CASE REPORT

Wiskott–Aldrich syndrome with bronchiectasis

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Summary
The Wiskott–Aldrich syndrome (WAS) is a rare X-linked immunodeficiency disease with a characteristic clinical phenotype that includes thrombocytopenia with small platelets, eczema, recurrent infections caused by immunodeficiency, and an increased incidence of autoimmune manifestations and malignancies. We present a patient who was diagnosed with WAS in adulthood and was found to have bilateral bronchiectasis. Although recurrent infections are common with Wiskott–Aldrich syndrome the association with bronchiectasis has not been previously reported.

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Introduction
The Wiskott–Aldrich syndrome (WAS) is a rare X-linked immunodeficiency disease with a characteristic clinical phenotype that includes thrombocytopenia with small platelets, eczema, recurrent infections caused by immunodeficiency, and an increased incidence of autoimmune manifestations and malignancies.\textsuperscript{1} Without aggressive treatment, such as bone-marrow transplantation, most patients die by 10 years of age due to recurrent infections, haemorrhage or autoimmune diseases.\textsuperscript{2,3} Here, we present a case of Wiskott–Aldrich syndrome that we diagnosed in an adult patient based on clinical findings. The patient presented with a respiratory infection and was found to have bilateral bronchiectasis. Although recurrent chest infections are common due to an immunodeficient syndrome the occurrence of bronchiectasis in patients with Wiskott–Aldrich Syndrome has not been previously reported.

Case report
A 27 year old male patient with a history of life long eczema, recurrent bacterial infections (cellulitis, pneumonia and sinusitis), viral infections (Herpes zoster, molluscum, genital warts) and a bleeding disorder requiring platelet transfusions in the past presented with a 3 day history of productive
cough, fevers and shortness of breath. His family history was notable for a brother, maternal uncle and grandfather who had all succumbed at ages of <30 due to recurrent infections and bleeding disorders (Figure 1).

On admission to the hospital he was alert awake and oriented. He was febrile with a temperature of 101.2°F, tachycardic with pulse rate of 116 and tachypneic with a respiratory rate of 24. ENT examination was notable for nasal congestion. Cardiovascular system revealed tachycardia with no murmurs, gallop or rub. Chest examination showed coarse crackles with expiratory rhonchi in both bases. Skin examination was significant for diffuse eczema with vesicles on the left side along the distribution of upper intercostal nerves suggestive of herpes (Figure 2) and petechiae. He also had extensive genital warts. Other physical examination was unremarkable.

His laboratory data were as follows: WBC count of \(4.8 \times 10^3\) cells/mcL with lymphocyte count of \(0.6 \times 10^3\) cells/µL, CD4 376(590-1060), CD8 200(280-760), CD4/CD8 1.8(2-4) and hemoglobin was 12.1 gm/dL. He was thrombocytopenic with platelet count of 12,000 cells/mcL. Peripheral blood smear showed thrombocytopenia with normal and small sized platelets (Figure 3). Serum immunoglobulins showed an IgM level of 31(77-220), IgA 161(68-378) and IgG 1180(590-1618) (mg/dL). HIV test was negative. Other laboratory tests including CMP, blood cultures were negative. X-ray and CT scan of the chest (Figure 4) showed bilateral basal bronchiectasis. Skin biopsy confirmed eczema. His HIV test was negative. He was admitted to the hospital and treated with intravenous Vancomycin, Piperacillin and Acyclovir for 7 days, received platelet transfusions and topical moisturising agents for eczema. Sputum cultures grew \(S.\) Pneumoniae which was pan sensitive. The diagnosis of Wiskott–Aldrich Syndrome was clinically suspected based on the presentation and later confirmed by genetic testing for WASP gene mutation on X chromosome using PCR-SSCP (Polymerase chain reaction-Single strand conformation polymorphism) technique which revealed missense mutation located in exons 2–3 of WASP gene. He improved dramatically on antibiotics and was discharged home with a plan to perform bone marrow transplantation.

Discussion

Wiskott–Aldrich Syndrome (WAS) is a rare X-linked recessive disease that was first recognized as a clinical syndrome comprising of immunodeficiency, thrombocytopenia, bloody diarrhea and eczema by Wiskott in 1937. The X-linked mode of inheritance was subsequently demonstrated by Aldrich. The incidence of WAS is estimated between 1 and 10 in 1 million live births, although this is likely to be an underestimation, as patients lacking the classic phenotype are often unrecognized. Clinical manifestations suggesting WAS are often present at birth and consists of petechiae, bruising, bloody diarrhea and persistent eczema. WAS always causes persistent thrombocytopenia and, in its complete form, also causes small platelets (mean platelet volume is also decreased: 3.8 to 5.0 fl in WAS males, compared with 7.1 to 10.5 fl in normal subjects), atopy, cellular and humoral immunodeficiency, and an increased risk of autoimmune disease and hematologic malignancy. WAS is fatal without curative bone marrow transplantation, but life expectancy has increased over time.

Although Aldrich demonstrated an X-linked pattern of inheritance for WAS in 1954, the molecular and genetic defect of Wiskott–Aldrich Syndrome was not identified until 1994. WAS results from a genetic defect in a protein that
has now been termed as Wiskott–Aldrich syndrome protein (WASp). The gene resides on Xp11.22-23, and its expression is limited to cells of hematopoietic lineage. Several hundred mutations associated with disease have now been discovered in the WASP gene. A broad range of phenotypes has also been associated with these mutations leading to differences in severity of the presentation.9 The exact function of WASp is not fully elucidated, but it seems to function as a bridge between signaling and movement of the actin filaments in the cytoskeleton.10,11 Many different mutations have been identified that interfere with the protein binding to Cdc42 and Rac GTPases, among other binding partners, most of which are involved in regulation of the actin cytoskeleton of lymphocytes.12 The actin cytoskeleton is responsible for cellular functions such as growth, endocytosis, exocytosis, and cytokinesis. This also leads to defects in innate immune function of macrophages in particular phagocytosis and chemotaxis of macrophages to the site of infection. Several other immune deficiencies have also been noted in patients with WAS. The severity of the immune deficiency varies depending on the mutation and its effect on protein expression. Both T and B lymphocytes are affected. The number of B cells might be normal or moderately decreased. Serum IgM levels are moderately decreased or can be normal and increased. IgA and IgE levels are frequently increased whereas serum IgG levels are within normal range. These immune deficiencies lead to recurrent bacterial and viral infections.10–12

Recurrent sinopulmonary infections are a hallmark of WAS. In a large multiinstitutional study Sullivan et al. surveyed 154 patients with WAS and found that the most common infection in patients with WAS is otitis media (78%)
followed by pneumonia (45%) and sinusitis (24%). Thus although recurrent upper and lower respiratory infections are common in patients with WAS the occurrence of bronchiectasis has not been previously reported in these patients. This may be related to the fact that many of these patients succumb at a young age often within eight years of life. In a more recent survey an average age of eleven years has been reported and occasional cases of patients with WAS who live up to second and third decade have been described. As the understanding of the pathogenesis of the disease and therapeutic options broaden it is likely that the outcome in these patients will improve. With increasing survival the association of bronchiectasis with this immunodeficient syndrome is likely to increase.

The patient described showed classic clinical findings of WAS including a persistent eczema, recurrent infections both skin and respiratory and thrombocytopenia with small platelets. His family history was significant for three male members who had succumbed to bleeding disorder and infections early in life. Thus the diagnosis was evident based on clinical criteria. This was further confirmed by performing genetic testing for WAS protein and he was found to have a missense mutation in exons 2–3 of the WASP gene on X chromosome. His infection was appropriately treated with broad spectrum antibiotics. Patient has also been offered stem cell transplantation. WAS is fatal without curative bone marrow transplantation.

In conclusion this case demonstrates the importance of complete medical and family history as well as necessity of a multidisciplinary approach and a broad differential diagnosis when a congenital disease in adults is suspected. Although there are few reports of WAS in adults, one should consider this diagnosis in an appropriate clinical setting because of variable penetrance of the disease. This case also illustrates that Wiskott–Aldrich Syndrome should be considered in patients with bronchiectasis in an appropriate clinical setting.

Conflict of Interest Statement

The authors do not have any conflict of interest.

References