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Wiskott-Aldrich syndrome complicated by an atypical lymphoproliferative disorder: a case report

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Wiskott-Aldrich syndrome (WAS) is an X-linked syndrome consisting of eczema, recurrent pyogenic infection, and thrombocytopenia with decreased platelet volume. Immunologic studies reveal normal immunoglobulin G (IgG), decreased IgM, elevated IgA and IgE levels, and decreased T-cell function. Patients with WAS often have increased susceptibility to lymphoproliferative disorders (LPDs). We report a 3-year-old boy who had persistent thrombocytopenia with bleeding, recurrent infections, and chronic eczema with frequent skin infections since birth. A blood smear revealed small platelets (50% of normal size). Immunologic studies showed normal IgG (1880 mg/dL), decreased IgM (76 mg/dL) and increased IgA (228 mg/dL) and IgE (14,282 IU/mL) levels. The relative proportions of immune cells were CD2 52.2%, CD3 41.1%, CD4 23.4%, CD8 16.8%, CD19 8.0%, CD57 7.7% and active T cells 14.6%. T-cell dysfunction was detected on the multitest for cell-mediated immunity. The WAS diagnosis was confirmed by mutation analysis which demonstrated a 4-base pair deletion in WAS protein gene exon 1. His thrombocytopenia was uncontrolled despite intravenous immunoglobulin infusions, so splenectomy was performed. The platelet count then rose to about 60,000 to 80,000/μL. However, about 2 weeks after splenectomy, he developed generalized lymphadenopathy and lymphoma was misdiagnosed based on lymph node biopsy at another hospital where he was admitted for urgent care. However, our analysis of his lymph node pathology led to the diagnosis of atypical LPD (ALPD). The lymphadenopathy regressed spontaneously 1 month later without chemotherapy. Early and correct diagnosis of WAS complicated with ALPD is important to avoid unnecessary chemotherapy.

Key words: Differential diagnosis, lymphoproliferative disorders, thrombocytopenia, Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome (WAS) is a rare X-linked recessive disorder comprising the triad of eczema, thrombocytopenia and immunodeficiency. Infections and hemorrhage are the major causes of WAS-related infant mortality [1]. However, with advances in the prevention and treatment of infections, children with WAS can expect to survive into their second and third decades. This improved early prognosis, however, has led to the emergence of autoimmune diseases and certain cancers as major life-threatening consequences [2].

There is a high prevalence of lymphoproliferative disorders (LPDs) in patients with primary immunodeficiency. Children at greatest risk for LPD are those with ataxia-telangiectasia, occurring in 10% of affected children, WAS (7.6%), and common variable immunodeficiency (1.4-7%) [3,4]. LPD have been reported to include reactive lymphoid hyperplasia, atypical LPD (ALPD) and malignant lymphoma [5,6]. These represent a spectrum of pathologic processes primarily involving B cells [7]. The exact pathogenesis is unclear, the usual explanation being a lack of antitumor surveillance in patients with immunodeficiency [4]. ALPD or reactive hyperplasia are the most common forms of LPD in patients with congenital immunodeficiencies [8]. We report a boy with WAS who developed ALPD.

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Case Report

A 3-year-old boy had ecchymoses and petechiae immediately after birth. His platelet count was 25,000/μL. He frequently received platelet transfusion because of persistent thrombocytopenia and recurrent epistaxis. There was no family history of ecchymosis, bleeding or infection but his 4-month old elder brother had died of unknown cause (Fig. 1). Bone marrow study when he was 3 months and again at 30 months old revealed normal results. The initial diagnosis was platelet dysfunction of unknown etiology. He had been

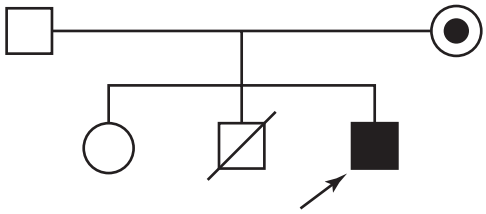

Fig. 1. Pedigree of the family described in this article. Squares denote males and circles females. The filled symbol denotes the patient and crossed symbol a deceased family member. A dot in a circle represents a carrier.

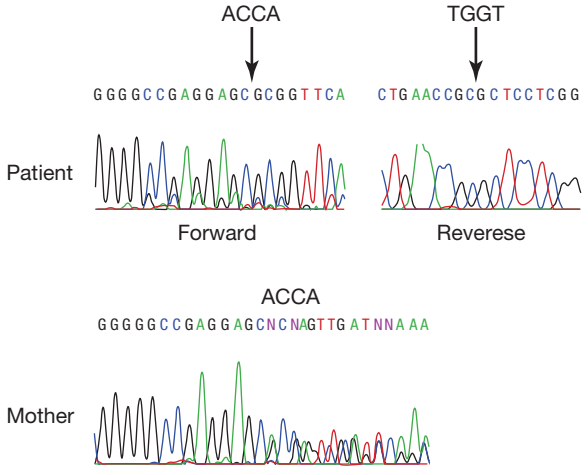

Fig. 2. Mutation analysis of Wiskott-Aldrich syndrome protein (WASP) gene in the patient and his mother.

hospitalized several times for recurrent otitis media, furunculosis with chronic eczema, and respiratory and gastrointestinal tract infections. He had had 1 episode of pseudomonas sepsis with generalized ecthyma gangrenosa at the age of 9 months. Because of the persistent thrombocytopenia, recurrent epistaxis, hematuria, melena, and infections despite intravenous immunoglobulin (IVIG) infusions, he was transferred to our hospital for further management of presumed WAS.

On admission, the spleen was palpable 2 cm below the left costal margin. White blood cell count was 2100/μL, with 49% neutrophils, 22% lymphocytes, 9% eosinophils and 7% monocytes. Red blood cell count was 3.24×10^6/μL, Hb 9.0 g/dL, and platelet count 6000/μL. Blood smear revealed small platelets (50% normal size). Serum immunoglobulin levels were immunoglobulin G (IgG), 1880 mg/dL; IgA, 228 mg/dL; IgM, 76 mg/dL; IgE, 14282 IU/mL; IgD, <48 IU/mL. The relative proportions of immune cells were CD2 52.2%, CD3 41.1%, CD4 23.4%, CD8 16.8%, CD19 8.0%, CD57 7.7% and active T cells 14.6%. Multitest for cell-mediated immunity (CMI) was uniformly negative (including *Candida albicans*, *Trichophyton* spp., coccidioidin, histoplasmin, tuberculin purified protein derivative, mumps and tetanus toxoid antigen). Later mutation analysis demonstrated that the patient had a 4-base pair deletion in WAS protein (WASP) gene exon 1, i.e., c.45delacca, which predictably caused the WASP codon 16 change from proline to arginine and then frameshift and premature stop at codon 44 (p.P16RfsX44). His mother was a carrier with heterozygous mutation in the WASP gene. Mutation analysis was not performed in his sister as she was less than 18 years old (Fig. 2). Because of persistent thrombocytopenia, splenectomy was performed. After the operation, he no longer had epistaxis or melena, and his platelet counts rose to about 60,000 to 80,000/μL. He was discharged with a prescription of oral penicillin and trimethoprim-sulfamethoxazole for chemoprophylaxis.

Thirteen days after splenectomy, he developed a spiking fever that persisted for 2 weeks. Generalized lymphadenopathy (nodes more than 2×2 cm) was noted in the neck, axilla, and inguinal areas. An excision biopsy of a lymph node was done at another hospital, where malignant lymphoma was diagnosed. He was referred to our hospital for further management. Our evaluation included a chest X-ray, which showed thickening of the right paratracheal space and an ill-defined soft tissue mass superimposed on the left atrium of the heart. Computed tomography scan of the brain, chest and abdomen revealed mass lesions in the paratracheal, subcarinal and retroperitoneal para-aortic space. A Tc-99m methylene diphosphonate body scan showed no evidence of osseous metastasis. Our pathologists reviewed the pathology of the lymph node biopsy and diagnosed ALPD, based on atypical interfollicular proliferation of transformed B cells (immunoblasts and plasmacytoid lymphocytes), atrophy of follicles and mantle zones, and depletion of small round lymphocytes in the T zones (Fig. 3). Immunophenotyping results were polyclonal with expression of both kappa and lamda light chains in the lymph node tissue. A needle biopsy of the bone marrow disclosed an increased number of megakaryocytes, ongoing active erythropoiesis, a slight increase in the number of small lymphocytes and intermediate-size B immunoblasts, consistent with WAS and ALPD. Polymerase chain reaction (PCR) for Epstein-Barr virus (EBV) in the lymph node was negative. Spontaneous regression of lymphadenopathy was noted

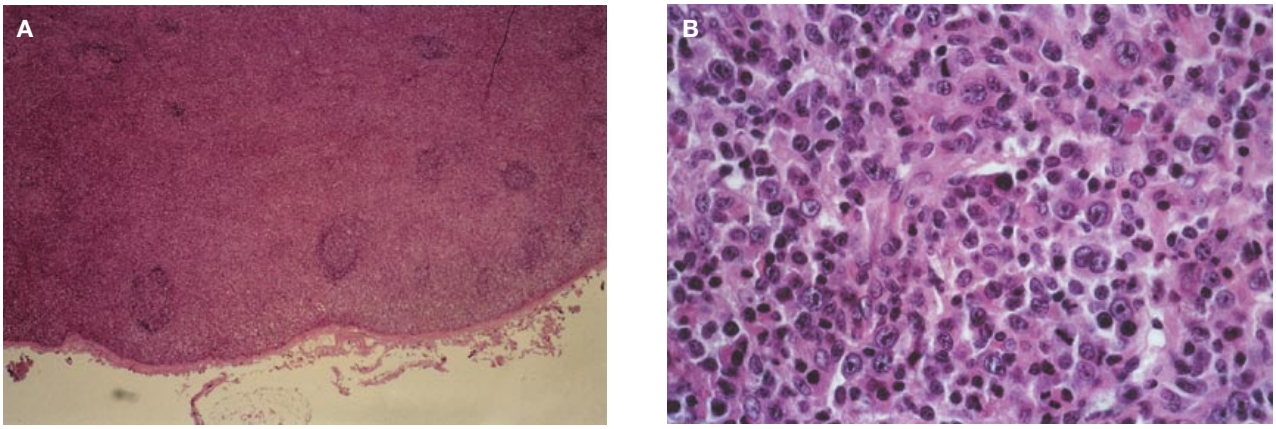

Fig. 3. Pathology of a lymph node. (A) Atrophy of follicles and mantle zones with wide interfollicular space (hematoxylin and eosin stain, × 20). (B) Atypical interfollicular proliferation of transformed B cells, including immunoblasts and plasmacytoid lymphocytes (hematoxylin and eosin stain, × 400).

and was also detected on a chest film 1 month later. The patient's parents refused bone marrow transplantation (BMT) for the WAS, preferring palliative treatment.

Discussion

WAS is caused by mutations in an intracellular protein (WASP) involved in signal transduction and regulation of the rearrangement of the actin cytoskeleton. Most affected boys present with normal levels of serum IgG, depressed IgM, and markedly elevated IgA and IgE in addition to defective T-cell function. The definitive diagnosis is to identify a mutation of the WASP gene. Since patients with WAS often have abnormal antibody responses, IVIG is indicated if they have frequent infections. Bone marrow or cord blood stem cell transplantation is the only definitive therapy for WAS. Human leukocyte antigen (HLA)-identical siblings are the preferred donors [1]. Our patient had an elder sister, but her HLA type (A11A33B58B62Cw4) was incompatible with his (A11A24B60B62Cw4). The most common causes of death in patients not treated with a transplant are infections (44%), malignancies (26%) and bleeding (23%) [1].

LPD is particularly common in individuals with primary immunodeficiencies. In WAS, the risk of malignancy is approximately 100 times greater than that of the age-matched normal population [3]. The factors contributing to the increased risk of LPD include the ubiquity of EBV, host defects in immunoregulation, and genetic defects resulting in imprecise rearrangement of immunoglobulin and T-cell receptor genes during lymphopoiesis. EBV infection is a major cofactor but is not present in all patients with LPD [2,5]. EBV infection was apparently not a factor in our patient, as shown by a negative EBV PCR result.

A substantial number of patients with LPD present with unusual clinical features, and their biopsies have pathologic findings that, while mimicking neoplastic conditions, are not apparently clearly malignant. These findings are termed ALPD. The definition of ALPD is hyperplasia with atypical histologic or cytologic features in the lymph nodes, suspicious but not diagnostic of lymphoma [9]. The main features of ALPD are an acute onset, generalized lymphadenopathy, hepatosplenomegaly, hypersensitivity, recurrent infections, dysgammaglobulinemia, and bone marrow plasmacytosis [10]. Our patient presented with the acute onset of generalized lymphadenopathy compatible with ALPD.

ALPD is apparently a process somehow intermediate between reactive, self-limiting lymph node growth (hyperplasia) and autonomous, clonal proliferations (neoplasia). The lymphoid lesions of ALPD feature florid cell proliferation and disturbance of organ architecture [4]. Our patient's lymph node pathology disclosed a marked increase of transformed B cells with uneven distribution.

There are some common histopathologic characteristics in ALPD that allow its distinction from malignant lymphoma. First, an extensive disturbance of the nodal architecture is present, but some basic topographic markings are preserved. ALPD evolves by expanding the architectural components of the lymph node rather than by destroying them, as do malignant lymphomas. The lymph node pathology of our patient was compatible with this basic architectural preservation. Second, there is a prominent interfollicular activation caused

by immunoblastic transformation. Unlike lymphomas, there is little or no nuclear atypicality in the transformed cells in ALPD. Our patient had the entire spectrum of plasmacytoid immunoblasts, immature and mature plasma cells in areas between residual germinal centers [4]. In addition, immunophenotyping of ALPD most commonly shows polyclonality of light chain immunoglobulins on the membranes of B cells [4,9]. Most malignant lymphomas associated with WAS are of monoclonal B cell origin [3,6]. Our patient, however, had polyclonal immunophenotyping. His pathology was thus compatible with ALPD. ALPD must also be differentiated from reactive lymphoid hyperplasia, which may have a similar histologic pattern. Reactive lymphoid hyperplasia, however, does not have disturbed architecture, cellular atypia (not so many immunoblasts in the paracortical area) and generally does not raise a suspicion of malignancy [9].

The clinical presentation and evolution of ALPD associated with primary immunodeficiency are variable. ALPD can transform directly to malignancy in some cases. However, the disorder may resolve spontaneously [10-12]. Even with resolution, careful, long-term clinical observation is required because of the continued risk of recurrence or frank malignancy. If malignancy does occur, the prognosis is poor because of limited tumor response, excessive toxicity of chemotherapy, and the high risk of fatal infections during chemotherapy [5]. Hence, prevention of the onset of immunodeficiency-associated LPD is important. Prompt and successful immunologic reconstitution with BMT may substantially reduce the risk of malignancy [13]. HLA-identical BMT is a safe and effective treatment for WAS, with 80-90% of patients achieving complete reversal of the immunodeficiency and platelet abnormalities [14]. Full immunologic reconstitution after BMT is important. Patients with only partial engraftment and incomplete immunologic reconstitution by haploidentical BMT have continued increased risk of LPD [13].

In conclusion, the differentiation of benign ALPD from malignant lymphoid lesions is essential to avoid unnecessary chemotherapy, which immunodeficient patients tolerate poorly. Given the poor prognosis if ALPD does progress to malignancy, immunoreconstitution by BMT should be pursued if possible in patients with immunodeficiency. If immunologic reconstruction is successful, the outlook for prolonged life is excellent.

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