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Job's syndrome with an atypical presentation

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Abstract

Hyper Immunoglobulin E syndrome also called Job's or Buckley Syndrome is a rare primary immunodeficiency disease characterized by elevated serum IgE levels (>2000 IU/ml), recurrent infections and eosinophilia. Other features include coarse facies and non-immunologic abnormalities of the dentition, bones, vasculature and connective tissues. We are reporting a case of a twenty four years old male with coarse facies who presented with severe pallor and upper gastrointestinal bleeding. Investigations revealed markedly elevated serum IgE levels (11,800 IU/ml), severe anaemia, esophageo-duodenal erosions, Helicobacter pylori (H. pylori) gastritis and oro-esophageal candidiasis.

Keywords: Hyper IgE syndrome, H.pylori infection, Job's syndrome.

Introduction

Hyper IgE syndrome (HIES), also known as Job's or Buckley Syndrome is a rare, genetic disorder characterized by recurrent infections with many bacteria, fungi and some viruses. There is a frequent involvement of skin, sinuses and lungs. Other manifestations include abnormalities of bones, teeth and vasculature.^{1,2} The symptoms may appear early in childhood or present late in adult life. This syndrome is characterized by very high IgE levels, usually more than 2000 IU/ml. The mutation in the signal transducer and activator of transcription 3 (STAT3) gene has been identified in autosomal dominant variety of HIES3. We describe here a case of Job's syndrome with an atypical presentation, diagnosed on the basis of characteristic facies, fungal infection and laboratory investigations.

Case Report

Twenty-four years old male, labourer by occupation was referred to our outpatient facility in September 2010 with complaints of epigastric pain, heartburn and black stools for two weeks and exertional dyspnoea for five days. There was no history of haemetemesis or changes in



Figure-1: Characteristic facies of patient with Job Syndrome (taken with permission of the patient).

bowel habits. He had been admitted recently in his native town with chest infection and anaemia. He had two to three episodes of diarrhoea in the past which resolved within 2-3 days by fluids and anti-diarrhoeal treatment. He had normal dietary habits and there was no history of addiction. He was born of a consanguineous marriage but his family history was unremarkable. On examination his weight and height were 47kg and 165cm respectively and he had stable vitals and was severely anaemic. Coarse atypical facies were noticed with a prominent forehead, deep set eyes, broad nasal bridge, wide fleshy nasal tip and mild prognathism as shown in Figure -1a and b. Oral examination showed a high arched palate with a normal dentition.

The skin examination revealed multiple boils on the arms. An evidence of phlebitis was evident two days after admission in the area where the intravenous line was placed. The systemic examination and digital rectal examination were unremarkable

The complete blood picture revealed haemoglobin of 4.0gm/dl with an MCV of 57.5 fl, total leukocyte count 10,600/mm³ (neutrophils 46.4%, lymphocytes 13%, monocytes 3.8%, eosinophils 36.6%, basophils 0.2%) and platelets 336,000/mm. The peripheral blood film showed hypochromia and microcytosis. The ESR, reticulocyte count and LDH were within normal limits and Coomb's test was negative. C reactive protein was low (0.1mg/dl; reference limit 0.8mg/dl) and serum transferrin saturation

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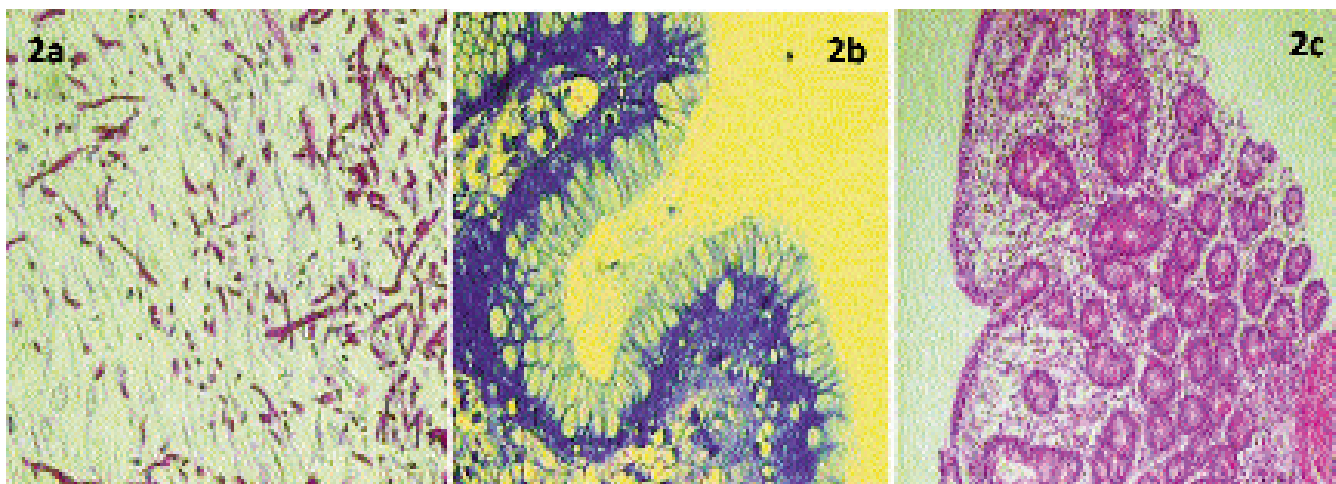


Figure-2: (a) Esophageal mucosal biopsy showing pseudohyphae suggestive of candidiasis. (b) Antral mucosal biopsy showing *Helicobacter pylori* infection. (c) Duodenal mucosa showing villous stunting and increased intra-epithelial lymphocytes suggestive of sprue.

was 0.8%. Serum B12 and folate levels were normal. The liver and renal function tests were normal and so was the bone chemistry. The stool detail report showed no ova or worms but it was positive for occult blood. Serum anti-HCV and anti-HIV antibodies were negative. Upper gastrointestinal (GI) endoscopy showed two large linear ulcers and whitish exudates in the distal esophagus, pangastric erythema and duodenal erosions. Esophageal biopsy showed severe candida infection (Figure-2a) while the antral biopsy revealed severe degree of *H. pylori* infection (Figure-2b). Duodenal biopsy depicted features consistent with sprue (Figure-2c). The lower GI endoscopy was unremarkable except recto-sigmoid biopsy which showed mild chronic nonspecific colitis. Serum IgE was very high at 11,800 IU/ml (Reference range <150 IU/ml) while serum IgG, IgA and IgM were within normal limits. Anti tissue transglutaminase and anti gliadin antibodies were absent. Serum anti-nuclear antibodies (ANA) were weakly positive (titer= 1:40). Ultrasound abdomen showed mildly enlarged liver with increased echogenecity. No pleuro-pulmonary pathology or skeletal abnormality was seen on radiographs of chest and spine respectively.

Final diagnosis was made as Hyper IgE syndrome (typical facies, invasive fungal infections, very high serum IgE levels and very low CRP) with an unusual presentation of severe anaemia, *H. pylori* infection and atypical tropical sprue.

Patient was treated with fluconazole for esophageal candidiasis and anti- *Helicobacter pylori* regimen (clarithromycin, amoxicillin and omeprazole). Phlebitis

and boils on extremities were managed with amoxicillin/clavulenate with good response. Intravenous iron supplementation was provided for correction of the documented iron deficiency. Ascorbic acid was given as it has been reported to improve the chemotactic responsiveness of neutrophils from patients with recurrent infection and high IgE levels.¹ Patient's condition improved after getting treatment with ciprofloxacin and folic acid for atypical tropical sprue.

Discussion

HIES is a rare multisystem primary immunodeficiency disorder in which there is an abnormal chemotaxis of leucocytes often accompanied by abnormalities of connective tissues, dentition and skeleton. It affects both males and females of all ethnic backgrounds. Exact pathogenesis is unclear and under debate. According to few reports it may be due to an imbalance in Th(helper) 1/ Th2 cytokines.⁴

Patients with HIES present with prominent forehead, deep set eyes, broad nasal bridge, wide fleshy nasal tip and mild prognathism.^{1,2} Dermatitis is present in more than 80% of these patients that usually begins in early childhood and may mimic atopic dermatitis. The skin and soft tissue infections may present in the form of cellulitis, furunculosis, paronychia, suppurative adenitis and 'cold' abscesses.¹ IgE level in HIES is usually higher than 2000 IU/ml however, it does not correlate with disease severity. Eosinophilia is also reported as a common finding in majority of these patients.²

The syndrome is mostly inherited as autosomal dominant

(AD-HIES) with variable expressivity however autosomal recessive (AR-HIES) and sporadic cases are also reported. Autosomal dominant variety is caused by mutations in signal transducer and activator of transcription 3 (STAT3) gene and is characterized by the presence of skin and lung infections, elevated serum IgE, and various connective tissue, skeletal, and vascular abnormalities.³ STAT3 mutation leads to diminished Th17 response resulting in absent IL-17. This results in decreased chemotaxis and acute phase response that is responsible for recurrent infections.³

The etiology of AR-HIES is under debate. The AR-HIES manifests as eczema, recurrent bacterial and viral skin infections but lacks the connective tissue and skeletal manifestations.⁵ HIES may be caused by the mutation of a single or multiple genes, or deletion of contiguous genes in a short chromosomal region.¹

Our patient had multiple features suggestive of HIES. His typical facies and high serum IgE levels together with eosinophilia, esophageal candidiasis, and skin infections were highly suggestive of HIES.^{1,2} Absence of skeletal, dental and pulmonary pathology indicates autosomal recessive pattern of inheritance however genetic analysis is needed for confirmation.⁶ The candidal infection noted in the esophagus is in conformity to the description of Job's syndrome.¹⁻³

The work-up for initial presentation of severe anaemia

revealed *Helicobacter pylori* infection and features of tropical sprue. This is an unusual mode of presentation for a primary immunodeficiency and hence can be missed or can cause a delay in the diagnosis if not properly investigated.

Consent

Written consent was taken from the patient to publish this case report.

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