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A Rare Cause of Recurrent Pneumonia: Common Variable Immunodeficiency

Sık Tekrarlayan Pnömonilerin Nadir Bir Nedeni: Yaygın Değişken İmmün Yetmezlik

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Abstract

Common Variable Immunodeficiency (CVID) is a rare underlying cause of frequent recurrent pneumonia in adults. The primary pathophysiology of CVID is impaired antibody response to the antigens associated with immunoglobulin deficiency, resulting from B lymphocyte pathologies. Frequent recurrent upper and lower respiratory tract infections, accompanying autoimmune comorbidities, and significant associations with malignancies make the early diagnosis and treatment of the condition crucial. We present here the case of a 68-year-old patient diagnosed with CVID following etiological investigations for recurrent pneumonia, discussed in the context of the current literature.

Keywords: *Immunoglobulin, Recurrent Pneumonia, Common Variable Immundeficiency.*

Öz

Erişkin yaş gruplarında sık tekrarlayan pnömonilerin altta yatan nadir bir nedeni de Yaygın Değişken İmmün Yetersizlik hastalığıdır. B lenfosit hücrelerin patolojisi sonucu meydana gelen immuünoglobulin yetersizliği sonucu antijenlere karşı antikor yanıtının bozulması temel fizyopatolojiyi oluşturur. Sık tekrarlayan alt ve üst solunum yolları enfeksiyonları, eşlik eden otoimmün ek hastalıklar ve azımsanmayacak oranda eşlik eden malignitlerden dolayı erken tanı ve tedavi elzemdir. Bu yazıda 68 yaşında sık tekrarlayan pnömoiler nedeni ile etyolojik araştırmalar neticesinde Yaygın Değişken İmmün Yetersizlik hastalığı tanısı alan bir olgu güncel literatür eşliğinde sunulmuştur.

Anahtar Kelimeler: *İmmünglobulin, Tekrarlayan Pnömoni, Yaygın Değişken İmmün Yetersizlik.*

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Common Variable Immunodeficiency (CVID) is the most common primary immunodeficiency (PID) in adults, characterized by impaired immunoglobulin (Ig) production due to defects in B lymphocyte differentiation. This results in defective antibody responses to antigens and an increased susceptibility to infections (1).

The most common clinical presentation of CVID is a recurrent bacterial infection, although it can also develop under various other heterogeneous clinical scenarios, including chronic lung disease, gastrointestinal disorders, increased autoimmune conditions, lymphoproliferative and granulomatous diseases, and, albeit rarely, in cases with an elevated risk of malignancy (2).

The pathophysiology of CVID remains unclear. In contrast to many other primary immunodeficiencies, over 90% of documented CVID cases lack a definitive molecular genetic diagnosis or other causal explanation. Only 10–20% of cases have a positive family history, as the majority occurs sporadically (3).

CVID diagnoses are based on reduced serum IgG levels accompanied by decreased IgM or IgA levels and poor vaccine response, after all other causes of hypogammaglobulinemia have been excluded. The cornerstone treatment includes antibiotics for infections and immunoglobulin replacement therapy (4).

We present here the case of a 68-year-old female patient diagnosed with CVID – a condition that is typically identified in childhood or early adulthood – aiming to highlight the need to consider CVID when making advanced evaluations of recurrent pneumonia, especially in older patients.

CASE

A 68-year-old female patient presented to the Pulmonology outpatient clinic with complaints of chills, shivering, coughing and stabbing chest pain during inspiration. Her medical history revealed a diagnosis of chronic lymphocytic leukemia (CLL) 10 years ago and a COVID-19 infection 2 years earlier. Her family history included a cousin with CLL. The patient had a 1-pack/year smoking history and no history of tuberculosis exposure.

On physical examination, the patient's vital signs were stable, while rales were identified in the right upper lung zone on auscultation. Additionally, a 1.5 cm lymphadenopathy was identified in both the right and left inguinal regions on palpitation. A posterior-anterior chest X-ray revealed an increased density in the right upper lung zone (Figure 1), while a thoracic computed tomography (CT) revealed an area of consolidation containing air bronchograms in the posterior segment of the right upper lobe. Also noted in the report were "several mediastinal lymph nodes, the largest measuring 1 cm in diameter, and bilateral axillary lymph nodes with the largest measuring 11 mm in diameter with prominent cortical thickening" (Figure 2). Laboratory tests revealed elevated acute-phase reactants, lymphocyte-predominant leukocytosis and increased C-reactive protein (CRP) levels (Table 1).

The patient was admitted to our department for follow-up and treatment with a preliminary diagnosis of pneumonia. Given her history of antibiotic use 1 month prior, antibiotic therapy of piperacillin-tazobactam (4x4.5 grams) and ciprofloxacin (2x500 milligrams) was initiated.

Table 1: Laboratory Values of the Case

Sr. No.	Foods items	Common points
WBC (103Ul)	46.2	4.00-10.00
CRP (µg/L)	250	0-5
Procalsitonin (mg/dL)	1.06	<0,5
Urea (g/dL)	45	16.6-48.5
Creatinin (mg/dL)	1.03	0.7-1.2
IgG (g/L)	5.9 / 6.5 (c)	7.0-16.0
IgA (g/L)	0.7 / 0.68 (c)	0.7-4,0
IgM (g/L)	0.22 / 0.3 (c)	0.4-2.3
IgG-1 (g/L)	5.19	4.05-10.11
IgG-2 (g/L)	0.55	1.69-7.86
IgG-3 (g/L)	0.108	0.11-0.85
IgG-4 (g/L)	0.046	0.03-2.01
CMV PCR (Iu/mL)	Negative	20-190000
EBV DNA IgG (U/mL)	Undetected	Negative
EBV DNA IgM(U/mL)	Undetected	Negative
Sedimentation mm/saat	22	0-15

c: Control, CRP: C-Reaktif Protein, EBV: Ebstein Bar Virus, mm: Milimetre, Ig:Immunoglobulin, WBC: Leucocyte, LDH: Lactat Dehidrogenase

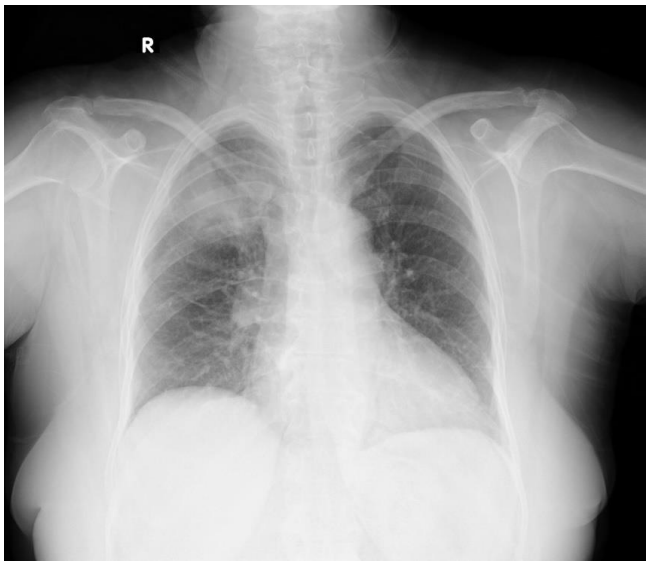

Figure 1: Non-homogenous density increase observed in the right upper zone on PA chest X-ray at the time of hospital admission

A deeper investigation of her medical history revealed frequent upper and lower respiratory tract infections in childhood, tonsillectomy and a history of recurrent pneumonia that had led to multiple hospital admissions. A review of the patient's previous radiological lung images and thoracic CT scans taken 6 and 12 months earlier revealed areas of pneumonic consolidation in different locations (Figures 3 and 4).

In the patient with a history of frequent pneumonia, immunoglobulin (Ig) A, M and G levels and vaccine responses were requested with a preliminary diagnosis of CVID, revealing IgG, A and M levels, as well as control values measured 1 week later, to be low (Table 1). An immunology consultation was requested, and after further investigations, the diagnosis of CVID was confirmed. Intravenous immunoglobulin (IVIG) therapy was initiated upon the recommendation of immunology. The patient was subsequently discharged with follow-up instructions for Pulmonology and Immunology outpatient clinics.

DISCUSSION

This case report relates to a patient diagnosed with Common Variable Immunodeficiency (CVID), a condition most commonly diagnosed in childhood that is relatively rare in adults. If not considered in clinical practice of pulmonology, a diagnosis of CVID may be overlooked. As evidenced by our case and a review of the literature, CVID should be suspected even in older adults with a history of recurrent pneumonia, radiological findings of pneumonic consolidations in different locations and associated malignancies, and in those with lymphoproliferative or autoimmune diseases.

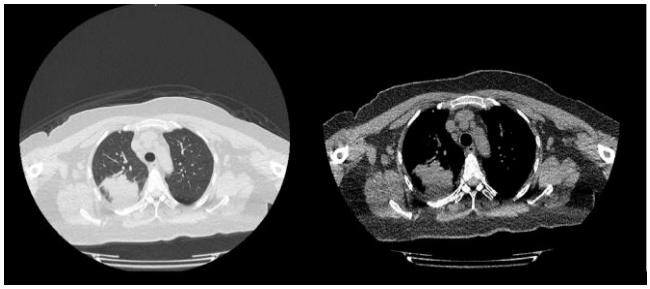

Figure 2: *Consolidated area containing air bronchograms observed in the posterior segment of the right upper lobe of the lung*

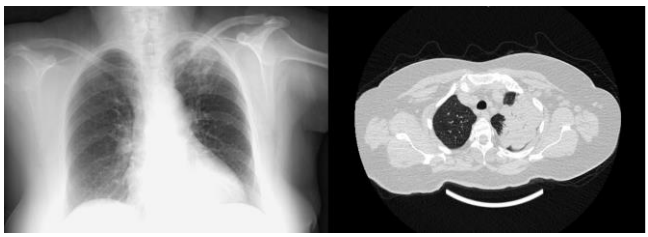

Figure 3: *Chest X-ray and thoracic CT taken 5 years earlier revealing consolidations in the left upper zone and the left upper lobe*

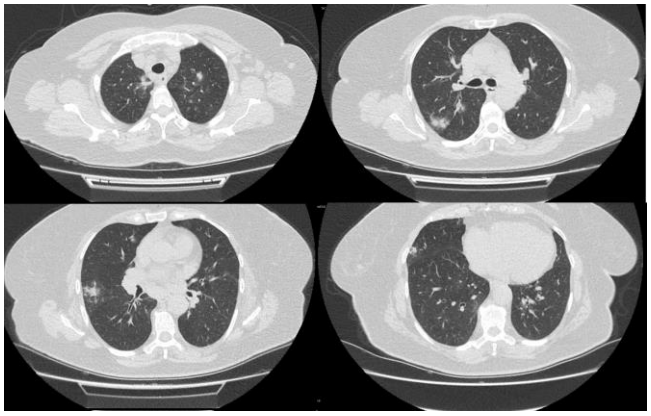

Figure 4: *Thoracic CT of the patient taken 12 months earlier revealing scattered areas of consolidation in both lungs*

CVID is the most common symptomatic primary immunodeficiency in adults. While studies generally report no gender predisposition, a recent meta-analysis of 51 studies detailing 8,521 cases reported a bimodal gender distribution, with males predominating in childhood (62%) and females in adulthood (58%). The reason for the female predominance in adults is not fully understood, although it has been suggested that sex hormone effects, epigenetic factors and environmental exposure may play a role (3–5).

CVID is typically diagnosed before adulthood, and late diagnosis in adults is relatively rare. Adult CVID is typically diagnosed after puberty, with most cases being identified between the ages of 25 and 45 years. Diagnoses in those over 65 years of age are extremely rare, accounting for only 8% of all adult CVID cases. Significant diagnostic delays can be witnessed in adulthood, as clarified by Bezrodnik et al. (6) in a study reporting an average diagnostic delay of 9.5 years in the adult population. At 68 years of age, the patient in the present study is a rare example of CVID in this age group, making the case worth reporting (7).

Impaired immunoglobulin production and inadequate antibody response to antigens due to defects in B lymphocyte differentiation form the pathophysiological basis of the disease and its predisposition to infections. Impaired immune response is most commonly blamed for frequent and severe lower and upper respiratory tract infections, as well as recurrent pneumonia. Diagnosis is based on the demonstration of hypogammaglobulinemia (IgG and IgA and/or IgM) and inadequate vaccine responses, and the exclusion of other causes of hypogammaglobulinemia (8,9).

A recent study reported the most common initial presentation of CVID to be pneumonia (36.8%), followed by diarrhea (19.1%) (10). Our patient's history of recurrent pneumonia and low immunoglobulin levels aligns with the literature in this regard.

Clinically, three different types of CVID are observed: the infectious type, characterized by an increase in the severity or frequency of infections; the autoimmune-autoinflammatory type, including such conditions as autoimmune thyroiditis and inflammatory bowel disease; and the type associated with malignancies. Autoimmune-granulomatous diseases and malignancies are more prevalent in CVID patients than in the general population. Although the exact cause has yet to be fully elucidated, the most widely accepted hypothesis is that genetic variants leading to primary immunodeficiency may directly predispose the patient to cancer, or that frequent/severe infections (oncogenic infections) may indirectly support carcinogenesis. A recent meta-analysis reported a malignancy prevalence of 8.6% in CVID, with lymphomas and gastric cancers being the most commonly associated forms (11–13), and the presence of both CVID and CLL in our case aligns with the literature in this regard. The most frequently detected microorganisms in CVID patients are encapsulated bacteria, such as *Haemophilus influenzae* and *Streptococcus pneumoniae*, resulting from defective B lymphocyte responses, and so any empirical antimicrobial therapy should cover these pathogens. The mainstay treatment is antibody replacement therapy with intravenous or subcutaneous immunoglobulin (400–600 mg/kg), typically administered once a month (14). In our case, the patient was successfully treated with both antibiotic therapy and IVIG treatment.

The increasing prevalence of HIV and the widespread use of various immunosuppressive therapies nowadays lead many patients to require immunological evaluation. Systemic disease development after live vaccination, the risk of being HIV-positive, and abnormal routine laboratory findings such as lymphopenia, neutropenia, and hypo/dysgammaglobulinemia can be observed. HIV causes progressive damage to CD4 T lymphocytes, which are vital for the maintenance of host immune response, and can lead to clinical scenarios similar to CVID, and so HIV should always be considered in adult cases of immunodeficiency. In our case, Anti-HIV was negative (15).

In conclusion, CVID should be considered even in older patients with recurrent pneumonia, and it should be kept in mind that the disease can be associated not only with recurrent infections, but also autoimmune disorders and malignancies.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - C.D., Z.Ç.; Planning and Design - C.D., Z.Ç.; Supervision - C.D., Z.Ç.; Funding - C.D., Z.Ç.; Materials - C.D., Z.Ç.; Data Collection and/or Processing - C.D., Z.Ç.; Analysis and/or Interpretation - C.D., Z.Ç.; Literature Review - C.D., Z.Ç.; Writing - C.D., Z.Ç.; Critical Review - C.D., Z.Ç.

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