

Hypereosinophilic Syndrome

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Hypereosinophilic syndrome is a rare disease with variable outcome. It is usually a disease of young adults. Involvement of the heart and or lungs occurs in 40-60% of cases which can lead to severe heart and lung failure. Direct tissue eosinophilic infiltration and release of their toxic granules are the main underlying pathology. In this study, we report a young lady presented with a short history of fever, easy fatigability, weight loss and bilateral lung infiltrates. The diagnosis was consistent with Hypereosinophilic syndrome and despite treatment with pulses of intravenous Methylprednisolone, oral Prednisolone, Hydroxyurea and Imitinab Mesylate, the patient unfortunately died because of severe respiratory failure. The age group, striking eosinophilia and fulminant fatal course without neoplasia warranted reporting.

Bahrain Med Bull 2006; 28(1):

The commonest cause of eosinophilia is reactive mainly in response to infection, parasitic infestation, allergic diseases and non-haematological malignancy. Clonal causes of eosinophilia account for less than 1% and include acute and chronic eosinophilic leukemia, chronic myeloid leukemia, acute myeloid leukemia, chromosome 16 variants, 8p 11 myeloproliferative syndromes, T lymphoblastic lymphoma and others. Persistent blood eosinophilia greater than $1.5 \times 10^9/L$ for 6 months or more with damage to end organs such as heart and lung and no ascertainable cause are the three defining criteria for hypereosinophilic syndrome (HES), as described by Hardy and Anderson in 1968^{1,9}. It is usually a disease of young adults commonly affects persons aged 41-50 years with a higher incidence in men than women and whites than blacks. Its manifestations are protean. The significant cause of morbidity and mortality is the tissue damage either due to direct infiltration by eosinophils or secondary to thrombotic problems. Involvement of the heart occurs in 60% of cases in the form of endomyocardial fibrosis, myocarditis and restrictive cardiomyopathy. Pulmonary involvement occurs in 40-60% of cases commonly with chronic persistent dry cough and lung infiltrates. Herein we report a young lady with HES who had an unfavorable outcome.

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THE CASE

A previously healthy twenty-eight year old Pakistani lady presented to hematology clinic in December 2003, with two weeks history of fever, easy fatigability and weight loss. There was no history of bleeding, cough nor bone or joints pain. She was a housewife and a mother of two children. There was no history of recent travel or use of any medications. On examination, she was significantly pale, febrile and had mild tachycardia. Systemic review was unremarkable. Initial laboratory investigations disclosed the following findings: WBC $54 \times 10^9/L$ (54,000 /mm), Eosinophils: $48 \times 10^9/L$ (48,000 /mm), Haemoglobin: 8.8g/dl of normochromic and normocytic indices, Platelets: $305 \times 10^9/L$, Reticulocytes: 1%, Peripheral Blood Film revealed absolute mature eosinophilia with some degranulation^{3,9}. Neither immature leukocytes nor eosinophil blasts were seen. Biochemical studies showed normal electrolytes, renal, thyroid and liver function tests. C-reactive protein was 125 mg/L, LDH was 405 units /liter and uric acid level was normal. Antinuclear antibody titer was 1:80 (equivocal). Both Smith antibodies for extractable nuclear antigens and Sjogren syndrome A+ B extractable nuclear antigens were negative. Hepatitis B surface antigen, hepatitis C virus antibody and HIV 1+2 antibodies were negative. Stool and urine analysis were repeatedly normal with no evidence of parasitic infections. Thick and thin Blood films were negative for malaria and Zeihl-Nelsen staining of sputum was negative for Tuberculous Acid Fast Bacilli (AFB). Septic screening revealed no organisms. IgE level was 151 KU/L (n=0-195 KU/L). Bone marrow aspirate and biopsy showed hypercellularity with myeloid hyperplasia. Sheets of eosinophils and their precursors were seen.

Figure 1

There were no blasts nor fibrosis. Cytogenetic analysis was normal and molecular analysis of BCR-ABL Philadelphia chromosome was negative. The mediastinal lymph node was biopsied and revealed the presence of eosinophilic granulomas with no evidence of lymphoma.

Figure 2

Arterial blood gases showed PH: 7.5, PO₂: 7.66, PCO₂: 4.09, HCO₃: 23.6 mmol/L, and O₂ saturation: 92.6% on room air. Chest X-ray showed mediastinal enlargement and bilateral lung infiltrates, more on the left side.

Figure 3

High resolution C.T. scan (HRCT) of the lung with contrast showed sizeable amalgamated lymph nodes in the superior mediastinum, preaortic, aortopulmonary, subcranial, left hilar and infrahilar areas. No calcifications or necrosis were seen. Thin ground-glass patchy opacities were seen in the left middle and lower lobes of the lungs.

Figure 4

Transbronchial lung biopsy revealed eosinophilic infiltration of the parenchyma and invasion of bronchi. Abdominal ultrasonography showed hepatomegaly, with no focal lesions. The spleen was moderately enlarged with multiple hypodense areas. Her kidneys, pancreas and other organs were morphologically normal. Initial ECG and echocardiography studies showed sinus Tachycardia. The patient was admitted to the major care and started on pulse doses of Methylprednisone (1gram intravenously daily for 3 days), with Allopurinol and hydration. The eosinophil count was reduced to normal levels on Hydroxyurea one gram twice daily and oral prednisone 0.5 mg /kg/day. The patient was maintained in stable condition and eosinophils count dropped to less than $0.4 \times 10/L$ ($0.04-0.4 \times 10/L$)⁹. She was sent home on oral Prednisolone 30 mg daily with weekly follow up in haematology clinic. One month later, she developed chest pain and dyspnea. Chest examination revealed bilateral fine crepitations. Blood tests showed an increase in white cell count to $44 \times 10/L$ and eosinophilis $38 \times 10/L$ ⁹. Other indices were within normal ranges. ECG showed sinus tachycardia and repeated chest x-ray showed worsening in her lung infiltrates.

Figure 5

The repeated HRCT scan study revealed diffuse patchy consolidations with air bronchogram in both lungs. The echocardiography showed moderate restrictive cardiomyopathy, minimal pericardial effusion, but no thrombi. The second course of pulse Methylprednisone was given with resumption of Hydroxyurea to two grams twice daily. This was followed by oral Prednisone 1 mg/ kg /day. The eosinophil count dropped to $2.4 \times 10/L$ (0.27% of total WBC)⁹. Despite cardiac and respiratory supportive measures, her lung condition did not improve and she was started on Imatinib Mesylate STI- 571 (Gleevic) 100 mg daily. This was increased gradually to 400 mg daily for a total of four weeks. However, her general condition deteriorated and required mechanical ventilation due to severe hypoxemia and persistent cardiac failure. She developed bilateral pleural effusions, which required repeated pleural tapping and right-sided chest tube insertion. The pleural fluid yielded significant numbers of mature eosinophils, whereas the peripheral eosinophil count was maintained to less than $3 \times 10/L$ ⁹. The skin around the chest tube became inflamed and swollen and the patient was started on broad spectrum intravenous antibiotics immediately. The cultures from the chest tube site and blood revealed the growth of *Pseudomonas Aeruginosa* which was sensitive to the antibiotics. Her condition continued to deteriorate and the patient died despite full supportive therapy.

DISCUSSION

Hypereosinophilic syndrome is defined as persistent eosinophilia characterized by the presence of more than 1500 eosinophils per micro liter, for more than six months, with multi organ involvement in the absence of other causes of eosinophilia and absence of eosinophil blast cells in the bone marrow or blood. Its presentation varies from asymptomatic to a life-threatening multisystem disease. It appears to be influenced by cytokines, including IL-3, IL-5 and GM-CSF². IL-5 is the most specific for eosinophil lineage, especially their differentiation and release. The migration of eosinophils into tissue is initiated by local chemo attractant molecules such as leukotrienes³. Eosinophils can survive in tissues for extended periods with unknown life span. Their granules contain major proteins that are very toxic to the tissues involved, causing fibrosis,

thrombosis and infarction⁴. Virtually any organ system can be involved and damaged in HES, most commonly the cardiovascular system, lungs, nervous system and the skin. The heart is involved in 60% of cases and the most serious involvements are endomyocardial fibrosis, myocardial infarction and restrictive cardiomyopathy. The most likely mechanism is deposition of eosinophilic toxic granular contents. This ultimately will cause endomyocardial fibrosis, mural thrombus formation and valvular insufficiency⁵. This patient developed severe restrictive cardiomyopathy and pericardial effusion, but there was no clinical evidence of thrombosis. Pulmonary involvement can be seen in 40-60% of cases⁵. The most common respiratory symptoms are persistent cough, wheezing and dyspnea, which may lead to confusion with bronchial asthma. However pulmonary function tests typically reveal no airflow limitation⁵. Chest radiography may reveal non-specific focal or diffuse, interstitial or alveolar infiltrates. In addition, HRCT scan usually reveals pulmonary nodules with a halo of ground-glass attenuations, as well as non-specific focal or diffuse, interstitial, or alveolar infiltrates. Pulmonary involvement in HES may be secondary to congestive heart failure or emboli originating from right ventricular thrombi or may reflect primary eosinophilic infiltration of lung parenchyma⁵. Bronchoalveolar lavage may recover large number of eosinophils in HES patients. In this patient, the chest x-ray initially showed mediastinal and hilar lymph nodes with diffuse interstitial lung infiltrates, while in the late stage her chest x-ray showed extensive pleural effusion and diffuse patchy consolidation with air bronchogram. HRCT Scan of the lung showed the classical ground-glass attenuations on both lung fields. Bronchoalveolar lavage showed large number of mature eosinophils. Almost 50% of HES patients develop neurological involvement⁶. This could be due to intracardiac microthrombi or diffuse central nervous system dysfunction of unknown etiology, causing behavioral changes, confusion and dementia⁷. Peripheral neuropathies, motor and sensory can be found in 50% of HES cases, possibly, due to direct peripheral eosinophil infiltration⁸. This patient had depression and mood changes but no peripheral neuropathies. However, the neurological examination was normal and the CT scan of the brain showed no obvious abnormalities.

The aim of management is to lower the eosinophil count and to decrease the symptoms produced by eosinophilic end-organ damage. Prednisolone is usually the drug of choice with a dose of 1 mg/kg/day. It reduces the effect of released eosinophil contents, reduces blood eosinophilia and suppresses inflammation⁹. Other drugs such as Hydroxyurea can be used for steroid-resistant patients at a dose of 1-2 g/day. Similar cases have been reported in the literature. Four Arab patients were found to have HES, with variable presentations. They were treated with steroids. Two of them have shown complete response, to steroid therapy, while the other two were treated additionally with Hydroxyurea and other immunosuppressive agents¹⁰. All had good outcome with the therapy regimen used. The use of Vincristine, Chlorambucil and Etoposide should be restricted to patients with persistent non-responsive end organ damage because of the small risk of myelodesplastic syndrome or secondary leukemia¹¹. Alpha-interferon showed benefits in steroid-resistant cases¹². Recently, Imatinib Mesylate (Gleevec), a small molecule inhibitor of tyrosine kinase, has been reported to be effective in the treatment of HES. Patients with hypereosinophilia and fusion of the fip-1-like 1 gene (FIP₁L₁) and the gene that encodes platelet-derived growth factor receptor α (PDGFRA) were found to have a good response to Imatinib Mesylate¹³. The starting dose of Gleevec is 100 mg orally daily; the dose can be escalated to 400 mg/d in case of disease progression or lack of response¹⁴. Five patients with HES and two patients with eosinophilia-associated chronic myeloid disorders were included in a prospective

study for the effectiveness of Imatinib Mesylate. This study showed that Imatinib was very effective in resolution of the peripheral eosinophilia and attaining clinical remission in two patients whereas the treatment was abandoned in a third patient due to drug toxicity¹⁵. This patient had transient response to corticosteroids, with no additional benefit from Hydroxyurea. Imatinib was started at a dose of 100 mg per oral per day, and then it was escalated to 400 mg/day for a total of 4 weeks with no signs of response. Despite the multiple therapies, the patient didn't improve and died. Recently a neutralizing anti-interleukin-5 antibody (mepolizumab) was reported to be effective in controlling this disease¹⁶. It is essential to look for cytogenetic, molecular, and other evidence of clonality as up to 25% of patients will be found to have a clonal disease of T-cells. Tissue eosinophilia involvement is not always directly related to the level of blood eosinophils, emphasizing the importance of frequent regular out-patient follow up in which thorough patient assessments should be done including radiological and molecular tests¹⁷. Some cases of HES with progressive disease or bone marrow fibrosis may benefit from allogenic bone marrow or peripheral stem cells transplantation¹⁸. Death generally results from primary heart damage, secondary cardiac complications such as endocarditis or from the thromboembolic complications of the syndrome. In the past, HES was almost always a fatal disease mainly due to late presentation and the mean survival duration was nine months. At present, a prolonged survival over decades has been reported in some cases because of the advanced methods for diagnosis, intervention and prevention of the complications²⁰. It is likely that the next few years will see an improvement in our understanding of this disease through extensive clinical and laboratory studies, with obvious implications for improved management.

CONCLUSION

The patient described here is notable because of her fulminant course with progressive lung and heart infiltration and subsequent complications, without evidence of clonality or neoplasia. Different modalities of therapy were used including Imatinib mesylate, which is a promising medication in HES, but in this patient was ineffective

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