone was tapered off at 2.5 months. Repeated CT chest at 6 months revealed complete resolution of pulmonary infiltrates. Patient followed with hematology/oncology service every 3 months. He continued to be asymptomatic with excellent performance status and no limitation in daily activities. However,

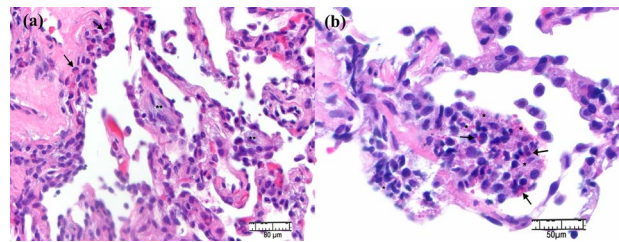


Figure 2: Histologic findings in the transbronchial biopsy (a) interstitial eosinophils (arrows) and small foci of organizing pneumonia (**), H&E, 20 \times , ruler 80 μ m. (b) Intra-alveolar eosinophil clusters (arrows) and eosinophilic granules from degranulated eosinophils (*), H&E, 40 \times , ruler 50 μ m.

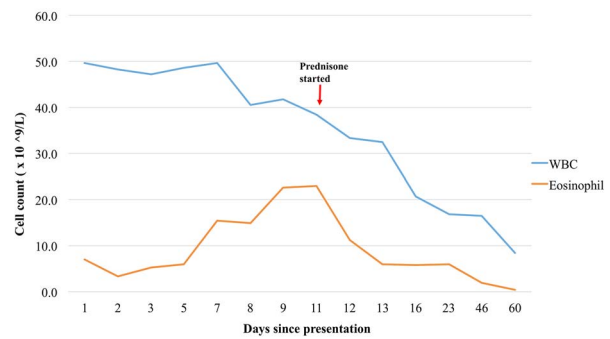


Figure 3: Trending of white blood cell (WBC) and eosinophil counts.

11 months after hospital discharge, CBC showed gradual worsening erythrocytosis (hemoglobin 18.8 g/dl and hematocrit 56%) with low serum erythropoietin level, and increase in eosinophils (3.2 k/ μ l). Bone marrow biopsy with NGS for myeloid mutation panel was performed at 4 months and 11 months post discharge. It revealed recurrent somatic STAT5b N642H mutation and ten-eleven translocation 2 (TET2) mutation. Although no overt myeloid neoplasm was found, given reported association of STAT5b N642H mutation with myeloid neoplasm with eosinophilia [4], the working diagnosis evolved toward myeloid neoplasm with eosinophilia. To control worsening erythrocytosis and eosinophilia, hydroxyurea 500 mg once daily was started. Cell counts subsequently improved. Given the inability to rule

out myeloid neoplasm, patient was committed to long-term anticoagulation therapy.

DISCUSSION

HES with lung involvement can present as acute eosinophilic pneumonia [5]. The radiographic manifestations can resemble pulmonary edema in the active phase with bilateral areas of ground glass opacity and smooth interlobular septal thickening [6]. Persistent eosinophil infiltrates in the lungs can lead to intraluminal fibrosis that resembles organizing pneumonia [6]. HES is a hypercoagulable disorder. Thromboembolism, both arterial and venous thrombosis, is a common complication of HES and can be life-threatening [7].

Recently, NGS targeting genes that are known to be associated with myeloid neoplasms have been increasingly applied to patients with idiopathic HES, especially when a clonal eosinophilia is suspected, but conventional cytogenetic testing is negative [2, 3]. Frequently detected mutations by NGS are genes involving DNA methylation and chromatin modification, such as TET2 [2, 3]. These mutations have also been frequently found in elderly general population (affecting about 10% of persons older than 70 years of age) and are associated with age-related clonal hematopoiesis [8]. Thus the detection of such mutations needs to be interpreted in the context of other clinical and pathological findings when establishing a diagnosis of clonal hypereosinophilia [2]. Recurrent somatic activating STAT5b N642H mutation was recently found in seven cases of idiopathic HES and 20 cases of myeloid neoplasms with eosinophilia [4]. Mutated STAT5b N642H causes enhanced stability of STAT5b dimerization with alteration of downstream gene expression profiles [4]. The overall survival of STAT5b-mutated idiopathic HES cases was only 30 months [4], compared with previously reported 87% of 5-year survival in a cohort of 98 patients with idiopathic HES [3]. Further studies with long-term follow-up are needed to elucidate the clinical significance of STAT5b N642H mutation in patients with HES.

In summary, we reported a case of HES with recurrent somatic STAT5b N642H mutation, suggesting possible underlying myeloid neoplasm. We highlighted the importance of long-term follow-up for disease monitoring in patients with HES.

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CONFLICT OF INTEREST STATEMENT

None.

ETHICAL APPROVAL

Ethical approval is waived for this study.

CONSENT

Written informed consent was obtained.

GUARANTOR

Sudhir Krishnan MD (corresponding author).

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