X-Linked Ectodermal Dysplasia With Immunodeficiency Caused by NEMO Mutation

Early Recognition and Diagnosis

Anthony J. Mancini, MD; Leslie P. Lawley, MD; Gulbu Uzel, MD

Background: X-linked ectodermal dysplasia with immunodeficiency (XL-EDA-ID) is described in patients with hypomorphic mutations in IKBKG (the inhibitory kB kinase gene), which encodes nuclear factor kB essential modulator (NEMO). Features include hypohidrosis, dental anomalies, alopecia, and immunodeficiency. Boys with NEMO mutations often present with serious infections, but the NEMO mutations are rarely diagnosed early in infancy. Cutaneous features in these patients are poorly elucidated.

Observations: A 12-week-old male infant presented with a recalcitrant skin eruption, intertrigo, atopiclike dermatitis, and erythroderma. Alopecia, frontal bossing, and periorbital wrinkling were present, and family history revealed incontinentia pigmenti in his mother. Laboratory evaluation revealed leukocytosis with eosinophilia, low IgG and IgM levels, and absent IgA. Flow cytometry revealed lymphocytosis with elevated CD3⁺ and CD4⁺ counts and low levels of natural killer cells. Amplification and sequencing of IKBKG revealed insertion of cytosine at nucleotide 1167 (1167-1168insC) in exon 10, with frameshift mutation in the zinc-finger domain. Peripheral blood stem cell transplantation led to initial engraftment and improvement in his skin findings, but his engrafted cell counts diminished, and a second stem cell transplantation was planned.

Conclusions: Mutations in NEMO should be considered in male infants with recalcitrant seborrheic or atopic dermatitislike eruptions and intertrigo, especially when features of ectodermal dysplasia are present. Early recognition and diagnosis are desirable, prior to the onset of manifestations of immunodeficiency.

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with the following growth parameters: weight at the 10th to 25th percentile for age, length at the 10th to 25th percentile for age, and head circumference at the 50th percentile for age. His scalp revealed diffuse alopecia and diffuse, yellow, greasy scales superimposed on erythema (Figure 1). He was noted to have mild frontalbossing, periorbital wrinkling, and an everted lower lip (Figure 2). His axillary and inguinal folds and perianal region revealed erosive erythema (Figure 3), and his umbilicus was erythematous and moist. His oral mucosa was clear, and he had no lymphadenopathy or hepatosplenomegaly.

He was initially diagnosed with severe intertrigo and seborrheic dermatitis and treated with oxiconazole nitrate, 1%, and alclometasone dipropionate, 0.05%, creams, oral cephalixin, and oral fluconazole. A prior culture had revealed heavy growth of *Staphylococcus aureus* that was pansensitive. Findings from fungal and repeated bacterial cultures from affected skin fold areas were negative. Given the severity of involvement, a laboratory evaluation for immunodeficiency was performed. Subsequently, his mother reported having been diagnosed with incontinentia pigmenti as a child, with apparent mild expressivity. She recalled her history of blisters with eventual spontaneous involution. She denied any history of dental or musculoskeletal defects, ophthalmic abnormalities (aside from myopia), and developmental abnormalities or seizures. Her hair and nails were normal, and findings of her most recent skin examination were notable only for faintly hyperpigmented linear and whorled streaks following the lines of Blaschko on the posterior aspects of her legs and flanks.

Throughout his early course, the patient’s skin involvement varied. He developed intermittent erythroderma with patchy clearing (Figure 4), yet the intertrigo was a fairly persistent finding. He had occasional atopic dermatitislike, erythematous, scaly plaques superimposed on a background of faint erythroderma. Dur-
Skin biopsy yielded methicillin-resistant Staphylococcus aureus, and he was treated with intravenous vancomycin with clearance. Also during the pretransplantation course, he displayed poor weight gain, diarrhea, and vomiting with feeding. Gastrointestinal evaluation and endoscopy were performed, revealing normal-appearing mucosa. Biopsy specimens of the duodenum and sigmoid colon showed nonspecific findings without viral inclusion bodies or granulomas. Of note, he had no radiologic evidence of osteopetrosis and no lymphedema of the limbs.

**LABORATORY FINDINGS**

Complete blood cell count revealed leukocytes at 22,710/µL (normal range, 5,000-19,500/µL) and platelets at 597,000/µL (normal range, 150,000-450,000/µL). Hemoglobin level was 11.3 g/dL (normal range, 9.0-14.0 g/dL). The differential analysis revealed 6% monocytes (normal range, 3%-10%), 55.8% lymphocytes (normal range, 44%-74%), 30.4% neutrophils (normal range, 14%-34%), 6.4% eosinophils (normal range, 0%-6%), and 1.4% basophils (normal range, 0%-2%).

Results of chemical analysis were normal. Findings of a chronic granulomatous disease flow study were normal, as were the expression of CD11b integrin (ruling out leukocyte adhesion deficiency) and mitogen stimulation assays (phytohemagglutinin, concanavalin A, and pokeweed mitogen). Tetanus titer showed undetectable levels, and a quantitative assay for immunoglobulins revealed a normal level of IgE, no detectable IgA, and diminished levels of IgG (128 mg/dL; normal range, 169-558 mg/dL) and IgM (11.5 mg/dL; normal range, 23-85 mg/dL).

Flow cytometry revealed overall lymphocytosis (lymphocyte count, 12,672/µL; normal range, 3,886-10,750/µL) with significantly increased numbers of CD3⁺ and CD4⁺ T lymphocytes (7,476/µL; normal range, 1,392-5,210/µL) expressing activation markers and increased numbers of double-negative T lymphocytes (CD3⁺ CD4⁺ CD8⁺) but very few natural killer cells (CD3⁺ CD16⁺ CD56⁺). His T-cell receptor Vβ repertoire suggested polygonal T cells, which made maternal transplacental T-cell engraftment unlikely. Review of peripheral blood smear findings revealed no features suggestive of hematologic malignancy. The recombination activating genes RAG1 and RAG2 as well as interleukin 7 (IL-7) receptor sequences revealed no mutations, ruling out Omenn syndrome and a severe combined immunodeficiency (SCID) with maternally engrafted cells.

To convert leukocytes and lymphocytes to number of cells × 10⁶/L, multiply by 0.001; platelets to number of platelets × 10⁹/µL, multiply by 1.0; hemoglobin to grams per liter, multiply by 10.0; and IgA and IgM to milligrams per liter, multiply by 10.0.

Sequencing of the coding region ofIKBKG revealed insertion of cytosine at nucleotide 1167 (1167-1168insC) in exon 10, resulting in a predicted frameshift at codon 390 (E390fsX394), and a short protein without the zinc-finger domain. Molecular testing of his mother revealed heterozygosity for the same mutation. Both sisters were tested and found to be homozygous for the wild-type gene.

**HISTOPATHOLOGIC FINDINGS**

Skin biopsy was performed during a follow-up visit at age 4 months (prior to confirmation of the NEMO mutation) to assess for possible graft-vs-host disease (GVHD). Hematoxylin-eosin staining revealed acanthosis and spongiosis of the epidermis and a superficial interface and perivascular lymphohistiocytic infiltrate with focal satellite cell necrosis (Figure 5). Numerous necrotic keratinocytes were noted as were pigment-laden macrophages. The changes were considered to be consistent with GVHD with a superimposed eczematous process. Interestingly, the findings from his variable number of tandem repeats (VNTR) studies for maternal engraftment in both peripheral blood and skin biopsy specimens were reported as negative, ruling out the possibility of GVHD.

**THERAPY**

The patient was initially treated with intravenous immunoglobulin, trimethoprim-sulfamethoxazole (Pneumocystis prophylaxis), azithromycin (mycobacterial pro-
Defects in the NF-κB pathway have been linked to several human diseases, including incontinentia pigmenti, ED, EDA-ID, osteopetrosis and/or lymphedema with EDA and ID (OL-EDA-ID), familial cylindromatosis, von Hippel-Lindau disease, primary lymphedema, a variety of osteoclast diseases, inflammatory bowel disease, Blau syndrome, familial cold autoinflammatory syndrome, and Muckle-Wells syndrome. Nuclear factor κB dimers are involved in the development and function of the immune system, with activation affecting a diverse array of immunity- and inflammation-associated genes, including acute-phase reactants, cytokines, chemokines, growth factors and receptors, adhesion molecules, and regulators of apoptosis and cellular proliferation. Nuclear factor κB also plays an essential role in ectoderm development through its association with (and activation through) the EDAR/ectodysplasin A pathway. Nuclear factor κB essential modulator, or NEMO, has been the topic of frequent scientific and clinical interest in recent years. Large-scale deletions of IKBKG, the gene encoding NEMO, result in incontinentia pigmenti, an X-linked dominant genotype. Around 80% of new mutations are caused by deletions in exons 4 to 10, with truncation and loss of protein function. The effects of this mutation lead to death for most affected male fetuses, while female fetuses survive because of the moderating effects of skewed X-inactivation, with selective elimination of cells expressing the mutation.

Hypermorphic mutations in IKBKG, which result in some preservation of NEMO function, are well described as a cause of XL-EDA-ID. The exact incidence of XL-EDA-ID caused by NEMO mutation is unknown, and clinical features vary in severity based on the residual function of the mutated protein. Hypohidrosis, delayed tooth eruption, coarse hair, and immunodeficiency with frequent bacterial infections may be present. Hair may be absent (atrichosis) or minimally present (hypotrichosis), and hypohidrosis may result in heat intolerance or heat stroke. Other dental findings include hypodontia or anodontia with conical incisors and gapped teeth. An autosomal dominant form of EDA-ID has been described, associated with a gain-of-function mutation of IkBe (an inhibitor of the IKK complex), thereby impairing NF-κB activation. This form is distinguished by a severe T-cell immunodeficiency. Immunodeficiency without EDA has also been recognized with IKBKG mutations, suggesting that different mutations in this gene may result in distinct clinical and immunologic phenotypes. While mutations in the coding region of IKBKG are associated with EDA-ID, stop codon mutations cause a more severe syndrome with associated osteopetrosis and lymphedema (OL-EDA-ID). Hence, hypomorphic mutations in this gene cause 2 allelic conditions.

The type of immunodeficiency seen in patients with XL-EDA-ID varies. The most consistent finding is impairment of antibody response to polysaccharides. Other reported defects include defective natural killer cell activity, impairments in CD40-mediated B-cell activation and isotype class switching, impaired response to lipopolysaccharide stimulation, and decreased production of tumor necrosis factor and IL-12. Patients with XL-EDA-ID are predisposed to infections with pyogenic bacteria during early infancy, including Streptococcus pneumoniae, because they are unable to mount a specific antibody response against the polysaccharide antigens. Other common pathogens include Haemophilus influenzae, S aureus, Klebsiella, Salmonella, and Pseudomonas species, as well as mycobacteria (including Mycobacterium avium intracellulare), cytomegalovirus, herpes simplex virus and Pneumocystis carinii. Infections may present as sepsis, pneumonia, otitis media, sinusitis, lymphadenitis, bronchiectasis (secondary to recurrent pyogenic pulmonary infections), skin and soft tissue infections, and infections of the bones and gastrointestinal tract.

The skin abnormalities in patients with XL-EDA-ID (aside from the classic features associated with ED) largely lack mention in the existing literature. Dry, pale, wrinkled, and/or hyperpigmented skin are all noted. In 1 cohort, prominence of superficial veins was present in 3 of 7 affected siblings. A chronic, atopiclike dermatitis with prominent involvement of the neck and intertriginous areas has been described.

Our patient presented with extensive and recalcitrant intertrigo and seborrheic dermatitis, with progression to erythroderma, a cutaneous phenotype reminiscent of that described in patients with other congenital immunodeficiencies such as severe combined immunodeficiency and Omenn syndrome. The possibility of cutaneous GVHD was considered before his immune defect was known, and while the skin biopsy findings were consistent, the demonstrated lack of maternal engraftment did not support this diagnosis. Other potential explanations include a GVHD-like clinical presentation from autoreactive T lymphocytes or a GVHD-like histologic mimic resulting from keratinocyte apoptosis related to the NEMO mutation. Our patient’s facial appearance evolved over time, with a gradually increasing prominence of periorbital wrinkling, inferior periorbital diskiness, flattening of the malar ridges, a thickened lower lip, and frontal bossing, all consistent with the facial features noted in HED/EDA.

The mutation noted in our patient (1167-1168insC) has been described in several patients. A trend noted...
in several of these patients includes decreased serum levels of IgA (noted in our patient) and elevation of IgM levels. Infectious complications varied, but bacterial sepsis was common, and 3 of the reported patients with this mutation developed disseminated mycobacterial (M avium intracellulare) infection. In 1 series of 7 patients with NEMO mutation and ID, the 2 with this mutation were noted to have the most severe clinical courses.\textsuperscript{18} Clarification of genotype-phenotype correlations is desirable and will likely evolve with further observations and reports of patients with XL-EDA-ID.

The optimal therapy and prognosis for patients with XL-EDA-ID are unclear. Ectodermal dysplasia is managed supportive, with the goals of minimizing overheating and preventing long-term preventable sequelae such as impaired speech development and cosmetic disfigurement. Early dental intervention with use of dental prostheses and/or implants is indicated, and referral to the National Foundation for Ectodermal Dysplasias (www.nfed.org) is important for patients and families. Treatment for the immunodeficiency may include immune-based therapies (such as intravenous immunoglobulin) and aggressive management of infections, including prophylaxis against (and/or treatment for) gram-positive and gram-negative bacteria, mycobacteria, cytomegalovirus, herpes simplex virus, and P carinii.\textsuperscript{14,18,19} Hematopoietic stem cell transplantation offers the potential advantage of immune reconstitution but bears the risks of obligatory immunosuppression, including disseminated infection (especially mycobacterial) and organ toxic effects.\textsuperscript{20,24} Following peripheral blood stem cell transplantation, our patient showed improvement in his skin appearance and evidence of initial engraftment from his sister’s donor cells, but eventually the good effect waned. Because of the immunologic dysregulation and infectious risks associated with NEMO mutations, a second stem cell transplantation is planned.

In summary, we describe a patient with XL-EDA-ID due to a hypomorphic mutation in NEMO diagnosed at age 5 months. Subsequent to his diagnosis, the patient’s mother recalled her prior diagnosis of incontinentia pigmenti (with very mild expressivity), and molecular testing revealed her heterozygosity for the same mutation. The NEMO mutation should be considered in male infants presenting with extensive or recalcitrant seborrheic or atopic dermatitis-like skin eruptions and intertrigo, especially when facial features of ED or maternal history of incontinentia pigmenti are present.

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Correspondence: Anthony J. Mancini, MD, Division of Dermatology, Children’s Memorial Hospital, 2300 Children’s Plaza No. 107, Chicago, IL 60614 (amancini@northwestern.edu).

Author Contributions: Dr Mancini had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Mancini. Acquisition of data: Mancini and Lawley. Analysis and interpretation of data: Mancini and Uzel. Drafting of the manuscript: Mancini. Critical revision of the manuscript for important intellectual content: Mancini, Lawley, and Uzel. Administrative, technical, and material support: Mancini. Study supervision: Mancini and Uzel.

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REFERENCES


