Monoclonal Gammopathy in a Pediatric Patient with Ataxia-Telangiectasia: A Case Report, Review of the Literature, and Preliminary Differential Diagnosis

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Abstract

Ataxia-Telangiectasia (A-T) is an autosomal recessive disorder characterized by immunodeficiency and neurodegeneration. An additional consequence of mutations in the ATM gene is a predisposition to monoclonal and oligoclonal gammopathies, which are reported in 8% of A-T patients. They have been hypothesized to originate from exposure of lymphocytes to events causing double stranded DNA breaks, such as ionizing radiation. Persistence of these breaks, along with the abnormal thymic development and defective cell cycle regulation seen in A-T, has the potential to lead to clonal dysregulation of B cells and to gammopathies. Of gammopathies present in the pediatric population, etiologies vary from autoimmune disorders, hematologic malignancies, myelodysplasias, and renal and hepatic disorders. Herein we discuss the unusual case of a pediatric patient with A-T, IgA deficiency, and asthma, who was found to have a monoclonal gammopathy. Further studies did not reveal the presence of an underlying malignancy or autoimmune disorder but the patient will continue to be closely monitored.

Introduction

Ataxia-Telangiectasia (A-T) is an autosomal recessive disorder characterized by immunodeficiency and neurodegeneration. The disorder is caused by mutations in the Ataxia Telangiectasia Mutated (ATM) gene on chromosome 11q22-23, which encodes a Phosphatidylinositol 3-Kinase (PI3-K) involved in regulation of cell death, the cell cycle, DNA repair and maintenance, and immune gene recombination [1-5]. Clinical features of the disorder include movement disorders, neurological symptoms, cutaneous and conjunctival telangectasias, possible increased risk of malignancy, and immunodeficiency [2,3].

Due to the involvement of the ATM gene in cell cycle progression and DNA repair, A-T patients are sensitive to ionizing radiation and have an increased susceptibility to cancer, particularly to hematolymphoid malignancies [1-10]. Immunodeficiency in A-T often involves T-cell lymphopenias, thymic hypoplasia, and deficiencies in immunoglobulin production, mainly IgA, IgE, and IgG2, which places A-T patients at an increased risk for recurrent sinopulmonary infections [1-3,10].

An additional consequence of mutations in the ATM gene is a predisposition to gammopathies, both monoclonal and polyclonal [1,10-13]. In a recent study, 39% of A-T patients showed hypergammaglobulinemia, with 8% of patients having a monoclonal or oligoclonal gammopathy [1,12]. The differential diagnosis for monoclonal gammopathies in the general pediatric population includes congenital, autoimmune, and infectious diseases, hematologic conditions, solid organ malignancies, and renal or hepatic disease [12]. However, no studies have specifically described the differential diagnosis for gammopathies in A-T patients. Here in, we describe a case of a child with A-T who was found to have a monoclonal gammopathy and propose a preliminary differential diagnosis for monoclonal gammopathy in A-T patients.

Case Report

The patient is a pediatric patient with a past medical history of A-T, IgA deficiency, presumed epilepsy, and asthma who was born at term to a 26 year old G1P1 mother. The patient’s family history was contributory for A-T in a sibling and a treatment with leg braces for undocumented
Figure 1: Monoclonal spike on serum protein electrophoresis. Protein electrophoresis depicting relative and absolute concentrations of serum proteins after densitometric evaluation of SPEP areas. A blood sample was drawn from the patient and analyzed for total serum proteins on SPIFE 3000 (Helena, Beaumont, TX, USA). High Resolution Protein Electrophoresis equipment per the manufacturer’s protocol. A monoclonal spike is present in the gamma region at a concentration of 0.56 g/dL. Mild hemolysis of the sample is indicated by the peak between the alpha 2 and beta regions.

conditions in distant relatives. The patient experienced irregular breathing postnatally and was observed in the neonatal intensive care until discharge at 5 days old. The patient met developmental milestones within the first few months of life. However, at 1 year of age, the child’s parents noted that the patient began walking but preferred to toe-walk with knees hyperextended, resulting in falls. This prompted a neurological evaluation. Brain magnetic resonance imaging, cerebrospinal fluid studies, complete metabolic panel, creatine phosphokinase, lactic acid, lysosomal enzyme battery, very long chain fatty acid levels, and an acyclcarnitine profile were all normal. However, IgA was found to be absent (normal 15 mg/dl to 80 mg/dl) and alpha-fetoprotein was found to be elevated at 87 ng/mL (normal range 0-15 ng/mL). The patient was referred to genetics for sequencing of the ataxia-telangiectasia mutated gene.

Full gene sequencing of the patient’s ATM gene was performed and two alterations were detected: a variant heterozygous change from G to A at nucleotide 331+1 of the ATM gene (c.331+1 G>A) and a positive heterozygous change from C to A at 1931, resulting in a nonsense change at codon 644 (c.1931 C>A; p.Ser644*). The first alteration involved the highly conserved canonical splice donor site of a nonsense change at codon 644 (c.1931 C>A; p.Ser644*). The first alteration would obliterate the normal splice donor site and thus result in a different pathogenic ATM mutation was previously documented at this site [15]. The second alteration results in premature termination of the transcript, which is an alteration previously documented in A-T [16]. Both mutations were predicted to be deleterious [14-16].

At diagnosis, total serum IgG was elevated at 1340 mg/dL (580 mg/dL to 1256 mg/dL), with IgG1-IgG4 subtypes within normal limits. Total serum protein was elevated at 8.6 g/dL (6.0 g/dL to 8.0 g/dL). The patient also had a neutrophilia of 81% (12% to 54%) and lymphopenia of 8% (3% to 75%). Serum Protein Electrophoresis (SPEP) was performed which showed a monoclonal protein (M-protein, M-spike, monoclonal gammaglobulin) detected with an approximate concentration of 0.56 g/dL (Figure 1). Immunoelectrophoresis (IEP) identified the monoclonal protein as either IgG λ or free λ (Figure 2). Repeat SPEP and IEP showed a monoclonal protein at an approximate concentration of 0.32 g/dL that was either IgG λ or free λ light chain. Serum IEP for IgD and IgE was also performed, which showed no IgD λ or IgE λ.

Three sets of serum free light chain testing were performed and showed a mean κ concentration of 16.0 mg/L ± 1.7 mg/L (Mean ± SEM) (normal 3.3 mg/dL to 19.4 mg/L) and a mean λ concentration of 10.3 mg/L ± 0.3 mg/L (normal 5.7-26.3 mg/L). The average κ/λ ratio was 1.54 ± 0.1 (normal range 0.26-1.65).

The patient was referred to hematology-oncology for further testing, but it was felt that the patient’s risk of malignancy was low due to a normal lymph node exam, and complete blood count, lactate dehydrogenase level, and uric acid level that were within normal limits. The patient will, however, continue to be closely monitored henceforth for changes in clinical status.

Discussion

A-T is an autosomal recessive disorder arising from mutations in the ATM gene that result in neurodegeneration, cutaneous and ocular telangectasias, cancer susceptibility, and immunodeficiency [2-3]. Clinically, the neurodegeneration manifests as oculomotor apraxia, dysarthria, and movement disorders such as choreo-athetosis, dystonia, Parkinsonism, among other neurological dysfunctions [2-3].

Due to the involvement of the ATM gene in cell cycle progression and DNA repair, homozygous mutated A-T patients are sensitive to ionizing radiation and may have an increased risk of hematologic or gastric malignancy, dysgerminoma, medulloblastoma, and gonadoblastoma, among other cancers [1-9]. A-T patients are most likely to develop hematologic malignancies, with Caucasian A-T patients and African-American A-T patients carrying a 250-fold and 750-fold increased risk of lymphoma, respectively, as compared with the general population [5,10]. There is an increased risk of developing both T and B cell tumors, with B cell non-Hodgkin’s lymphoma being...
the most common B cell tumor and T acute lymphocytic leukemia, 
T cell lymphoma, and T prolymphocytic leukemia, being the most 
common T cell neoplasms [5]. Additionally, female carriers of an 
ATM gene mutation have a documented increased risk of breast 
cancer [3,17].

Immune deficiency in A-T is variable in each individual patient 
but also in one patient across time. The most common immune 
defects in A-T involve cellular and humoral immunity: CD4+T 
cell lymphopenia, reduced delayed-type hypersensitivity reactions, 
and deficiencies in IgA, IgE, and IgG2 [1,10]. Thymic hypoplasia is 
observed as an absence of Hassall’s corpuscles and decreased 
corticomedullary differentiation [1]. Lymphocytes of A-T patients 
 exhibit telemicular erosion and fusions, as well as cell cycle dysfunction, 
which may also play a role in immunodeficiency in A-T [18]. Due 
to these factors, A-T patients have a predilection for recurrent bacterial 
sinopulmonary infection which, worsened by neurodegenerative 
dysphasia, leads to the most common cause of death in the disorder: 
 aspiration pneumonia [1-3].

Additional sequelae of ATM gene mutations are monoclonal 
and polyclonal gammapathies [1,10-13]. Gerritsen et al. [11] studied 
monoclonal gammapathies in the general pediatric population. They 
detected all immunoglobulin isotype monoclonal gammapathies 
except for IgA monoclonal gammapathies and identified a 
predominance of lambda light chain gammapathies. Conversely 
Akha et al. specifically studied gammapathies in A-T patients. They 
found that 39% of A-T patients showed hypergammaglobulinemia, 
with 8% of patients having a monoclonal gammapathy [1,12]. They 
also found that all immunoglobulin isotypes were represented in A-T 
patients with monoclonal gammapathy and did detect A-T patients 
with lambda light chain gammapathies, although the lambda light 
chain did not predominate [1,12].

Our patient exhibited a monoclonal gammapathy involving the 
lambda light chain, but the immunoglobulin isotype was unable to 
be determined. It is unlikely that the gammapathy represented free 
light chain lambda, as the free κ/λ ratio was only mildly elevated in 
two measurements, with the mean ratio being within normal limits. 
Urine protein electrophoresis and immunoelctrophoresis would be 
helpful to further characterize the isotype, however the clinical team 
did not order these studies. Although our data cannot be directly 
compared to the Gerritsen et al. study, as they were not specifically 
evaluating A-T patients with monoclonal gammapathy and did detect A-T patients 
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The differential for monoclonal gammapathies in the general 
pediatric population has been established by Gerritsen et al. and 
Karafin et al. and includes congenital, autoimmune, and infectious 
diseases, hematologic conditions, solid organ malignancies, and 
renal and hepatic diseases [11,12]. In this classification, A-T is 
included in the spectrum of congenital diseases. It is likely that 
the causes of gammapathies in A-T patients may predominantly include 
malignancy, autoimmunity, and infection, considering the unique 
susceptibility of these patients to cancer and immunodeficiency. 
Indeed, case reports published on gammapathies in A-T patients 
have described prior oral and genital herpetic infections and diffuse 
plasmocytosis of the kidney, liver, bone marrow, and lungs [10,13].

It has been hypothesized that monoclonal and polyclonal 
gammapathies in A-T may result from exposure of lymphocytes to 
events that increased double stranded DNA breaks, such as ionizing 
radiation, chemotherapy, or infections [1,11]. The lack of repair 
of these breaks, coupled with abnormal thymic development and 
defective cell cycle regulation, could then lead to clonal dysregulation 
of B cells and gammapathies [1]. Data supporting this includes 
abnormalities in TCR rearrangements in A-T and an increased 
incidence of translocations involving TCR and immunoglobulin 
genes [3,8]. In fact, these translocations can be detected in 10% of 
circulating T cells in A-T patients throughout their lifetime [19]. In 
many cases, these monoclonal gammapathies appear to be short-lived 
[11], as is the case in the general pediatric population [11]. However, 
it is wise for clinicians to be aware of the unique susceptibility of A-T 
patients to malignancy and immunodeficiency and screen for the 
possibility of an underlying malignancy, autoimmune disorder, or 
infection.

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