Case Report

Spontaneous Regression of Diffuse Large B-cell Lymphoma in a Patient with Ataxia–Telangiectasia

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Abstract

Ataxia–telangiectasia (AT) is a type of primary immunodeficiency characterized by an autosomal recessive mode of inheritance and usually presents with progressive cerebellar ataxia in early life. This complex disease is associated with humoral and cellular immune dysfunction and other features including characteristic oculocutaneous telangiectasia and increased predisposition to cancers, particularly lymphoma and leukemia. An 11-year-old Iranian girl presented with primary immunodeficiency and was diagnosed as having AT according to her clinical manifestations and molecular findings. She had a history of two types of non-Hodgkin's lymphoma and showed spontaneous regression of her diffuse large B-cell lymphoma without any specific treatment. Gene mutations and dysfunction in patients with AT result in different manifestations including abnormal development of the thymus, immunodeficiency, increased susceptibility to malignancies, and increased radiosensitivity. No standard treatment is available for these patients. The use of immunotherapeutic strategies in patients with primary immune deficiency disease-associated tumors is potentially important.

Keywords: *Ataxia–telangiectasia, diffuse large B-cell lymphoma, non-Hodgkin's lymphomas, spontaneous regression*

Introduction

Ataxia–telangiectasia (AT) is an autosomal recessive genetic defect caused by mutations in the Ataxia telangiectasia-mutated (*ATM*) gene. This large gene is located on chromosome 11q22-23 and codes for ATM kinase, which plays a role in cell cycle control, signal transduction, and DNA repair.[1] More than 500 *ATM* mutations have been described so far which cause AT syndrome, comprising a variety of apparently unrelated but complex features such as progressive cerebellar ataxia, oculocutaneous telangiectasia, increased radiosensitivity, growth retardation, and Type 2 diabetes mellitus.[2,3]

A small, abnormally developed thymus and immune system dysfunctions are hallmarks of AT that affect primary cellular and humoral immunology. The manifestations of AT are variable and include impaired V (D) J recombination and class-switching and consequently decreased or absent serum immunoglobulin A (IgA) and IgG subclasses, increased IgM levels, a decreased B-cell receptor (BCR) and T-cell receptor repertoire, reduced numbers of circulating T- and B-cells, defective BCR signaling, reduced response to mitogens, impaired capacity to produce cytotoxic T lymphocytes, enhanced levels of oxidative stress, and premature cell death induction.[4] Immunodeficiency and chromosomal instability in patients with AT lead to pulmonary disease, recurrent infections, and increased susceptibility to malignancies. Among patients with AT, the frequency of cancer is about 38%, with 5% of patients developing more than one malignancy. The most common cancer in this group is lymphomas, which usually appear in early childhood.[5]

Non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of aggressive lymphomas that have been defined on the basis of clinical, morphologic, immunophenotypic, and molecular features.[6] Among human tumors, NHL has the fastest doubling time, and at present, there is no standard care for salvage regimens.[7] These aggressive neoplasms are the most frequent malignancy associated

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with primary immune deficiency disease (PID).[8] Despite some advances, relapsed and refractory disease represent major treatment challenges, and spontaneous regression is extremely rare.[9]

In this report, we describe a girl with AT who had two types of NHL: Burkitt's lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL). Her DLBCL showed spontaneous regression in the absence of any antineoplastic treatment.

Case Report

The patient was an 11-year-old Iranian girl from a consanguineous family with a diagnosis of AT. Her family history disclosed that her parents were cousins, and that her mother's cousin had died at 6 months of age. She was first referred to the hospital at the age of 2 years and 9 months.

She had a history of recurrent fever, ataxia, failure to thrive, speech delay, congenital fistula in front of her right ear, nail clubbing, recurrent bacterial and viral infections, mucocutaneous candidiasis, mouth ulcers and tooth caries, recurrent sinusitis, rhinitis and upper respiratory tract infections, persistent conjunctivitis-otitis media, and recurrent chronic diarrhea. She presented with low serum levels of IgG and IgA and markedly increased IgM and a high level of alpha-fetoprotein. The laboratory findings for this patient are shown in Table 1. Furthermore, she had a history of hypothyroidism (thyroid-stimulating hormone: 6 mU/L), anemia (hemoglobin: median 8 g/dL leukopenia with granulocytic predominance, and thrombocytopenia. Hematological studies showed hypochromic red cells and moderate anisopoikilocytosis with ovalocytes, teardrop shapes, and stomatocytes.

Table 1: Immunopathological findings of ataxia-telangiectasia patient

Test	Result	Unit	Normal range
Protein electrophoresis			
Albumin	47.1	Percentage	45-62
Alpha 1	3.3		2-5
Alpha 2	12.9		6-15
Beta	13.7		6-18
Gamma	23		7-21
Ig			
IgG	<0.192	g/L	4.82-12
IgG2	<200	mg/L	360-2250
IgG3	<17	mgLl	173-676
IgM	22.484	g/L	0.4-2.63
IgA	0.072	g/L	0.22-1.18
IgE	0.4	IU/mL	<20 allergy unlikely
Serologic tumor markers			
Alpha-fetoprotein	146.9	ng/mL	Negative: ≤10
Autoimmune disease			
CH50	35.7	Percentage	63-145
Antiphospholipid IgG	0.1	IU/mL	Negative: <10
Antiphospholipid IgM	14.5	IU/mL	Negative: <10
Anticardiolipin Ab (IgG)	0.5	IU/mL	Negative: <10
Anticardiolipin Ab (IgM)	9.2	IU/mL	Negative: <7
NBT test		Normal	

NBT: Nitroblue tetrazolium, Ig: Immunoglobulin

In light of her clinical manifestations, we analyzed the *ATM* gene and detected a homozygous c.5623C >T mutation in exon 39 (p. Arg1875). This mutation gives rise to a stop codon and leads to instability and loss of the ATM protein from both alleles. Therefore, this girl was considered a typical AT patient.

According to the referring clinician, antibiotics and intravenous immunoglobulin (IVIG) were used at both therapeutic and prophylactic doses. She had received monthly infusions of IVIG beginning at the age of 3 years. Two months later, nasal lymph node swellings were seen, and she developed a mass in her left nose. Magnetic resonance imaging revealed a tumor measuring 3 cm × 2 cm × 1 cm in the left nasal cavity.

Microscopic examination of the tumor biopsy showed sheets of a uniform population of round, small-size lymphoid cells with coarse chromatin and several nucleoli, indicating a high mitotic index and proliferative activity. Moreover, the starry sky appearance was seen. Immunohistochemical staining of the tumor sections was positive for leukocyte common antigen, CD20, and Ki-67 (in more than 95% of tumor cells) and negative for CD10, terminal deoxynucleotidyl transferase, and vimentin. Based on the histopathological findings, a diagnosis of NHL, probably, BL was made. She was started on chemotherapy consisting of cyclophosphamide, vincristine, methotrexate, and Adriamycin. After two cycles of treatment, the mass completely disappeared, and she was in complete remission on follow-up. During follow-up, the patient was evaluated with bone marrow aspiration and cerebrospinal fluid cytology, neither of which showed evidence of tumor cell infiltration nor malignancy.

Four years later, when she was 7 years old, the patient complained of a mass in her neck at a regular follow-up visit. Abdominal cavity ultrasound examination disclosed massive splenomegaly, mild hepatomegaly, and multiple small mesenteric and left para-aortic lymphadenopathy images. Tumor resection was carried out, and the diagnosis of DLBCL was made by microscopic and pathologic examination. Immunohistochemical analysis showed that the tumor was positive for CD5 (in a few small lymphocytes), CD10 (focally), CD20 (strongly positive), and Ki-67 (in approximately 60% of tumor cells). Several months after tumor resection, the swollen lymph nodes and spleen decreased in size spontaneously without any specific treatment for DLBCL.

After frequent hospital admissions, on her last admission, she had severe malnutrition (body mass index 7.5), diarrhea, temporal atrophy, muscle atrophy, cachexia, dyspnea, and

massive hemoptysis. She died of pressure drop, ischemia, and bradycardia at 10 years and 8 months of age.

Discussion

ATM gene dysfunction in patients with AT results in different manifestations including reduced survival, abnormal development of the thymus, and immunodeficiency. These patients are prone to malignancies, especially lymphoma, and cancer is the main cause of death in this group.[10] Nevertheless, there is no consensus regarding the optimal strategy for treating hematopoietic malignancies associated with AT in children, especially since these patients have reduced tolerance to chemotherapy.[11] Moreover, management of cancer in these patients may be further complicated by increased sensitivity to ionizing radiation and radiomimetic drugs. Accordingly, the development of new therapeutic strategies to replace conventional chemotherapy in the treatment of patients with AT who develop cancer is a highly desirable goal. Recent advances in our understanding of antitumor immunity have suggested some treatment modifications, for example, combining molecular targeting agents such as rituximab and immunotherapy to favor the induction of immunogenic cell death (ICD).[12,13]

Our patient had classical AT, with the loss of ATM function confirmed by molecular analysis. She suffered from recurrent infections and fever during her follow-up. She developed BL at 3 years of age, and the tumor subsided with two-phase chemotherapy. However, DLBCL developed 4 years later, with diffuse lymphadenopathy, which was not treated specifically. A few months later, the lymph nodes and spleen lesions regressed. In general, DLBCL is a metastatic phenomenon, so spontaneous regression is rare particularly in patients with primary immunodeficiency.[14] The leading hypothesis regarding spontaneous regression of NHL involves modulation of the host immune system during overstimulation of immune cells by viral or bacterial infection, chronic inflammation, or traumatic effects.

Based on the available data, it is clear that chemotherapeutic agents such as cyclophosphamide or doxorubicin, alone or combined with others, can induce ICD.[15] Doxorubicin is routinely used for lymphoma and is an excellent candidate drug for ICD induction. It effectively controls tumor growth, enhances tumor antigen uptake by dendritic cells, and increases the numbers of tumor-infiltrating cytotoxic T lymphocytes, while decreasing expression levels of the immunosuppressive enzyme.[16] ICD generates a series of signals that stimulate the immune system to recognize and clear tumor cells, and as a result, it not only favors the removal of the existing tumor but also prevents the development of subsequent tumors.[17] It is noteworthy that the chemotherapy regimens were prescribed for our patient contained cyclophosphamide, vincristine, methotrexate, and Adriamycin (doxorubicin).

The patient received both antibiotics and IVIG at prophylactic doses, but these are unlikely causes of tumor regression, because the tumors developed while the patient was receiving these drugs. On the other hand, recurrent systemic inflammation during sinopulmonary infections, together with the traumatic effects of several biopsies, is hypothetical mechanisms that may explain DLBCL regression in this young girl. Another factor that may have contributed to spontaneous regression is ICD induction by chemotherapeutic drugs used for primary BL. However, more research is required to elucidate the mechanisms underlying the regression of this patient's lymphoma.

Conclusion

To the best of our knowledge, this is the first report of spontaneous regression of DLBCL in a patient with AT. As exemplified by our patient, management of the cancer may be complicated by the increased sensitivity to ionizing radiation and radiomimetic drugs. Systematic clinical studies and the accumulation and sharing of numerous research experiences will be needed to improve the treatment options for malignancies in these patients. These rare cases also merit attention because their clinical course may be relevant to future potential immunotherapeutic strategies in patients with PID-associated tumors.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parents has given their consent for her images and other clinical information to be reported in the journal. The patient and the parents understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Rothblum-Oviatt C, Wright J, Lefton-Greif MA, McGrath-Morrow SA, Crawford TO, Lederman HM. Ataxia telangiectasia: A review. Orphanet J Rare Dis 2016;11:159.
2. Chun HH, Gatti RA. Ataxia-telangiectasia, an evolving phenotype. DNA Repair (Amst) 2004;3:1187-96.
3. Yanofsky RA, Seshia SS, Dawson AJ, Stobart K, Greenberg CR, Booth FA, *et al.* Ataxia-telangiectasia: Atypical presentation and toxicity of cancer treatment. Can J Neurol Sci 2009;36:462-7.

4. Staples ER, McDermott EM, Reiman A, Byrd PJ, Ritchie S, Taylor AM, *et al.* Immunodeficiency in ataxia telangiectasia is correlated strongly with the presence of two null mutations in the ataxia telangiectasia mutated gene. Clin Exp Immunol 2008;153:214-20.
5. Haas OA. Primary immunodeficiency and cancer predisposition revisited: Embedding two closely related concepts into an integrative conceptual framework. Front Immunol 2018;9:3136.
6. Thandra KC, Barsouk A, Saginala K, Padala SA, Barsouk A, Rawla P. Epidemiology of Non-Hodgkin's Lymphoma. Med Sci (Basel) 2021;9:5.
7. Chao MP. Treatment challenges in the management of relapsed or refractory non-Hodgkin's lymphoma-novel and emerging therapies. Cancer Manag Res 2013;5:251-69.
8. Kiykim A, Eker N, Surekli O, Nain E, Kasap N, Aktürk H, *et al*. Malignancy and lymphoid proliferation in primary immune deficiencies; hard to define, hard to treat. Pediatr Blood Cancer 2020;67:e28091.
9. Snijder J, Mihyawi N, Frolov A, Ewton A, Rivero G. Spontaneous remission in diffuse large cell lymphoma: A case report. J Med Case Rep 2019;13:28.
10. Moslemi M, Moradi Y, Dehghanbanadaki H, Afkhami H, Khaledi M, Sedighimehr N, *et al.* The association between ATM variants and risk of breast cancer: A systematic review and meta-analysis. BMC Cancer 2021;21:27.
11. Tomioka H, Kaneoya A, Mochizuki Y, Harada H. Primary diffuse large B-cell lymphoma arising in the tongue accompanied by ataxia-telangiectasia: A case report. J Clin Diagn Res 2015;9:D25-7.
12. Machida S, Tomizawa D, Tamaichi H, Okawa T, Endo A, Imai K, *et al.* Successful treatment of diffuse large B-cell lymphoma in a patient with ataxia telangiectasia using rituximab. J Pediatr Hematol Oncol 2013;35:482-5.
13. Makkouk A, Joshi VB, Lemke CD, Wongrakpanich A, Olivier AK, Blackwell SE, *et al.* Three steps to breaking immune tolerance to lymphoma: A microparticle approach. Cancer Immunol Res 2015;3:389-98.
14. Abe R, Ogawa K, Maruyama Y, Nakamura N, Abe M. Spontaneous regression of diffuse large B-cell lymphoma harbouring Epstein-Barr virus: A case report and review of the literature. J Clin Exp Hematop 2007;47:23-6.
15. Garg AD, More S, Rufo N, Mece O, Sassano ML, Agostinis P, *et al.* Trial watch: Immunogenic cell death induction by anticancer chemotherapeutics. Oncoimmunology 2017;6:e1386829.
16. Huang FY, Lei J, Sun Y, Yan F, Chen B, Zhang L, *et al.* Induction of enhanced immunogenic cell death through ultrasound-controlled release of doxorubicin by liposome-microbubble complexes. Oncoimmunology 2018;7:e1446720.
17. Gebremeskel S, Johnston B. Concepts and mechanisms underlying chemotherapy induced immunogenic cell death: Impact on clinical studies and considerations for combined therapies. Oncotarget 2015;6:41600-19.