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Job Syndrome in a Patient with Seronegative Refractory Celiac Disease: A Case Report

Hussain SZ[2], Khan RTY[*1], Tasneem AA[2], Jariko AA[2], Majid Z[2], Metlo HA[2], Khalid MA[2], Ali I[2], Laeeq SM[2], and Luck NH[2]

[1]Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan

[2]Department of Gastroenterology and Hepatology, Sindh Institute of Urology and Transplantation

[*]Corresponding author:

Raja Taha Yaseen Khan,
Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan, E-mail: raja_taha101488@hotmail.co

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1. Abstract

Job syndrome is a rare genetic immunodeficiency disorder characterized by recurrent infections, cutaneous abscesses and elevated serum IgE levels. Here we report a case of Job syndrome in a patient with seronegative refractory celiac disease. Refractory celiac disease is defined as persistent malabsorptive symptoms with villous atrophy despite of a person being adherent to a strict gluten free diet for a period of 6 to 12 months without any other cause of non-responsive celiac disease and in the absence of overt malignancy. This patient presented with the history of chronic diarrhea, recurrent skin infections like folliculitis, hypereosinophilia (eosinophil >20%) and elevated serum IgE level (IgE 7800UI/ml). He was also labelled as seronegative refractory celiac disease type I based on the clinical presentation and histopathological examination. To the best of our knowledge, Job syndrome in a patient with seronegative type I refractory celiac disease has not been reported earlier in literature

2. Introduction

Hyper IgE Syndrome (HIES), also called Job syndrome, is a rare clinical entity which is defined by the presence of elevated levels of immunoglobulin E (IgE) and recurrent childhood infections and coarse facial features [1, 2]. The symptoms may occur in the early childhood or later in adulthood. Serum IgE levels are usually above 2000 IU/ml [1]. HIES is divided into Autosomal Dominant (AD) and Autosomal Recessive (AR) types of HIES. In majority of the cases there is mutation in signal transducer and activation of transcription (STAT3) [3] which is seen in AD-HIES variety (Type I) of Job syndrome. In contrast, type II or AR–HIES is associated with tyrosine kinase 2 (TYK 2) deficiency [4]. The type II HIES usually presents with recurrent lung infections, eczema and elevated Ig E but it lacks the connective tissue manifestations that are a part of AD-HIES. Life span is shorter in children as compared to their matched adults, while some of them may survive up to their mid adulthood [4]. Recurrent chest infections are the most common cause of death in AR-HIES [4].

Celiac Disease (CD) is an immune mediated disease caused by the gluten hypersensitivity leading to the characteristic small intestinal inflammation [5]. Celiac disease may present variably, some patients presenting with diarrhea and malabsorption (classical CD), while others with constipation, fatigue and depression (non-classical CD) [6]. To the best of our knowledge, Job Syndrome has never been reported earlier in a patient with Celiac disease. We, hereby, describe a case of Celiac disease who was also found to have Job Syndrome.

3. Case Report

A thirty years old male, tailor by occupation, presented to our outpatient clinic with complaints of persistent diarrhea and weight loss of 10 kg over a period of three months. He had no history of dysphagia, fever, jaundice, loss of appetite, altered bowel habits or joint pains. His stool was loose watery in consistency, large in volume and seldom sticky, containing mucus. He denied any history of blood in stool, urgency or tenesmus. He also reported an unin-

tentional weight loss, which was not associated with decrease in appetite or any chronic disease. His past history was significant for recurrent respiratory (pneumonia) and skin infections (folliculitis, cellulitis) since childhood for which he had been seeking medical advice from his local general practitioner. On examination, he appeared emaciated with visible temporal wasting and thin extremities (Figure 1). He was anemic and wasted with a weight of 40 kg, height of 1.57 meters, and a body mass index of 16 kg/m2.

His laboratory investigations revealed hemoglobin of 11 gm/dl, total leucocyte count 5200 cells/mm3, eosinophil count 20%, platelet count 345,000/mm3 and erythrocyte sedimentation rate (ESR) of 18mm in first hour. The peripheral blood smear showed hypereosinophilia with no atypical cells. Serologies for chronic viral hepatitis (HbsAg, HCV antibody) and human immunodeficiency virus (HIV) were negative. Serum iron profile, vitamin B12 and serum folate levels were within normal limits. Lactate dehydrogenase (LDH) and reticulocyte count were within normal range. No pleuro-pulmonary or skeletal abnormalities were noted on chest or spine radiographs, respectively. Ultrasound of abdomen was unremarkable.

Based upon his symptoms, both upper and lower gastrointestinal endoscopies were performed. The upper GI endoscopy showed fissuring of distal duodenal mucosa while gastric and esophageal mucosa appeared normal. Colonoscopy revealed normal colonic mucosa and few erosions in terminal ileum. The distal duodenal biopsy showed features of sprue (Marsh class III b: increased intra-epithelial cells, crypt hyperplasia and moderate blunting of duodenal villi), while rectosigmoid and terminal ideal biopsies showed normal findings. The serum tissue transgulatiminase antibodies (tTG IgA & IgG) and deamidated gluten peptide (DGP) were negative. However, the human leukocyte antigen (HLA) analysis demonstrated presence of HLA DQ 2. Based upon his symptomatology, laboratory and histopathological findings, he was diagnosed as seronegative Celiac disease. Consultation of an expert nutritionist was sought and the patient was advised strict gluten free diet. Since, the complete blood picture showed presence of eosinophilia, further workup was performed including serum immunoglobulin levels. A raised seum Ig E level (7800 IU/ml) and normal IgA (2.53 g/L) (normal range: 0.82 - 4.53 g/dl and IgG 14 g /L (normal range: 7.5-15.6 g/L). As the patient had history of recurrent childhood infections (pneumonias, colitis), typical skin manifestations (folliculitis, celllulitis) and very high IgE levels, immunologist opinion was sought and finally a diagnosis of hyperactive immunoglobulin E syndrome (HIES or Job Syndrome) was established

The patient remained in our follow up on outpatient basis for monitoring of his symptoms. However, despite adherence to gluten free diet (GFD), he continued to have frequent episodes of diarrhea. A repeat upper GI endoscopy was performed one year after commencement of GFD, which showed fissuring of distal duodenal mucosa and decreased height of mucosal folds. Histopathology of duodenal mucosa demonstrated Marsh class III b, which had also been observed before starting gluten restriction (Figure 2A, B). The Immunohistochemical (IHC) markers were applied on the biopsy specimen, which showed positivity for CD3 and CD8, consistent with a diagnosis of refractory celiac disease type 1 (Figure 2C, D). The patient was advised to continue GFD and advised steroid therapy (Prednisone 10mg daily orally), with regular follow-up and family screening.

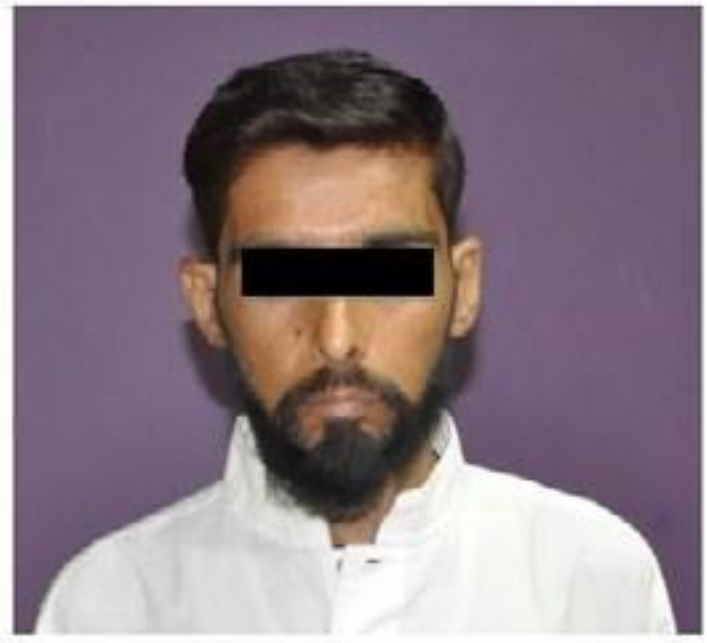

Figure 1: Facies of the patient with seronegative refractory Celiac disease and Job Syndrome.

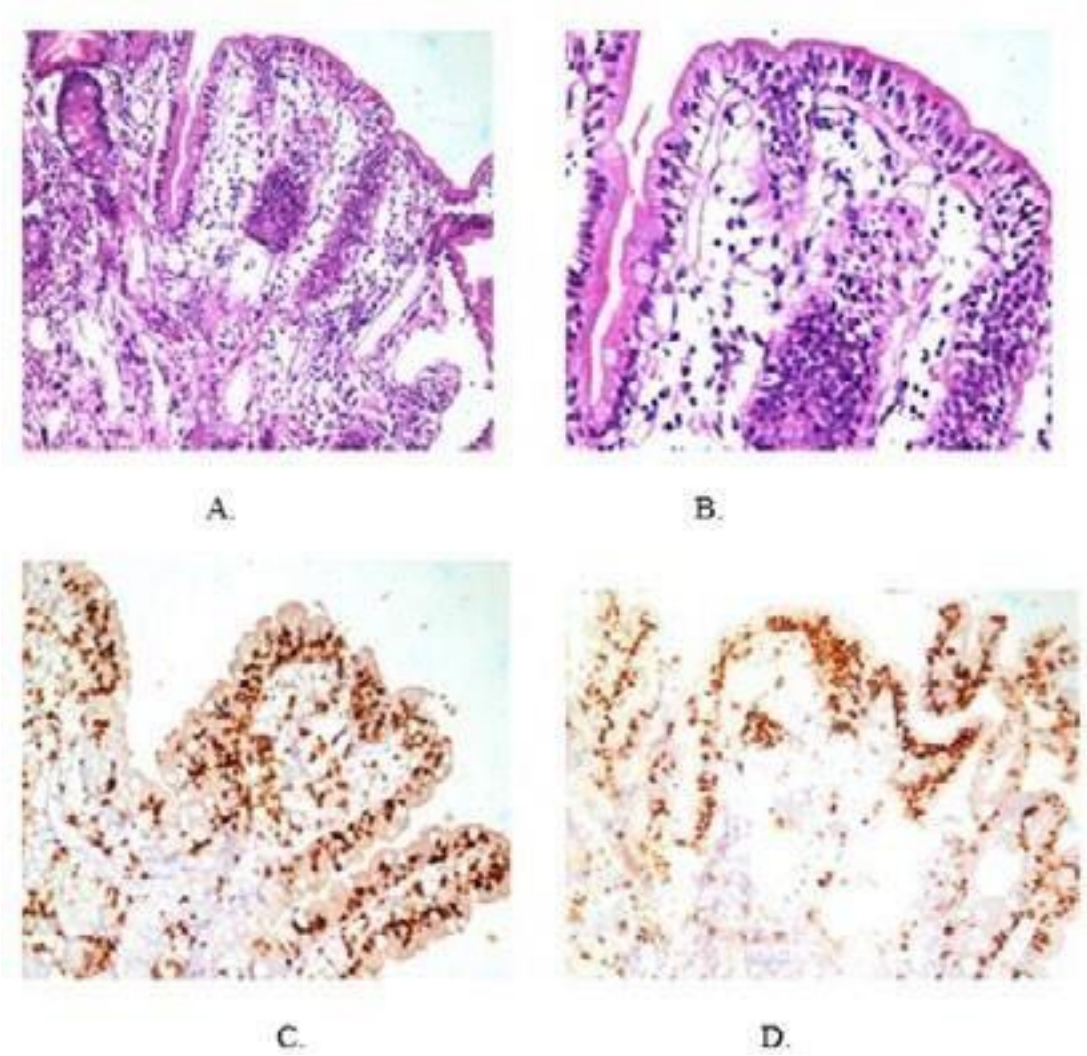

Figure 2: Histologic findings of duodenal biopsy. A. Medium power view of small bowel mucosa with moderate stunting of villi and intraepithelial lymphocytosis (H&E, x 200). B. High power view of small bowel showing increased intraepithelial lymphocytes (>30/100 enterocytes) (H&E, x 400). C &D. Immunohistochemical stains CD3 and CD8 showed expression of CD8 in majority of CD3 positive intraepithelial lymphocytes (IHC, x 400)

4. Discussion

Job syndrome (Hyper IgE syndrome) is a rare, multisystem, primary immune deficiency disorder that was first described in 1966 in two patients with eczema, recurrent pulmonary infections, and cold lung abscesses. Later, in 1972, Buckley et al., [7]. Reported the association of this condition with raised serum immunoglobulin E levels and a series of phenotypic features called HIES or Job syndrome. Patients with Job syndrome were characterized as having eczema, recurrent boils, pneumonia and extremely elevated IgE levels [3]. Patients with AD-HIES have coarse facies, prominent forehead, deep set eyes, broad nasal bridge with fleshy nasal tip and mild prognathism [8]. It is associated with STAT3 mutation which results in impaired neutrophilic chemotaxis leading to recurrent infections [4]. In contrast, patients with AR-HES have same characteristic features except they lack musculoskeltal manifestations of AD-HIES.

Various cases of Job syndrome associated with different kinds of clinical conditions have been reported previously. James et al reported a patient of Job syndrome having cheilitis, depapillation and fissuring of the tongue, high arched palate, multiple keratotic/erosive areas on tongue and buccal mucosa, multiple non-specific ulcers on gingiva and poor oral hygiene [9]. Another case reported by Arora et al showed the retinal detachment with complicated cataract in Hyper IgE syndrome [10]. Another study reported the common gastrointestinal manifestations of Hyper IgE syndrome including gastroesophageal reflux disease (GERD) observed in 41%, dysphagia in 31%, and abdominal pain in 24%. In this study, the most serious complications were food impaction in 13% and colonic perforation in 6% [11]. Furthermore, a report by Alyasin et al., [12] demonstrated Hyper IgE syndrome in a child with presence of unusual skin manifestation such as keratoacanthoma and brain abscess. In our case, the patient had the typical symptoms of Job syndrome including a history of recurrent respiratory infections (pneumonia) and skin infection (folliculitis and cellulitis) with hypereosinophilia and elevated IgE levels (IgE 7800U/ml). Many other cases of HIES have been reported earlier including a case of Non-Hodgkin lymphoma in a patient with Job syndrome

by Gregory et al., [13]; and a report by Sham Berger RC et al. who demonstrated the presence of pneumatocoele in a patient with Job syndrome [14]. This pneumatocoele resulted in a persistent bronchopleural fistula and a pulmonary abscess that required pneumonectomy [14]. Seronegative refractory celiac disease in the setting of Job syndrome has never been described in the literature previously. These patients are likely to have a poor prognosis because development of infections in the presence of already compromised bowel function can further worsen the clinical scenario and overall outcome.

5. Conclusion

This case highlights the importance of extensively investigating a patient, which can reveal very useful information in terms of making an accurate diagnosis, and planning a more efficient therapeutic strategy. Had this extensive work up not been done, there would have been various loopholes in the management leading to imperfectly addressing the problems of the patient. The early diagnosis of this condition is very crucial in preventing the long-term fatal consequences related to this disorder.

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