ASSOCIATION OF PULMONARY HEMOSIDEROSIS AND CELIAC DISEASE

Murat Doğan MD,[1] Mehmet Selçuk Bektaş MD,[2] Şekibe Zehra Doğan MD,[2] Fesih Aktar MD,[2] Yaşar Cesur Prof. MD,[1]

[1] Department of Pediatric Endocrinology, Faculty of Medicine, Yuzuncu Yil University, Van

[2] Department of Pediatrics, Faculty of Medicine, Yuzuncu Yil University, Van

ABSTRACT

Idiopathic pulmonary hemosiderosis (IPH) is a rare disease of unknown autoimmune etiology mainly affecting children and adolescents. We report the case of an 6-years-old boy with cough and tiredness. There were no gastrointestinal symptoms were not determined. Body weight and height were in normal percentiles. Physical examination revealed cutaneous and mucosal pallor, due to severe anemia (hemoglobin 3 g/dL). Infiltrations were seen at the chest X-rays at both lungs, but markedly at left lung. In sputum examinations, hemosiderin-laden macrophages were seen. The diagnosis of IPH was made. The association of IPH and Celiac disease (CD) is well known. Searching associated CD was performed and then confirmed by biological and histological examinations. A gluten-free diet was initiated. Evolution was favorable. Searching for CD in IPH should be done, even in the absence of gastrointestinal symptoms.

Key Words: *Celiac disease, idiopathic pulmonary haemosiderosis.* ***Nobel Med 2011; 7(2): 103-105***

PULMONER HEMOSİDEROZİS VE ÇÖLYAK HASTALIĞI BİRLİKTELİĞİ

ÖZET

İdiyopatik pulmoner hemosiderozis (IPH) çoğunlukla çocuk ve adölesanları etkileyen otoimmun etyolojisi bilinmeyen nadir bir hastalıktır. Biz vakamızda hastanemize öksürük ve halsizlik şikayetleri ile başvuran 6 yaşında erkek bir hastayı sunduk. Hastada gastrointestinal semptomlar saptanmadı. Boy ve kilosu normal persentillerdeydi. Fizik muayenede ciddi anemiye bağlı (hemoglobin 3 g/dL) kutanöz ve mukozal solukluk vardı. Akciğer grafisinde özellikle sol akciğerde belirgin olmak üzere her iki akciğerde infiltrasyonlar görüldü. Balgam incelemesinde, hemosiderin yüklü makrofajlar görüldü. IPH tanısı konuldu. IPH ve Çölyak hastalığı birlikteliği iyi bilinmektedir. Vakamızda da Çölyak hastalığı ile birliktelik araştırıldı ve sonrasında biyolojik ve histolojik incelemelerle doğrulandı. Hastaya glutenden fakir diyet başlandı. Sonraki takiplerde klinik ve radyolojik olarak belirgin düzelme gözlendi. Gastrointestinal semptomlar olmasa bile sistematik bir şekilde IPH'da özellikle Çölyak hastalığı da araştırılmalıdır.

Anahtar Kelimeler: Çölyak hastalığı, İdiyopatik pulmoner hemosiderozis. **Nobel Med 2011; 7(2): 103-105**

INTRODUCTION

Idiopathic pulmonary haemosiderosis (IPH) is a rare disease of unknown autoimmune etiology mainly affecting children and adolescents[1-3]. The diagnosis of pulmonary hemosiderosis is made by combining particular clinical findings (hemoptysis, cough, and dyspnea) and specific roentgenographic and laboratory findings (reticulonodular infiltration on chest X-ray and iron deficiency anemia) together with sputum, bronchoalveolar fluids, or lung biopsy specimens showing hemosiderin laden macrophages[1,2,4,5]. IPH is sometimes associated with celiac disease, especially in children[6]. Evidence for a causal relationship between pulmonary hemosiderosis and celiac disease is lacking.

Treatment with a gluten-free diet alone has beneficial effects not only on the intestinal disease but also on→

the pulmonary disease. We report a new pediatric case of IPH associated with Celiac Disease (CD).

CASE REPORT

A 6-years-old-boy who was healthy before, was brought to our hospital because of no appetite and tiredness that had begun three weeks ago. He had dyspnea and palpitation during playing. Cough and paleness had been realized, 15 days after first complaints beginning. The patient had expectorated non bloody sputum. There was no family history. Body weight and height was between 20 and 25 percentiles, vital signs were normal except respiratory rate (62/minute). On physical examination, tachypneic respiration, crepitant rales on inferior of both lungs and sufl tuber on apex of the left lung. 3-4/6 degree of murmur on mesocardiac focus were found. On laboratory examination, hemoglobin (Hb) was 3 g/dL, hematocrit was 10%, white blood cell count (WBC) was $13.3x10^{9}L^{-1}$, mean corpuscular volume, mean corpuscular Hb, mean corpuscular Hb concentration were 52 fL, 15 pg, 29 pg/dL respectively. Platelet count was $206x10^{9}L^{-1}$. Low serum iron (14.3 ug/dL), ferritin (11.3 ng/mL), vitamin B12 (<150 pg/mL) levels, increased iron binding capacity (388 ug/dL), negative polyspecific direct coombs test were determined and reticulocyte ratio was <1%. Prothrombin time, partial thromboplastin time, serum electrolytes levels, liver and renal function tests were normal. C-reactive protein and erythrocyte sedimentation rate were 3 mg/dL and 20 mm/h respectively. Salmonella, brucella serologies, hepatitis markers, helicobacter pylori serologies were negative.

Anti nuclear antibody, P-ANCA, C-ANCA, anti double stranded DNA were negative and hemoglobin electrophoresis was normal. Tissue transglutaminase antibody immunoglobulin (Ig) G and Ig A, antigliadin Ig G and A were positive and the jejunal biopsy revealed villous atrophy consistent with the diagnosis of CD. Villous atrophy with hyperplasia of the crypts and increased intraepithelial lymphocyte count was found on biopsy examination. Haemosiderin-laden macrophages were seen in sputum examinations (performed for the three times). X-ray roentgenogram was showed infiltrations on both lung, but markedly left lung (Figure 1). On computerized tomography examinations, ground glass appearance, increased alveolar density and consolidations areas were seen. Echocardiographic examination was normal. The patient was hospitalized because of the deep anemia. Although he had tachypneic respiration, bacterial pneumonia was not thought at the diagnosis because of feverless. The patient diagnosed as CD and pulmonary haemosiderosis because of deep

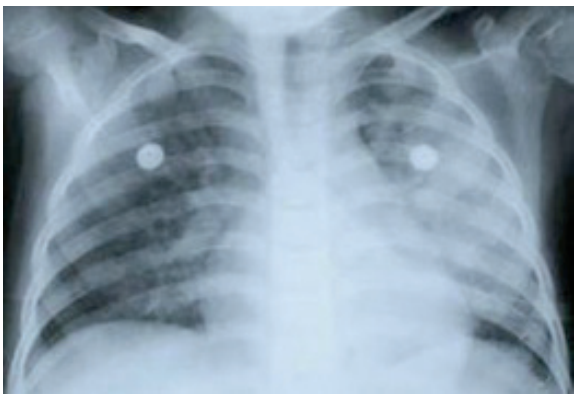

Figure 1. The chest X-ray roentgenogram of patient before the treatment shows infiltrations on both lung, but markedly left lung

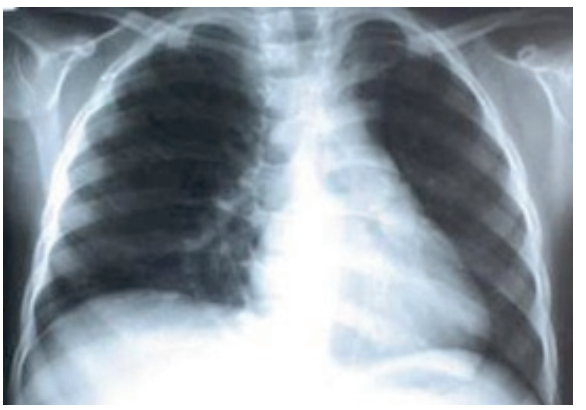

Figure 2. The chest X-ray roentgenogram of patient after the treatment shows normal examination findings.

anemia, feverless, ground glass appearance on thorax tomography examination, negativity of other serologic examinations but positivity of celiac markers and hemosiderin-laden macrophages. Anemia was related to pulmonary hemorrhage and iron deficiency anemia. Gluten free diet was. One week after the diet, his complaints resolved completely (Figure 2). He has been followed for the six months without symptom by the endocrinology policlinic.

DISCUSSION

The triad of anemia, haematemesis and recurrent alveolar hemorrhage doubts diagnosis and the finding of haemosiderin-laden macrophages in bronchoalveolar lavage fluid confirms diagnosis of pulmonans haemosiderosis.[7] In infants with IPH, the co-occurrence with CD has been described, underlining the importance of autoimmune phenomena in this disorder. The combination of IPH and CD has been rarely reported in literature.[8] Our patient had deep anemia, alveolar haemorrhage and heamosiderin-laden macrophages in sputum. So IPH diagnosis was confirmed. However, these symptoms →

did not have a recurrent characteristic. Therefore, we thought that this attack could be the first.

Currently, children with CD manifest clinical signs of malabsorption with significant diarrhoea, steatorrhea, impaired growth, abdominal distension and muscle wasting[9]. Our patient had no signs of classic or non-classic CD. He had only severe iron-deficient anemia. For this and since CD had been previously reported in association with IPH, serological test and intestinal biopsy were performed. The diagnosis of CD is established by positive results of serological testing and evidence of characteristic histopathology on intestinal biopsy[10]. Characteristic histologic features of CD include varying degrees of villous atrophy, with hyperplasia of the crypts and increased intraepithelial lymphocyte count. The criteria proposed by Marsh are often used to grade the disease (from 0 to 4) in terms of these features[11]. Most symptomatic patients have partial, subtotal or total villous atrophy, which are Marsh type 3 lesions. Positive identification of these abnormalities leads to a presumptive diagnosis of CD and institution of a gluten-free diet. Clear clinical improvement while the patient is following the diet yields a definitive diagnosis. As consistent with literature, in our case; anti tissue transglutaminase anticores, anti gliadin anticores were highly rate positive and villous atrophy with hyperplasia of the crypts and increased intraepithelial lymphocyte count was found on examination of biopsy. Therefore, diagnosis of CD was confirmed. The patient was started on a gluten-free diet with iron supplementation. She has had no recurrence of hemoptysis over a follow-up of six months. The resolution of symptoms with gluten free diet is support the diagnosis too.

The mechanism of CD and IPH togetherness is not clear. But, immunological mechanism is suggested to play a role in both CD and IPH[1–5]. There are some hypotheses about the pathogenic mechanism of the association of IPH with celiac disease. The first pathogenic hypothesis is the deposition of circulating immune complexes involving food allergens on the basal membrane of alveolar capillaries. The second one is the cross-reaction between the antireticulin antibodies and the alveolar basal membrane antigens. The third hypothesis is that adenovirus 12, a possible cause of celiac disease, may also have some effects on the lungs[12-14]. Corticosteroids and other immunosuppressants have been used in the treatment of IPH.[1–5] However, in children and adolescents, the long-term treatment can be problematic because of side-effects, and a higher rate of recurrence on trial to taper/discontinue the steroids. We had not used corticosteroids or any other immunosuppressant in our patient. He has remained well on a gluten-free diet alone. His symptoms regressed, and he had no recurrences of hemoptysis over 6 months follow-up.

CONCLUSION

Our case shows that IPH should be considered in patients with deep anemia and infiltration on X-ray roentgenogram without fever, and CD should be specifically looked for in patients with IPH despite the absence of signs of classic or non-classic CD.

C **CORRESPONDING AUTHOR:** Murat Doğan, MD. Department of Pediatric Endocrinology, Faculty of Medicine, Yuzuncu Yil University, Van doganmurat.md@gmail.com

✔ **DELIVERING DATE:** 12 / 01 / 2009 • **ACCEPTED DATE:** 26 / 02 / 2009

REFERENCES

1. Malhotra P, Aggarwal R, Aggarwal AN, Jindal SK, Awasthi A, Radotra BD: Coeliac disease as a cause of unusually severe anaemia in a young man with idiopathic pulmonary haemosiderosis. Respir Med 2005; 99: 451–453.
2. Ioachimescu OC, Sieber S, Kotch A: Idiopathic pulmonary haemosiderosis revisited. Eur Respir J 2004; 24: 162–170.
3. Turay UY, Ergun P, Erdogan Y, Biber C, Demirag F, Keyf IA: Idiopathic pulmonary haemosiderosis. Tuberk Toraks 2004; 52: 382–385.
4. Chu SH, Shyur SD, Peng YH, Wu CY, Chang CL, Lai CL, Wu WC: Juvenile idiopathic arthritis with pulmonary hemosiderosis: a case report. J Microbiol Immunol Infect 2002; 35: 133–135.
5. Hartl D, Belohradsky BH, Griese M, Nicolai T, Krauss-Etschmann S, Roos D, Wintergerst U: Celiac disease and pulmonary hemosiderosis in a patient with chronic granulomatous disease. Pediatr Pulmonol 2004; 38: 344–348.
6. Bouros D, Panagou P, Rokkas T, Siafakas NM. Bronchoalveolar lavage findings in a young adult with idiopathic pulmonary haemosiderosis and celiac disease. Eur Respir J 1994; 7: 1009–1012
7. Collard HR, Schawarz MI.: Diffuse alveolar hemorrhage. Clin Chest Med 2004; 25: 583–92.
8. Reading R, Watson JG, Platt JW, Bird AG: Pulmonary haemosiderosis and gluten. Arch Dis Child 1987; 62: 513–515.
9. Alessio F: Coeliac disease in children. Best Pract Res Clin Gastroenterol 2005; 19: 467–478.
10. Hill ID, Dirks MH, Liptak GS et al. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2005; 40: 1-19.
11. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992; 102: 330-354.
12. Perelman S, Dupuy C, Bourrillon A. The Association of pulmonary hemosiderosis and celiac disease. Apropos of a new case in a child. Ann Pediatr (Paris) 1992; 39: 185–188.
13. Ploier R, Emhofer J, Dorninger L, et al. Immunological aspects of a child with idiopathic pulmonary hemosiderosis and celiac disease. Klin Padiatr 1998; 210: 409–412.
14. Reading R, Watson JG, Platt JW, Bird AG. Pulmonary haemosiderosis and gluten. Arch Dis Child 1987; 62: 513–515.