ORIGINAL RESEARCH PAPER

Medical Science

HYPEREOSINOPHILIC SYNDROME

KEY WORDS:

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The hyper eosinophilic syndrome (HES) is a rare and heterogeneous condition characterised by persistent eosinophilia and multi organ involvement. HES are pleomorphic in clinical presentation and can be primary or secondary to underlying conditions such as haematological disorders, allergic and autoimmune diseases. We describe a case of a patient with idiopathic hypereosinophilic syndrome with cardiac, pulmonary and cutaneous involvement. He was not steroid responsive and needed a second line agent to suppress his eosinophil counts. Although corticosteroids are the main first line agent for HES, there are new novel therapeutic agents such as tyrosine kinase inhibitors and monoclonal antibodies that have provided with alternative treatment options.

A 51-year-old male presented to the emergency department with a one year history of worsening shortness of breath, wheeze and productive cough. These symptoms were previously investigated by his GP and respiratory physician and was managed as adult onset asthma with steroid and ventolin inhaler. His subsequent lung function test showed no airway reversibility thus this diagnosis was excluded. He also developed a new maculopapular rash over his trunk days prior to admission with no new medications or treatment. He did not have any orthopnoea or paroxysmal nocturnal dyspnoea.

On systems review, he denied having any arthralgia, myalgia, fevers, night sweats, sore throats, abdominal pain, change in bowel or urinary symptoms. No history suggestive of any unintentional weight loss.

On admission he was on symbicort 200/6mg two puffs twice daily and had just completed a weaning dose of prednisolone.

The patient's past medical history was significant for allergic rhinitis and sinusitis for the last two years. He had a functional endoscopic sinus surgery (FESS) with an ear, nose throat surgeon with minimal relief. He had been experiencing post nasal drip which he has been taking inhaler. He was previously employed as automotive industry and reported asbestos exposure for 20 years. He was a lifelong non smoker. There is a family history of atopy but no asthma.

On examination he was noted to have a respiratory rate of 20, blood pressure 135/75, heart rate 95 and afebrile. On respiratory examination, there was reduced air entry bilateral with decreased vocal resonant. HS dual with no added murmurs. His abdomen was soft non tender with soft calves. There was no hepatosplenomealy or lymphadenopathy. There was no chest wall deformity or clubbing. THere was no evidence of any nasal deformity.

Initial blood tests of the patient showed haemoglobin level of 130, a white blood cell count of 27.8 with a raised eosinophil count of 14.62, monocytes 1.31), neutrophils 10.31. The eosinophilia had been persistently high for the past one year, with a previous number of 11.58. Electrolytes, urea, creatinine, liver function tests and coagulation profile of the patient were within normal ranges. He had a Creactive protein (CRP) of 214 (<5), erythrocyte sedimentation rate (ESR) 84 total IgE- 2580, mildly elevated IgG-16.4. Urine examination was normal. Other results such as CMV, HIV, HepB, Hep C, ANA, ENA, ANCA, flow cytometry, C4 and C3 were all within normal ranges. An infective screen was also done which included PJP PCR, mycoplasma PCR, Bordetella serology, three acid fast bacillus, aspergillus precipitins and Galactomannans which all yielded to be negative.

The patient's routine chest xray showed bilateral hazy opacities. Computed tomography (CT) scan of the chest revealed new nodule opacities in both lower lobes with a new left sided pleural effusion. There were also changes in the upper lung zones with ground glass opacities and prominent interstitial markings. There was also suggestion of a left phrenic nerve palsy with an elevated L) diaphragm. There was also evidence of mild cardiomegaly. The CT sinus scan showed evidence of mucosal thickening of the ethmoidal air cells and the frontal sinuses.

The histology of the skin biopsy taken from the area of rash showed interstitial eosinophils with no evidence of small vessel vasculitis. A bone marrow biopsy was done which showed normal cellular marrow with mild increase in eosinophilic precursors.

A lung function test that was done showed a mild restrictive ventilatory defect with mild impairment in gas transfer. FEV1 2.69 (64% predicted), FVC 3.38 (64%), FEV1/FVC 80 (101%), 23.64 (61% predicted) and KCO 4.83. An echocardiogram that was performed showed a normal LV size and function with an EF of 55%. Mildly increased LV wall thickness. Normal RV size and systolic function. No significant valve dysfunction.

The working diagnosis for Mr D.F is that he had hypereosinophilia with pulmonary, cutaneous, cardiac and left phrenic nerve involvement. It was unclear if it was ANCA negative Churg-Strauss or FIP1L1PDGFRA negative hyperoesinophilic syndrome. The lack of previous history of asthma and no vasculitis on the biopsy made Churg-Strauss less likely. He was subsequently diagnosed as having idiopathic hyperoesinophilic syndrome (FIP1L1-PDGFRA negative hyperoesinophilic syndrome) given the persistent eosinophils count

He was restarted on 25mg Prednisolone course and continued his inhaled Symbicort. Mepolizumab was subsequently added as he had persistent eosinophilia despite steroid use. He responded to treatment well and follow up on her eosinophil count was 7.63. Unfortunately, due to the high doses of steroids he developed oesophageal candidiasis which needed fluconazole treatment.

DISCUSSION:

Hypereosinophilic syndrome (HES) is a subset of idiopathic eosinophilia first described in 1968 by Hardy and Anderon[1]. It is a myeloproliferative disorder characterized by an abnormal accumulation of eosinophils in blood and peripheral tissues that can lead to organ failure.HES is a rare syndrome that comprises a heterogeneous group of conditions Approximately one-third of HES cases are secondary to neoplastic diseases, with the remaining cases are classified as reactive or idiopathic. Lung involvement is seen in up to 67% of cases and may be the presenting manifestation of the disorder.

It primarily affects males with a male-to-female ratio of 9:1. There is no racial predilection, it is commonly diagnosed in those aged being between 20-50 with a peak incidence in the forth decade of life. A prior literature review observed the 5 years survival rate to be at 80%, decreasing to 42% at 15 years. Poor prognostic factors include other myeloproliferative syndrome, lack of response to corticosteroids, existence of cardiac disease, male sex, and the

degree of eosinophilia6. Cardiac/thromboembolic diseases such as cardiomyopathy accounts for 43% of the estimated mortality rate in HES, followed by neurological causes (33%) and infection 19%[2,3].

The diagnostic criteria for the diagnosis of idiopathic hyper eosinophilic syndrome is outlined below[2]:

- A sustained absolute eosinophil count (AEC) greater than >1500/µl, which persists for longer than 6 months
- No identifiable etiology for eosinophilia (such as parasitic infection or allergic disease)
- Signs and symptoms of organ involvement

The differentials for hypereosinophilia can be divided into the following groups[10]:

- Allergic/hypersensitivity diseases: Asthma, rhinitis, drug reactions, allergic bronchopulmonary aspergillosis
- Infections strongyloidiasis: Toxocara canis, Trichinella spiralis, coccidioidomycosis and cryptococcus
- Connective tissue diseases: Churg-Strauss syndrome, Wegener granulomatosis
- Pulmonary diseases Bronchiectasis, cystic fibrosis, Loeffler syndrome, eosinophilic granuloma of the lung
- Cardiac diseases Tropical endocardial fibrosis, eosinophilic endomyocardial fibrosis or myocarditis
- Skin diseases Atopic dermatitis, urticaria, eczema, bullous pemphigoid, dermatitis herpetiformis, episodic angioedema with eosinophilia (Gleich syndrome)
- Gastrointestinal diseases Eosinophilic gastroenteritis, coeliac disease
- Malignancies Hodgkin and non-Hodgkin lymphoma, acute lymphoblastic leukemia, Langerhans cell histiocytosis
- Immune system diseases/abnormalities Wiskott-Aldrich syndrome, hyper-IgE (Job) syndrome, hyper-IgM syndrome, IgA deficiency

The primary goal of HES is to reduce the eosinophil levels in the blood and tissues. Treatment for HES has revolutionised since the discovery of FIP1-like1–platelet-derived growth factor receptor (FIP1L1PDGFRA). This is the result of interstitial deletion on chromosome 4q12 and subsequently fusion of the 5' segment of the FIP1L1 gene to the 3' portion of the PDGFRA gene. This activated fusion tyrosine kinase transforms haematopoietic cells leading to an excessive eosinophil growth[3,4].

The first like therapy for patients without FIP1L1-PDGFRA gene mutation is glucocorticosteroid medications such as prednisone. It is indicated for those with organ damage and useful for eliciting rapid reductions in the eosinophil count. For those that lack steroid responsiveness, the second line therapy is cytotoxic therapy. Hydroxyurea is an effective second-line chemotherapeutic for HES, some benefits has also been reported for other agents including vincristine, chlorambucil, cyclophosphamide and interferon alpha. Remissions have been associated with clinical improvement and organ disease such hepatosplenomegaly, cardiac and thromboembolic complications, mucosal ulcers and skin involvement. Bone marrow/peripheral blood stem cell allogeneic transplantation can be attempted in patients with aggressive disease. Disease-free survival ranging from 8 months to 5 years has been reported with one patient relapsing at 40 months. Allogeneic transplantation using nonmyeloablative conditioning regimens has been reported in 3 patients, with remission duration of 3 to 12 months at the time of last reported follow-up[11].

Patients with FIP1L1-PDGFRA mutation are commenced on imitanib, a tyrosine kinase inhibitor. The majority of patients achieve haematological and cytogenetic remission as shown in various cases. The first case of imatinib treatment in HES was reported in 2001. The patient was resistant or intolerant to prior therapies including corticosteroids and hydroxyurea. He was commenced on imatinib and achieved a rapid and complete hematologic remission after taking 100 mg imatinib daily for 4 days. Complete disappearance of peripheral eosinophils occurred by day 35. Imatinib was decreased to 75 mg daily for headaches. It is generally well tolerated with minimal side effects, and most HES patients respond to low doses of imatinib (100 mg/day)[6]. A study conducted in China estimated that 94% with F/P mutated achieved a complete hematologic remission (CHR), and 97% achieved a complete molecular remission (CMR) after a median of 3 (1.5-12) months. Twenty-four cases received maintenance therapy, with a median CMR duration of 43 months. Imatinib therapy was discontinued in 4 cases who experienced relapse[8].

Mr D.R was commenced on Mepolizimub a humanised anti–interleukin-5 monoclonal immunoglobulin G1 antibody. Rothenberg et al examined the use of mepolizimub in patients with HES, the primary end point was the successful tapering of the prednisone dose to 10 mg or less per day for 8 or more consecutive weeks, without any clinical relapse. The primary end point was reached in 84% of patients in the mepolizumab group, as compared with 43% of patients in the placebo group. The results were statically significant. A blood eosinophil count of less than 600 per microliter for 8 or more consecutive weeks was achieved in 95% of patients receiving mepolizumab, as compared with 45% of patients receiving placebo[9].

CONCLUSION:

HES is a heterogenous condition with that have various clinical presentations and prognosis. Recent advances of targeted therapies such as imatinib and IL-5 antibodies have provided us with treatment options as second line agents. Early diagnosis and treatment is essential to prevent organ dysfunction and improve overall morbidity and mortality.

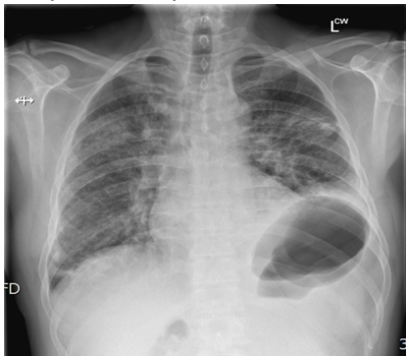

Figure 1: chest xray

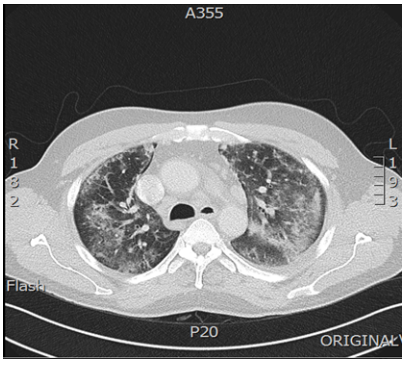

Figure 2: CT chest

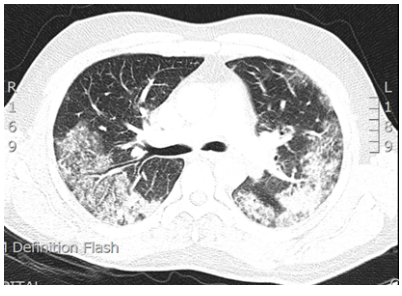

Figure 3: Peripheral ground glass opacities noted in the upper lobes

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