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Atypical combined immunodeficiency due to Artemis defect: A case presenting as hyperimmunoglobulin M syndrome and with LGLL

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ABSTRACT

SCID can be caused by various genetic mutations leading to distinctive phenotypes according to the presence of T, B and NK cells. Artemis is a gene encoded on chromosome 10p. The deficiency of this molecule causes an inability to repair DNA double strand breaks and is one of the causes of radiosensitive T-B-NK+ SCID. The syndrome usually presents with opportunistic infections in the first years of life that leads to death if not treated with stem cell transplantation. The spectrum of the disease can be wide because of the heterogeneity of the mutations. Herein we present an atypical SCID (CID) patient with Artemis defect mimicking hyper IgM syndrome. Our patient had high serum IgM with low IgG and IgA levels, lymphocytosis and recurrent infections, intractable diarrhea, growth retardation, systemic CMV infection and sclerosing cholangitis. He also developed large granular lymphocytic leukemia and survived until the age of 6.5 years.

1. Introduction

Severe combined immunodeficiency (SCID) disease is the most severe form of the primary immunodeficiencies. The defining characteristic is always a defect in T cell differentiation and function with primary or secondary defects in B-lymphocytes and, in some genetic types, in NK production as well. A great number of T-B-NK+ SCID patients were shown to have mutations in the recombination activating genes (RAG1 and RAG2). Several T-B-NK+ SCID patients without RAG gene mutations were found to have fibroblasts sensitive to ionizing radiation (Noordzij et al., 2003). These patients have been shown to have defects in the nonhomologous end-joining (NHEJ) DNA repair pathway, the major pathway for repairing DNA double-strand breaks (DSBs). DSBs caused by a variety of exogenous and endogenous agents, cause cell death if left unrepaired and pose a major threat to genome integrity (Chu, 1997; Kanaar et al., 1998; Kurosawa and Adachi, 2010). Five genes involved in the NHEJ pathway, Artemis, DNA-PKcs, DNA ligase 4, Cernunnos-XLF and DNA end-binding complex Ku70-Ku80 are involved in B cell negative radiosensitive SCID (Cagdas, 2012; Schwarz et al., 2003). Artemis is one of the genes that is involved in the NHEJ pathway, encoded on chromosome 10p and it belongs to the metallo-β-lactamase superfamily (Buckley, 2011).

The Artemis (named after the Hellenic goddess of the hunt who aids in childbirth and protect young children) was identified as a multi-functional protein in the maintenance of genome integrity and DNA double-strand breaks (DSBs) repair, and has the function as a nuclease required for the resolution of hairpin coding ends during V(D)J recombination. V(D)J recombination is a process in the early B and T lymphocyte development. It takes place to assemble the variable (V) region of the T cell receptor and Ig genes, giving rise to a large repertoire of specificities (Jung et al., 2006).

We present a patient who admitted with recurrent infections, intractable diarrhea, growth retardation, sclerosing cholangitis, serum Ig profile suggestive for hyperimmunoglobulin M syndrome and large granular lymphocyte leukemia with a defect of the Artemis gene and died of septic shock at the age of 6.5 years.

2. Case report

A 5.5-year old boy who was the first child of third cousin healthy parents was referred to our center. He was learned to be healthy and weighed 3000 g at birth. Beginning from the first months of life, he suffered from recurrent oral ulcers, upper respiratory tract infections, otitis media, bronchitis, intractable diarrhea and hospitalized

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Table 1
Immunological findings of the patient.

Patient (age)	2 years old	5 years old	5.5-year-old[a]	5 years 9 months old	6 years old	6 years 5 months old
Complete blood count						
Hb (g/dL)	9.6	8.15	10.6	10.4	12.1	10.7
WBC (/mm^3)	9410	6420	20,400	38,600	12,500	4800
Plt (/mm^3)	336,000	174,000	45,000	99,000	337,000	223,000
ALC (/mm^3)	2000	3780	7548	11,580	8125	3360
ANC (/mm^3)	3000	2010	1224	1003	3375	960
Immunoglobulins						
Ig A (g/dL)	23(21–480)	23(57–282)	<6.67(57–282)	22(57–282)	25(57–282)	27(57–282)
Ig G (g/dL)	660(488–1774)	250(745–1804)	1080(745–1804)	440(745–1804)	300(745–1804)	340(745–1804)
Ig M (g/dL)	668(49–318)	670(78–261)	2000(78–261)	401(78–261)	94(78–261)	37(78–261)
Lymphocyte subsets (% and absolute counts (/mm^3))						
CD3	92(39–73)	NT	86(55–78)	88(55–78)	77(55–78)	75(55–78)
	1840(1400–8000)	NT	6491(700–4200)	10,190(700–4200)	6256(700–4200)	2520(700–4200)
CD4	28(25–50)	NT	5(27–53)	4(27–53)	9(27–53)	10(27–53)
	560(900–5500)	NT	377(500–2400)	810(500–2400)	731(500–2400)	336(300–2000)
CD8	79(11–32)	NT	83(19–34)	85(19–34)	68(19–34)	58(19–34)
	1580(400–2300)	NT	6264(300–1800)	9843(300–1800)	5525(300–1800)	1948(300–1800)
CD19	0.5(17–41)	NT	0(10–31)	0(10–31)	0(10–31)	0(10–31)
	10(600–3100)	NT	0(200–1600)	0(200–1600)	0(200–1600)	0(200–1600)
CD16+56	6(3–16)	NT	8(4–26)		22(4–26)	22(4–26)
	120(100–1400)	NT	603(90–900)		1787(90–900)	739(90–900)
CD45 RA (%)	NT	NT	NT	NT	NT	29(66–77)
CD45 RO (%)	NT	NT	NT	NT	NT	56

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; NA, not available; NT, not tested. Numbers in parenthesis indicates the values of healthy controls. IVIG treatment started at age 1.5.

[a] First admission to Hacettepe University.

for several times. At 18 months, he was admitted to a hospital again with intractable diarrhea and abdominal distension and the physical examination revealed hepatosplenomegaly. The immunologic study showed high immunoglobulin M with low immunoglobulin A and immunoglobulin G levels and was diagnosed as hyper IgM syndrome in a regional center. Trimetoprim/sulfamethaxazole, triflucan prophylaxis and monthly IVIG treatment have been started. Despite these treatments he continued to fail gaining weight, the size of the liver and spleen increased, he hospitalized several times and received wide-spectrum antibiotics. At the age of 5.5 years he was referred to Hacettepe Children's Hospital with fever, abdominal distension and respiratory distress. Physical examination revealed growth retardation (weight: 11 kg – 50% for 22 months, length: 89 cm – 50% for 36 months, head circumference: 47.5 cm – 50% for 26 months), massive hepatosplenomegaly (both 8–10 cm below the respective costal margines) and ascitic fluid. Complete blood count showed mild anemia, elevated white blood cells and thrombocytopenia; Hgb: 9.3 g/dL, Hct: 28.3%, MCV: 86 fL, WBC: 19.2×10^9/L, platelet: 53×10^9/L Peripheral blood smear revealed atypical lymphocytosis of 86%, in addition to 8% neutrophils and 6% monocytes. The morphology of atypical lymphocytes was prominent with large granular lymphocytes. Blood biochemistry revealed AST 341 IU/L, ALT 118 IU/L, GGT 379 IU/L, total bilirubin 3.49 mg/dL, direct bilirubin 2.7 mg/dL, total protein 6.9 g/dL, albumin 3 g/dL. The microbiological work-up revealed Anti CMV IgM positivity with positive CMV PCR. Repeated stool tests for Cryptosporidium antigen were negative.

Chest radiographs showed pneumonia with pulmonary infiltrates suggestive for viral infection and gancyclovir treatment started. Histopathological findings of the liver biopsy that was performed for hepatosplenomagaly, ascites, hypertransaminasemia and direct hyperbilirubinemia was compatible with sclerosing cholangitis. Immunophenotyping of peripheral lymphocytes revealed absence of B cells; high absolute CD3 and CD8 positive T and normal NK cell counts. While the percentages of CD4 positive T cells were markedly low, the absolute numbers were low/low normal and remained the same during the follow-up period. Immunologic findings obtained before admission to and during follow-up at our center are given in Table 1. Lymphocyte proliferation response to pHA, conA and pMA + ionomycin were negative, some response was obtained against anti-CD3 (Table 2).

Bone marrow aspiration was performed at three different times within 3 months due to persistent fever, hepatosplenomegaly, atypical lymphocytosis and thrombocytopenia in order to rule out hemophagocytic lymphohistiocytosis and malignancy. Bone marrow aspiration smears were cellular with the atypical lymphocytosis similar to peripheral blood film. The HLH was ruled out since the patient did not fulfill the diagnostic criteria of HLH 2004 and hemophagocytosis was absent. The patient was diagnosed to have large granular lymphocytic leukemia of T cells composed of CD3+, CD4−, CD8+ cells. TCR rearrangement studies could not be done. Since the patient had persistently high fever with rapid detoriation of the condition, he was put on daily methylprednisolone (10 mg/kg) and weekly methotrexate (10 mg/m^2) treatments. After first month of chemotherapy, fever remitted, liver transaminases started to decrease, CMV viral load decreased and the patient discharged from the hospital. After he discharged from the hospital hepatosplenomegaly regressed and he started to gain weight, and he only had a few upper respiratory tract infections during the following nine months as learned from the parents. During these follow-ups, steroid treatment was slowly tapered to a dose of prednisolone 0.5 mg/kg/day and methotrexate was continued as weekly. Unfortunately, by the 9th month of the initiation of methylprednisolone and methotrexate treatments he came emergency

Table 2
In vitro lymphocyte proliferation test results of our patient compared with healthy controls.

Age	5.5 years old		5 years 9 months old	
	Patient	Control	Patient	Control
Stimulation with:				
PHA	1.15/1.29	79.9/0.8	1.46/1.07	255.7/1.2
ConA	1.3/1.29	23.7/0.8	0.48/1.07	82/1.2
antiCD3	1.12/1.29	46.3/0.8	30.7/1.07	74.1/1.2
PMA + I	1.07/1.29	12.5/0.8	0.94/1.07	114/1.2

PHA, phytohemaglutinin; con A, concavalin A; PMA + I, phorbol myristate acetate and Ionomycine. In vitro lymphocyte proliferation test, cpm $\times 10^{-3}$ (stimulated/unstimulated).