Osteopetrosis, Lymphedema, Anhidrotic Ectodermal Dysplasia, and Immunodeficiency in a Boy and Incontinentia Pigmenti in His Mother

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ABSTRACT. A child with X-linked osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia, and immunodeficiency (OL-EDA-ID) was recently reported. We report the clinical features of a second boy with this novel syndrome and his mother, who presented with signs of incontinentia pigmenti (IP). The child had mild osteopetrosis without neurosensory complications, unilateral lymphedema of the left leg, and characteristic features of anhidrotic ectodermal dysplasia with sparse hair, facial dysmorphy, delayed eruption of teeth, and sweat gland abnormalities. He died at 18 months of severe immunodeficiency with multiple infections caused by Gram-negative (*Salmonella enteritidis*) and Gram-positive (*Streptococcus pneumoniae*) bacteria, nontuberculous mycobacteria (*Mycobacterium kansasii*), and fungi (*Pneumocystis carinii*). His 30-year-old mother's medical history, together with residual cutaneous lesions, was highly suggestive of IP without neurologic impairment. In this patient with OL-EDA-ID, we detected the same NF-κB essential modulator stop codon hypomorphic mutation identified in the previous patient. The occurrence of the same clinical features in 2 unrelated patients with the same genotype demonstrates that OL-EDA-ID is a genuine clinical syndrome. The clinical and biological descriptions of the proband and his mother further corroborate the relationship between IP and EDA. Both syndromes are allelic and are associated with mutations in NF-κB essential modulator, with a genotype-phenotype correlation in hemizygous males. In contrast, loss-of-function mutations and hypomorphic mutations may cause IP in females. *Pediatrics* 2002;109(6). URL: http://www.pediatrics.org/cgi/content/full/109/6/e97; *children, osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia, incontinentia pigmenti, immunodeficiency, bone marrow transplantation.*

ABBREVIATIONS. IP, incontinentia pigmenti; NEMO, NF-κB essential modulator; OL-EDA-ID, osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia, and immunodeficiency; SD, standard deviation; Ig, immunoglobulin; IL, interleukin; TNF-α, tumor necrosis factor-α; HSCT, hematopoietic stem cell transplantation.

Recently, X-linked dominant incontinentia pigmenti (IP) was found to be caused by loss-of-function mutations in NF-κB essential modulator (NEMO), which encodes an essential component of the NF-κB signaling pathway.[1] Hemizygous males die in utero,[2] whereas heterozygous females have the symptoms of IP, consisting of a characteristic neonatal rash and hyperpigmentation, in some cases associated with a variety of malformations of eyes, teeth, skeleton, and central nervous system.[3] Most loss-of-function NEMO mutations are large deletions that encompass the coding region.

Remarkably, NEMO mutations were found also in 2 unrelated boys with a hitherto unknown syndrome that consisted of osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia, and immunodeficiency (OL-EDA-ID).[4] Both patients with OL-EDA-ID were hemizygous for the same NEMO stop codon hypomorphic mutation. The clinical features of 1 child with OL-EDA-ID were recently described.[5] We describe herein the clinical features of the second boy with OL-EDA-ID and his mother, who presented with major criteria for the diagnosis of IP.

CASE REPORT

The proband was born at 38 weeks of gestation. The pregnancy was uncomplicated, and a boy was delivered by cesarean section for breech presentation. At birth, he weighed 2920 g (−1 standard deviation [SD]), was 48 cm long (−1 SD), and had a head circumference of 34.5 cm (mean). The child had chronic diarrhea with persistent vomiting from birth. However, he developed normally until 2 months of age, when growth retardation was observed, reaching −3 SD for weight and −1 SD for length at 4 months of age. Despite the administration of a medium-chain triglyceride diet and continued gastric nutrition, he failed to thrive, and total

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parenteral nutrition was initiated at 9 months of age. At 15 months of age, improvements were recorded in growth for weight (−1 SD) and length (mean). Duodenogastroscopy and rectosigmoidoscopy with biopsies performed at 2 months and 5 months of age were normal. No infectious agents were found in the stools and in biopsy samples.

At 1 month of age, the patient was hospitalized for noninflammatory asymmetric lymphedema of the left leg, resulting from deficient lymphatic drainage, as shown by lymphoid scintigraphy after the injection of 18 MBq rhenium sulfide (labeled with technetium) at 0, 30, 60, and 90 minutes. Arterial pulses were present, and there were no visible venous abnormalities. The lymphedema extended to the genitals at 6 months of age. Skin biopsy showed no lymphangiectasis. There were no clinical signs of intestinal or pleural lymphangiectasis. The lymphedema responded transiently to lymphatic "drainage."

The first skeletal radiographs taken at 2 months of age showed a dense cortex and a narrow but visible medulla with diffuse osteosclerosis, particularly of the cranial vault. The vertebrae had end-plate thickening, and iliac wings showed a "bone-within-bone" appearance (Fig 1). Clear metaphyseal bands were observed for long-bone extremities (Fig 2). Bone biopsy (Fig 3) confirmed the diagnosis of mild osteopetrosis, with the large, dense, and irregular bone trabeculae typical of osteopetrosis. All of these enlarged trabeculae had a central core of cartilage. Osteoclasts were present in normal numbers and were morphologically normal on conventional microscopy. Electron microscopy to examine the ruffled borders of osteoclasts was not performed. Moderate hypocalcemia (2.09 mmol/L) was observed. Clinical examination revealed splenomegaly without hepatomegaly, and the leukocyte count was high (17 200/mm^3) with 7200 polymorphonuclear neutrophils/mm^3, 1100 monocytes/mm^3, 55 myelocytes/mm^3, 5500 lymphocytes/mm^3, and hyporegenerative anemia (Hb 8 g/dL; reticulocytes: 100×10^9/L). Bone marrow aspirate revealed progenitors from all lineages with no abnormal cells visible. Medullary karyotype was normal (20 cell mitoses analyzed). Neurologic and neurosensory (ophthalmologic examination, electroretinogram) investigations were normal. Overall, clinical, biological, and radiologic investigations confirmed the diagnosis of type 2 osteopetrosis, a more benign form than lethal type 1 osteopetrosis.

Distinctive mild facial dysmorphy was observed with relative frontal bossing; saddle nose; and fine, lightly pigmented, sparse hair. Eyebrows were absent, but eyelashes were normal. These facial features were not specific, but their association with a dry, nonsweating skin and a lack of teeth at 1 year of age suggested a diagnosis of EDA. Mandibular radiograph confirmed hypodontia. The skin biopsy showed normal epidermis and dermis, and no eccrine sweat glands were observed in the samples.

Primary immunodeficiency was diagnosed after multiple infections (Table 1). *Pneumocystis carinii* pneumonitis was diagnosed by bronchoalveolar lavage after respiratory distress with a diffuse chest infiltrate that required oxygen treatment and responded well to intravenous sulfamethoxazole-trimethoprim. Disseminated *Mycobacterium kansasii* infection was diagnosed on papular and erythematous skin eruption with lung involvement (positive gastric aspiration with normal chest radiograph) and bone involvement with metatarsal fracture at 14 months of age. The mycobacterial infection responded partially to a combined regimen of antibiotics and γ interferon. At 16 months of age, the patient developed a self-healing adenoviral infection (conjunctivitis and rhinitis).

During infectious episodes, the patient had a poor inflammatory response, with absent or delayed fever and increases in blood concentrations of markers of inflammation. For example, during *Streptococcus pneumoniae* meningitis, his body temperature was normal on day 1 after diagnosis and moderately high on days 2 to 4 (38.5–39°C); the C-reactive protein level was normal on day 1 (16 mg/L) and increased only 4 days after diagnosis (135 mg/L). The child's immune status was assessed (Table 2). The number and morphology of blood monocytes and polymorphonuclear cells were normal. T- and B-cell counts and proliferative responses to protein antigens were normal. Serum immunoglobulin (Ig) levels were normal for age except for IgG levels, which were normal to low. Titers of antibodies directed against polysaccharide antigens, such as blood isohemagglutinin A (titers 1:4), and serum antibodies against *S pneumoniae* were low (0.4 μg/mL), despite proven infection, at 1 year of age. The response of immune cells to lipopolysaccharide, interleukin (IL)-1β, IL-18, tumor necrosis factor-α (TNF-α), and CD154 was poor, as reported elsewhere.[4] No clinical or biological signs of autoimmunity were found (Coombs' test, antigliadin and antiendomysial antibodies, antinuclear antibodies, anti-liver-kidney-muscle antibodies, and anti–smooth muscle antibodies). There were no clinical or biological signs of allergy.

Finally, as a result of the severity and recurrence of infectious diseases, the patient underwent matched unrelated donor stem cell transplantation at 17 months of age, after a conditioning regimen consisting of Thymoglobulin (5 mg/kg), busulfan (20 mg/kg), and cyclophosphamide (200 mg/kg). The first injection of Thymoglobulin resulted in massive cardiovascular toxicity with collapsus, generalized seizures, and necrosis of the skin of the extremities (feet and hands). The outcome was favorable after 5

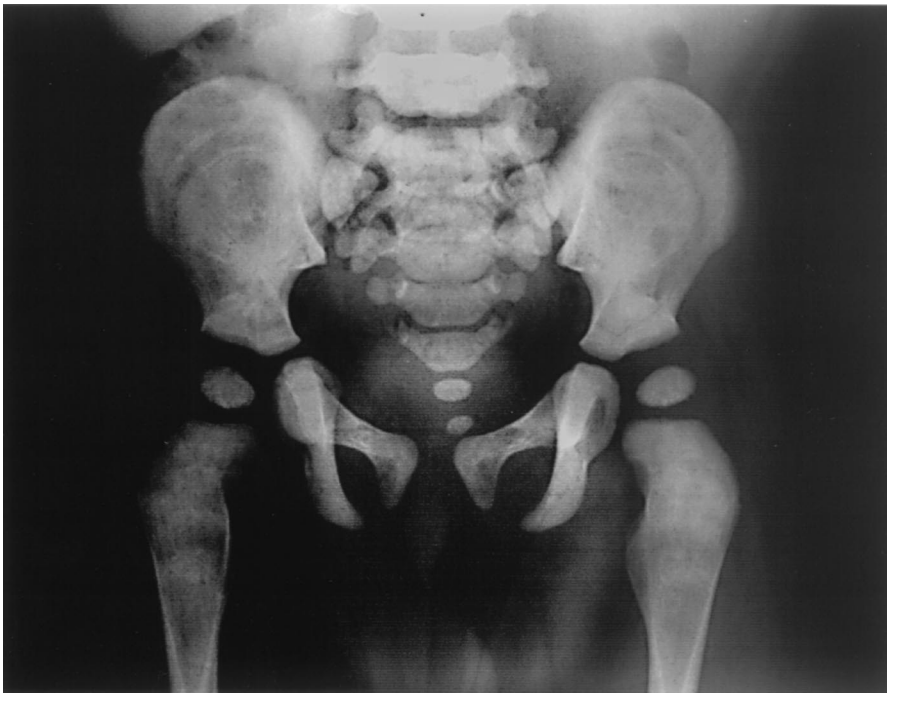

Fig 1. Skeletal radiograph of iliac wings demonstrating a "bone-within-bone" appearance.

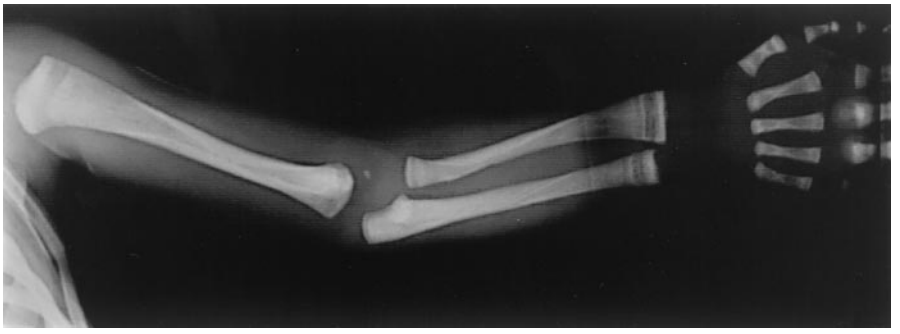

Fig 2. Skeletal radiograph of long bones.

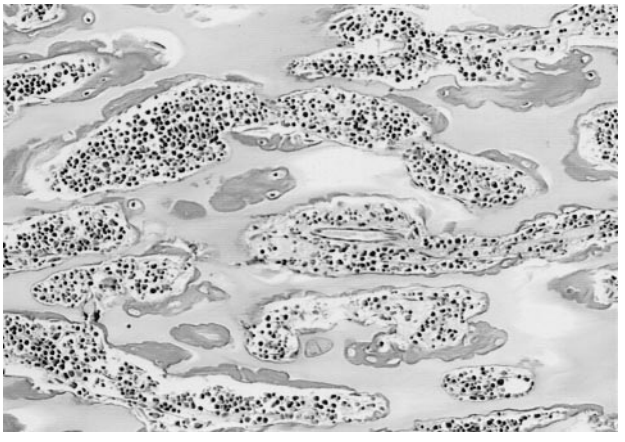

Fig 3. Iliac bone marrow biopsy. Microscopy of bone biopsy samples revealed large, dense, irregular bone trabeculae typical of osteopetrosis. All of these enlarged trabeculae had a central core of cartilage (hematein-eosin, ×100).

days of intensive care requiring mechanical ventilation and inotropic drugs. Unfortunately, the patient experienced severe hepatic toxicity from the conditioning regimen 6 days after hematopoietic stem cell transplantation (HSCT) and died from liver failure 11 days after transplantation. This hepatic toxicity was thought to correspond to veno-occlusive disease of the liver because of the association of painful hepatomegaly that appeared 4 days after transplantation, fluid retention with edema, ascites, sudden weight gain, and hyperbilirubinemia (54 μmol/L). Severe hepatic cytolysis was observed at the time of diagnosis with high serum aspartate aminotransferase levels (1874 IU/L and 5260 IU/L 8 and 9 days after HSCT).

The first-degree relatives of the proband underwent systematic physical examination. The proband's mother, a 30-year-old woman, presented pale, atrophic, hairless, linear lesions on the back of the lower legs, a localized reticular hyperpigmentation pattern of the groin, hypohidrosis, and delayed dentition with normal teeth. She had developed chronic vesicular eruption at the extremities during the first months of life, and her intelligence was normal. All of these features were highly suggestive of IP without neurologic impairment.

DISCUSSION

We provide here a comprehensive clinical description of a second child with OL-EDA-ID syndrome and his mother with IP. The occurrence of the same clinical features in 2 unrelated patients with the same genotype demonstrates that OL-EDA-ID is a genuine clinical syndrome (Table 3). The clinical and biological descriptions of the proband and his mother clearly demonstrate the relationship between IP and EDA. Both syndromes are allelic and are associated with mutations in NEMO, with a genotype-phenotype correlation in hemizygous males. In contrast, loss-of-function mutations and hypomorphic mutations may cause IP in females.[4,5]

The child's mother fulfills the classic criteria for IP diagnosis in adults. In affected females, it causes highly variable abnormalities of skin, hair, nails, teeth, eyes, and central nervous system. The cutaneous manifestations are diagnostic and classically occur in 4 regressive stages: vesicular and verrucous stages, which occur during the neonatal period and resolve spontaneously; the hyperpigmented stage, which disappears by the age of 20 years, although pigmented lesions may remain and become a permanent feature; and the atrophic stage. However, residual localized hyperpigmentation, often in the groin, and pale, hairless, linear lesions most clearly visible on the lower legs, as in this case, may be the only lesions observed in adult females and require great care in detection. Their association with a vesicular eruption on the extremities, during the first months of life, as in the case of the proband's mother, make possible the firm diagnosis of IP. The proband's mother also presented with mild hypohidrosis and delayed dentition, common features of ectodermal disorders. A linear arrangement of sweating and nonsweating skin similar to that described in X-linked hypohidrotic ectodermal dysplasia has been observed in cases of IP.[6] Therefore, a diagnosis of classical but mild IP without neurologic involvement was unambiguously confirmed for the mother of our proband. IP was also diagnosed in the mother of the other patient[5] on the basis of skin abnormalities with hyperpigmentation in the right inguinal region and the right side of the trunk. Dentition abnormalities were more severe in the other case, with incomplete dentition. In our case, dentition was delayed but not incomplete.

Our proband did not develop clinical manifestations of IP, as he survived the postnatal period and did not develop characteristic skin lesions, but instead developed features of mild EDA with severe immunodeficiency, osteopetrosis, and lymphedema. The clinical features of EDA in the proband were not obvious. However, the distinctive facial dysmorphy of the child with frontal bossing, saddle nose, and fine, lightly pigmented, and sparse hair associated with a dry and nonsweating skin without sweat glands on cutaneous biopsy indicated a diagnosis of EDA, with none of the criteria for IP diagnosis. In the other case described,[5] facial dysmorphy was absent, but skin manifestations were more severe with hemangiomata at birth, hyperpigmentation of the

TABLE 1. Infections Experienced by the Proband

	1 Month	2 Months	3 Months	5 Months	5.5 Months	12 Months	13 Months	14 Months	15 Months
Blood cultures	*Escherichia coli*			*Streptococcus mitis* and *S vestibularis*	*S pneumoniae*	*S pneumoniae*			
Urine									
Lung aspiration		*E coli*	*Pneumocystis carinii*		*E coli*			*E coli*	*Candida albicans*
CSF						*S pneumoniae*			
Bone									*M kansasii*
Skin							*Mycobacterium kansasii*		
Otitis						*S pneumoniae* and *Haemophilus influenzae*			
Gastric aspiration							*M kansasii*		

CSF indicates cerebrospinal fluid.

skin, and eczema. Neither patient had mental retardation, but this is not an invariable feature of EDA. As shown elsewhere,[4] residual signaling probably accounted for the clinical features being milder than those of patients with EDA without ID. The same mutation (X420W) therefore caused IP in females and EDA in males from 2 unrelated kindred.

Osteopetrosis is clinically and genetically heterogeneous.[7] In this case, osteopetrosis was mild with extramedullary hematopoiesis but residual medullary cavities, not different from the type 2 osteopetrosis described elsewhere.[8] The other patient described seemed to have a more severe skeletal disease without residual medullary cavities.[5] One patient previously reported with EDA-ID[9] had extramedullary hematopoiesis of the dura, perhaps attributable to an even milder form of osteopetrosis, but there were no clinical, radiologic, or biological signs of osteopetrosis at autopsy (E. Reimund, personal communication). Two other recently described patients[10] had high bone density consistent with osteopetrosis, but the clinical, hematologic, and radiologic features were not reported. Therefore, only the 2 patients with the X420W NEMO mutation can unambiguously be described as having osteopetrosis in the context of OL-EDA-ID. The pathogenesis of osteopetrosis in this syndrome is not entirely clear, but NF-κB is essential in osteoclast development.[4]

Congenital lymphedema is a chronic swelling of 1 or more limbs, frequently affecting the legs, as a result of lymphatic vessel dysfunction. This disorder, also called Milroy disease, generally shows an autosomal dominant pattern of inheritance with reduced penetrance, variable expression, and variable age of onset. In our proband and in the other case described,[5] lymphedema developed very early, when the child was only a few weeks old, but in the case reported here, it was unilateral. As reported elsewhere, the pathogenesis of lymphedema in this patient may be related to impaired vascular endothelial growth factor-3 signaling.[4]

ID was first suspected on the basis of the multiple clinical infectious diseases presented by the patient. Children with EDA usually have hyperpyrexia as a result of aplasia of the sweat glands necessary for normal thermostasis.[11] In this case, fever was absent or delayed in the course of several infections, suggesting an impaired response to proinflammatory cytokines and/or microbial products, which may be a distinctive feature of OL-EDA-ID. The patient had multiple infections attributable to bacteria (Gram-negative bacilli, Gram-positive cocci, and nontuberculous mycobacteria) and fungi (*P carinii*). Conjunctivitis attributable to adenovirus infection had a benign clinical course, and no other viral diseases were documented, suggesting that viral immunity was not significantly affected. ID has been described in association with EDA but is classically associated with high fever, sinusitis, and otitis.[10,12,13] Recurrent infections were observed in the other case described[5] except for viral infections like our patient. On the contrary, the other patient did not develop fungal infections. The stop codon X420 NEMO mutation affects multiple signaling pathways.[4] An impaired

TABLE 2. Immunologic Status

	Age (Months)								
	2	3	4	5	6	8.5	11.5	13.5	14
Serum Ig levels (g/L)									
IgG before IVIG	2.11	1.37		0.91	0.69	6.9	2.75		
IgA	<0.07	<0.07		<0.07	<0.07	<0.07	0.1	0.46	
IgM	0.32	0.7		0.3	0.38	0.34	0.4	0.6	
Allohemagglutinins								(1/4)	
Serology									
Tetanus toxoid serology (IU/mL)			0.12					1.66	
Poliovirus serology type 1/type 2/type 3			160/40/40					160/320/40	
Mycobacterial antigen								Negative	
S pneumoniae serology								0.4 μg/mL	
Lymphocyte phenotype									
Absolute lymphocyte count (/mm^3)	9600	5500	6000	7300				10 000	5400
CD3(%)	72	83		63				70	76
CD4(%)	61	65		40				54	52
CD8(%)	9	13		15				16	13
CD16+CD56+(%)		0.4						3	
CD19(%)	17	15	26	32				26	
CD45 RO/CD4(%)				17					19
CD45 RO/CD8(%)				13					28
CD45 RA/CD4(%)				76					81
CD45 RA/CD8(%)				87					72
Lymphocyte proliferative function (10^3 cpm)									
PHA		96	43	171				268	
OKT3 50 ng/ml		206							
Candidin			9	9.5					
Tetanus toxoid			26	42					
Poliovirus			43						
Tuberculin				16					

IVIG indicates intravenous immunoglobulin; PHA, phytohemagglutinin.

cellular response to proinflammatory cytokines such as TNF, IL-1, IL-18, and bacterial products (lipopolysaccharide and other ligands of Toll receptor), may contribute to the development of infectious diseases. Patients previously described had low serum IgG levels with variable IgM and IgA levels and did not produce antibodies specific for polysaccharide antigens.[10,12–15] In this case, the T- and B-cell responses to antigens seemed to be normal, except that serum IgG levels were low (Table 1). The "normal" immunologic workup in these patients is indeed potentially misleading, particularly in children with EDA-ID before infections occur and before antibody response to polysaccharides can be tested (18–24 months of age). *P carinii* infections are thought to occur in CD40L-deficient (X-HIGM) and NEMO-deficient patients (EDA-ID) owing to impaired CD40-mediated activation of lung macrophages, either after impaired ligation by T-cell–expressed CD40L (X-HIGM) or impaired NEMO-dependent NF-kB activation within macrophages (EDA-ID).

Malabsorption and growth retardation as a result of chronic diarrhea were observed both in our patient and in the other case described.[5] The underlying mechanism is unclear, but both children failed to thrive and required total parenteral nutrition. In this case, no intestinal obstruction was observed, biopsies were normal, and gastrointestinal infections were not documented. In contrast, the other patient had more severe intestinal disease with obstruction, and histologic findings were suggestive of multiple vascular abnormalities of the small intestine. Infectious diseases probably contributed to malabsorption.

CONCLUSION

We described a second patient with the related and, until now, unrecognized syndrome of EDA-ID with osteopetrosis and lymphedema (OL-EDA-ID) caused by stop codon X420W NEMO mutation.[5] In addition, we provided an extensive description of his carrier mother. As previously described, OL-EDA-ID syndrome and IP are allelic.[4] Moreover, there is a genotype-phenotype correlation in males, with large-deletion loss-of-function NEMO mutations leading to a cellular phenotype of abolished NF-κB signaling and clinical IP phenotype, and stop codon X420W hypomorphic mutations leading to impaired but not abolished NF-κB signaling with the OL-EDA-ID phenotype. The same X420W NEMO mutation results in 2 different phenotypes in males and females: OL-EDA-ID syndrome in hemizygous males and IP in heterozygous females. The co-segregation of the NEMO X420W mutation with disease was previously reported.[4] The affected mother was the only female heterozygous for this mutation, and her affected son was the only hemizygous male for the mutation.

The value of HSCT in the treatment of patients with this life-threatening syndrome is unclear. Indeed, our patient experienced shock after Thymoglobulin treatment and died from severe hepatic toxicity shortly after the conditioning regimen. NF-κB is known to protect against TNF-induced apoptosis in several tissues.[16] We cannot exclude the possibility that the massive cardiovascular toxicity observed after Thymoglobulin injection and the lethal hepatic toxicity observed after the conditioning regimen

TABLE 3. Comparison of the Clinical Features of 2 Kindreds With OL-EDA-ID and X420W NEMO Mutation

	This Case	Case Reported by Mansour et al[5]
Mother		
Skin manifestations of IP	+	+
Incomplete dentition	− (Delayed dentition)	+
Neurologic impairment	−	−
	This case	Case reported by Mansour et al[5]
Child		
Birth weight	2920 g at 38 wk (50 percentile)	2600 g at 40 wk (2nd percentile)
Osteopetrosis	Residual medullary cavities, OP type II	Uniformly dense, sclerotic bones
Lymphedema	Unilateral	Bilateral
EDA		
Skin manifestations	Moderate, dry skin	Severe with eczema, multiple telangiectasis; generalized patchy, reticular, hyperpigmentation
Teeth	No teeth at 14 mo	No teeth at 15 mo
Infections	Severe	Severe
Gram-negative bacilli	+ *S enteritidis*	−
Gram-positive cocci	+ *S pneumoniae*	+ *S aureus*
Mycobacteria	+ *M kansasii*	+ *Mycobacterium spp*
Viruses	−	−
Fungi	+ *P carinii*	−
Gastrointestinal		
Malabsorption	+	+
Parenteral nutrition	+	+
Intestinal obstruction	−	+
Splenomegaly	+	+
Outcome	Died from toxicity after HSCT at 17 mo	Died at 31 mo from severe malabsorption and mycobacterial infection

Plus sign indicates present; minus sign indicates absent.

were favored by impaired NF-κB activation. An alternative conditioning regimen should be tried until gene therapy trials become possible.

Our next step will be to study patients with an incomplete form of this syndrome, associating ectodermal anhidrotic dysplasia and immunodeficiency (designated EDA-ID) but without lymphedema and osteopetrosis. This syndrome was recently described in patients from 11 families who carry mutations in the coding region of NEMO.[4,10,13–15] These patients differ clinically, and it would be of value to define clinical and biological differences of patients with EDA-ID in more detail.

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