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Rare Coexistence of Kartagener Syndrome and Granulomatous Polyangiitis: A Compelling Case Report

Granülomatöz Polianjit ve Kartagener Sendromunun Nadir Birlikteliği: İlginç Bir Olgu Sunumu

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Abstract

Primary ciliary dyskinesia (PCD) is predominantly an autosomal recessive disorder that is characterized by recurrent respiratory infections stemming from impaired ciliary motility. Granulomatous polyangiitis is a necrotizing vasculitic disease marked by granulomatous inflammation in the vascular wall that often manifests in the lungs with cavitating nodules, masses and consolidations. A 24-year-old female patient presented to our clinic complaining of dyspnea, productive cough and pleuritic chest pain, and was diagnosed with Kartagener Syndrome based on her situs inversus, bronchiectasis and sinusitis. Subsequent genetic tests and further clinical evaluations, including thoracic CT, revealed findings of cavitating nodules, PR3-ANCA positivity and leukocytic vasculitis from a skin biopsy pathology, confirming the coexistence of PCD and granulomatous polyangiitis.

Keywords: *Granulomatosis with polyangiitis, Kartagener's Syndrome, Primary ciliary.*

Öz

Primer siliyer diskinezi (PSD), yetersiz siliyer motilite kaynaklı tekrarlayan solunum yolu enfeksiyonları ile karakterize çoğunlukla otozomal resesif geçişli bir bozukluktur. Granülamatöz polianjit, sıklıkla akciğerlerde kaviter nodüller tutulumlar, kitleler ve konsolidasyonlar yapan damar duvarında granülamatöz inflamasyon ile seyreden nekrotizan bir vaskülittir. Yirmi dört yaşında kadın hasta, kliniğimize dispne, prodüktif öksürük ve plöretik göğüs ağrısı ile başvurdu. Hastanın situs inversus, bronşektazi ve sinüzit bulguları göz önüne alınarak, genetik testler ile Kartagener Sendromu tanısı konuldu. Toraks tomografisinde kaviteleşen nodüllerinin olması, PR3-ANCA pozitifliği ve cilt biyopisi sonucunda lökositik vaskülit saptanması üzerine PSD ve granülamatöz polianjit tanısı doğrulandı.

Anahtar Kelimeler: *Granülomatöz Polianjit, Kartagener Sendromu, Primer Siliyer Diskinezi.*

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Primary ciliary dyskinesia (PCD) is a predominantly autosomal recessive disease characterized by frequent respiratory system infections resulting from dysfunction in ciliary motility. Its reported incidence in the population is in the range of 1 in 15,000–20,000 live births. Patients may present with chronic rhinosinusitis, infertility and bronchiectasis caused by upper and lower respiratory tract infections (1). PCD accompanied by situs inversus totalis, bronchiectasis and recurrent sinusitis is referred to as Kartagener Syndrome (2). Although PCD is diagnosed in childhood and adolescence, it may also be detected rarely in adulthood. Differential diagnoses in suspected cases are ruled out based on advanced genetic examinations, evaluations of cilia structures by electron microscope and nasal nitrite oxide tests. The mutations most commonly associated with PCD are those of the dynein axonemal heavy chain 5 (DNAH5) and dynein axonemal medium chain 1 (DNA I1) (3). Given the lack of any curative treatment, the primary approach to bronchiectasis secondary to PCD is preventive education to reduce the risk of infections in the patient, and such precautions as frequent routine follow-ups and regular pneumococcal and influenza vaccines. In cases that develop an acute infection, an appropriate antibiotic treatment is applied based on sputum culture results (4).

Granulomatous polyangiitis is a rare necrotizing systemic vasculitis that progresses to granulomatous inflammation in the vessel wall, and can be fatal if left untreated. The prevalence of the disease is in the region of 3/100,000. Patients are usually diagnosed between the ages of 45 and 60 years (5). For a diagnosis of the disease, two of the following criteria must be met: involvement in the sinuses; involvement on chest X-ray or cavitary lesions; presence of hematuria or erythrocytes, along with urinary sediment; and histopathological detection of granulation in the perivascular area around the artery or arteriole, or in the artery itself. Lung involvement may be observed in 50–90% of cases. Patients may be asymptomatic or may present with such symptoms as dyspnea, cough, chest pain and hemoptysis (6,7). Alveolar hemorrhage, single or multiple nodules in the parenchyma, and tracheal or subglottic stenosis may be observed (5). Nodular involvement is observed in 50% of patients. Such nodules can turn into necrotic cavities (7). c-ANCA is detected positive at a rate of 90% in patients with systemic involvement. PR3-ANCA positivity is more specific for disease involvement, and so its diagnostic value is quite high. The disease is treated with corticosteroids in combination with such immunosuppressive agents as cyclophosphamide and rituximab, with reported remission rates of up to 80% (6).

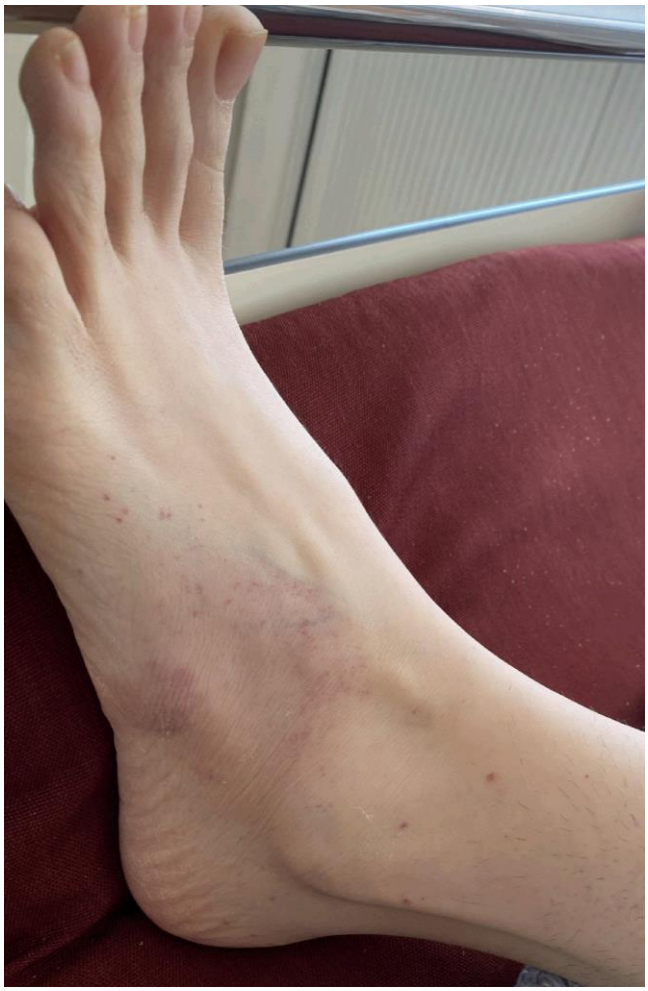

Figure 1: Maculopapular rashes on the lower extremities, unresponsive to pressure

CASE

A 24-year-old female nurse presented to our clinic with complaints of grade 4 dyspnea on the mMRC scale, cough, sputum, pleuritic pain, weight loss and fever, leading to an initial diagnosis of bronchiectasis exacerbation. A review of her medical history revealed a pattern of frequent lung infections, prior hospitalizations and Pseudomonas aeruginosa colonization in recent sputum cultures. The patient had been recently hospitalized for parenteral antibiotic treatments.

Her family history revealed no significant features, other than an aunt with a history of bronchiectasis. A physical examination revealed situs inversus totalis, along with widespread rales and rhonchi in the lungs. Maculopapular rashes on the lower extremities that were unresponsive to pressure were also observed (Figure 1).

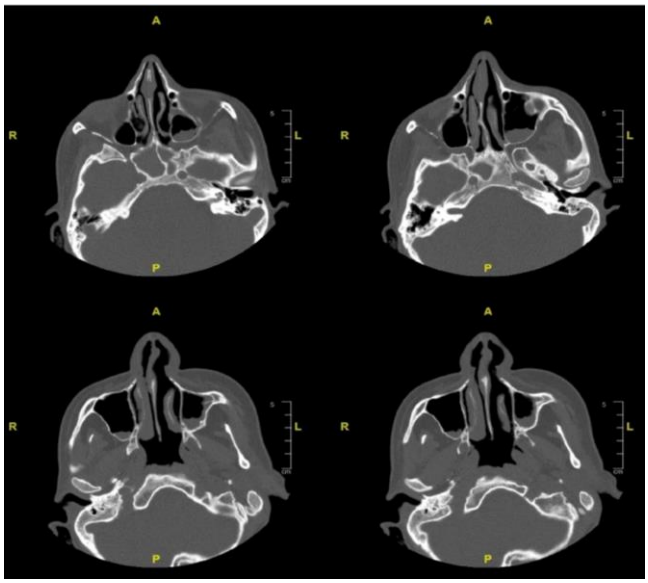

Figure 2: Paranasal sinus CT-demonstrated sinusitis

Laboratory tests revealed elevated CRP (290 mg/L), an increased sedimentation rate (57 mm/h), proteinuria (2268 mg/24 hours), albuminuria (980 mg/24 hours) and microscopic hematuria (349 erythrocytes in spot urine). The patient started on empirical parenteral antibiotic treatment with meropenem.

Paranasal CT scans revealed sinusitis, turbinate hypertrophy (Figure 2) and thoracoabdominal situs inversus totalis, as well as thick-walled cavitary lesions with air-fluid levels in the middle-lower zones of both lungs, bronchiectasis, mucus plugs, and nodules with a tree-in-bud pattern (Figure 3).

Systolic pulmonary artery pressure was measured through transthoracic echocardiography at 30 mmHg, and slight tissue thickening in the anterior mitral valve and a mild systolic collapse, not extending beyond the annulus level at its tip, were observed. Abnormal movement of the interventricular septum was noted, while no significant abnormalities were detected in other wall movements. The interatrial septum was found to have an aneurysmatic structure.

Various tests were conducted on the immunosuppressed patient, including sputum culture, sputum acid-resistant bacteria (ARB) screening test, sputum culture for tuberculosis, serum galactomannan level, beta-D-glucan antigen test and CMV-DNA screening. Immune biomarkers were also assessed due to the preliminary diagnosis of vasculitis, given the presence of cavitary nodules on thoracic CT, along with skin rash and sinusitis. Bronchoalveolar lavage was performed using fiberoptic bronchoscopy and Pseudomonas growth was identified in the sputum culture, leading to the initiation of broad-spectrum antibiotic treatment based on the antibiogram.

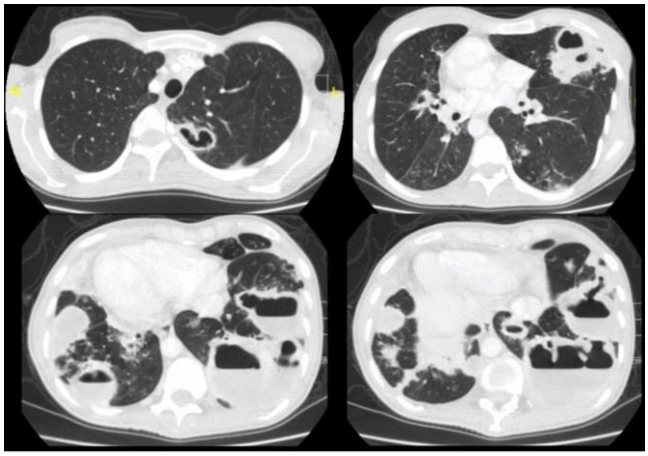

Figure 3: Thorax CT revealing thick-walled cavitary lesions with air-fluid levels, widespread in the upper-middle-lower zones of both lungs, bronchiectasis and mucus plugs

The PCD diagnosis was confirmed by genetic tests, which identified mutations in DNAI1 associated with defects in both the outer and inner dynein arms. Additionally, the patient was identified with positive ANCA and PR3 antibodies, proteinuria and hematuria were observed during follow-up, and vascular C3 positivity was detected in the dermal papillae, consistent with leukocytic vasculitis.

Considering the findings, long-term inhaler tobramycin treatment was initiated for P. aeruginosa colonization, and the patient was also placed on systemic steroid and rituximab treatment, leading ultimately to the diagnosis of Granulomatous Polyangiitis. A significant improvement in the patient's clinical condition was noted during follow-up, and an almost complete regression of symptoms. The patient returned to work, and a thorax CT scan at the 8th-month follow-up revealed a reduction in the cavitary lesions (Figure 4).

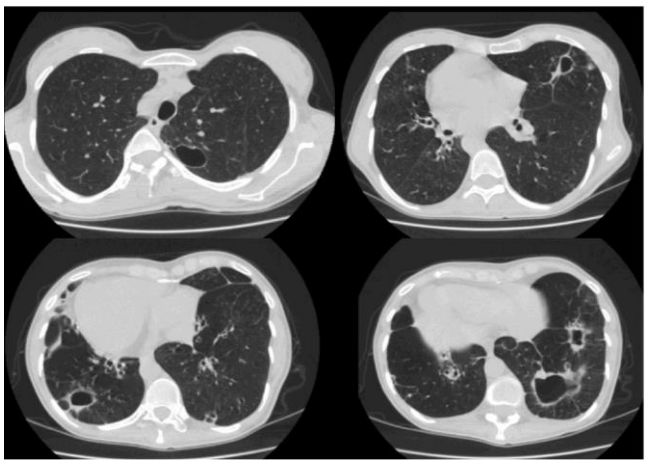

Figure 4: Regression in the cavitary lesions revealed on thorax CT at 8th month follow-up

DISCUSSION

PCD is typically diagnosed in childhood and adolescence, but may on rare occasions be diagnosed in adulthood. Characterized by frequent respiratory infections resulting from the impairment in ciliary motility, patients with chronic lung infections in PCD face the risk of lung function loss and structural deterioration in lung parenchyma (1). Controlling chronic infections with appropriate antibiotic treatments is thus crucial. Antibiotic therapy is tailored to previous culture results and sensitivities identified in upper and lower respiratory tract secretions (8).

Tsubouchi et al. (9) reported on a case with PCD and simultaneous intralobar pulmonary sequestration who was started on clarithromycin treatment upon the identification of a Staphylococcus aureus growth in a bronchoalveolar lavage culture for the effective management of the chronic lower respiratory tract infection prior to a surgical intervention. In the presented case, suitable antibiotic therapy was initiated upon the detection of pseudomonas in the sputum culture, and clinically significant improvement and a marked reduction in secretions were achieved.

Ciftci et al. (10) commented on the potential difficulties in diagnosing PCD due to the nonspecific and overlapping of symptoms with those seen in other chronic respiratory conditions, including refractory asthma, atypical cystic fibrosis, pulmonary sequestration, yellow nail syndrome and middle-lobe/lingula syndrome, potentially leading to delayed or misdiagnoses.

While studies in literature reporting concurrent or overlapping systemic vasculitis such as PCD and Granulomatous Polyangiitis are scarce, such systemic diseases should be considered in the differential diagnosis of patients presenting with cavitary and nodular lesions on thorax CT. A review of cases in literature suggests that granulomatous polyangiitis may often be confused with such conditions as lung malignancy, metastasis, sarcoidosis and tuberculosis due to its progression with nodular lesions and granulomatous inflammation in the lungs. Isolated lung involvement can lead to misdiagnosis, and tissue diagnosis and immunological markers should guide the differential diagnosis (11-13). Granulomatous polyangiitis can be fatal if left untreated. In the study by Arunsurat et al. (14) of two cases with systemic organ involvement and pulmonary nodular lesions, one case had nodular involvement accompanied by a cavitary lesion, and despite the initiation of methylprednisolone and cyclophosphamide, the patient yielded to infection after the third course of immunosuppressive treatment. The second case, treated with methylprednisolone and azathioprine, showed significant improvement in lung lesions after 6 months of treatment. Due to the nephrotic-level proteinuria in our patient, methylprednisolone and rituximab treatments were initiated based on rheumatology recommendations. Simultaneously, inhaler tobramycin was started due to persistent Pseudomonas growth in sputum cultures, and both clinical and radiological improvements were observed in the patient.

Recent studies have reported decreased NO levels in the airways of PCD patients. NO plays a role in immune system defense, bronchomotor tonus regulation, ciliary activity and airway clearance. Reduced NO levels may be linked to the neutrophilic inflammation response (15). Although the pathophysiology of granulomatous polyangiitis is as yet not fully understood, antineutrophil antibodies against neutrophilic proteinase 3 and myeloperoxidase enzymes have been associated with disease development (16). This may contribute to an increase in the frequency of coexistence of such rare diseases as PCD and granulomatous vasculitis. Given the rarity of the two diseases, however, it is no surprise that no detailed case studies of the issue were found in literature.

CONCLUSION

Lower respiratory system infections are more prevalent in patients with Kartagener Syndrome due to bronchiectasis and reduced mucociliary clearance. In cases with newly developed cavitary lesions, however, the potential for underlying systemic diseases should be considered. In our case, in which two rare diseases coexisted, significant improvement was achieved with the diagnosis and treatment of vasculitis.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - G.C.S., F.A., E.S., M.Ö., A.G.K., S.E., A.Ç., A.K.; Planning and Design - G.C.S., F.A., E.S., M.Ö., A.G.K., S.E., A.Ç., A.K.; Supervision - G.C.S., F.A., E.S., M.Ö., A.G.K., S.E., A.Ç., A.K.; Funding - G.C.S., F.A.; Materials - G.C.S., F.A.; Data Collection and/or Processing - G.C.S., F.A.; Analysis and/or Interpretation - G.C.S., F.A.; Literature Review - G.C.S., F.A.; Writing - G.C.S., F.A.; Critical Review - G.C.S., F.A., E.S., M.Ö., A.G.K., S.E., A.Ç., A.K.

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