

Wiskott-Aldrich Syndrome Presenting as Possible Allergy: Unusual Presentation for an Unusual Disease

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ABSTRACT

A 10-year-old white boy was evaluated for potential allergic rhinitis but had no laboratory evidence of IgE-mediated allergy. He also had a history of eczema since birth. Subtle historical findings, including the presence of recurrent respiratory infections, protracted herpangina, paronychia, and previous leukopenia, suggested the need for an immunodeficiency evaluation. A constellation of immunologic aberrations was observed, including alterations in immunoglobulin levels, lack of humoral antibody production to polysaccharide antigens, and depressed cell-mediated immunity. Platelet numbers were normal or elevated, but the platelet volume was invariably low. The combination of defective antibody response to polysaccharide antigens and low platelet volumes in a male child with eczema since birth is most compatible with a variant of the Wiskott-Aldrich syndrome. The presentation was not classic, since affected patients are usually infants with bleeding, thrombocytopenia, or recurrent, severe infections. This case was unique because of the advanced age (10 years) and the unusual presenting complaint (potential allergic rhinitis). Therapeutic options for this patient are discussed.

INTRODUCTION

WISKOTT-ALDRICH SYNDROME IS AN X-LINKED recessive immunodeficiency disorder. The usual manifestations of this syndrome are thrombocytopenia, eczema, and recurrent infections. The diagnosis is usually established during infancy.^(1,2)

The thrombocytopenia may result in petechiae or a bleeding episode. Common infectious agents affecting this population include cytomegalovirus, *Pneumocystis carinii*, herpes simplex, and varicella. Inability to form antibodies to polysaccharide antigens is a hallmark immunologic manifestation of this disorder. The eczema is similar to classic atopic dermatitis in appearance and distribution.

Several variant forms of the Wiskott-Aldrich syndrome have been reported, including boys with thrombocytopenia and low isohemagglutinins but without recurrent infection or eczema.⁽³⁾ Another patient had eczema and inability to form antibody to polysaccharide antigens, but without thrombocytopenia.⁽⁴⁾

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Another report described a 24-year-old man with defective T cell immunity, recurrent skin infections, and thrombocytopenia but with normal antibody responses to polysaccharide antigens.⁽⁵⁾

In this report, a patient with probable Wiskott-Aldrich syndrome with unusual symptoms is presented.

CASE REPORT

History of present illness

JM is a 10-year-old Caucasian male whose chief complaint was possible nasal allergy. He had nasal symptoms consisting of clear rhinorrhea, excessive sneezing, and nasal congestion but denied any accompanying allergic symptoms of the eyes. Increased severity during the winter months was identifiable, but specific triggers were not.

There was no documented wheezing or asthma, but he did complain of nighttime and exercise-induced cough during the winter months only. JM also had a history of severe, chronic, nonitchy eczema and dry skin since birth, which were more severe during infectious episodes. Despite a lack of known food sensitivity, a blood RAST test performed 3 months earlier showed allergy to corn but not to other foods. A corn elimination diet did not result in significant improvement in the eczema.

Review of systems

There was a history of numerous bouts of infection, including three episodes of pneumonia, the last of which 2 months earlier was caused by *Mycoplasma* and required hospitalization for antibiotic and nebulizer treatments. He also had a history of recurrent bronchitis and otitis media. He suffered a severe episode of herpangina 6 years earlier, manifested by throat and mouth ulcers, dehydration, and weight loss, which persisted for 6 weeks.

JM also had a history of recurrent, chronic paronychia lesions of the nails of the fingers and toes. Although *Candida albicans* was assumed to be the causal organism, this was not demonstrable by culture. He had been treated unsuccessfully with topical antifungal agents only.

The history of recurrent infections prompted a physician evaluating the eczema to perform two complete blood counts 2½ years earlier. These revealed the following: total leukocyte counts were 2100 and 2400 cells/mm³ (normal 5000–14,500), total lymphocyte counts were 525 and 888 cells/mm³ (normal > 2000), monocyte percentages were 20% and 4% (normal 3%–9%) and counts were 420 and 96 cells/mm³ (normal < 750), total neutrophil counts were 987 and 1320 cells/mm³ (normal > 1000), total eosinophil counts were 84 and 72 cells/mm³ (normal < 740), the hemoglobin concentrations were 11.3 and 11.0 g/dl (normal 10.5–12.7), the hematocrits were 31.9% and 31.8% (normal 32.0–38.0), platelet counts were “adequate” and 449,000 cells/mm³ (normal 150,000–450,000), and the value for mean platelet volume on one of these occasions was 5.5 femtoliters (normal 7.5–11.5).

The parents related that on a separate occasion, anemia was diagnosed. The evaluation revealed an elevated serum level of vitamin B₁₂. He was not receiving vitamin supplementation at that time.

There was no history of sepsis, meningitis, or arthritis, and JM had never had varicella. Risk factors for acquired immunodeficiency syndrome (AIDS) were not present. Additionally, he had no history of chronic diarrhea, petechiae, purpura, or frank bleeding episodes, although the family had noted intermittent “purplish” lesions of the skin of the trunk and forearms, which were more frequent and severe during infectious episodes and improved during antibiotic therapy.

Past medical history

JM’s medications included amoxicillin for otitis media and Eucerin cream and triamcinolone acetonide for eczema. He had received three primary diphtheria-tetanus (DT) immunizations and two booster immunizations, the last of which was administered at 5 years of age. HIB vaccine had not been given. Growth and development had been normal.

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Family history

There was a history of allergic rhinitis in the maternal grandfather but not of immune deficiency or early deaths. JM had two female siblings who were healthy. JM's mother had no history of bleeding or severe infections but did have severe, nonitchy eczema between the ages of 3 years and 19 years, anemia that was treated transiently with vitamin B₁₂, paronychia nail lesions that were similar to those of JM and have resolved, and intermittent pitting of the nails even up to the present time.

Physical examination

JM appeared well developed. His weight and height were at the 50th and 10th percentiles, respectively, for age. He had a fair complexion and blondish white hair. His skin had generalized xerosis and multiple red, slightly raised, slightly scaly lesions in a generalized distribution, with no evidence of excoriation. There were paronychia lesions involving the nails of the toes and fingers. He had slightly pale, boggy nasal turbinates but no rhinorrhea. There was scarring of the tympanic membranes bilaterally. Tonsillar tissue was absent, and only scant lymphoid tissue was palpable in the regional lymph nodes. The lungs were clear to percussion and auscultation. The heart had a regular rate and rhythm without murmurs. The abdomen was soft without organomegaly. Neuromuscular examination was unremarkable.

Laboratory evaluation

Hypersensitivity. Allergy skin tests were performed by the puncture and intradermal methods and revealed appropriate positive (histamine) and negative (saline) control responses but no reactions to house dust, ragweed, grass, English plantain, tree, *Penicillium*, *Epicoccum*, dust mite (*Dermatophagoides farinae*), cat, dog, cow's milk, egg, wheat, corn, and soybean allergens.

Humoral immunity. Immunoglobulin levels were as follows: IgG 1490 mg/dl (normal 504–1364), IgA 1090 mg/dl (normal 121–243), IgM 28 mg/dl (normal 35–85), and IgE 9.6 IU/ml (normal 0–570). IgG subtypes were as follows: IgG1 1484 (normal 350–950), IgG2 317 (normal 70–450), IgG3 22 (normal 20–90), and IgG4 29 (normal 3–90).

No monoclonal immunoglobulin molecules were detected in the patient's serum on immunoelectrophoresis, and total protein electrophoresis revealed the following: total protein 8.5 g/dl (normal 6.00–8.30), albumin 4.34 g/dl (normal 3.2–5.2), alpha₁ 0.24 g/dl (normal 0.10–0.40), alpha₂ 1.26 g/dl (normal 0.60–1.00), beta globulin 1.33 g/dl (normal 0.60–1.40), and gamma globulin 1.36 g/dl (normal 0.70–1.60). Aside from the increased level of alpha₂ globulins, the electrophoretic pattern suggested the presence of immune complexes.

The results of tests to evaluate production of functional antibodies against protein and polysaccharide antigens (prevaccine and postvaccine) are summarized in Table 1. This revealed normal antibody levels to protein antigens (tetanus) but defective antibody responses after immunization to polysaccharide antigens (*Haemophilus influenzae* and pneumococcus). He also had decreased ABO erythrocyte blood group antibodies.

Cell-mediated immunity. Delayed hypersensitivity skin tests to *Candida* and tetanus antigens at 1:100 dilutions were nonreactive, indicating the presence of cutaneous anergy.

Total leukocyte counts were 1900, 2200, and 1500 cells/mm³ (normal 5000–14,500) on three separate occasions, and total lymphocyte counts were 670, 550, and 450 cells/mm³ (normal > 2000) on these same occasions, respectively, whereas monocyte percentages were 17%, 19%, and 29% (normal 3%–9%), respectively, and counts were 320, 420, and 440 cells/mm³ (normal < 750), respectively. The total eosinophil counts were 60, 20, and 80 cells/mm³ (normal < 740), respectively.

Of a total lymphocyte count of 738 cells/mm³, 354 (48%) were T cells (normal 756–1664). Suppressor T cells (CD8) numbered 214 cells/mm³ (normal 207–587), and helper T cells (CD4) numbered 229 cells/mm³ (normal 392–930). This yielded a helper/suppressor ratio of 1.07 (normal 1.15–3.20). The total number of B

TABLE 1. FUNCTIONAL SERUM ANTIBODY RESPONSES

<i>Antigen</i>	<i>Prevaccine</i>	<i>Postvaccine</i>
Protein		
Tetanus	ND ^a	0.51 IU/ml (immune)
Polysaccharide		
Hamophilus influenza	ND	<0.55 µg/ml (nonprotective)
Pneumococcus		
Type 3	40 ng/ml ^b	90 ng/ml ^b
Type 7	30 ng/ml ^b	10 ng/ml ^b
Type 9	30 ng/ml ^b	30 ng/ml ^b
Type 14	50 ng/ml ^b	30 ng/ml ^b
ABO antigens ^c		
A1	1:8 (IgG)	ND
	1:4 (IgM)	ND
B	<1:1 (IgG)	ND
	1:1 (IgM)	ND

^aND, not done.^bProtective range 200–300 ng/ml.^cBlood type O⁺, normal titers > 1:16.

lymphocytes was 162 cells/mm³ (22%, with normal values of 7%–21%). The percent natural killer cells was 33% (elevated).

Lymphocyte proliferation tests revealed a reduced response to both phytohemagglutinin (PHA) and pokeweed mitogen (PWM). The tritiated thymidine incorporation by the patient's lymphocytes was 30,533 counts/minute in AB plasma and 26,525 counts/minute in autologous plasma (control 100,000 counts/minute). This indicates the presence of a reduced PHA response in both autologous and AB plasma, which suggests an abnormality of lymphocyte functional responsiveness to nonspecific mitogenic stimulation. Counts/minute for PWM stimulation were 12,977 in AB plasma (normal 59,000 counts/minute). This indicates a reduced lymphocyte response to PWM.

Complement and neutrophil quantity and function. The absolute neutrophil count was 710, 910, and 440 cells/mm³ (normal > 1000) on three separate occasions. A nitroblue tetrazolium test revealed the presence of 1% positive cells (normal < 5%) in the unstimulated (baseline) state and 99% positive cells (normal > 98%) after stimulation with phorbol myristate acetate.

Complement levels were as follows: C3, 115 mg/dl (normal 70–176), and C4, 24.1 mg/dl (normal 16–45). The total hemolytic complement (CH100) was 150 units (normal > 60).

Hematologic studies. The hemoglobin concentration was 12.1 g/dl (normal 10.5–12.7), and the hematocrit was 34.5% (normal 32.0–38.0). The red blood cell indices were as follows: mean corpuscular volume 80.9 femtoliters (normal 85–105), mean corpuscular hemoglobin 28.3 pg (normal 25–31), and mean corpuscular hemoglobin concentration 35 g/dl (normal 31–35). The reticulocyte count was 1.8% (normal 0.5–2%). Because of the history of anemia and elevated serum vitamin B₁₂ levels, serum vitamin B₁₂ and folic acid levels and erythrocyte folate levels were measured. The results were >2000 pg/ml (normal 150–1000), 6.4 ng/ml (normal 2.6–18.0), and 430 ng/ml (normal 169–707), respectively.

Platelet counts were 389,000 cells/mm³, 596,000 cells/mm³, and “adequate” on three separate occasions (normal 150,000–450,000). Values for mean platelet volume were 5.9, 5.6, and 6.2 femtoliters (normal 7.5–11.5) on these occasions, respectively.

Other studies. Pulmonary function testing revealed a forced vital capacity (FVC) of 2.07 liters (122% predicted), a forced expiratory volume in 1 second (FEV₁) of 1.86 liters (131% predicted), a peak expiratory flow rate (PEFR) of 3.01 liters/second (90% predicted), a forced expiratory flow (25%–75%) (FEF₂₅₋₇₅) of

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2.11 liters/second (99% predicted), and an FEV₁/FVC% of 90% (predicted 84%). As such, spirometry was within normal predicted limits. Chest radiograph showed a normal cardiomedial silhouette and clear lung fields.

Sinus radiographs revealed the presence of pansinusitis, and a lateral neck radiograph showed a small adenoid shadow. Urinalysis showed no abnormalities.

Family testing. A complete blood count was performed on the patient's mother. The hemoglobin was 13.6 g/dl (normal 11.7–15.7), and the hematocrit was 40.0% (normal 35.0–47.0). The red blood cell indices were as follows: mean corpuscular volume 87.3 femtoliters (normal 80.8–100), mean corpuscular hemoglobin 29.7 pg (normal 28.2–32.3), and mean corpuscular hemoglobin concentration 34 g/dl (normal 31.7–35.7). The total leukocyte count was 4300 cells/mm³ (normal 4500–11,000). Of these, 1900 (44%) were neutrophils, 1590 (37%) were lymphocytes, 470 (11%) were monocytes, and 300 (7%) were eosinophils. The platelet count was 375,000 cells/mm³ (normal 150,000–450,000), and the mean platelet volume was 8.0 femtoliters (normal 7.5–11.5).

The results of tests to evaluate the pattern of X chromosome inactivation (selective vs random) in the mother and female siblings are pending.

TREATMENT

The patient is being treated with intravenous gamma globulin, antifungal agents, and prophylactic antibiotics. The eczema has improved markedly since initiation of antibiotic prophylaxis.

DISCUSSION

This 10-year-old white boy had a history of potentially allergic nasal symptoms but had no laboratory evidence of IgE-mediated allergy. He also had a history of eczema since birth. Subtle historical findings, including the presence of recurrent respiratory infections, protracted herpangina, paronychia, and previous leukopenia, suggested that an evaluation for immunodeficiency was warranted. A constellation of immunologic aberrations was observed, including alterations in immunoglobulin levels, lack of humoral antibody production to polysaccharide antigens, and depressed cell-mediated immunity. Platelet numbers were normal or elevated, but the platelet volume was invariably low. Although these findings could potentially represent a variant of combined immunodeficiency syndrome, the combination of defective antibody response to polysaccharide antigens and low platelet volumes in a male child with eczema since birth is most compatible with the diagnosis of Wiskott-Aldrich syndrome (Table 2). An abnormality of both platelets and lymphocytes is one of the hallmarks of patients with the Wiskott-Aldrich syndrome. Moreover, small platelets are found almost exclusively in patients with the Wiskott-Aldrich syndrome.⁽⁶⁾ This case was unique because of the advanced age at presentation (10 years) and the unusual presenting complaint (potential allergic rhinitis).

However, the presentation was not entirely classic for Wiskott-Aldrich syndrome, since affected patients are usually infants with bleeding, thrombocytopenia, or recurrent, severe infections. The patient presented here had a relatively benign infectious disease history, and this case is best considered as a variant form of the Wiskott-Aldrich syndrome. Other investigators have reported several variant forms of classic Wiskott-Aldrich syndrome, including cases with and without thrombocytopenia, recurrent infections, or eczema.^(3–5)

The mode of inheritance of the Wiskott-Aldrich syndrome is X-linked recessive.⁽⁷⁾ As such, only males generally are affected. Females with the defective gene are considered carriers, with one normal and one defective copy of the causative gene. None of the males or females in the extended family of this patient suffered from an immunodeficiency disease, suggesting a sporadic mutation of the responsible gene. However, there are some indications that the mother may have been afflicted with a similar problem during her childhood years, which subsequently resolved on a clinical level. Indeed, subtle immunologic abnormalities (leukopenia, disproportionately high percentage of monocytes), which were similar but not identical to those in the patient, were present in the mother at the time of this evaluation. One might speculate that developmental changes in the expression of the defective gene were responsible for these phenotypic changes. This could be explained by developmentally controlled random vs selective inactivation of one of the X

TABLE 2. SUMMARY OF EVIDENCE FOR DIAGNOSIS OF WISKOTT-ALDRICH SYNDROME

Findings consistent with classical Wiskott-Aldrich syndrome
Historical/physical examination
Male with eczema since birth, recurrent infections
Laboratory
Low serum, IgM, elevated serum IgA
Defective antibody response to polysaccharide antigens
Normal antibody responses to protein antigens
Defective cell-mediated immunity
Low platelet volumes
Normal polymorphonuclear leukocyte function and normal complement levels
Findings not consistent with classic Wiskott-Aldrich syndrome
Historical/physical examination
Lack of bleeding, thrombocytopenia, and eosinophilia
Negative family history
Lack of splenomegaly, hepatomegaly, and cervical lymphadenopathy
Laboratory
Low serum IgE

chromosomes in a female. Selective inactivation of the defective gene could result in a normal phenotype, whereas full or partial expression of the defective gene at another time could result in some or all of the manifestations of the disease. In contrast, males with only one defective copy of the gene would not be expected to have a normal phenotype at any time.

The lack of acute, severe infections in this child may be explained by several potential compensatory mechanisms. One is the markedly elevated serum IgA level. Secretory IgA is keenly involved in defense against the invasion of mucosal surfaces by infectious agents. Another possible mechanism is the disproportionately high percentage of circulating monocytes. Cells of the monocyte/macrophage lineage are involved in HLA-restricted antigen presentation and initiation of the immune response to foreign antigens via the production of cytokines. Additionally, natural killer cells, which also produce cytokines and kill malignant or virally infected cells, were elevated in the circulation.

The marked serum elevation of vitamin B₁₂ in this patient is of interest. Diseases that have been associated with serum elevations of vitamin B₁₂ include leukemia, polycythemia vera, carcinoma with liver metastases, and acute and chronic hepatitis. Although an increased incidence of lymphoreticular malignancy has been reported in the Wiskott-Aldrich syndrome,⁽⁸⁾ this patient's course was not compatible with any of these diagnoses, and a plausible explanation for the elevated level is lacking. Any relationship that might exist between the elevated serum level of vitamin B₁₂ and the immune or hematologic defects in this patient with Wiskott-Aldrich syndrome is also unclear. However, one could speculate that the elevated level may have a role in disease pathogenesis or, alternatively, could merely represent an epiphenomenon.

Since Wiskott-Aldrich syndrome is an uncommon immunodeficiency disorder and since many variant forms have been identified, the therapeutic approach must be individually tailored to an affected patient. Bone marrow transplantation with busulfan and cyclophosphamide conditioning has emerged as a successful therapy for Wiskott-Aldrich syndrome when it appears in infancy with severe manifestations of bleeding or infection.⁽⁹⁾ Whether or not bone marrow transplantation is indicated in this 10-year-old child without serious bleeding episodes or infections is subject to careful consideration. In contrast, treatment with intravenous gamma globulin is clearly indicated because of the patient's inability to form functional antibodies to polysaccharide antigens. A similar argument applies for the use of prophylactic antibiotics. Due to the relatively benign infectious disease history and lack of bleeding episodes, therapy with intravenous gamma globulin and prophylactic antibiotics was elected, with the option of considering a bone marrow transplantation if disease manifestations become severe in the future.

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