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Case Report
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Monoclonal Gammopathy in a Pediatric Patient with Ataxia-Telangectasia: 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

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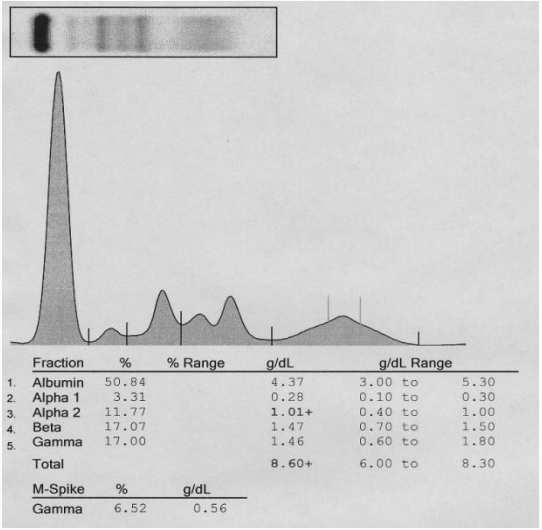

	Fraction	%	% Range	g/dL	g/dL Range
1.	Albumin	50.84		4.37	3.00 to 5.30
2.	Alpha 1	3.31		0.28	0.10 to 0.30
3.	Alpha 2	11.77		1.01+	0.40 to 1.00
4.	Beta	17.07		1.47	0.70 to 1.50
5.	Gamma	17.00		1.46	0.60 to 1.80
	Total			8.60+	6.00 to 8.30

M-Spike	%	g/dL
Gamma	6.52	0.56

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.

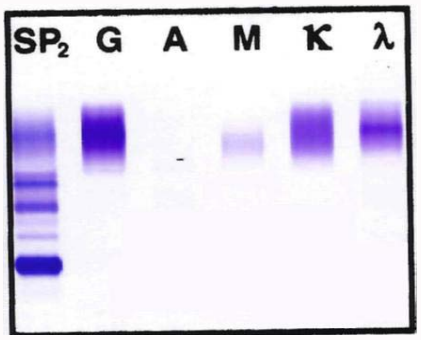

Figure 2: Monoclonal lambda light chain band on serum protein immunoelectrophoresis.
Immunoelectrophoresis (serum protein electrophoresis with immunofixation) depicting relative concentrations and clonality of serum proteins. A blood sample was drawn from the patient, serum was isolated and serum protein electrophoresis with immunofixation was performed on SPIFE 3000 (Helena, Beaumont, TX, USA) High Resolution Protein Electrophoresis equipment per the manufacturer's protocol. A distinct band is evident for the lambda light chain amid a polyclonal background. It is possible that a distinct IgG band is present but it is hidden by the predominantly polyclonal IgG staining. IgM is polyclonal, as is the kappa light chain. The barely visible polyclonal IgA population is consistent with the patients known IgA immunodeficiency.

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 241 mg/dL) and alpha-fetoprotein was found to be elevated at 87 ng/mL (normal < 20 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 intron 6 (also known as intron 4). *In silico* splicing analyses [14] predict that this alteration would obliterate the normal splice donor site and 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 alternation 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 to1256 mg/dL), with IgG1-IgG4 subtypes within normal limits. Total serum protein was elevated at 8.6 g/dL (6.0 g/dL to8.0 g/dL). The patient also had a neutrophilia of 81% (12% to 34%) and lymphopenia of 8% (45% 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 md/L 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 telemeric 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 gammopathies [1,10-13]. Gerritsen et al. [11] studied monoclonal gammopathies in the general pediatric population. They detected all immunoglobulin isotype monoclonal gammopathies except for IgA monoclonal gammopathies and identified a predominance of lambda light chain gammopathies. Conversely Akha et al. specifically studied gammopathies in A-T patients. They found that 39% of A-T patients showed hypergammaglobulinemia, with 8% of patients having a monoclonal gammopathy [1,12]. They also found that all immunoglobulin isotypes were represented in A-T patients with monoclonal gammopathy and did detect A-T patients with lambda light chain gammopathies, although the lambda light chain did not predominate [1,12].

Our patient exhibited a monoclonal gammopathy involving the lambda light chain, but the immunoglobulin isotype was unable to be determined. It is unlikely that the gammopathy 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 immunoelectrophoresis 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, our data is in agreement with Akha et al.'s finding that A-T patients can exhibit lambda light chain monoclonal gammopathies.

The differential for monoclonal gammopathies 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 gammopathies 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 gammopathies 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 gammopathies 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 gammopathies [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 gammopathies 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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