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A Case of Primary Ciliary Dyskinesia Syndrome with Situs Ambiguous

Situs Ambigous'lu Primer Siliyer Diskinezi Olgusu

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Abstract

Primary ciliary dyskinesia (PCD) is a rare autosomal recessive disease that develops as a result of ciliary dysfunction, and that presents with clinical findings that may vary depending on the affected system. Situs anomalies are common with PCD. Although approximately half of all cases are associated with situs inversus totalis, they may rarely be associated with situs ambiguous, which is a rare situs anomaly. We share this case of PCD with situs ambiguous due to its rarity.

Keywords: *Congenital anomalies, DNAAF3 gene mutation, primary ciliary dyskinesia, situs ambiguous.*

Öz

Primer siliyer diskinezi (PSD) nadir görülen, otozomal resesif geçişli, siliyer fonksiyon bozukluğu sonucu gelişen, etkilenen sisteme göre değişen klinik bulgular ile karşımıza çıkan bir hastalıktır. PSD ile birlikte situs anomalileri sık görülür. Olguların yaklaşık yarısı situs inversus totalis ile birlikte iken, nadir görülen bir situs anomalisi olan situs ambiguousun eşlik etmesi az rastlanılan bir durumdur. Nadir görülmesi sebebi ile situs ambiguouslu PSD olgusunu paylaşıyoruz.

Anahtar Kelimeler: *Konjenital anomali, DNAAF3 gen mutasyonu, primer siliyer diskinezi, situs ambigous.*

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Primary ciliary dyskinesia (PCD) is a rare hereditary disorder associated with impaired ciliary function. Normal ciliary function is important for respiratory host defense and sperm motility and ensures proper visceral orientation during embryogenesis (1). Congenital anomalies such as transpositions of great vessels, heterotaxia, cardiac anomalies, infertility and chronic respiratory tract infections may occur as a result of abnormal ciliary function (ciliary immotility or dyskinesia) (2).

During embryogenesis, monociliums in the embryonic nodes (9+0) cause the nodal current of the extra-embryonic fluid (to the left). The nodal current is behind the left-right body asymmetry and deteriorates in cases with abnormal ciliary structures and functions, and in the absence/inactivity of monocilia, allowing thoracoabdominal orientation to develop randomly. In this regard, derogated ciliary motility during embryogenesis leads to the transposition of thoracic and abdominal organs (3).

PCD is classified based on the accompanying situs anomaly, with situs solitus, situs inversus and situs ambiguous (SA) being the three most common situs anomalies. Organs show settlements in the body without complying with a specific order, and SA is a more serious disease than situs inversus, as 90–99% of patients with SA have cardiac anomalies (4,5).

We present here a rare case of PCD with SA diagnosed in adulthood.

CASE

A 31-year-old female patient presented to the emergency department with a recent increase in such symptoms as shortness of breath, cough and sputum, which had been present for the last 10 years. Her medical history included subaortic resection surgery due to a subaortic membrane in childhood, and frequent upper and lower respiratory tract infections since childhood, while her family history revealed her parents to be the children of two sisters. She had a 10-pack/year smoking history. An examination of her respiratory system revealed bilateral, middle and basal rhonchi and right basilary lung crepitations on auscultation, while laboratory findings were as follows: white blood cell count: 12,400/uL, hemoglobin: 12.1 gr/dL, platelet count: 234,000/uL, C-reactive protein: 80.16 mg/L and procalcitonin: 0.07 μg/L, while all other biochemical laboratory findings were unremarkable. A postero/anterior chest X-ray (PA) revealed left tracheal and mediastinal deviation, diffuse bronchiectasis in the left lung, increased air volume in the left lung and heterogeneous opacities in the right lower zone (Figure 1A). A chest computed tomography (CT) scan revealed the heart and mediastinum to be displaced to the left, diffuse atelectasis in the left lung, cystic and tubular bronchiectatic changes in both lung fields and bilateral pleural effusion (Figure 1B).

The patient was admitted to the chest diseases clinic, sputum cultures were obtained and *Haemophilus parahaemolyticus* was isolated, leading to the patient being started on broad-spectrum antibiotics and bronchodilators.

A further investigation for congenital lung diseases was planned due to the history of frequent childhood respiratory tract infections and great vessel operations, and the identification of bronchiectasis and organ location anomalies on thorax CT.

An abdominal CT also revealed left isomerism (polysplenia syndrome), inferior vena cava on the left side of the aorta, a midline position of the liver, and a direct opening of the hepatic veins to the right atrium. and a spleen location in the lower right quadrant. Also observed were appearances compatible with multiple splenosis, the largest of which was 75x40 mm in size (Figure 1C-D). The abdominal CT was reported in accordance with SA. A Waters radiograph taken for the assessment of a chronic upper respiratory tract infection revealed air-fluid levels and poor visualization of the air spaces in the right maxillary sinus, while a paranasal sinus CT revealed mucus retention cysts and mucosal thickenings in the paranasal sinuses (Figure 1E-F).

Echocardiography (ECHO) of the patient, who had a history of cardiovascular surgery, revealed stage-1 left ventricular dysfunction, left atrial dilatation, an LVOT obstruction in systole due to basal septum hypertrophy (1.6 cm) and a mitral valve obstruction (73/50 mmHg), coronary sinus dilatation, pulmonary hypertension (systolic pulmonary artery pressure [sPAP]: 55 mmHg), middle aortic valve insufficiency and mild mitral valve regurgitation.

Genetic consultation and analysis were requested, and the reported result was "consistent with PCD, a homozygous variant of NM_001256715.1:c.912+2T>A splice_donor_+2 was observed in DNAAF3 gene". The patient was discharged after her symptoms reduced significantly following treatment.

DISCUSSION

PCD almost always originates from mutations in genes related to cilia or ciliary movement, and so chronic sinopulmonary infections are usually the predominant clinical finding with this syndrome. PCD is classified according to the presence of concomitant situs anomalies, and the association of SA with DNAAF3 gene mutations is a less common condition than other situs anomalies. This rare case of PCD is presented to literature as PCD is usually diagnosed in childhood, and due to the rare gene mutation accompanying SA.

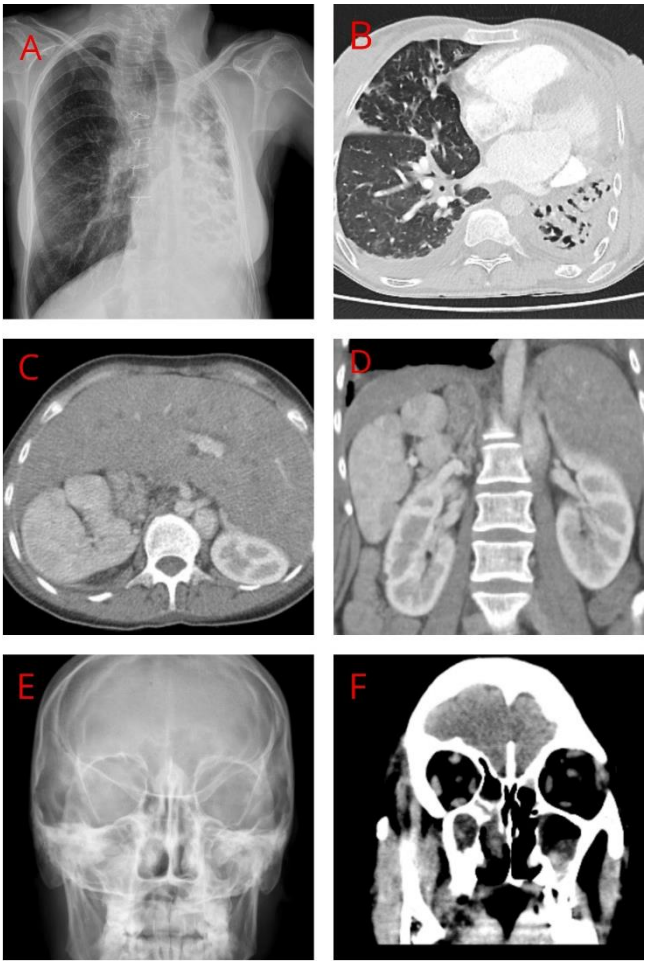

Figure 1: *Chest X-ray (PAAG) showing left tracheal and mediastinal deviations, diffuse bronchiectasis in the left lung, increased air volume in the left lung and heterogeneous opacities in the right lower zone* ***(A)****; A chest computed tomography (CT) scan revealing a displacement of the heart and mediastinum to the left, diffuse atelectasis in the left lung, cystic and tubular bronchiectatic changes in both lung fields, and bilateral pleural effusion* ***(B)****; Abdominal CT revealing the midline position of the liver and the right lower quadrant location of the spleen. Appearances compatible with multiple splenosis were also observed, the largest of which was 75x40 mm in size* ***(C, D)****; Water's radiography taken during an examination for a chronic upper respiratory tract infection showed air-fluid levels and poor visualization of air spaces in the right maxillary sinus, while paranasal sinus CT revealed mucus retention cysts and mucosal thickenings in the paranasal sinuses* ***(E, F)***

PCD is a genetically heterogeneous, typically autosomal recessive disease characterized by ciliary dysfunction and impaired mucociliary clearance. Every one of the ciliary cells that cover the apical cell surface of the upper and lower respiratory tracts contains hundreds of 9+2 microtubule cilia, creating the sweeping movement of mucus from the lower respiratory tract to the upper respiratory tract and out of the middle ear cavity. The reduced mucociliary clearance resulting from impaired ciliary movement can lead to chronic rhinosinusitis, chronic otitis media, recurrent lung infections, narrowing of the airways, chronic bronchitis and bronchiectasis, as well as infertility and sinus anomalies, and in rare cases, hydrocephalus may accompany (6). The case in the present study had bronchiectasis and recurrent rhinosinusitis. In the study by Hosie et al. (7) assessing 84 cases with PCD, 81% had chronic cough, 71% had rhinosinusitis and 49% had recurrent otitis media, while 32% had bronchiectasis at the time of admission. Based on the prevalence of SI and bronchiectasis, an incidence of PCD of around 1/16,000 births has been estimated (8). PCD can be diagnosed based on an ultrastructural examination of the nasal mucosa or bronchial brush biopsy specimens using electron microscopy, or from the detection of a mutation in one of the genes known to be associated with PCD. All abnormalities associated with PCD begin with mutations in the genes involved in cilia development or ciliary movement (9). In the early stages of embryogenesis, the position of the internal organs is determined, and asymmetry between the right and left sides of the body is normal, since the liver is on the right and the spleen is on the left. If a defect in asymmetry develops during embryogenesis, organ laterality defects called SI or SA, being mirror images of the situs, may develop (10). There are two subgroups of SA: SA with polysplenia, and SA with asplenia (11). In the presented case, SA polysplenia was identified, and an abdominal CT revealed the inferior vena cava to be located on the left side of the aorta, the midline positioning of the liver, a direct opening of the hepatic veins into the right atrium, and multiple splenosis, the largest of which was 75x40 mm in size. PCD is rarely accompanied by SA. In their study, Shapiro et al. (12) identified PCD in 12% of the 305 cases in their study, while Kennedy et al. (13) reported that 6.3% of the 337 cases with PCD in their study had SA, and of these cases, 143 (47%) had situs solitus, 125 (41%) had situs inversus totalis and 37 (12%) were in the SA group. One should keep in mind that situs anomalies like SA are commonly associated with congenital heart disease (CHD) (14). In a study by Kennedy et al. (13) reporting on 337 PCD cases, six (54.5%) of the 11 cases with left isomerism had polysplenia and cardiac/vascular anomalies, 12 (57.1%) of the 21 heterotaxia cases had cardiovascular malformations, four cases had only vascular abnormalities and eight had complicated cardiac anomalies requiring surgery. Our case had undergone surgery for a subaortic membrane. In cases with PCD, the risk of congenital heart disease due to heterotaxia has been reported to be 200 times greater than in the general population. It has been suggested that PCD is missing in many patients with heterotaxia and CHD (13,15).

Advances in DNA sequencing, genomics and proteomics in recent years have led to the identification of mutations in approximately 30 genes responsible for PCD cilia motility defects. DNAI1 and DNAH5 mutations are observed in more than 30% of cases, while mutations in the DNAAF1 and DNAAF3 genes have also been shown to

be associated with external dynein arm defects in cases with PCD (16,17). Furthermore, mutations in such genes as ZIC3, LEFTY, CRYPTIC and ACVR2B have been shown to play a role in cases of heart disease accompanying human heterotaxia syndrome (18). A genetic analysis of the case presented here revealed a mutation in the DNAAF3 (dynein axonemal assembly factor 3) gene that was first reported by Mitchison et al. (19), who suggested that this mutation caused immotile cilia as a result of the defects in both the inner and outer dynein arms, noting also left-right laterite defects in the DNAAF3 morphant embryo that were similar to the human situs inversus, thus showing the importance of the DNAAF3 gene in the movement of the cilia. DNAAF3 mutations in PCD patients were first reported by Guo et al. (20), identifying that condition in four cases with PCD, all of which had situs inversus, while our case had rare left isomerism with SA. The respiratory symptoms of Guo et al.'s cases were cough and sputum, as in the case presented here, although a computed tomography of the four cases revealed bronchiectasis in one case, localized consolidation in another, and no pathology in the lung parenchyma in the other two.

CONCLUSION

Based on the presented case of SA polysplenia accompanied by a rare PCD and an even rarer DNAAF3 gene mutation, we recommend that a diagnosis of PCD should be kept in mind in adults with frequent recurrent rhinopulmonary infections, even in the absence of situs inversus totalis.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - D.B., C.D., E.Y.G., H.İ.U.; Planning and Design - D.B., C.D., E.Y.G., H.İ.U.; Supervision - D.B., C.D., E.Y.G., H.İ.U.; Funding - H.İ.U., D.B.; Materials - H.İ.U., E.Y.G.; Data Collection and/or Processing - H.İ.U., E.Y.G.; Analysis and/or Interpretation - D.B., C.D.; Literature Review - D.B., C.D.; Writing - D.B., C.D.; Critical Review - C.D.

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