Spontaneous Regression of Angioimmunoblastic T-cell lymphoma in a Pediatric Patient with Ataxia-Telangiectasia: A case report and review of literature

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Abstract

Angioimmunoblastic T-cell lymphoma (AITL) is an uncommon subtype of Peripheral T-cell lymphomas (PTCLs) in children with less than 20 cases reported in the literature. In this paper, we present a case of AITL in a three years old male with Ataxia-Telangiectasia which regressed spontaneously without any therapy. A comprehensive review of the literature regarding treatment and outcome of pediatric patients with AITL has been also discussed in this article.

Title: Spontaneous Regression of Angioimmunoblastic T-cell lymphoma in a Pediatric Patient with Ataxia-Telangiectasia: A case report and review of literature Dima Abla[a], Abeer Al-Battashi[b] , Khalil Al Bayroti[a], Khuloud Abu Qasida[c], Nasser Al-Rahbi[ca] Pediatric Hematology and oncology Specialist, Department of Pediatric Hematology and Oncology, The National Oncology Centre, The Royal Hospital, Muscat, Sultanate of Oman.[b] Pediatric Hematology and oncology Consultant, Department of Pediatric Hematology and Oncology, The National Oncology Centre, The Royal Hospital, Muscat, Sultanate of Oman.[c] Department of Pathology, The Royal Hospital, Muscat, Sultanate of Oman. Corresponding author: Abeer Al-Battashi The Royal Hospital, Muscat, Sultanate of Oman PO Box 1191, PC 133 +968 97228888 Word count: Abstract; 68 words, Main text:1047 words. The number of Tables, Figures, and Supporting Information files: 1 Figure, 2 Tables A short running title: Angioimmunoblastic T-cell lymphoma in Ataxia-Talengiectasia Keywords: Angioimmunoblastic T cell lymphoma, spontaneous regression, pediatric patient. Abbreviations

AITL	Angioimmunoblastic T-cell lymphoma
PTCLs	Peripheral T-cell lymphomas
NHL	Non-Hodgkin's Lymphoma
WBC	White blood cell
PLT	Platelet
LDH	Lactate Dehydrogenase
EBV	Epstein-Barr Virus
VCA	Viral Capsid Antigen
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
NK	Natural Killer
AILD	angioimmunoblastic lymphadenopathy with dysproteinemia
ALL	Acute Lymphoblastic Leukemia
UKCCSG	United Kingdom Children's Cancer Study Group

Abstract:

Angioimmunoblastic T-cell lymphoma (AITL) is an uncommon subtype of Peripheral T-cell lymphomas (PTCLs) in children with less than 20 cases reported in the literature. In this paper, we present a case of AITL in a three years old male with Ataxia-Telangiectasia which regressed spontaneously without any therapy. A comprehensive review of the literature regarding treatment and outcome of pediatric patients with AITL has been also discussed in this article. Introduction: Peripheral T-cell lymphomas (PTCLs) are extremely rare in children and adolescents. They represent less than 2% of all childhood Non-Hodgkin's Lymphoma (NHL)[1] and divided into 28 subtypes by the 2016 World Health Organization Classification System[2]. Although the outcome of pediatric patients with PTCLs appears to be inferior to that of adult patients, the survival rates are still poor compared to other NHL types[1]. The management of this type of lymphomas in children remains challenging and no standard treatment strategy has been defined[3]. Here, we present a case of AITL in a 3-year-old pediatric patient with Ataxia-Telangiectasia who improved spontaneously without any chemotherapy. Case Presentation: In 2018, a 3-year-old male patient sought medical advice because of unsteady gait and recurrent upper respiratory tract infections. The diagnosis of Ataxia-Telangiectasia was confirmed at that time by identifying a novel homozygous mutation in the ATM gene. He presented again within few months of diagnosis with a one-week history of fever and cough. On physical examination, he had submandibular, cervical, axillary, and inguinal enlarged lymph nodes with no detectable hepatosplenomegaly. His chest X-ray showed bilateral perihilar peri-bronchial wall thickening without mediastinal widening. The abdominal ultrasound was unremarkable. Laboratory tests revealed severe neutropenia (neutrophil count 0.2 $\times 10^9$/L) with total white blood cells (WBC) of 3.9 $\times 10^9$/L, hemoglobin (HB) of 9 g/L, and platelets count (PLT) of 214 $\times 10^9$/L. His lactate dehydrogenase (LDH) was 275 U/L, and Epstein-Barr Virus (EBV) VCA (Viral Capsid Antigen) antibodies IgM were negative. Due to the presence of neutropenia and high suspicion of malignancy in patients with primary immunodeficiency, the patient underwent a right axillary lymph node excisional biopsy. Microscopic analysis demonstrated infiltration with atypical lymphoid cells having small, medium to large nuclei and clear cytoplasm localized around high endothelial venules. Immunohistochemical stains showed positivity of the atypical lymphoid cells for CD3, CD4, CD10, BCL6, and PD1 (FIGURE 1). The morphology and immunophenotype were both suggestive of AITL. The diagnosis was confirmed by molecular studies, which revealed detection of clonal T cell receptor gamma chain gene rearrangement as well as clonal B cell IgH/Kappa chain gene rearrangement. His bone marrow biopsy did not show any lymphomatous involvement. The patient was planned for chemotherapy with CHOP protocol: cyclophosphamide, doxorubicin, vincristine, and prednisone. Surprisingly before treatment initiation, he showed complete recovery of symptoms with absence of fever and regression of all previously affected lymph nodes. Therefore, the decision was taken to manage the patient conservatively with close observation and follow-up after extensive discussion with the parents and additional multidisciplinary team review. Since then, the patient remains asymptomatic, apart from EBV reactivation which was detected 1 year ago and was managed by several doses of Rituximab. The patient was still in remission at the last follow-up, 4 years from diagnosis. Discussion: PTCL is a very rare aggressive type of NHL in children[1]. It originates from mature T cells in the thymus and has rearrangement of T-cell receptor genes. The most common subtype in children is peripheral T-cell lymphoma–not otherwise specified, other reported phenotypes include Hepatosplenic T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, extra-nodal NK/T-cell peripheral T-cell lymphoma and AITL[4]. AITL, formerly known as angioimmunoblastic lymphadenopathy with dysproteinemia (AILD), was believed to be a benign immune response. It is now recognized as a subtype of PTCL[5]. There are only few cases of pediatric patients with AITL reported in the literature[1]. The first case was reported in 1976 by Howarth and Bird. They described a 7-year-old male who presented initially with fever and generalized lymphadenopathy and then died due to disease progression 13 months after diagnosis[6]. In 1981, Fiorillo et al reported the first case of AILD in childhood with spontaneous improvement[7]. Another case of AILD in a 14-month-old baby was reported by de Terlizzi et al. The patient died due to disease recurrence 100 months after initial presentation[8]. Horneff et al described neurological complications in a 13-year-old girl with AILD[9]. In a retrospective analysis of non-anaplastic peripheral T-Cell lymphoma in pediatric patients in Japan, Kobayashi et al reported one case of AITL in a 14-year-old male[10]. In a study of childhood PTCL in the United Kingdom, there were 3 cases of pediatric patients with AITL[4]. In the latest international review of 143

cases of pediatric PTCL, 4 patients had AITL[11]. Kraus et al reported a case of AITL in a pediatric patient post heart transplant presenting with cranial nerve palsy [12]. To our knowledge, this is the first case report describing AITL in a pediatric patient with Ataxia-Telangiectasia evolved toward spontaneous remission. Characteristics, treatment, and outcome of the previously described patients (including our case) are shown in (TABLE 1). There is no consensus about the optimal treatment for pediatric PTCL due to the absence of randomized clinical trials and the rarity of cases in pediatric patients[3]. Chemotherapy options include NHL or Acute Lymphoblastic Leukemia (ALL) regimens[11]. The United Kingdom Children's Cancer Study Group (UKCCSG) reported a superior outcome of ALL–like therapy compared to NHL therapy[4]. The association between other types of NHL and immune deficiency is well known. Many cases of AILD/AITL after immunosuppressive therapy have been reported in adults [13-14]. In the retrospective EICNHL/i-BFM analysis of 143 children, pre-existing conditions such as primary immune deficiency, immune suppressive therapy and/or previous transplantation were found in 25 % of the patients. A better outcome was observed in those patients [11]. Our patient was diagnosed with Ataxia-Telangiectasia 1 year before developing AITL. Spontaneous regression of malignancies is a fascinating phenomenon. It is defined as the complete or partial disappearance of cancer in the absence of anti-neoplastic therapy [15]. It was first described by Sir William Osler in 1906 [16] and has been reported in patients with low grade non-Hodgkin's lymphoma[17]. The exact mechanism of this phenomenon remains unclear and most likely can be explained by immunological factors[18]. Among pediatric patients with PTCL, only 12 cases with spontaneous regression have been reported in the literature. They are summarized in (TABLE 2). Conclusion: In summary, this is the first case report of spontaneous improvement of Angioimmunoblastic T-cell lymphoma in a 3-year-old pediatric patient with Ataxia-Telangiectasia. Due to paucity of cases of AITL in children, international collaboration is certainly needed to establish the best treatment recommendations to guide clinicians and pediatric oncologists worldwide. Conflict of interest statement: Authers declare there is no conflict of interest. References: Attarbaschi A, Abla O, Arias Padilla L, Beishuizen A, Burke GAA, Brugieres L, Bruneau J, Burkhardt B, d'Amore ESG, Klapper W, Kontny U, Pillon M, Taj M, Turner SD, Uyttebroeck A, Woessmann W, Mellgren K. Rare non-Hodgkin lymphoma of childhood and adolescence: A consensus diagnostic and therapeutic approach to pediatric-type follicular lymphoma, marginal zone lymphoma, and nonanaplastic peripheral T-cell lymphoma. Pediatr Blood Cancer. 2020 Aug;67(8):e28416. doi: 10.1002/pbc.28416. 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FIGURE 1: The lymph node biopsy findings and immunophenotypic features: -Effacement of lymph node architecture Hematoxylin-eosin (H&E) Stain.4X (A). -Atypical lymphoid cells with high endothelial venules proliferation. H&E stain.20X.(B). -The neoplastic lymphocytes are positive for CD3.10X (C). -CD21 highlights the expanded follicular dendritic meshwork.4X (D). -The neoplastic cells are positive for T follicular helper cell markers including CD10 , BCL6 (E&F respectively, 4x) and PD1 (not shown). TABLE 1: Characteristics, Treatment and Outcome of Pediatric Patients with Angioimmunoblastic Lymphoma.

Study	Number of patients
Howarth and Bird[6]	1
Fiorillo et al[7]	1
de Terlizzi et al[8]	1
Horneff et al[9]	1
Kobayashi et al[10]	1
Windsor et al[4]	3
Mellgren et al[11]	4
Kraus et al[12]	1
Our case	1
Abbreviations: y; years- m; months- NR; not reported- D; Death- L; Alive.	Abbreviations: y; years- m; months- NR; not

TABLE 2: Characteristics and Subtype of Pediatric Patients with PTCL and Spontaneous Regression.

Study
Fiorillo et al[7]

Study
Windsor et al[4]
Kobayashi et al[10]
Maciejka-Kemblowska et al[3]
Mellgren et al[11]
Our case

Abbreviations: y; years- m; months- NR; not reported- AILD; angioimmunoblastic lymphadenopathy with dysproteinemia-