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CLINICAL VIGNETTE

Class switch recombination defect in child with ataxia-telangiectasia with hyper IgM phenotype

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Abstract

Ataxia-telangiectasia (AT) is a rare autosomal recessive disease characterized by cerebellar ataxia, ocular and/or cutaneous telangiectasia, immune deficiency, enhanced radiosensitivity, and susceptibility to malignancy. It is caused by mutations in the AT mutated (*ATM*) gene. Hyper-IgM phenotypes are characterized by a class-switch recombination defect, IgG and IgA deficiencies, immune dysregulation, and lymphoproliferative disorders. In this case report, a 6.5-year-old Egyptian AT female had progressive hepatosplenomegaly, hypersplenism, generalized lymphadenopathy, and high levels of IgM. This patient had a class switch recombination defect (CSRD), leading to the diagnosis of HIgM-phenotype of AT with class switch defect (HIgM AT-CSD). In reporting this case, we hope to highlight its rarity and complexity in a pediatric patient with AT, as well as the potential role of an appropriate diagnostic assessment in achieving successful clinical outcomes. The presence of hepatosplenomegaly and lymphadenopathy in AT suggests malignancy or infection, but after exclusion of these causes, pediatricians must consider HIgM AT-CSD as a possible cause of lymphoproliferation.

Key words: ataxia-telangiectasia, HIgM AT-CSD, CSRD, lymphoproliferation

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Case report

A 6.5-year-old female child presented with progressive hepatomegaly and generalized lymphadenopathy to the Primary Immunodeficiency Unit of a university children's hospital in Egypt. She had been in good health until the age of one year when she began to exhibit recurrent respiratory tract infections and purulent otitis media. His parents were consanguineous, and there was a family history that was consistent with her presentation.

At the age of two, she presented with splenomegaly and chronic anemia. Investigations revealed low iron level, low transferrin, and normal metabolic and hemolysis workup. She was treated accordingly with iron supplementation and other supportive management with follow-up.

At the age of three, she developed bilateral ocular telangiectasia, truncal titubation, and disturbed gait. She was evaluated by a pediatric neurology specialist, who diagnosed cerebellar ataxia. She was referred to our Primary Immunodeficiency Unit at this age due to associated recurrent sinopulmonary and gastrointestinal tract infections.

Our initial laboratory workup revealed microcytic hypochromic anemia, high alpha-fetoprotein (AFP) levels, and mild chromosomal breakage induction. The results of an immunological workup revealed low IgG, low IgA, high IgM, and normal IgE. In lymphocyte subsets, CD20 percentage was reduced, but CD3, CD4, CD8, and CD56/16 percentages were normal (Table I). A diagnosis of ataxia-telangiectasia (AT) was made, and monthly intravenous immunoglobulin (IVIg) replacement and prophylactic treatment with trimethoprim-sulfamethoxazole were initiated at the age of three.

Table I. Laboratory and immunological data of a child diagnosed with HIgM-phenotype of ataxia-telangiectasia with class switch defect (HIgM AT-CSD)

Parameter	**Values at diagnosis (age 3 years)**	**Values at age 6**	**Reference value**
Total WBCs [1,000/μL]	6.6	3.1	5–15
Neutrophil [1,000/μL]	3.21	0.3	1.5–8.5
Lymphocyte [1,000/μL]	2.73	1	2–8
Hb [mg/dL]	10.7	8.3	11.5–15

MCV [fL]	68.9	76.2	75–87
Platelets [1,000/μL]	188	240	150–500
IgM [mg/dL]	1,090	3,300	(Normal value: 19–146)
IgG [mg/dL]	116	238	(Normal value: 453–916)
IgA [mg/dL]	Undetectable	29	(Normal value: 20–100)
IgE [IU/mL]	0.14	0.13	(Normal value: 0–60)
CD3+ [%]	84.7	65	(Normal value: 43–76)
CD4+ [%]	44	53	(Normal value: 23–48)
CD8+ [%]	24.2	10	(Normal value: 14–33)
CD4/CD8 ratio	1.8	5.3	(Normal value: 1.6–6.2)
CD3+ absolute count	2,397/μL	3,217/μL	(Normal value: 900–4,500)
CD4+ absolute count	1,245/μL	2,623/μL	(Normal value: 500–2,400)
CD8+ absolute count	685/μL	495	(Normal value: 300–1,600)
CD20+ [%]	1.7	1.5	(Normal value: 14–44)
CD56–/CD16+ [%]	2.4	2.8	
CD56+/CD16+ [%]	10.4	11.2	
CD56+/CD16– [%]	0.9	5	
Total NK cells [%]	13.7	19	(Normal value: 4–23)
HBe Ag (ECL)	Negative	Negative	
HBc Ag (ECL)	Negative	Negative	
HBs Ab (IU/L)	Negative	Negative	

HCV Ab (Index)	Negative	Negative	
Anti-EBV Ab (Index)	Negative	Negative	
Anti-CMV Ab (COI)	Negative	Negative	
Anti-HSV1+2 Ab (Index)	Negative	Negative	
Anti-HIV Ab (Index)	Negative	Negative	
Toxoplasma IgM (Index)	Negative	Negative	
Rubella IgM (Index)	Negative	Negative	
Alpha-fetoprotein [ng/mL]	99.1	149.9	Up to 8

WBC — white blood cells; Hb — hemoglobin; MCV — mean corpuscular volume; Ig — immunoglobulin; NK — natural killers; HCV — hepatitis C virus; EBV — Epstein-Bárr virus; CMV — cytomegalovirus; HSV1 — herpes simplex virus 1; HIV — human immunodeficiency virus

Her condition worsened at the age of five, and abnormal findings resulted, including generalized lymphadenopathy and hepatosplenomegaly. Lab and radiology workups were performed to exclude malignancies, autoimmune lymphoproliferative syndrome (ALPS), hemophagocytic lymphohistiocytosis (HLH), and infectious causes. In both bone marrow aspiration and bone marrow biopsy, normal cellularity was found with no malignancy or hemophagocytosis observed. A serology and polymerase chain reaction (PCR) for cytomegalovirus (CMV) showed positive results, and the patient was treated with antiviral therapy (gancyclovir) until complete eradication of the CMV infection, with a slight improvement in her clinical status. Results of repeated viral investigations were all negative. Blood, urine, and cerebrospinal fluid cultures (bacterial and mycobacteria) were sterile.

At the age of six, the patient developed hypersplenism, so a splenectomy was performed with subsequent improvement of pancytopenia. Six months later, hepatomegaly and lymphadenopathy worsened, and fever appeared. Therefore, she was admitted to the hospital once again. A multislice computed tomography (CT) chest, abdomen, and pelvis post intravenous contrast study showed bilateral axillary, supraclavicular, infraclavicular, mediastinal, and mesenteric lymphadenopathy, as well as hepatomegaly. After lymph node excision, the histopathology showed no evidence for malignancy and suggested

lymphoproliferative disease of immunodeficiency, including partly disturbed architecture with attenuation of lymphoid follicles and expansion of the interfollicular area by marginal zone cells. The interfollicular area showed an abundance of plasma cells and histiocytes admixed with small lymphocytes, and a few scattered mononuclear cells were seen.

Due to the presence of lymphoproliferative disease and elevated IgM levels, we tested for class switch recombination (CSR) in this patient by evaluating the ability of peripheral blood mononuclear cells to produce a normal level of IgE after being cultured for 12 days at 37°C in a humidified atmosphere with 5% CO_2 in the presence of recombinant interleukin 4 (IL-4) and CD40L. CSR is considered defective if the quantity of IgE produced after stimulation is less than 0.35 IU/mL [1]. As this patient had a class switch recombination defect, we concluded that she had HIgM-phenotype ataxia-telangiectasia with a class switch defect (HIgM AT-CSD).

Discussion

Patients with primary immune deficiency are susceptible to hepatosplenomegaly, a lymphoproliferative complication that is generally caused by infection or immune dysregulation. According to some reports, hepatosplenomegaly is a characteristic feature of AT patients with HIgM profiles [2, 3].

Class switch recombination defect (CSRD) is an immunodeficiency disorder characterized by low levels of serum IgG, IgA, and IgE, with normal or raised levels of IgM [1, 4, 5].

In this AT patient, having high levels of serum IgM in association with low levels of IgG and IgA led to a presumptive diagnosis of a HIgM-phenotype. CSRD was diagnosed based on the absence of IgE production by B-lymphocytes stimulated by IL-4 and anti-CD40, leading to the diagnosis of HIgM-phenotype of ataxia-telangiectasia with class switch defect (HIgM AT-CSD). Muhammadinejad et al. [1] also reported three Iranian girls and a German boy of Turkish origin with high IgM serum levels and a diagnosis of AT and defective CSR processes.

Whenever there is a disseminated disease, a pediatric immunology service should be consulted as soon as possible to rule out any underlying immunodeficiency disease, and to optimize treatment [6].

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