Wiscott Aldrich Syndrome With Oral Involvement: A Case Report

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ABSTRACT

Wiskott Aldrich syndrome is an X-linked recessive disorder characterized by thrombocytopenia with microplatelets, eczema, recurrent infections, and predisposition to autoimmune disease and malignancy. It is a rare syndrome, and the incidence rate is approximately 4 in every 1 million live male births with no clear ethnic or racial predilection. The purpose of this paper was to report a case of Wiskott Aldrich syndrome with oral involvement demonstrated by 2 male siblings.

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Wiskott Aldrich syndrome (**WAS**) was first described by Alfred Wiskott in 1937[1] as a triad of discharging ears, eczema, and thrombocytopenia. The syndrome was rediscovered in 1954 by Robert Aldrich et al.[1], who demonstrated an X-linked mode of inheritance in a family with 16 affected males within 6 generations. By the mid-1960s, many additional cases had been recognized and the clinical syndrome became known by the names of both pediatricians.[1,2] Subsequently, other WAS features were recognized, including immunodeficiency involving: humoral, cellular, and innate immunity; a high rate of autoimmunity; malignancies; abnormal apoptosis; and defective cell motility.[2]

WAS occurs due to an X-linked recessive mutation, which is expressed phenotypically in all the males who receive it and which only rarely manifests in heterozygotic females.[3] In 1994, the gene responsible for WAS was identified by positional cloning. It was demonstrated that the mutations of the WAS protein (**WASp**) result in 4 clinical phenotypes: (1) classic WAS; (2) X-linked thrombocytopenia; (3) intermittent thrombocytopenia; and (4) neutro-penia.[2] Zhu et al., scored WAS from 1 to 5, based on severity of the associated symptoms.[4,5]

The features associated with WAS include dysfunction of nearly all effector arms of the immunity, as well as thrombocytopenia with platelet dysfunction. As a consequence of these abnormalities, children and adults with this syndrome have recurrent bleeding, recurrent and significant infection with common opportunistic organisms, autoimmune diseases, and lymphoreticular malignancies.[6,7]

Antibiotic prophylaxis, intravenous immunoglobulin, splenectomy, and bone marrow transplantation are the treatment options available presently.[6] Hematopoeitic stem cell transplantation and gene therapy are expected to cure the disease.[2]

A literature search revealed no case report of WAS with oral involvement. Very few papers reported in the literature have addressed the issue of dental management of WAS. The present case report is intended to describe a case of Wiskott Aldrich syndrome with oral involvement demonstrated by 2 male siblings.

CASE REPORT

A 6-year-old male patient and his 4-year-old brother (Figure 1) reported to the outpatient Department of Oral

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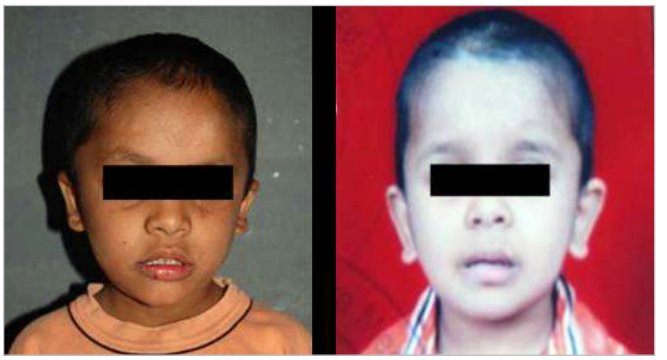

Figure 1. Petechiae seen over the facial skin of older and younger siblings.

Medicine and Radiology, M. S. Ramaiah Dental College and Hospital, Bangalore, Karnataka, India. The older brother complained of pain of 3 days duration in the upper right posterior region of his jaw; the younger brother presented with spontaneous gingival bleeding. The older sibling's dental history revealed previous episodes of pain and swelling around his primary maxillary right first molar. Spontaneous bleeding upon tooth-brushing and overnight bloody staining of pillows had been observed in the younger sibling over the previous 2 weeks. A family history revealed that they were the first 2 of 3 children from second-degree consanguineous parents and had a younger, healthy sister. A detailed family history revealed that 13 previous children of this same family, 12 sons and 1 daughter, had succumbed to death within 2 to 3 years of birth due to bleeding disorders and recurrent infections. The pedigree chart (Figure 2) with abbreviations explains the family tree of this large family, in which WAS affected 16 total children—13 of whom are deceased and 3 of whom have survived.

The patient's maternal cousin was reported to have WAS, and the human leukocyte antigens-matched bone marrow of his younger sibling was used for treatment.

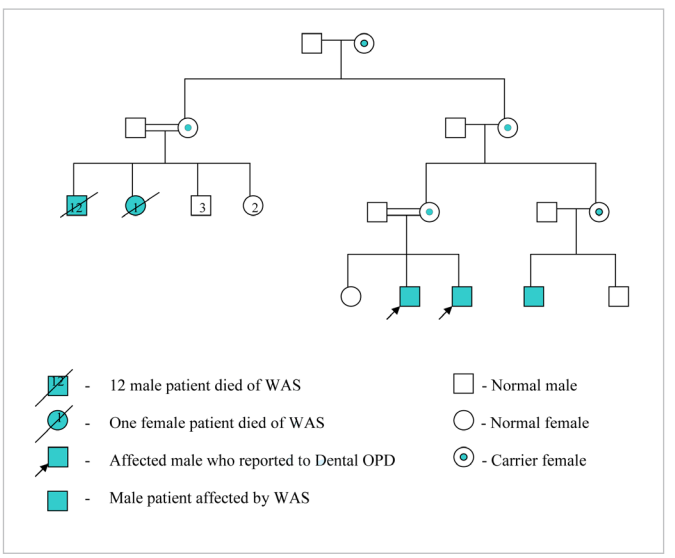

Figure 2. Pedigree chart with abbreviations depicting family tree.

The child is reported to be doing well following bone marrow transplantation.

The older sibling's medical history revealed that soon after birth the patient presented with severe anemia, icterus, subgaleal hemorrhages, and thrombocytopenia, for which a blood transfusion and phototherapy were given. This was followed by: recurrent episodes of epistaxis and bleeding in the stool since 17 days after birth; repeated gastrointestinal tract and lower respiratory tract infections since infancy; multiple episodes of fever and ear discharge reported 1 month after birth; and skin eczema observed since 6 months of age. The patient was diagnosed with WAS at 7 months of age.

The 4-year-old brother has also had similar complaints since birth. He presented with epistaxis, gastroenteritis, pyrexia, eczema, and multiple echymotic spots across his body during his first month of life. The child was diagnosed with a low platelet count since he was 2 months old. Intracranial bleeding was diagnosed at 8 months of age and WAS at 11 months of age.

Both siblings experienced spontaneous nasal and gastrointestinal tract bleeding whenever the platelet count was less than 50,000 µl. The patients were repeatedly given platelet and blood transfusions since birth to stop the bleeding. Bone marrow transplantation was advised for both patients, but was not carried out, because a suitable donor was not available. Table 1 shows the normal[8] and the observed hematological values in both the siblings.

Intraorally, both siblings presented with petechiae on their buccal mucosa, palate, and gingiva (Figure 3). The older sibling's oral hygiene was fair, with minimal deposits of calculus. Bleeding on probing and dental caries were observed around the primary maxillary right central incisor, canine, and second molar and primary maxillary left central incisor, canine, and first and second molars. The primary maxillary right first molar was grossly decayed and was associated with abscess formation. A conservative line of treatment was followed, including a pulpotomy of the primary maxillary right first molar and restoration of the remaining decayed teeth. Fluoride application was carried out, as the older sibling was prone to dental caries.

The younger sibling's oral hygiene was fair; however, spontaneous gingival bleeding was noted (Figure 4). Following oral prophylaxis, topical application of astringent gum paint (tannic acid 2%, zinc chloride 1%, cetrimide 0.1%) was advised, which acts as a local hemostatic agent.

Spontaneous bleeding and bleeding upon slight provocation was noted in both patients on clinical examination which was inconsistent with local factors, that can be attributed to underlying WAS. Platelet transfusion was performed, following which gingival bleeding and epistaxis stopped. The patients were recalled for regular follow-up once in 3 months. The parents were

Table 1. Showing the Normal[8] and Observed Hematological Values in Both Siblings.

Value	Normal range	Older sibling	Younger sibling
Hemoglobin concentration (g/dL)	11.5-15.5	11.6	9.6
Platelet count (lakhs/cumm)	1.5-4	20,000	15,000
Total white blood cell count (cells/cumm)	5,500-15,500	9,300	21,000
Neutrophils (%)	54-62	30	41
Lymphocytes (%)	25-33	56	42
Eosinophils (%)	1-3	9	8
Basophils (%)	0-1	0	1
Monocytes (%)	3-7	0	2
Myelocytes (%)	0	0	2
Bandform (%)	3-5	5	4
Mean platelet volume (fL)	7-13	4.2	3.9
Immunoglobulin profile (mg %):			
IgA	14-159	133	129
IgG	345-1,236	1,435	1,441
IgM	43-207	269	273
Bone marrow		Small-sized platelets and anisocytosis	Very small-sized platelets

however advised to report to the clinicians whenever they observe spontaneous oral bleeding.

DISCUSSION

WAS is an X-linked disorder believed to affect approximately 4 in every 1 million boys worldwide.[4,6,9] This disorder previously was thought to be uniformly fatal, with a life expectancy of 8 months before 1935. After 1964, life expectancy increased to 6.5 years; in the most recent known survey, approximately 10% of living WAS patients were older than 18 years.[6]

The gene responsible for WAS has been isolated, cloned, and sequenced. It is encoded by 12 exons and composed of 1,823 basepairs; the cDNA encodes a 502-amino acid, proline rich protein (WAS protein), which is a signaling molecule and instrumental for cognate and innate immunity, cell motility, and protection against autoimmune diseases.[2,5,10] WASp's function as a major regulator of actin polymerization and cytoskeleton reorganization explains many, though not all, clinical features of the disease as consequences of impaired intracellular actin-dependent events. The inability to establish functional contact between T cells and antigen-presenting cells accounts for the T-cell immunodeficiency that is characteristic of WAS patients.[10]

WAS is a well-recognized triad of eczema, bleeding diathesis, and recurrent infections that occurs in males. In a typical case of severe WAS, petechiae, bruising and bloody diarrhea may develop in the first few days of life due to thrombocytopenia with platelets (low platelet volume) and dysfunctional platelets. Possibly severe eczema typically ensues, and throughout childhood there may be frequent episodes of otitis media, pneumonia, and diarrhea. Sepsis or meningitis may occur.[10] They are prone to lymphoma and other malignancies in adolescence.[4,11] This syndrome was the first condition in which predisposition to cancer was postulated to be due to impaired immune surveillance.[11]

As many as 40% of WAS patients may eventually suffer from an autoimmune disorder, with an increased chance of developing a malignancy such as lymphoma, leukemia, and Epstein-Barr virus-associated brain tumors. Vasculitides and hemolytic anemia are the 2 most common autoimmune diseases to occur and often cause considerable morbidity and mortality. Chronic inflammation, interleukin deficiency, and increased apoptosis may play a role in the loss of peripheral tolerance to self-antigens in this disease.[4] Autoimmune hemolytic anemia is significantly observed in patients with a high serum IgM level.[12]

A diagnosis of WAS often relies on a panel of compatible diagnostic studies because both the clinical presentation and the laboratory features are so variable,

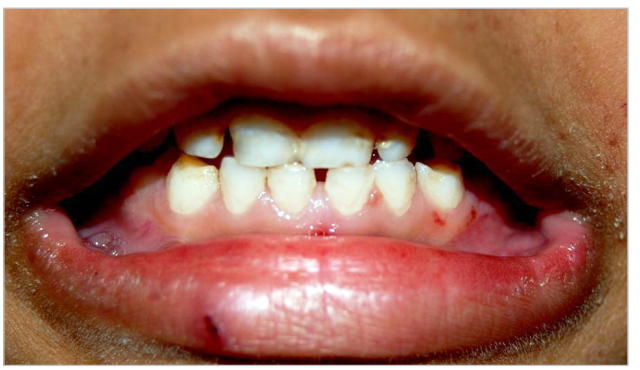

Figure 3. Petechiae over the gingiva of older sibling.

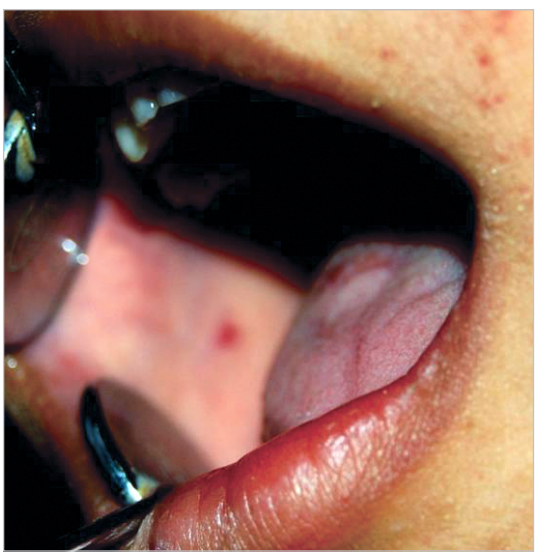

Figure 4. Petechiae over the buccal mucosa of the younger sibling.

and the treatment must be individualized for each patient, depending on his or her needs.[6] Patients suffering from WAS require vigilant medical care. Prompt and aggressive treatment of infections and bleeding is mandatory. Surveillance for malignancy is an important aspect of care. Treatment often utilized for these patients includes prophylactic antibiotics, elective use of splenectomy, and bone marrow transplantation.[4,13] Clinical trials of gene therapy to reconstitute WASp expression in autologous hematopoietic stem cells are now under development.[6]

The advent of bone marrow transplantation and elective use of splenectomy have more recently led to a substantially increased life expectancy for these patients, a considerable portion of whom are older than 20 years.[6] With its wide spectrum of clinical manifestations and complications, it is important for specialists in several disciplines—including dentistry—to be aware of this syndrome and its fatal consequences.[5] Optimal clinical management requires a coordinated multidisciplinary approach. Invasive dental procedures should be deferred until the platelet count is adequate to prevent excessive blood loss. Infection control also poses a problem in these patients; hence, strict asepsis should be followed during treatment procedures.

This case highlights the need for awareness among dentists about this rare syndrome, and WAS should be considered under the differential diagnosis for various bleeding disorders among male children.

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REFERENCES

1. Loan W, McCune K, Kelly B, Maxwell R. Wiskott-Aldrich syndrome: Life-threatening hemorrhage from aneurysms within the liver, small bowel mesentery, and kidney requiring both surgical and radiological intervention. J R Coll Surg Edinb 2000; 45:326-8.
2. Notarangelo LD, Miao CH, Ochs HD. Wiskott-Aldrich syndrome. Curr Opin Hematol 2008;15: 30-6.
3. Nussbaum RL, McInnes RR, Willard HF. Thompson and Thompson Genetics in Medicine. 7th ed. Philadelphia: WB Saunders Company; 2007:115-49.
4. Schurman SH, Candotti F. Autoimmunity in Wiskott-Aldrich syndrome. Curr Opin Rheumatol 2003;15:446-53.
5. Zhu Q, Zhang M, Blaese RM, et al. The Wiskott-Aldrich syndrome and X-linked congenital thrombocytopenia are caused by mutations of the same gene. Blood 1995;86:3797-804.
6. Sullivan, Kathleen E. Recent advances in our understanding of Wiskott-Aldrich syndrome. Curr Opin Hematol 1999;6:8-19.
7. Heidelberger KP, Legolvan DP. Wiskott-Aldrich syndrome and cerebral neoplasia: Report of a case-with localized reticulum cell sarcoma. Cancer 2006; 33:280-4.
8. Pesce MA. Reference ranges for laboratory tests and procedures. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, eds. Nelson textbook of pediatrics. 18th ed. Volume II. Phildelphia, Elsevier, Saunders; 2007:2943-54.
9. John TS. Wiskott-aldrich syndrome. Indian J Dermatol Venereol Leprol 1992;58:388-90.
10. Watanabe N, Yoshimi A, Kamachi Y, et al. Wiskott-Aldrich syndrome is an important differential diagnosis in male infants with juvenile myelomonocytic leukemialike features. J Pediatr Hematol Oncol 2007;29:836-8.
11. Puck JM, Candotti F. Focus on research: Lessons from the Wiskott-Aldrich syndrome. New Engl J Med 2006;355:1759-61.
12. Dupuis-Girod S, Medioni J, Haddad E, et al. Autoimmunity in Wiskott-Aldrich syndrome: Risk factors, clinical features, and outcome in a single-center cohort of 55 patients. Pediatrics 2003;111: e622-7.
13. Mathew LG, Chandy M, Dennison D, et al. Successful bone marrow transplantation in an infant with Wiskott-Aldrich syndrome. Indian Pediatr 1999;36:707-10.