Common Variable Immunodeficiency Mimicking Systemic-Onset Juvenile Idiopathic Arthritis: Differential Diagnosis

Sistemik Başlangıçlı Juvenil İdiyopatik Artriti Taklit Eden Yaygın Değişken İmmün Yetmezlik

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ABSTRACT Primary immune deficiencies are a group of genetic disorders in which one or more components of the immune system are lacking or dysfunctional. Dysregulation in the immune response may lead to bone and joint abnormalities in patients with primary immune deficiencies, with arthritis being the most common. Common variable immunodeficiency is the most common symptomatic primary antibody deficiency syndrome. In this report, a male patient was described who presented with arhritis, intermittant fever and hepatosplenomegaly mimicking systemic onset juvenile idiopathic arthritis and finally was diagnosed with common variable immunodeficiency. This case suggested that serum immunoglobulin levels should be screened in patients with suspected juvenil idiopathic arthritis in order to rule out immunodeficiency states.

Key Words: Arthritis, hypogammaglobulinemia, common variable immunodeficiency

ÖZET Primer immün yetmezlikler, immün sistemin bir ya da daha fazla bileşeninin eksik ya da işlev göremez olduğu bir grup genetik hastalıktır. İmmün cevabın düzenlenmesindeki bozukluk, içlerinde artritin en sık olduğu kemik ve eklem anormalliklerine yol açabilir. Yaygın değişken immün yetmezlik en sık görülen semptomatik primer antikor eksikliği sendromudur. Bu çalışmada sistemik başlangıçlı juvenil idiyopatik artrit tablosunu taklit eden, ateş, hepatosplenomegali ve artrit ile başvuran, sonuçta yaygın değişken immün yetmezlik tanısı alan bir olgu sunulmuştur. Bu hasta, juvenil idiyopatik artrit şüphesi olan hastalarda immün yetmezlikleri dışlamak için serum immünglobülin düzeylerinin taranması gerektiğini düşündürmüştür.

Anahtar Kelimeler: Artrit, hipogamaglobülinemi, yaygın değişken immün yetmezlik

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Primary immune deficiencies (PIDs) are a group of disorders in which one or more components of the immune system are lacking or dysfunctional. Dysregulation in the immune response may lead to bone and joint abnormalities in patients with PIDs, with arthritis being the most common.[1] Arthritis occurs mainly in humoral immune deficiencies. Common variable immunodeficiency (CVID) is the most common symptomatic primary antibody deficiency syndrome. Here we report a patient who presented with arhritis, intermittent fever and hepatosplenomegaly mimicking systemic onset juvenile idiopathic arthritis and finally was diagnosed with CVID.

A 4-year-old boy was referred to the Pediatric Immunology-Rheumatology Department with fever of unidentified origin lasting for two months. He had used a 3-week course of antibiotics prior to admission without any improvement. He had been treated with oral cefuroxime (20 mg/kg/day)

for one week followed by intravenous seftazidime (150 mg/kg/day) and amikacin (15 mg/kg/day) combination for two weeks. The fever pattern was intermittent. He suffered from pain and swelling of the right knee especially during the bouts of fever for the last week. He was the only child of healthy unrelated parents. The past medical history revealed recurrent upper respiratory tract infections since two years old. He had no history of hospitalization.

On physical examination, he was growing within normal centiles for weight and height. He had fever, generalized lymphadenopathy, hepatosplenomegaly, and arthritis of the right knee. There were no rashes. The remainder of the examination was unremarkable.

Complete blood count revealed elevated white blood cell count, 21.9×10^3 cells/mm^3 (N: 5.5-15.5 $\times$ 10^3 cells/mm^3). The hemoglobin concentration was 10.2 mg/dL (-2 SD: 11.5 mg/dL) and platelet count was normal. Direct Coombs test was negative. Blood smear showed predominance of polymorphonuclear leukocytes. Erythrocyte sedimentation rate was 42 mm/hour (N: 0-15 mm/hour) and C-reactive protein was 9 mg/L (N: 0-5 mg/L). Serologic markers for salmonellosis, brucellosis, hepatitis A, B, C, *Borrelia burgdoferi*, Epstein-Barr virus, cytomegalovirus, toxoplasmosis, parvovirus B19, and human immunodeficiency virus antigen were negative. Repeated cultures of the blood did not yield any bacteria. Chest X-ray was normal and tuberculin skin test was negative. The thymus was apparent on chest X-ray. The serum liver and kidney function tests were normal. He had no proteinuria and the serum protein level was normal. Complement components (C3 and C4) were normal. Anti-nuclear antibodies, anti-double-stranded DNA antibodies, and anti-neutrophile cytoplasmic antibodies were negative. A bone marrow aspiration biopsy showing hypercellularity with increased number of myeloid precursors excluded malignancy. Upon the lack of an infectious proof by cultivation and serology, systemic onset juvenile idiopathic arthritis (JIA) was suspected in this patient with intermittent fever and arthritis. He was put on naproxen sodium, which provided partial pain relief. Regarding his past medical history of recurrent infections, immunoglobulin levels were assessed. The diagnosis of immune deficiency was considered when hypogammaglobulinemia was detected. Immunological studies showed decreased levels of immunoglobulin (Ig)G, IgA, and IgM, decreased percentage of peripheral blood B lymphocytes, increased percentages of cluster of differentiation 8 (CD8) + T lymphocytes, and a reduced CD4/CD8 ratio (Table 1). Common variable immunodeficiency or secondary hypogammaglobulinemia due to an infection were considered for differential diagnosis. However, the absence of infectious proof by cultivation and serology suggested CVID was most likely. Intravenous immunoglobulin (IVIG) substitution therapy (400 mg/kg/dose) resulted with the resolution of arthritis and fever, as well as hepatosplenomegaly and lymphadenopathy. Lymphocyte function tests such as PHA and anti-CD3 could not be studied. The Bruton tyrosine kinase gene mutation was studied in Karolinska Institute in Stockholm and did not reveal any mutations.

During the 6-year follow-up, his serum immunglobulins as well as B cell numbers remained low consistent with primary immunodeficiency. He did not experience any further attack of arthritis. He had recurrent sinusitis. At the age of 10, a thorax computerized tomography was performed for his prolonged coughing, which revealed minimal bronchiectatic changes. Tuberculin skin test was 9 mm (he had 2 BCG scars) and repeated cultures of sputum for *Mycobacterium tuberculosis*

TABLE 1: Immunologic parameters of the patient.

	Patient	Normal
Absolute lymphocyte count (×10^9/L)	6.57	1.7-6.9
IgG (mg/dL)	267	345 -1236
IgA (mg/dL)	12	14 -159
IgM (mg/dL)	4	43 -207
CD3 (%), absolute counts (×10^9/L)	(88%), 5.78	(65-83%), 1.1-3.9
CD4 (%), absolute counts (×10^9/L)	(24%), 1.57	(26-49%), 0.6-2.0
CD8 (%), absolute counts (×10^9/L)	(62%), 4.04	(9-35%), 0.3-1.3
CD19 (%), absolute counts (×10^9/L)	(8%), 0.52	(11-31%), 0.3-1.2
CD4/CD8 ratio	0.36	0.9-2.9

(Reference ranges for Igs were derived from Nelson Textbook of Pediatrics, 18th edition and for CD cells from "İkincioğulları A et al. Peripheral blood lymphocyte subsets in healthy Turkish children. Turkish J Pediatr 2004;46:125-130").

were negative. He continues to take regular immunoglobulin therapy every month.

The discovery of hypogammaglobulinemia in a patient with arthritis is a challenging diagnostic problem. Several possibilities should be considered. A careful analysis of the time of onset of hypogammaglobulinemia and investigations for causes of secondary hypogammaglobulinemia may help to establish the diagnosis. In a child, a combination of arthritis and hypogammaglobulinemia should suggest a PID syndrome, when investigations are negative for an iatrogenic, infectious, or lymphoproliferative cause.

Primary immune deficiencies typically manifest as recurrent infections that usually start in childhood. Among the other clinical manifestations, bone and joint abnormalities occur mainly in humoral PIDs.[1] In patients with CVID, the prevalence of joint manifestations before treatment has ranged between 10% and 20%.[2] Importantly, while arthritis can be expected as the presenting symptom in children with PID, it is rarely the presenting symptom in adults.

There are several causes of arthritis in PIDs. Certain evidence of infection is found in some cases, whereas in others a dysimmunity-related synovial disorder seems to be the reason for arthritis. The most notable microorganism causing arthritis in PID is *Mycoplasma*.[3] Unfortunately, we could not study the cold agglutinin for mycoplasma. The other bacteriologic and serologic test results revealed no infectious causes in our patient. Besides, arthritis can be the presenting symptom of a lymphoproliferative syndrome responsible for immunodeficiency affecting both humoral and cell-mediated defenses, although this is exceedingly rare. In our patient, disappearance of lymphadenopathy and hepatosplenomegaly after IVIG therapy excluded lymphoproliferative syndrome.

Transient hypogammaglobulinemia of infancy (THI) was another condition to be considered in the differential diagnosis in this patient. THI is a relatively common primary immunodeficiency disease that affects infants and young children, which is characterized by decreased serum IgG and IgA levels in the first years of life but with normal to near-normal antibody responses to protein immunizations. These levels usually increase to the reference range by 2-6 years of age in children with THI.[4] We could not measure the polio and tetanus antibody levels; however, his immunoglobulins did not reach normal levels during the 6-year follow-up rendering THI unlikely. X-linked agammaglobulinemia was ruled out by the lack of Bruton tyrosine kinase gene mutation. Adenosine deaminase deficiency was also considered unlikely because the patient had normal numbers of T cells.

Autoimmune disorders should also be carefully monitored because they are common in CVID such as rheumatoid arthritis.[5] Persistent antigen stimulation, secondary to a defective eradication of pathogens followed by a compensatory exaggerated chronic inflammatory response is considered to be the primary cause leading to autoimmunity.

In conclusion, autoimmunity and immune deficiency conditions may present with symptoms overlapping each other in pediatric patients. This case suggested that serum immunoglobulin levels should be screened in patients with suspected JIA in order to rule out immunodeficiency states.

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