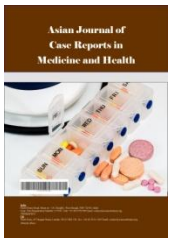

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An Elderly Patient with Abdominal Pain: Hypereosinophilic Syndrome

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Authors' contributions

This work was carried out in collaboration among all authors. Author CSV collected the history, examination, investigation results and its interpretation information from the patient. Author KCH was responsible for radiographic collection, interpretation and description. Author NNT analysed and compiled investigation results, as well as responsible in writing introduction. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Hypereosinophilic Syndrome (HES) is diagnosed when there is peripheral hypereosinophilia with eosinophil count of more than >1500/µL. 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. This case report details a case of hypereosinophilic syndrome in an 80-year-old man with multiple co-morbidities, who presented with unexplained peripheral eosinophilia, intermittent skin rashes, cardiac, respiratory, and abdominal symptoms. 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: Peripheral eosinophilia; skin rash; cardiac symptoms; respiratory symptoms; abdominal symptoms; hypereosinophilic syndrome.

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1. INTRODUCTION

Eosinophilia is commonly seen in clinical practice, in which it is often attributed to parasitic infection, allergy, autoimmune diseases, and drug reactions. Hypereosinophilic Syndrome (HES) is diagnosed when there is peripheral hypereosinophilia with eosinophil count of more than >1500/µL [1]. 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 [1,2]. In recent years, the guidelines have been revised [1,3], 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/µL. 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 not well characterised [1]. The European Medicines Agency estimated the prevalence of HES in 2004 at 1.5/100,000 [4]. The disease commonly affects adults between 20-50 year-old [5,3], predominantly affecting male [1], with no predilection for race [5]. 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% [6]. However, a recent analysis from France noted an 80% survival at 5 years and a 42% survival at 15 years [7].

2. 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, and a recent history of successful cardioversion for symptomatic slow atrial flutter presented with passing dark tarry stool (suggestive of melena) for 2 days. Patient also had a few months history of intermittent non-pruritic rashes (Fig. 1) affecting his upper limbs, which transiently improves with application of hydrocortisone cream 1%. In addition, there was 2-week history of dry cough. He was also on Frusemide 40 mg OD, Apixaban 5 mg BD, Clopidogrel 75 mg OD, Enalapril 10 mg OD, Gliclazide MR 120 mg OD, Atorvastatin 40 mg OD, Metformin 1 g BD, Acarbose 100 mg TDS, Bisoprolol 2.5 mg OD. His elder brother had pulmonary tuberculosis. His son had psoriasis, and gouty arthritis. Till date, there was no known history of allergy to any substances or drugs.

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, consistent with lower lobes of the lungs. He was hemodynamically stable, with blood pressure of 119/55 mmHg and pulse rate of 81 beats/ minute. The cardiac, abdominal, and neurological examinations were normal. He had no lymphadenopathy or evidence of melenic stool on per rectal examination.

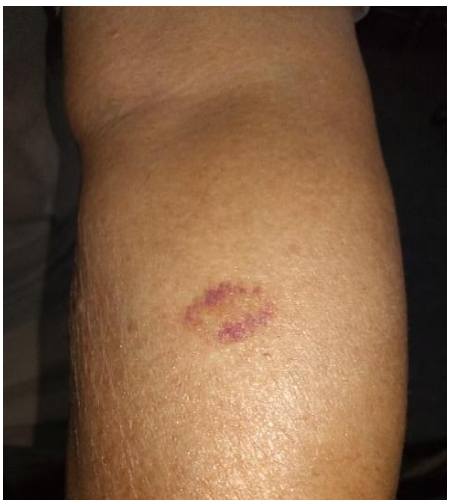

Fig. 1. An annular lesion on left forearm with erythematous-edematous margins and a clear center

He was admitted a few days earlier (prior to the current admission), when he experienced severe episodic generalised abdominal pain, with increasing difficulty to defecate, which patient described as “constipation” During investigation, plain abdominal radiograph showed faecal laden large bowel loops, Haemoglobin was 13 g/dL with haematocrit of 36.9%, and white blood count was 12 x 10^9/L with 34.2% of eosinophils. Erythrocyte sedimentation rate (ESR) was 45 mm/hour. Electrocardiograph detected atrial flutter and variable block, with heart rate of 42 beats per minute (Fig. 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 45 mmHg. 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 (Fig. 3). He was prescribed a course of anti-parasitic medication and Apixaban for thromboembolic prevention. Elective cardioversion was performed. The patient was treated for community acquired pneumonia, and was prescribed Augmentin and Doxycycline, as he was noted to have bibasal coarse crepitations and hypoxia, with oxygen saturations of 92% under air. His condition improved after the antibiotics.

In the current admission, several investigations were repeated. Hemoglobin was 12.7 g/dL with haematocrit of 38.4%, white blood count 15.9 x 10 ^{9}/L, platelets of 376 x 10 ^{9}/L, with eosinophil counts increased to 8300/µL, and eosinophils 52%. There was no blast cell seen on peripheral blood film. Erythrocyte Sedimentation rate was 40 mm/hour at this juncture. 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 (Fig. 4) showed marked upper zone consolidation and computed tomography of the thorax (Fig. 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 (Fig. 5). 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.

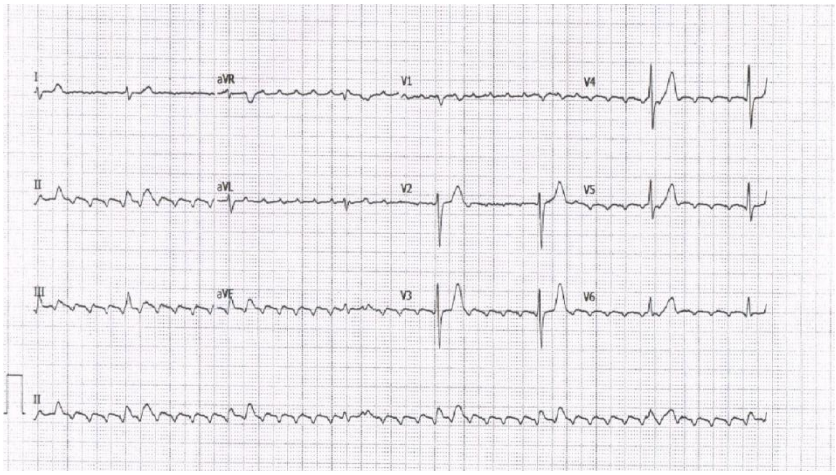

Fig. 2. Atrial flutter with variable atrio-ventricular block, heart rate of 42 beats/minute

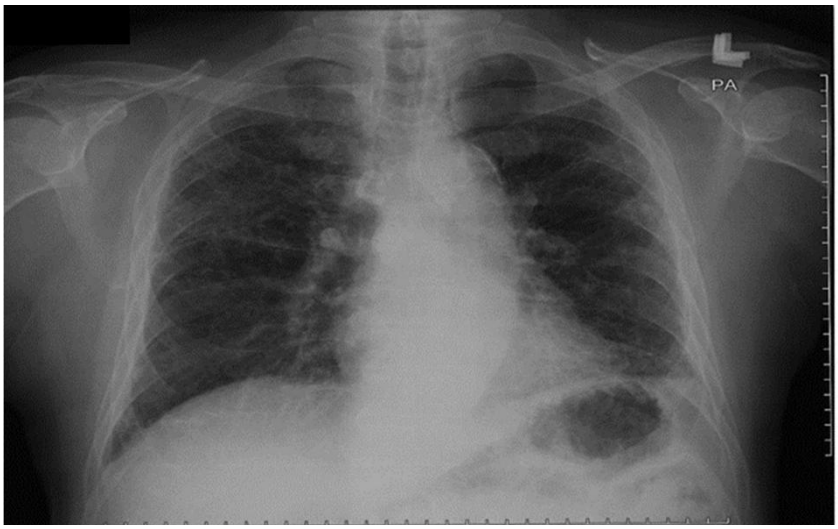

Fig. 3. Bilateral pulmonary fibrosis and bronchiectatic changes associated with calcified mediastinal and right hilar lymph nodes

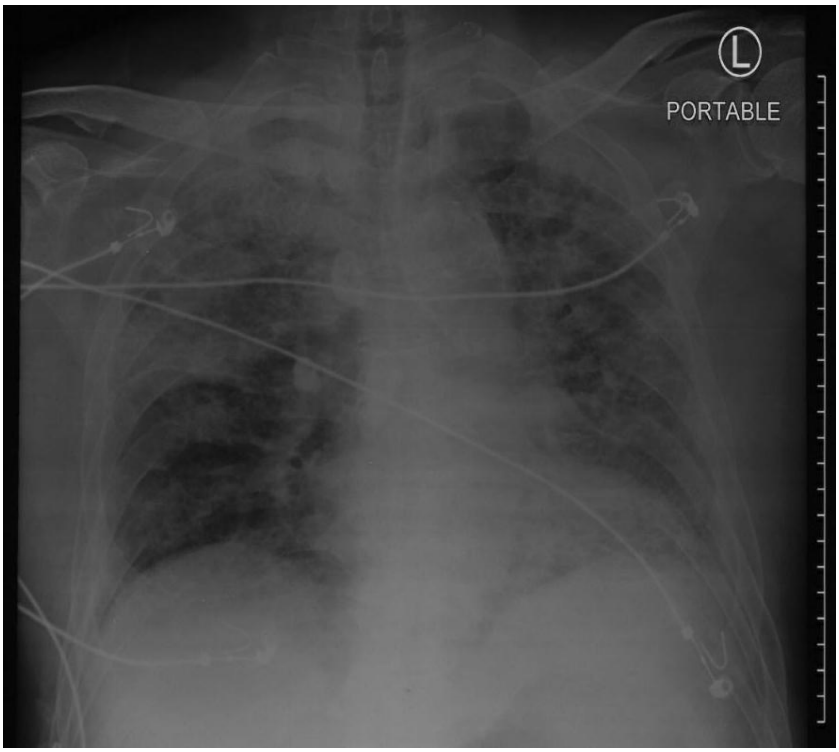

Fig. 4. Marked upper lung zone consolidation, predominantly on the right side

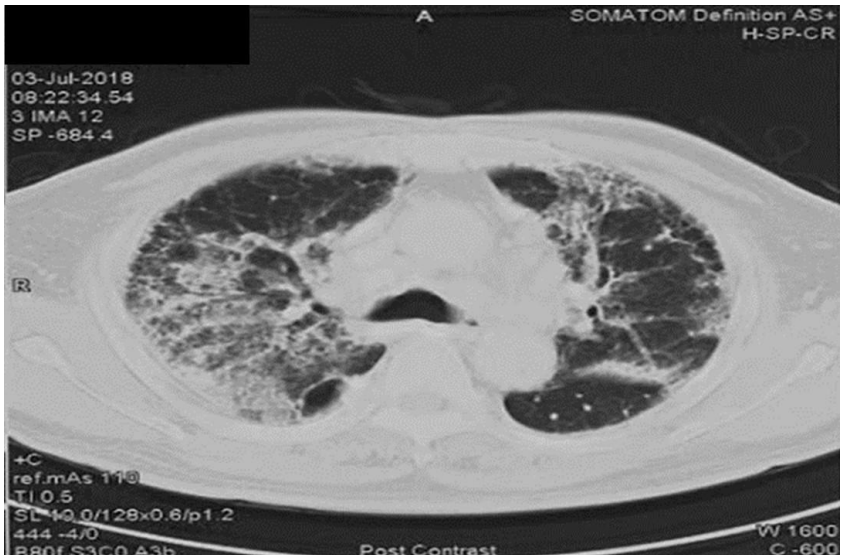

Fig. 5. CT thorax showing bilateral upper lobe alveolitis and peripherally located patchy consolidation

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) was ordered to identify myeloid neoplasms with eosinophilia, which is commonly associated with aberrant gene. He was noted to have negative platelet-derived growth factor receptor A (PDGFRA) and platelet-derived growth factor receptor B (PDGFRB). 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.

Oral Gastro-Duodenoscopy (OGDS) was unremarkable. The patient was treated conservatively for upper gastrointestinal bleed secondary to anticoagulant therapy. He received intravenous Pantoprazole of 40 mg OD, and Apixaban was withheld. He was also treated for eosinophilic pneumonia. The patient received prednisolone of 35 mg twice a day. After 5 days, the eosinophilic count dropped markedly, from a level of 5200/µL or eosinophilic % of 37.6, to 0. A repeated chest radiograph after a few days also showed significant improvement (Fig. 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/µL, with eosinophil % of 1.9. Prednisolone was stopped 10 months after the initial presentation. He remains well and in sinus rhythm a year later.

3. DISCUSSION

This is a case of an elderly patient who initially presented with abdominal pain and difficulty in passing motion. He 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.

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. Myeloid neoplasm with eosinophilia was less likely [1], as the FISH test for the PDGFRA and PDGFRB were negative [1]. In addition, the patient responds dramatically to prednisolone, without the needs for other cytotoxic drugs (such as imatinib) typically seen in patient with myeloid neoplasms with eosinophilia [1]. Chronic eosinophilic leukemia, not-otherwise-specified (CEL-NOS) [1], is less likely as there are no peripheral blast cells identified. Lymphoproliferative variant of HES (L-HES) is a less likely diagnosis, too, as he has a normal level of IgE and immunoglobulin. Thus, by exclusion, this patient is most likely to have idiopathic hypereosinophilic syndrome [1].

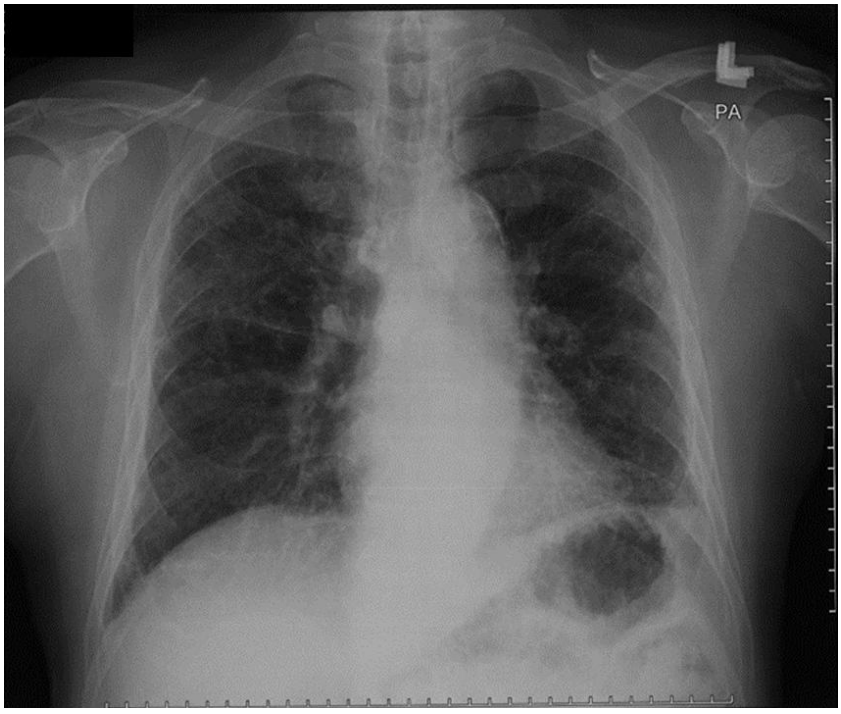

Fig. 6. Improved CXR with resolved consolidation over both upper lung zones

The gastrointestinal and liver involvement are seen in a third of patients with hypereosinophilic syndrome [1,3,8]. 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 [3]. Patients with eosinophilic gastroenteritis typically presents with acute bowel obstruction with nausea, vomiting, crampy abdominal pain, with malabsorption and bloating. Patients can either present with diarrhoea or constipation [9]. Alternatively, the abdominal symptoms could be due to eosinophilic vasculitis [10], as shown in a patient who had perforated colon, with marked eosinophilc infiltration noted in the resected colon histologically [10]. Hence, the worsening of "constipation" with acute abdominal pain in the elderly gentleman here, could be attributed to either eosinophilc gastroenteritis or eosinophilic vasculitis. His symptoms resolved with the initiation of prednisolone. No colonoscopy was done subsequently.

Cardiac involvement occurs in more than 60% of patients with HES [11]. This patient developed significant cardiac involvement with arrhythmia. 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 [1,3]. 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 [3]. Endomyocardial fibrosis is the most common cardiac involvement in HES patients, but it also carries a worse prognosis [11]. The cardiac involvement occurs seemingly early in this patient's presentation. 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 [11]. 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 of prolonged non-productive cough [3,10] and prompt response to oral prednisolone was typical of pulmonary involvement in HES. Other common pulmonary presentations include bronchospasm with nocturnal cough, dyspnoea [11], and transudative pleural effusion [10]. Bronchoalveolar lavage may recover a large number of eosinophils (more than 25%) in HES patients [11]. However, this patient has normal bronchospcopy result, despite a radiological picture consistent with eosinophilic pneumonia. Most patients with HES present with chronic respiratory symptoms [11]. However, in this patient, the presentation was rather acute, with symptoms spanning over a period of 2 weeks, reversible peripheral pulmonary infiltrate within a week. This is suggestive of a more acute presentation of eosinophilic pneumonia. He had no pleural effusion, otherwise.

Dermatologic involvement is seen in more than half (68%) of HES patients [1]. Skin involvement is seldom the only manifestation of HES [12]. Patients usually present with pruritus, atypical urticaria, angioedema [3], atypical rash, or dermatographism [13,14]. Presence of urticaria or angioedema lesion is suggestive of a better long term prognosis of hypereosinophilic syndrome. The cutaneous manifestations in this patient were retrospectively linked to hypereosinophilic syndrome. There was erythematous ring-like margin of the lesion, as shown in Fig. 1. The lesion was non-itchy and bears resemblance to eosinophilic annular erythema [15]. The skin lesion has since disappeared following the initiation of the oral prednisolone.

Prednisolone produces a response in approximately 85% of patients with hypereosinophilic syndrome [1], as in this patient. Corticosteroids are the mainstay of the treatment for HES patients. They usually achieve a rapid response in the number of the eosinophils, as well as a swift return of normal organ function [10]. This is clearly exhibited in this patient with prompt improvement of the eosinophil count and the resolution of the respiratory symptoms, and abdominal symptoms within days, Prednisolone was stopped after 9 months of treatment in this

patient. This patient has a prompt positive response to prednisolone. With no evidence of congestive cardiac failure, the outlook of the disease is favourable [11].

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.

4. 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.

ETHICAL APPROVAL

As per international standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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