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Case Report PEDIATRICS

A rare disease: ZAP70 deficiency

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ABSTRACT

Zeta associated protein (ZAP) 70 deficiency is a rare disease. ZAP70 deficiency results in an autosomal recessive form of severe combined immunodeficiency (SCID) that is characterized by a selective absence of CD8 T cells. The diagnosis should be suspected in patients presenting with a severe combined immunodeficiency phenotype and selective deficiency of CD8 T cells. Sequencing of the ZAP70 gene can confirm the diagnosis. We wanted to emphasize that immunodeficiencies should also be remembered in the differential diagnosis by presenting a 5-month-old patient who applied to our clinic with complaints of skin rash and cough, was given respiratory support with mechanical ventilation for a long time, and was diagnosed with ZAP70 deficiency.

Keywords: Protein kinase; severe combined immunodeficiency; ZAP70.

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Severe combined immunodeficiency (SCID) is a rare but fatal syndrome characterized by marked deficiency of T and B lymphocyte functions. ZAP70 deficiency is a rare autosomal recessive disease in severe combined immunodeficiencies. ZAP70, a zeta chain-associated protein kinase, plays a role in T cell receptor (TCR) signaling, T cell differentiation and T cell function. Children with ZAP70 deficiency have frequent infections in the first two years of life, but diagnosis may be delayed due to the presence of lymphoid tissue and normal lymphocyte counts in most patients. Patients with ZAP70 deficiency have very low levels of CD8 + T cells in the peripheral circulation, while CD4 + T cells are within normal limits.

ZAP70 deficiency was first described in 1989 in a patient of the Mennonite race. It has been found that approximately 30% of the patients in the literature are of Mennonite origin, followed by Turkish, Japanese and Caucasian ones, respectively [1–3].

CASE REPORT

A five-month-old girl presented with a cough and rash on her arms and legs. In her medical history, she was born by vaginal delivery, there is a third degree of kinship between parents, vaccinations are made according to her age and she had no previous hospitalization history.

In her physical examination, body weight was 5800 g (25th–50th percentile), height 65 cm (>97th percentile), and head circumference was 41.5 cm (50th percentile). There were erythematous papule-like rashes with a diameter of

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1–2 mm on her hands and legs. Heart rate 152/min, respiratory rate: 55/min, oxygen saturation ($satO_2$) 82% in room air, $satO_2$: 99% under oxygen therapy with reservoir breathing mask. Her other system examination findings were normal. In her abdominal ultrasonography, the liver was heterogeneous and diffuse hypoechoic areas in the mesenteric tissue adjacent to the spleen and reactive lymph nodes with the largest size of 9x5 mm were observed. In laboratory examinations; WBC: 24.1 10^3/uL, neutrophil: 10.4 10^3/uL, hemoglobin 8.5g / dL, platelet: 143 10^3/uL, ANC: 12.6 10^3/uL, AEC: 0.3 10^3/uL, CRP: 0.2 mg/dL, procalcitonin: 0, 17 ng/mL, LDH: 958 U/L, INR: 1.45, ferritin: 1035 ng/mL, thyroid function tests were within normal limits.

No pathology was found in the stool examinations of the patient who had watery stool in the follow-up. The respiratory viral panel was negative. Tetanus antibody: 0.12 IU/mL. The detected IgA was: 33 g/dL, IgG: 324 g/dL, IgM: 81 g/dL, IgE: 14.1 IU/mL. Lymphocyte subgroups are shown in Table 1. Ceftriaxone, azithromycin and oseltamivir treatments were started. Skin punch biopsy was taken due to increased rashes and it was evaluated as non-immunogenic lymphocytic vasculopathy. Oxygen therapy was started with a high flow nasal canal for the patient who developed respiratory failure in the ward. Thoracic CT was performed on the patient with a ground-glass image on the controlled chest X-ray, it was observed that ground glass density and inter / intralobular septal thickening in the upper lobes of the lung formed a cobblestone appearance and consolidated, collapsed areas were commonly observed. Bronchoscopy was performed under operating room conditions, alveolar macrophages, bronchial epithelial cells and sparse lymphocytes were observed in bronchoalveolar lavage examination, mycobacteria were not detected in microbiological examination and there was no growth in the culture.

The patient, who was intubated after bronchoscopy and followed up in the pediatric intensive care unit and whose extubation failed, was given respiratory support with a mechanical ventilator. Ganciclovir was added to the treatment upon detection of CMV PCR positivity in the bronchial tissue biopsy of the patient, who was treated with meropenem, vancomycin and fluconazole. Plasma CMV PCR: found 427,895 IU/mL. The patient received two intravenous immunoglobulin (IVIG) replacements. On the 37th day of her admission to the PICU (Pediatric Intensive Care Unit), the patient was disconnected from the mechanical ventilator and received oxygen therapy with a high-flow nasal cannula. The patient whose clinical findings were stable during the follow-up was transferred to the pediatric service. With this clinical picture, the immunodeficiency and interferonopathy genetic panel was planned, considering that the patient might have immunodeficiency. Informed consent was taken from the patient and the patient's family.

Table 1. Patient's lymphocyte subgroups

	%
CD8	15.5
CD4	79.8
NK cells	6.5
NK-T lymphocytes	1.2
B lymphocytes	23.4
T lymphocytes	68.9

CD8: Cluster of differentiation 8; CD4: Cluster of differentiation 4; NK cells: Natural killer cells; NK-T lymphocytes: Natural killer T lymphocytes.

Molecular Analysis

Clinical exome sequencing was planned to clarify the molecular etiology for possible immunodeficiency. Automatic DNA isolation was performed in accordance with the standard protocols of the QIAAmp DNA Mini (Qiagen) kit from peripheral blood samples. Within the scope of the test, the sequencing was done on the Illumina NextSeq 500 platform using SOPHIA Clinical Exome Solution using Illumina V2 chemicals. The gene content of the kit is available on request. Sequence analysis covers coding regions of each gene, including all coding exons, +/- 10 base pairs of adjacent intronic sequences. In the patient sample, the ZAP70 (NM_001079), c.1520C>T, p. (Ala507Val) missense homozygous variant was detected. This variant was absent in homozygous state from controls in GnomAD and in-silico prediction algorithms MVP, EIG-EN, SIFT, and MutationTaster show that this variant has a destructive effect at the protein level. The variant had also been previously reported as a disease-causing mutation associated with Immunodeficiency-48 (PMID: 18509675). In segregation analysis, parents were found to be heterozygous for the variant.

The patient was followed up by pediatric genetics and pediatric immunology clinics. One month after discharge, the patient, who presented with a swelling of 3 cm in the left axillary region, was planned to be hospitalized in the pediatrics service and examined and treated, but the treatment was rejected by the family.

DISCUSSION

ZAP70 deficiency is a rare disease which results in an autosomal recessive form of severe combined immunodeficiency (SCID) that is characterized by a selective absence of CD8 T cells. The diagnosis should be suspected in patients presenting with a severe combined immunodeficiency phenotype and selective deficiency of CD8 T cells. In the study published in 2020 in which 49 patients with ZAP70 deficiency were systematically evaluated it was reported that; 81.8% of these patients had recurrent respiratory tract infections; 57.9% had clinical findings with cutaneous lesions, 32.4% had clinical findings with lymphoproliferation, 19.4% had clinical findings with enteropathy and 8.1% had clinical findings with increased risk of malignancy. The most common infectious complications were listed as pneumonia, diarrhea, sinusitis, bilateral otitis, and acute nasopharyngitis. In addition to hematological diseases such as non-immune and immune hemolytic anemia, hemophagocytic syndrome, immune thrombocytopenic purpura and bicytopenia, neurological involvements such as brain infarcts, VZV encephalitis, viral cerebellitis, facial paralysis, renal involvement such as nephrotic syndrome and IgA nephropathy can also be seen [4]. In addition, cases with cardiovascular findings such as cholestatic liver disease, persistent hypertension and atrioventricular block have been reported [5, 6].

The general approach in patients with ZAP70 deficiency, as in primary combined immunodeficiencies; It includes follow-up of growth, evaluation of agents that cause common opportunistic viral, bacterial and fungal infections; laboratory examination (liver and kidney function tests, complete blood count, lymphocyte subgroups and quantitative immunoglobulin level), hematology consultations in terms of genetics, immunology and bone marrow transplantation (BMT). Basic approaches; Antibacterial, antifungal and antiviral treatments and P. jiroveci prophylaxis, use of CMV-negative and leukocyte-free irradiated blood products and immunoglobulin replacement for the control and reduction of opportunistic infections. In patients with ZAP70 deficiency, cure can only be achieved by bone marrow transplantation. However, before BMT, busulfan and cyclophosphamide treatments should be given with or without antithymocyte globulin. HLA-compatible sibling is the best donor option for BMT, but in conditions where it cannot be provided, other tissue-compatible donors may be an option [7]. In the review by Sharifinejad et al. [4], 18 of the 25 patients who underwent stem cell transplantation survived, 2 lost and 3 survived after the second stem cell transplant, 8 patients were prophylactic and 18 patients were prophylactic steroid and intravenous immunoglobulin for the control of transplantation side effects. They stated that their treatment was given.

Infectious cutaneous presentations included disseminated molluscum contagiosum, oral and cutaneous warts, varicella zoster virus dermatitis fungal abscess. Noninfectious skin lesions such as erythematous urticarial rash, bullous pemphigoid, eczema perineal ulcers, widespread xerosis, ichthyosis, and subcutaneous nodule have also been described [8]. Our patient also presented with a skin rash and had a severe lower respiratory tract infection that required respiratory support with a mechanical ventilator and day intensive care stay in the follow-up.

CID is characterized by cellular and humoral insufficiency caused by T and B cell dysfunction. ZAP70 deficiency may manifest itself with classical form SCID, atypical SCID (Omenn syndrome), lymphoma, BCG infection, congenital nephrotic syndrome, brain infarctions, and allergic symptoms [9, 10]. It is known that all forms of CID have a risk of developing lymphoma [11]. The diagnosis of lymphoma was ruled out with the examination findings and bone marrow aspiration of our patient. It has been shown that BCG vaccination in patients with SCID can cause localized or disseminated complications in 17% and 34% [12]. BCG vaccine was administered to our patient, but no complications were detected. Mycobacteria were not detected in the gastric fasting water and BAL taken.

In conclusion, early clinical suspicion due to severe infections is the first step for the diagnosis of acute combined immunodeficiency. However, acute combined immunodeficiency, which is in pediatric emergencies, is a disease that has the potential to be diagnosed in the first days after birth due to lymphopenia and in the prenatal period if there is a family history. ZAP70 deficiency in this disease group should be remembered and necessary genetic tests should be studied.

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