FT35

A case report of cystic fibrosis with von Willebrand disease

Kistik fibrozis ile von Willebrand hastalığı birlikteliği olan bir olgu sunumu

Büşra ÖZYALVAÇ[1], Sevgi PEKCAN[2], HüseyinTOKGÖZ[3]

1 Necmettin Erbakan University, Meram Faculty of Medicine, Department of Pediatrics, Konya

2 Necmettin Erbakan University, Meram Faculty of Medicine, Department of Pediatrics, Division of Pediatric Pulmonology, Konya

3 Necmettin Erbakan University, Meram Faculty of Medicine, Department of Pediatrics, Division of Pediatric Hematology, Konya

Abstract: Cystic fibrosis, is a common genetic disease in the white race with autosomal recessive inheritance. It occurs as a result of a defect in the chlorine channel called CFTR (Cystic Fibrous Transmembrane Regulatory Protein) in the epithelial cell membrane. Clinical findings are heterogeneous in cystic fibrosis due to involvement of more than one system. Lung findings are the most common findings at all age groups. Hemoptysis is not an uncommon complication of lung involvement and usually occurs as a result of the destruction of the airway wall due to infections due to bronchiectasis. Here, we report a case of von willebrand's disease which was followed up for cystic fibrosis and investigated for recurrent minor hemoptysis.

Keyword: *cystic fibrosis, von willebrand disease, hemoptysis*

Özet: Kistik fibrozis, otozomal resesif kalıtılan beyaz ırkta sık görülen genetik bir hastalıktır. Epitel hücresi membranındaki KFTR (Kistik Fibröz Transmembran Regülatör Protein) adlı klor kanalının defekti sonucunda ortaya çıkar. Birden fazla sistemi tutması nedeniyle kistik fibroziste klinik bulgular heterojendir. Akciğer bulguları tüm yaş gruplarında en sık görülen bulgulardır. Hemoptizi de akciğer komplikasyonu olarak nadir görülmeyen bir komplikasyondur ve genellikle bronşektazi gelişen havayolu duvarının enfeksiyonlar nedeniyle harabiyete uğraması sonucu ortaya çıkar. Burada kistik fibrozis nedeniyle takip edilen hastanın tekrarlayan minör hemoptizleri nedeniyle araştırılırken von willebrand hastalığının birlikte saptandığı bir vaka sunulmuştur.

Anahtar kelimeler: *kistik fibrozis, von willebrand hastalığı, hemoptizi*

Introduction:

Cystic fibrosis is a disease with a autosomal recessive mode of inheritance with an incidence of 1 in 2.000-3.500 live births and a carrier rate of 1/25. (1) CF gene is located in the q22-31 region of chromosome 7. (2) The most common mutation is F508 del. (3) A protein called CFTR (Cystic fibrosis transmembrane regulator) is synthesized from the CF gene. Structural and functional impairment of CFTR protein causes disruption of ion transport in the epithelial cell plasma membrane of organs such as lung, pancreas, liver, intestine, sweat glands and epididymis. (4) Although lung is the most commonly involved organ in CF, clinical findings vary according to the age of the patient, the involved systems and the severity of the disease. (5)

Hemoptysis is a common complication of lung involvement in patients with cystic fibrosis. Bronchiectasis is usually encountered as a clinical evidence of pulmonary endobronchial hemorrhage; the cause of this hemorrhage is the destruction of the airway wall due to infections. Vitamin K deficiency and thrombocytopenia due to hypersplenism also play a role in the development of hemoptysis. (6)

Von Willebrand disease (vWd) is an autosomal inherited bleeding diathesis due to deficiency or dysfunction of von Willebrand factor (vWf). (7) It is one of the most common hereditary bleeding diathesis. Incidence rates obtained by community screening are around 1%. (8) It is typically characterized by mild to moderate skin-mucosal bleeding. (9) There are 3 types and these include Type 1, relative quantitative lack of vWF; type 2, qualitative vWF disorder; and type 3 is a complete quantitative deficiency of vWF. (10) Diagnosis is based on clinical findings and laboratory tests. Initial tests for vWd include vWF antigen (vWF: Ag), ristocetin cofactor activity (vWF: RCo) and Factor VIII activity. (11)

Case:

A 16 year-old girl with cystic fibrosis presented with recurrent minor hemoptysis. The patient who had cough and wheezing since infancy, had productive cough and was found to have less weight than her peers; she was diagnosed with cystic fibrosis based on the clinical findings of cystic fibrosis, and 110 mEq/L sweat test and delF508 homozygous genetics at 11 years of age. Polypectomy was performed three times because the patient had recurrent nasal polyps during follow-up and treatment.There was no bleeding problem after polypectomy. The patient had growth of Pseudomonas aeruginosa for the first time at 14 years of age. He received cefepime + amikacin intravenous treatment for 14 days and then chronic pseudomonas colonization developed. She is currently receiving regular inhaled tobramycin therapy and has had intermittent respiratory exacerbations while taking inhaled tobramycin. He had intermittent minor hemoptysis three times. Her platelet count was 250.000 mm3/uL in hematological examination and platelets were abundant and clustered in the peripheral smear. Among coagulation parameters; APTT was determined to be 34.6 sec (22.5-32) and factor levels were requested, because PT and PTT should be prolonged if the hemorrhage was due to vitamin K deficiency as a result of cystic fibrosis. Laboratory results were found to be as follows: Factor 8 level: 39.2% (70-150), von Willebrand factor antigen level 44% (50-160), and ristocetin cofactor level 42% (50-160). Other factor levels were also studied and were within normal range. The patient was determined to have mild type 1 vWd. Bronchoscopy performed to determine the etiology of hemoptysis showed mild bronchiectasis and no active bleeding foci were observed. On computed tomography, areas of mild bronchiectasis were observed in bilateral lower lobes. No major bleeding problems were observed in the patient who was followed up and treated for cystic fibrosis. Family screening for vWd was planned. The patient was informed about the procedures to be done before interventional procedures and in cases of bleeding. As in our case, it was explained that specific treatment is not required in patients with mild disease and those requiring a minor surgery but desmopressin treatment can be administered when needed, and VWF containing factor VIII concentrates have to be used in vWd's that do not respond to desmopressin or require major surgical intervention. It was also told that tranexamic acid can be used locally and systemically for mucosal bleeding.

Discussion:

Cystic fibrosis is an autosomal recessive inherited disease and the incidence of the disease varies between populations. (1) In countries where consanguineous marriages are common, the incidence of autosomal recessive inheritance increases. Our case is known to be a child of first cousins.

Clinical findings are heterogeneous in cystic fibrosis and vary according to the age of the patient, the systems involved and the severity of the disease. (5) DeltaF508 mutation, which is common for this disease and detected in our case, belongs to the class II mutation group, where clinical findings, especially lung findings, are never synthesized by CFTR protein. (13) Bleeding problems can also be seen in cystic fibrosis and may be in the form of anemia and bleeding diathesis due to deficiencies of fat-soluble vitamins (A, D, E, K). Focal biliary cirrhosis caused by obstruction of intrahepatic ducts may also cause portal hypertension and esophageal bleeding. (12) Hemoptysis is a common complication of lung involvement in patients with cystic fibrosis. Bronchiectasis is usually encountered as a clinical evidence of pulmonary endobronchial hemorrhage (6). In our case, she was diagnosed with von Willebrand disease while investigating for intermittent hemoptysis. Von Willebrand disease is an inherited in an autosomal manner and is a common bleeding diathesis. (7) Clinical presentation is highly variable and depends on the severity and type of vWd. Due to the extremely low FVIII level, type 3 vWd is at risk for deep tissue bleeding and hemarthrosis seen in classic hemophilia and life-threatening bleeding. Clinically, disease severity is typically mild in most type 1 vWd individuals. (14) Our case did not have evidence of serious bleeding. This is wished to be reported because of the fact that although both diseases are inherited in an autosomal manner, the association of these two conditions is a rare situation. Due to the high frequency of consanguineous marriages in our country, the reasons for incidental other bleeding diathesis should be kept in mind and it may not be related to cystic fibrosis.

Conclusion:

Although there are bleeding problems in cystic fibrosis patients, thrombocytopenia or coagulopathy secondary to vitamin deficiency is due to liver dysfunction or local inflammatory damage. It should be remembered that hematological disorders should be investigated in patients with prolonged complaints as in our case.

References:

1 *Romeo G, Devoto M, Galietta LJV. Why is the cystic fibrosis gene so frequent? Hum Genet 1989; 84: 1-5.*

2 *Kerem B, Rommens JM, Buchanan JA, et al. Identification of the cystic fibrosis gene: genetic analysis. Science 1989; 245: 1073-80.*

3 *Bobadilla JL, Macek M, Fine JP, Farrell PM. Cystic fibrosis: a worldwide analysis of CFTR mutations--correlation with incidence data and application to screening. Hum Mutat 2002; 19: 575-606.*

4 *Gadsby DC, Vergani P, Csanády L. The ABC protein turned chloride channel whose failure causes cystic fibrosis. Nature 2006; 440: 477-83.*

5 *Yalçın E. Kistik fibroziste klinik bulgular ve tanı. In: Dağlı E, Karakoç F; eds. Çocuk Göğüs Hastalıkları. İstanbul: Nobel Matbaacılık, 2007; 225-30.*

6 *Boat TF, Acton JD. Cystic Fibrosis. In: Kliegman RM, BehrmanRE, Jenson HB, Stanton BF; eds. Nelson Textbook of Pediatrics. 18 th ed. Philadelphia: Saunders, 2007; 1813.*

7 *Rick ME: von Willebrand disease . Hematology 2003, American Society of Hematology Education Program Book. p:567-572.*

8 *RodeghieroF, Castaman G, Dini E. Epidemıological investigation of the prevalence of von Willebrand's disease. Blood 1987; 69:454.*

9 *Italian Working Group.Spectrum of von Willebrand disease Br.J.Haematol 1977;35:101.*
10 *De Meyer, S.F., H. Deckmyn, and K. Vanhoorelbeke, von Willebrand factor to the rescue. Blood, 2009. 113(21): p. 5049-57.*
11 *Nichols, W.L., et al., Clinical and laboratory diagnosis of von Willebrand disease: a synopsis of the 2008 NHLBI/NIH guidelines. Am J Hematol, 2009. 84(6): p. 366-70.*
12 *McCormick J, Green MW, Mehta G, Culross F, Mehta A. Demographics of the UK cystic fibrosis population: mplications for neonatal screening. Eur J Hum Genet 2002; 10: 583-90.*
13 *Rowntree RK, Harris A. The phenotypic consequences of CFTR mutations. Ann Hum Genet 2003; 67: 471-85.*
14 *De Meyer, S.F., H. Deckmyn, and K. Vanhoorelbeke, von Willebrand factor to the rescue. Blood, 2009. 113(21): p. 5049-57.*