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Acute Myeloid Leukemia in a Patient with Wiskott Aldrich Syndrome: A Case Report

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Abstract
Wiskott-Aldrich syndrome is a rare X-linked primary immunodeficiency disorder characterized by thrombocytopenia, eczema, and recurrent infections. It is caused by mutations of the WAS gene. It is also associated with autoimmunity and increased predisposition to develop malignancies. Here we report a case of acute myeloid leukemia in a 3yr old child with Wiskott-Aldrich syndrome.
Keywords: *Wiskott-Aldrich syndrome (WAS), thrombocytopenia, leukaemia.*

Introduction

Wiskott-Aldrich syndrome (WAS) is a rare X-linked disorder caused by a mutation in the Wiskott-Aldrich syndrome gene (*WAS*)[1]. *WAS* mutations give rise to a wide spectrum of phenotypes with differing severity. The most severe form, referred to as classical WAS, is characterized by a triad of thrombocytopenia, recurrent infections, and eczema with an increased chance of developing autoimmune conditions and malignancy. The milder form of WAS, known as X-linked thrombocytopenia (XLT), is characterized by thrombocytopenia with absent or mild eczema/immunodeficiency[1,2].

The incidence of this rare X-linked primary immunodeficiency disorder is approximately one to four cases per 1,000,000 live male births, with an average age at diagnosis of 24 months in families without a previously affected family member.2 The gene responsible for WAS is located on the short arm of the X chromosome at Xp11.22–p11.23.[3] The *WAS* gene encodes the WAS protein (WASp), which is a 501-amino acid protein expressed within the cytoplasm of nonerythroid hematopoietic cells.[3] WASp is involved in actin polymerization and associated coupling of receptor engagement, signaling events, and cytoskeletal rearrangement.[3] Heterogeneous mutations spanning the entire *WAS* gene have been described.[3] These mutations in *WAS* alter the function and/or expression of the intracellular protein, WASp.[3] Perturbation in the function and/or expression of WASp is correlated with the spectrum of clinical findings of "classic" WAS and its associated phenotypic variations, such as X-linked thrombocytopenia (XLT) and X-linked neutropenia (XLN).[3]

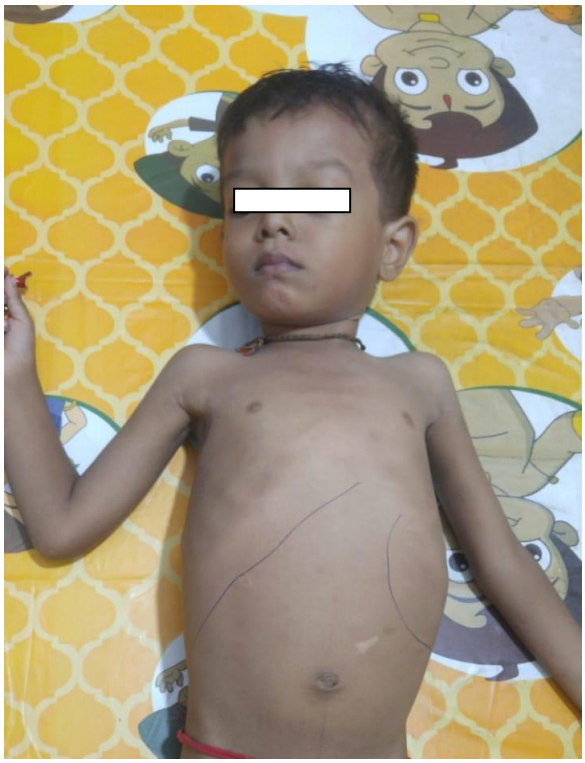
The development of malignancy is a frequent occurrence in the setting of WAS. Sullivan et al noted that 13% of patients with WAS developed malignancy at a mean age of 9.5

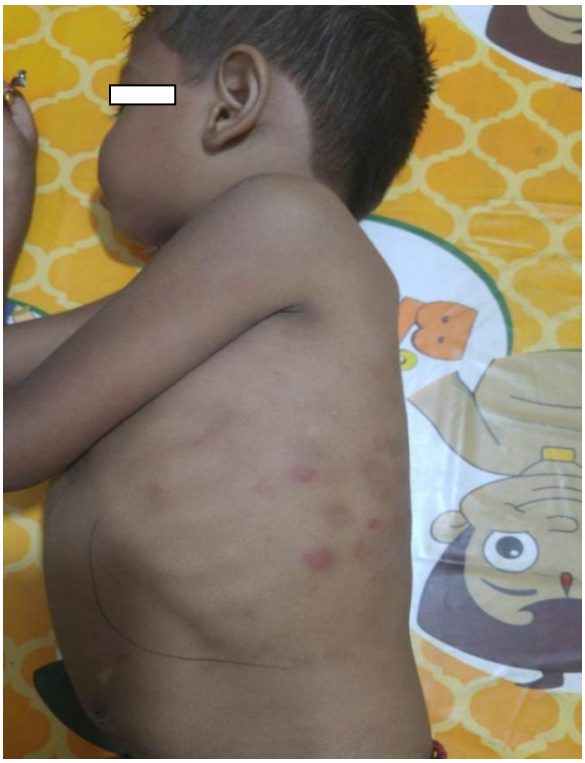
years.[4] Lymphomas were the most commonly observed malignancy in the setting of WAS.2 Moreover, there is a preponderance of non-Hodgkin's lymphoma (NHL) in patients with WAS when compared to Hodgkin's lymphoma. Other malignancies, including myelodysplasia, leukemia, and myeloproliferative disorders, have also been described.[5] The aggressive nature of malignancy in the setting of WAS portends a poor prognosis, as demonstrated by historical data suggesting >95% mortality among those affected.[4] Genetic susceptibility conferred by abnormal WASp function, associated abnormalities in tumor-surveillance mechanisms (eg, impairment in NK cell cytotoxicity), and environmental factors (eg, Epstein–Barr virus [EBV]) are examples of factors that increase the risk of malignancy in patients with WAS.[5]

Case Report

A 3yr old male child born out of non-consanguineous marriage came to our hospital with complaints of multiple erythematous nodules over left chest wall for last 1 month. Past history revealed multiple episodes of respiratory tract infections for which patient was prescribed anti-histaminics and antibiotics on several occasions. There was also past history of eczematous lesions over scalp and limbs. On examination there was mild pallor, axillary lymphadenopathy, erythematous nodules over left infraaxillary area. Abdominal examination revealed hepatosplenomegaly with other system being within normal limits. Laboratory investigations Hb-11.3gm%, TLC-16,500/cmm (N-46%, L-48%, E-4%, B-2%), TPC-41000/cmm, CPS- mild anisocytosis with thrombocytopenia, sicking test-negative, serum IgE-433IU/ml thus ruling out hyper IgE syndrome/ Job syndrome.

The child was diagnosed to have Wiskott Aldrich syndrome and was discharged. On follow up after 6 months, CBC showed Hb-12.8gm%, TLC-28000(N-46%, L-44%,E-02%, large immature cells-6%), TPC-20000/cmm, bone marrow examination revealing subleukemicleukemia (myeloid type). Patient was started on chemotherapy.





Discussion

Wiskott-Aldrich syndrome (WAS) is an X-linked disorder caused by mutations in the gene that encodes the Wiskott-Aldrich syndrome protein (WASp). The originally described features of WAS include susceptibility to infections (subsequently associated with adaptive and innate immune deficiency), microthrombocytopenia, and eczema. As an X-linked disorder, it is seen almost exclusively in males. Approximately 50 percent of patients with *WAS* gene mutations have the WAS phenotype, and the other half have the X-linked thrombocytopenia (XLT) phenotype.

Abnormalities in immune system function (i.e. cell-mediated, humoral, and innate immunity) among patients with WAS result in susceptibility to a wide variety of infectious pathogens. Despite this, infectious complications as a sole first manifestation of WAS are uncommon (<5% of cases).[6] Patients with WAS are susceptible to opportunistic infections with organisms such as *Pneumocystis jirovecii*. Patients with WAS may develop severe and disseminated forms of viral infections, with herpes simplex virus I or II (6% of cases) and varicella (3% of cases) as the most common pathogens. Invasive yeast and fungal infections (10% of cases) have also been described. Sinopulmonary infections are the most common infectious complications prior to diagnosis, including otitis media (64% of cases) and pneumonia (25% of cases). Other severe infectious complications may occur, such as sepsis (7% of cases) and meningitis (4% of cases).[6]

The immunodeficiency in WAS involves T cells and is associated with both quantitative and qualitative defects in T cells. Humoral immune responses are abnormal in patients with WAS. Serum levels of immunoglobulin IgG, IgM, and IgA are often low and IgE levels often high in patients with WAS. Functional antibody responses may be abnormal as demonstrated by abnormal isohemagglutinintiters (84% of cases) and diminished vaccine responses to protein.

Patients that suffer from primary immunodeficiency are at risk to develop haematological malignancies often associated with Epstein-Barr virus infection and of poor prognosis.[7] The reason for increased cancer risk could be failure of the immune system to eradicate tumors or due to intrinsic failure during myelopoiesis and lymphopoiesis. Mutations in the *WAS* gene that encodes for the cytoskeletal regulator WASp are associated with two immunodeficiency syndromes, Wiskott-Aldrich syndrome (WAS) and X-linked neutropenia (XLN). WAS is caused by loss-of-function mutations in WASp leading to severe immunodeficiency. The tumor incidence in WAS is estimated to be 13–22% with a median age of onset of 9.5 years and with poor prognosis.[8] WAS patient tumors include non-Hodgkin lymphoma, EBV positive and EBV negative lymphoma, Hodgkin lymphoma, Burkitt lymphoma, and less frequently myelodysplasia, acute lymphoblastic leukemia, myelomonocytic leukaemia, and nonhematopoietic malignancies.

Treatment is directed mainly at control of bleeding by infusion of blood and platelets, control of infections with proper antibiotics and IVIG infusion. IVIG is useful in the prophylaxis of both bacterial and viral infections but not in thrombocytopenia. Patients should be immunized with conjugated and unconjugated vaccines; however, the avoidance of live viral and attenuated viral vaccines is necessary. All patients with a diagnosis of WAS should be placed on Bactrim or an equivalent agent to prevent *P. jirovecii* pneumonia. Eczema is difficult to manage and is usually treated with emollients and topical steroids. Currently the only therapeutic option available for WAS is hematopoietic stem cell transplantation.

We know that genetic conditions like Down syndrome, fragile X syndrome, ataxia-telangiectasia, fanconianemiaetc are pre-leukemic conditions. By reporting this case we want to give the message to clinicians that primary immunodeficiency disorders (PID) like WAS can develop malignancies in the long run. So, regular followup and serial hematologic investigations

can lead to early diagnosis and favourable outcome.

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