

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

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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 Zagazig 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. Her 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.

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 (ganciclovir) 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

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

| Parameter | Values at diagnosis (age 3 years) | Values at age 6 | Reference value |
|-----------------------------|-----------------------------------|-----------------|---------------------------|
| Total WBCs [1,000/ μ L] | 6.6 | 3.1 | 5–15 |
| Neutrophil [1,000/ μ L] | 3.21 | 0.3 | 1.5–8.5 |
| Lymphocyte [1,000/ μ L] | 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/ μ L] | 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/ μ L | 3,217/ μ L | (Normal value: 900–4,500) |
| CD4+ absolute count | 1,245/ μ L | 2,623/ μ L | (Normal value: 500–2,400) |
| CD8+ absolute count | 685/ μ L | 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 |

WBCs – white blood cells; Hb – hemoglobin; MCV – mean corpuscular volume; Ig – immunoglobulin; NK – natural killers; ag – antigen; ECL – electrochemoluminescence assay; HCV – hepatitis C virus; EBV – Epstein-Barr virus; CMV – cytomegalovirus; HSV1 – herpes simplex virus 1; HIV – human immunodeficiency virus

IgE after being cultured for 12 days at 37 °C in a humidified atmosphere with 5% CO₂ 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 HlgM-phenotype ataxia-telangiectasia with a class switch defect (HlgM 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 HlgM 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). Mohammadinejad 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.

Summary

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].

Authors' contributions

MA – clinical analysis, writing the manuscript. EGB – clinical analysis, writing the manuscript. TAA – clinical analysis, writing the manuscript. All authors critically revised and approved the manuscript.

Conflict of interest

None.

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None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to Biomedical journals.

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