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Misclassification of Ataxia Telangiectasia with Hyper IgM Immune Profile

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Abstract

Ataxia-telangiectasia is a rare primary immunodeficiency and multisystem DNA repair disorder, resulting from mutation in *ataxia telangiectasia mutated (ATM)* gene. The ATM protein plays a significant role in detecting DNA double-strand breaks (DSB), oxidative stress and other genetic stresses. The ATM can directly mention DNA ends in repair complexes and directly involve in the repairment of DSBs that are induced during T cell and B cell rearrangement. Therefore, increase in the level of serum IgM and mainly sinopulmonary recurrent infection, which is indistinguishable from hyper IgM syndrome, can be a symptom of some AT patients. AT patients with class-switched defect are more prone to severe infections, autoimmunity, and lymphoproliferative disorders. In this study an AT patient with characteristic features of hyper IgM phenotype and lymphoproliferation is investigated.

Keywords Ataxia telangiectasia, Class switch recombination, Hyper IgM syndrome, Lymphoproliferation.

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Introduction

Ataxia-telangiectasia (AT) is a rare, autosome recessive disorder that results from mutation in *ataxia telangiectasia mutant (ATM)* gene. This disorder is characterized by progressive cerebellar ataxia, oculocotaneous telangiectasia, abnormalities of endocrine, growth retardation, chromosomal instability, radiosensitivity and increase in predisposition to cancer (1). *ATM* gene encodes a protein kinase, which is a member of the phosphatidylinositol 3 kinase-related protein family, and plays an important role in cellular response to DNA damages including phosphorylation of the targets that mediate control of cell cycle checkpoints, repairment of DNA double-strand break, monitoring of telomere length and apoptosis (2).

After B cell is activated, B cell receptor genes will be diversified by class switch recombination (CSR) as well as somatic hypermutation (SHM), since both SHM and CSR can be activated by activation-induced cytidine deaminase (AID) - an enzyme that detects cytidines in single-stranded DNA. ATM has a vital role in the CSR process of double strand break (DSB) repair (3). Impairment in the molecular mechanism and the signals involved in CSR and SHM are observed in a group of disorders called class switching recombination defect (CSRD) (4,5). In recent years, it has been noted that a subgroup of AT patients manifest CSRD in correlation with severe phenotypes.

In this study, an AT patient with CSR symptom and severe lymphoproliferation is investigated.

Case presentation

The patient is a 30 months old boy who is the third child of consanguineous parents. There is no history of immunodeficiency and autoimmunity in the family. The patient had a healthy condition until reaching 12 months of age. At 12 months old he was admitted to hospital because of fever, hepatosplenomegaly and cytopenia. After numerous multisystem workups including infectious, hematologic, metabolic, and rheumatologic workups, no definite diagnosis was established. Consequently, he was transferred to our hospital for further examination. The pathologic findings of the physical examination included the following: temperature:38.5°C, respiratory rate:34 per minute, pulse rate: 95 per minute, blood pressure:90/60 mmHg, pale conjunctiva, and a grade 2 systolic ejection type murmur which was prominent in the left sternal border. However, other findings of chest examination were normal. Neurologic and dermatologic examinations yielded normal results. Common antibiotics were prescribed and workups of immunologic, infectious, metabolic and oncologic disorders were undertaken. Bone marrow aspiration and bone marrow biopsy were found to be normal, as no malignancy and hemophagocytosis was observed. Bone marrow smear for Leishman body, acid-fast staining, and mycobacterium PCR were found to be negative. Blood culture, urine culture and bone marrow cultures for bacteria and fungus were also negative. The result of rheumatological examination was normal. Based on the ophthalmologist's examination, the results of fundoscopy were normal. Levels of β glucocerebrosidase and acid sphingomyelinase were normal. The findings of immunologic examinations such as complete blood count, immunoglobulin (Ig) levels, CD markers, vaccine antibodies, and infectious panels are illustrated in **Table 1**. In the immunological workup, hyper IgM syndrome (HIgM) was observed for this case which was due to significantly high levels of serum IgM and low IgG and IgA. Therefore, genetic study was requested for confirmation of AID or UNG deficiency.

The patient received intravenous Ig (IVIG) and underwent Ig replacement therapy on a monthly basis. He was discharged with a prophylactic antibiotic and in a good condition. We did not visit him until he reached 23 months of age. Although he was receiving IVIG and prophylactic antibiotics, his parents complained of recurrent sinusitis, otitis and pneumonia. A persistent fever was observed from 1 month ago and generalized lymphadenopathy (bilateral cervical, axillary and inguinal lymphadenopathy) was developed. Consequently he was admitted to the hospital once again because of these new complications. In the first step, Vancomycin and Meropenem with granulocyte-colony stimulating factor (GCSF) were prescribed, while oncology and infectious consultation were being done. No evidence of malignancy in the lymphadenitis was detected in the excisional lymph node biopsy.

Table 1. Laboratory data of the AT case manifested by HIgM syndrome

	Values at age 1y (Diagnosis age)
Complete blood count	
WBC(cell/ul)	3970
Neutrophils (% of WBC)	63
Lymphocytes (%of WBC)	26
Platelets (10^3/UL)	78
Hemoglobin (g/dL)	8.2
CD markers	
CD3+ (% of lymphocytes)	64
CD4+(%of lymphocytes)	28
CD8+ (% of lymphocytes)	28
CD16+ (%of lymphocytes)	21
CD56+ (%of lymphocytes)	10
CD19+ (%of lymphocytes)	10
HLA-DR (%of lymphocytes)	11
CD45(%of lymphocytes)	100
Serum immunoglobulins	
IgM (mg/dL)	1500
IgG (mg/dL)	15
IgA (mg/dL)	Undetectable
IgE (IU/ml)	Undetectable
Vaccine antibodies	
Anti-tetanus (IU/mL)	Undetectable
Anti-diphtheria (IU/mL)	Undetectable
Infections panels	
HBe Ag (ECL)	Negative
HBc Ag (ECL)	Negative
HBs Ab (IU/L)	Negative
HCV Ab (Index)	Negative
Anti-EBV Ab (Index)	Negative
Anti-CMV Ab (Index)	Negative
Anti-HSV1+2 Ab (Index)	Negative
Anti-HIV Ab (Index)	Negative
Alpha-fetoprotein(ng/mL)	62

Abbreviations: WBC; white blood cells, Ig; Immunoglobulins, CD; Cluster of Differentiation, HLA; human leukocyte antigen, HBe Ag; Hepatitis B e-antigen, HBc Ag; Hepatitis B c-antigen, HBs Ab; Hepatitis B s- antibody, HCV; Hepatitis C, EBV; Epstein-Barr virus, CMV; Cytomegalovirus, HSV; Herpes simplex virus, HIV; Human immunodeficiency virus

Genetic analysis for *UNG* and *AID* showed no mutations. Considering that mutations in other genes associated with HIgM phenotype -such as *CD40L, CD40, nuclear factor-kappa-B essential modulator (NEMO/IKBKG), inhibitor of kappa light chain gene enhancer in B cells, alpha (IKBA), nuclear factor kappa-B subunit 1 (NKFB1), MutS Homolog 6 (MSH6), MutS Homolog 2 (MSH2), post meiotic segregation increased 2 (PMS2),I-NO80, Nibrin/Nijmegen breakage syndrome 1 (NBS1/NBN),* and *meiotic recombination 11-like protein A (MRE11)*- could result in class-switched recombination defect, the sample of the case was sent for whole-exome sequencing. At 30 months of age, the patient showed signs of ataxia. In this respect, the genetic examination confirmed a mutation in *ATM* gene and the diagnosis changed to AT disorder.

Considering that the case suffered lymphoproliferation disorders, corticosteroid pulses (methyl prednisolone 10mg/kg/day for 2 days) were administered to him and treatment was followed by dexamethasone (10mg/m2/day) along with cyclosporine syrup. After 2 months the fever was gone and lymphoproliferations regressed. Liver function tests yielded normal results and neutrophil counts fell within the normal range.

Discussion

We investigated a patient with a history of recurrent infection in upper respiratory tract and lymphoproliferation, who was initially diagnosed with HIGM syndrome with respect to the level of serum Ig. Subsequently, his lymphoproliferation progressively heightened and ataxia and an increase in the level of alpha-fetoprotein and ATM mutation were observed, and he was diagnosed with AT disorder.

CSRD or HIGM syndrome is a primary immunodeficiency disorder that is characterized by a reduction in the level of serum IgG, IgA and IgE with normal or raised IgM level. CSRD is an outcome of defects in class switch recombination and somatic hypermutation. After antigen is presented in the mature B cell, Ig class switch recombination and somatic hypermutation occur and lead to production of Ig isotypes other than IgM with high affinity. In the process of CSR, the constant region of heavy chain undergoes changes; however, the variable domain remains unchanged. Activation-induced cytidine deaminase initiates CSR and SHM and uracil DNA glycosylase and mismatch repair enzymes process them to produce DNA double-strand breaks (DSB). DSBs regions are then repaired by non-homologous end-joining. The ATM, which is a member of phosphatidylinositol 3 kinase-related protein family, plays a vital role in detecting and responding to DNA damage along with several other DNA repairment factors (4,6-8). The ATM protein involves in checkpoint responses induced by double-stranded DNA breakage. As a result, its function is critical for the development of B and T cell, recombination of V(D)J in diversification of Ig and recombination of T cell receptor chain, proliferation of B cell and T cell, and survival after interconnection of receptors (9). With this respect, CSRD could be observed in patients offerings from AT. Decrease in serum IgG and IgA with normal or raised IgM level is observed in 10-20% of AT patients and they are diagnosed as hyper IgM phenotype (AT-CSD) (7,10,11). Thus, AT-CSD patients are likely to be misdiagnosed as classical HIGM (10-12). Furthermore, some clinical indications of the AT disorder, including ataxic gait and telangiectasia might not be observed in early stages of the disease, consequently the diagnosis of patients is likely to be misclassified as HIGM (13).

These patients receive a poor prognosis and undergo a more severe course of the disease. The main cause of death in this group of AT patients in respiratory failure. In AT-CSD patients' neutropenia is more frequent. Lymphoproliferation disorders (e.g. splenomegaly, hepatomegaly, and lymphadenopathy) and autoimmunity are also frequent in AT-CSD patients (11). For patients with HIGM profile without mutation in relevant candidate genes (e.g. *CD40, CD40L, AID, UNG*), checking αFP level, analysis of ATM mutation, assay of radiosensitivity or detection of ATM protein is recommended. It has been proven that the main immune-related sign of AT-CSD group is lymphoproliferative disorder and autoimmunity (11,14).

AT-CSD patients are usually characterized by early-onset infections, whereas AT patients without CSD commonly show ataxia and other neurologic signs (7,10,11). Ghiasy et al. reported that some of the non-infectious immunological signs are more frequently observed in AT-CSD patients; such as lymphoproliferative disorders in 42.9%, splenomegaly in 42.9%, hepatomegaly in 28.6%, lymphadenopathy in 21% and autoimmunity in 42.9% (11). Moreover, in the reports of AT-CSD patients' neutropenia was observed more frequently. Our patient suffers from lymphoproliferation disorders, huge splenomegaly, hepatomegaly and generalized lymphadenopathy and neutropenia. The course of the disease is more severe in AT-CSD patients than other patients with AT, which leads to a decline in quality of life, poor prognosis, and early death mainly as a result of respiratory failure.

The lack of class-switched immunoglobulins in AT-CSD patients results in deficiency in secondary function of antibodies, such as complement activation, opsonization, antibody-dependent cell cytotoxicity, and neutralization (4,11). Higher frequency of lymphoproliferation in this group of AT patients might be the outcome of dysregulated and highly proliferating B cell which is a result of which is a result of continues stimulation by antigens and cytokines.

Conclusion

Patients with HIGM phenotype, especially those with increased AFP and lymphoproliferative disorders, should be investigated for AT disorders. Given that AT-CSD patients show a more severe phenotype than other AT patients, management and follow up of this group of patients must be undertaken with further precision.

Conflicts of interest: There is no conflicts of interest.

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