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Primary Immunodeficiency and Malignant Disease Coexistency: Two Case Reports

Primer İmmün Yetmezlik ve Malign Hastalık Birlikteliği: İki Olgu Sunumu

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Abstract

Primary immunodeficiency diseases are that predispose to malignancies other than recurrent infections. Genomic instability due to some unknown mechanisms and defective DNA repair processes in patients with primary immunodeficiency causes an increase in cancer risk, and it is thought that the risk of developing cancer in these patients varies between 4.7-5.7%. After infections, the most common cause of death in patients with primary immunodeficiency is malignancies. In this article, our first case was admitted to the hospital with a cough and was diagnosed with Burkitt lymphoma in the follow-up. A low level of immunoglobulins was detected in the tests performed, and it was diagnosed as common variable immunodeficiency at the same time. In our second case, acute lymphoblastic leukemia developed while she was being followed up due to transient hypogammaglobinemia of infancy. Here, we draw attention to the fact that the unusual first presentation of patients with a primary immunodeficiency may be associated with malignancy. In addition, we aimed to increase the awareness of clinicians following primary immunodeficiency patients about the development of malignancy.

Keywords Acute Lymphoblastic Leukemia, Burkitt's lymphoma, Common Variable Immunodeficiency

Özet

Primer immun yetmezlikler tekrarlayan enfeksiyon dışında malignitelere yatkınlık oluşturan hastalıklardır. Primer immun yetmezlikli hastalarda bazı bilinmeyen mekanizmalar ve kusurlu DNA onarım süreçleri nedeniyle oluşan genomik instabilite, kanser riskinde artışa neden olur ve bu hastalarda genel olarak kanser gelişme riskinin % 4,7- 5,7 arasında değiştiği düşünülmektedir. Primer immun yetmezlikli hastaların enfeksiyonlardan sonra en sık ölüm nedeni malignitelerdir. Bu makalede sunmuş olduğumuz ilk olgumuz öksürük şikâyetiyle hastaneye başvuran ve takibinde Burkitt Lenfoma tanısı alan, bu aşamada tetkiklerinde immünglobülinlerinde düşüklük saptanarak lenfoma tanısına eş zamanlı olarak yaygın değişken immün yetmezlik tanısı eklenen hastamızdır. İkinci olgumuz primer immun yetmezlik nedeniyle takipliyken akut lenfoblastik lösemi gelişen hastamızdır. Burada primer immun yetmezlikli hastaların olağanın dışında ilk başvurusunun maligniteyle beraber de olabileceğine dikkat çekmeyi ve primer immun yetmezlikli hasta takip eden klinisyenlerin malignite gelişimine karşı farkındalıklarını arttırmayı amaçladık.

Anahtar Kelimeler *Akut Lenfoblastik Lösemi, Burkitt Lenfoma, Yaygın Değişken İmmun Yetmezlik*

GİRİŞ

Primary immunodeficiency disease (PID) or Inborn errors of immunity (IEI) is a heterogeneous group of diseases characterized by a disorder of the immune system. Patients with IEI may present with variable symptoms, the most common clinical manifestations being recurrent infections, autoimmunity, and malignancies. In 2019, the International Union of Immunological Societies (IUIS) published an updated phenotypic classification of IEI. There are 430 single gene IEI diseases underlying various phenotypes such as infection, malignancy, allergy, autoimmunity, and autoinflammation. In addition, the European Society for Immunodeficiencies (ESID) working definitions for clinical diagnosis of PID are available. Common variable immunodeficiency (CVID) and transient hypogammaglobinemia of infancy (THI) are included in these classifications.[1,2]

The susceptibility to tumor formation seen in these patients is associated with various reasons such as defects in DNA damage repair, irregularities in the immune response that plays a role in the clearance of oncogene viruses such as EBV and HPV, and chronic antigenic stimulation, and deterioration in apoptosis. In some PIDs, malignancies are more common. The most common malignancy is lymphoma, and it is known to be associated with EBV infection in some patients.[3,4] In this case report, we wanted to draw attention to the coexistence of PID and malignancy by presenting our patients who were diagnosed with CVID simultaneously with Burkitt lymphoma and developed pre-B acute lymphoblastic leukemia (ALL) during follow-up with the diagnosis of THI.

CASE-1

A 6-year-old female patient applied to the pediatric emergency department with complaints of fever and cough that started 3 days ago. The patient had a history of obesity, asthma, and dust mite allergy. There was no feature in the family history of the patient. On physical examination, respiratory sounds were found to be decreased in the right baseline. Other system examinations were unremarkable. In laboratory examinations, white blood cell count: 10.980/mm3, absolute neutrophil count: 7.590/mm3, absolute lymphocyte count 2.560/mm3, Hemoglobin: 12.4 gr/dl, platelet: 537.000/µL, and CRP: 83.5 mg/dl. Thoracic ultrasonography (USG) was performed because of the increase in opacity in the right hemithorax in the chest X-ray of the patient. Thoracic USG revealed pleural effusion. A thorax tube was inserted by the pediatric surgeon and thoracentesis was performed. The patient's thoracentesis fluid was compatible with the exudate and he was admitted to the ward with antibiotherapy. On the 9th day of hospitalization of the patient, who responded to the treatment in the control chest X-ray, respiratory sounds could not be obtained from bilateral baselines. One day later, the patient's respiratory effort increased and her general condition deteriorated, and hepatomegaly, intra-abdominal mass, and free fluid were detected in the abdominal USG of the patient who developed abdominal distension. The patient with uric acid: 10.57 mg/dl and LDH: 2.439 U/L was transferred to the Department of Pediatric Hematology and Oncology for further examination and treatment with a preliminary diagnosis of malignancy. The cytological examination was sent from the thoracentesis fluid and PET/CT was taken to the patient, and EBV-VCA immunoglobulin G (IgG) was positive. The patient was consulted by the Department of Pediatric Immunology and Allergy, when the tests taken during this period showed IgG: 196 mg/dL, IgM 21.7 mg/dL, and IgA: 35.7. Anti-B titer was ¼ positive in the patient's antibody responses, but vaccine antibody responses (Rubella, hepatitis B, etc.) were low (table-1). The patient was diagnosed with CVID. Intravenous immune globulin (IVIG) treatment was started once every 4 weeks. The patient, who was diagnosed with Burkitt's lymphoma, continues to receive IVIG treatment together with chemotherapy. (Informed consent was taken from the parents of the patient for this presentation.)

Table 1. Immunological data of patients at the time of diagnosis

	Ig A (g/L)	Ig G (g/L)	Ig M (g/L)	Anti-A/ Anti-B	Anti-HbS (0-10)	Anti-Rubella IgG
Case 1	37.6	194	184	1/4	14.6	negative
Case 2	34	523	75	1/2	negative	82.9

CASE-2

She was 3.5 years old and had transient hypogammaglobinemia of infancy for the last 1.5 years (table-1). The patient applied to the outpatient clinic to receive monthly IVIG treatment. From her anamnesis, it was learned that she last received IVIG treatment 4 months ago. The patient had bone pain for 1 month. She was examined by an adult rheumatologist due to bone pain in the last month, and pediatric hematology outpatient control was recommended to the patient without any further examination. She didn't want to step on his feet anymore. She had a fever and weakness for the last 4 days. The patient looked sluggish. Other than that, the systemic examination was normal. There was no organomegaly and focus of fever. Her examinations were requested and she was admitted to the service for IVIG. In the examinations of the patient, white blood cell: was 63.890/mm3, absolute neutrophil: was 4.290/mm3, and absolute lymphocyte count could not be calculated. Hgb: 11.6 g/dl, platelet: 17.000/μL, uric acid: 7.1 mg/dl, and LDH: 668 U/L. She was consulted by the Department of Hematology and Oncology. The patient, who had atypical cells in her peripheral smear, was diagnosed with pre-B acute lymphoblastic leukemia as a result of further investigations. The patient is still receiving chemotherapy and concomitant IVIG. (Informed consent was taken from the parents of this patient for this presentation.)

DİSCUSSİON

Primary immunodeficiencies are rare diseases with a wide variety of genetic inheritances. The clinical phenotype varies according to the affected immune system cells, impaired immune functions, and associated infectious or neoplastic processes. As seen in our two different cases, the first clinical picture may be infection, sometimes malignancy, sometimes autoimmune diseases, and lymphoproliferative disease may develop in patients diagnosed with PID over time.

The World Health Organization (WHO) evaluated lymphoproliferative lesions seen in immunocompromised patients as a separate section in the 2017 lymphoma classification. In this section, the clinical pictures of lymphoproliferative lesions are collected under 4 main headings and their distribution among PID cases according to the data of different studies. According to this classification; incidence rates in combined T and B cell deficiencies: 9-18%, in immunodeficiency cases including CVID and other antibody deficiencies, especially in immunoglobulin deficiency: 53-72%, and incidence rates in defined immunodeficiency syndromes such as Ataxia Telangiectasia, Nijmegen Syndrome, Bloom Syndrome: 5-22%, incidence rates in diseases such as immune regulation disorder, an autoimmune lymphoproliferative syndrome characterized by X-linked lymphoproliferative disease: 1-3%.[5,6]

Common variable immunodeficiency is one of the most common congenital immunodeficiency encountered in clinical practice.[7] Diagnosis is made by demonstrating decreased serum concentrations of IgG, IgA, and IgM with loss of protective antibodies.[2] The genetics of this syndrome are complex and still under investigation. The term "variable" in its name describes the heterogeneity of the clinical picture in this disease (infections, chronic lung disease, autoimmune diseases, gastrointestinal disorders, malignancy, etc.). Non-infectious autoimmune or inflammatory conditions may be the first and only sign that a patient has a significant immune defect. These manifestations include splenomegaly, generalized or alarmingly large lymphadenopathy and malignancy, particularly lymphoma, episodes of immune thrombocytopenia, autoimmune

hemolytic anemia, or neutropenia.[8,9] Supporting this situation, the finding of our first patient at the time of diagnosis was malignancy and she was diagnosed with CVID. There were no complaints of frequent infections.

Non-Hodgkin lymphoma (NHL) is the most common type of B-cell lymphoma with a rate of 32%. B-cell lymphomas identified in approximately 31% of the patients were found to be associated with EBV.[3] Our case was positive for EBV serology, and our patient was diagnosed with Burkitt's lymphoma, one of the subtypes of NHL. In addition, although lymphoma is the most common malignancy in patients with PID, leukemia may also develop, as in our other case.

CONCLUSİON

It should be kept in mind that the first presentation of patients with PID may also be with unusual findings and malignancy every malignancy is the result of an immune disorder. We suggest that clinicians following patients with PID should pay attention to the precursor examination findings of lymphoproliferative diseases such as organomegaly and lymphadenopathy in their patients at each visit and be aware of this issue.

Declaration

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