
Characteristics of mycobacterial infection in patients with immunodeficiency and nuclear factor- κ B essential modulator mutation, with or without ectodermal dysplasia

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Hypomorphic mutations of the nuclear factor κ B essential modulator gene cause ectodermal dysplasia and immunodeficiency. Affected patients have increased susceptibility to mycobacterial disease including cutaneous manifestations. We describe clinical and histopathologic characteristics of 5 patients with nuclear factor κ B essential modulator gene mutations and mycobacterial infections, two of whom had mycobacterial cutaneous infections. (J Am Acad Dermatol 2004;51:718-22.)

Ectodermal dysplasia (ED) can result from an impaired ability to activate the transcription factor nuclear factor (NF)- κ B after an interaction between ectodysplasin A (EDA) and the EDA receptor (EDAR).^{1,2} This can occur as a result of specific mutations in the genes coding for EDA, EDAR, or an EDAR-associated death domain adaptor protein.³⁻⁶ Genetic aberrations that cause ED by disrupting the pathway to activation of NF- κ B more distally include point mutations of the genes encoding the NF- κ B essential modulator (NEMO) protein (which only partially impair the protein function, ie, hypomorphic mutations)⁷⁻¹¹ and the inhibitor of NF- κ B protein (which induces persistent protein function, ie, hypermorphic mutations) (Fig 1).¹² Larger frameshift or deletion mutations that completely impair NEMO function (ie, amorphic mutations) result in incontinentia pigmenti in women and are prenatally fatal to male fetuses.¹³ The NEMO protein is a scaffold for assembly of the

Abbreviations used:

ED:	ectodermal dysplasia
EDA:	ectodysplasin A
EDAR:	EDA receptor
MAI:	<i>Mycobacterium avium-intracellulare</i>
NEMO:	NF- κ B essential modulator
NEMO-ID:	NEMO mutation and immunodeficiency
NF- κ B:	Nuclear factor κ B

inhibitor of NF- κ B kinase, which affects the degradation of inhibitor of NF- κ B allowing cytosolic NF- κ B to travel into the nucleus to induce gene transcription. NEMO mutations impair the function of the ectodysplasin system and result in ED. NEMO mutations also cause combined immunodeficiency, as activation of NF- κ B is required for the function of receptors critical to the immune system.

The immunodeficiency in patients with ED and a hypomorphic NEMO mutation is characterized by hypogammaglobulinemia, defective specific antibody production, and impaired innate immunity.^{7-10,14} The latter probably results in the hallmark susceptibility to mycobacterial infections in patients with a hypomorphic NEMO mutation and immunodeficiency (NEMO-ID). Several boys with NEMO-ID have been reported to have atypical mycobacterial infections including disseminated *Mycobacterium avium-intracellulare* (MAI)^{7,10} and *M kansasii*,¹⁴ and of the patients with NEMO-ID reported, 51% have a history of atypical mycobacterial disease. The specific characteristics of these mycobacterial diseases in a group of patients with NEMO-ID, however, have not been evaluated. It is also unclear if the

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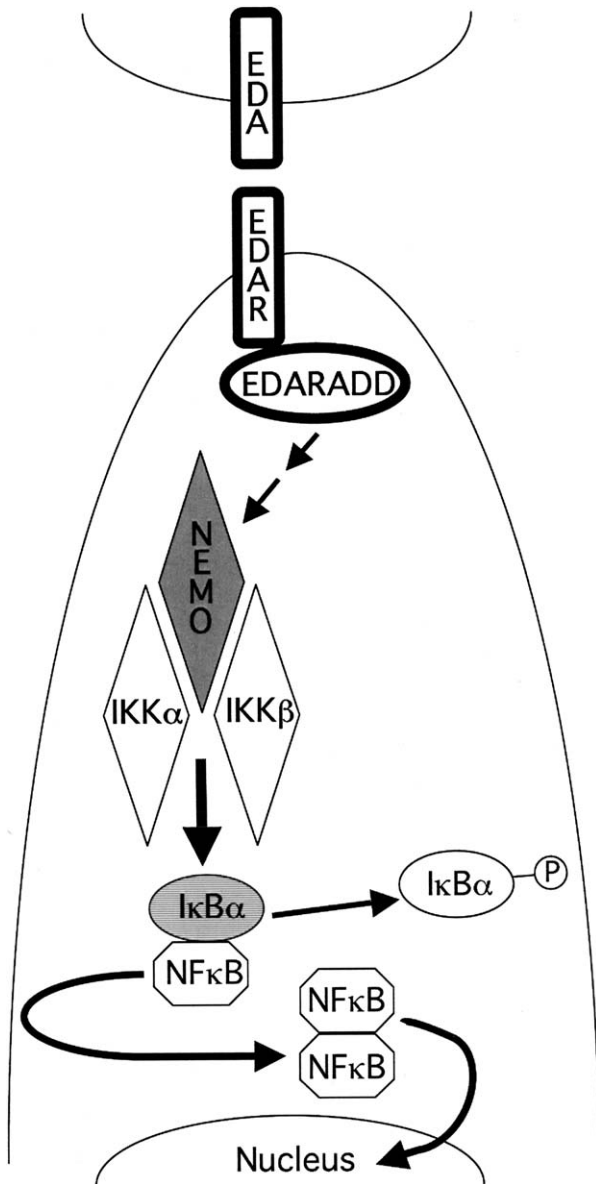


Fig 1. Distinct gene mutations affecting proteins involved in the NF- κ B activation pathway can cause ED. These include the *ED1* gene encoding the tumor necrosis factor (TNF) superfamily member ectodysplasin A (EDA), the EDA receptor gene (*EDAR*) encoding the TNF superfamily receptor EDAR, the EDAR-associated death domain gene (*EDARADD*) encoding the EDAR associated death domain, the *IKBA* gene encoding the inhibitor of NF- κ B alpha ($I\kappa B\alpha$), or the *IKKBG* gene encoding the NF- κ B modulator (NEMO) protein. The *ED1*, *EDAR* and *EDARADD* mutations are amorphic (*proteins outlined in bold*), whereas the *IKBA* mutation is hypermorphic (*protein striped*) and the *IKKBG* mutation is hypomorphic (*protein shaded*). All mutant proteins share the same disruptive effect on appropriate signals that would be normally induced by EDA. *ED1* and *IKKBG* are on the X chromosome and cause disease with an X-linked recessive pattern of inheritance. *EDAR* and *EDARADD* are on chromosomes 2 and 1, respectively and are inherited in an autosomal

abnormal ectoderm in concert with the immunodeficiency in these individuals results in a preponderance of cutaneous manifestations. To address these issues we report the manifestations of mycobacterial infection in 5 patients with NEMO-ID.

MATERIALS AND METHODS

A total of 5 boys with mycobacterial infections evaluated at Children's Hospital, Boston, Mass, between 1984 and 2002 were ultimately given the diagnosis of NEMO-ID. This represents 71% of the patients given the diagnosis of NEMO-ID at our institution. NEMO gene sequence analysis was pursued as a result of the combination of ED and mycobacterial infection (patients No. 1-3) or mycobacterial infection with combined immunodeficiency (patient No. 4). The immunologic characteristics and details related to NEMO mutations in these boys have been previously reported or submitted for publication.^{9,10,15} Manifestations and history of their mycobacterial diseases were obtained from retrospective chart review and re-evaluation of pathologic specimens. Studies were performed with the approval of the committee for clinical investigation.

RESULTS

All patients had a mutation predicted to affect the C-terminus of NEMO (Table I).^{9,10,15} All boys had obvious ED as characterized by the presence of oligodontia or conical teeth, frontal bossing, fine sparse hair, and absent perspiration,^{9,10,15} except patient 4. Mycobacterial infections occurred at a median age of 7 years (range: 14 months-14 years) and were culture proven in all cases (Table I). Patients 1a, 1b, and 2 had disseminated disease. Patients 1a and 1b presented with recurrent fevers and had MAI isolated from their blood, and had granulomas and acid-fast bacilli in lymph nodes and liver (Fig 2, A to C). Patient 2 presented with skin lesions that demonstrated noncaseating granulomas (Fig 2, D and E) and yielded MAI on culture. Ten months later, he developed recurrent fever and MAI was cultured

recessive pattern. *IKBA* is on chromosome 14, but because of its hypermorphic nature is inherited in an autosomal dominant manner. As the *IKBA* and *IKKBG* mutations impair the function of receptor-ligand systems other than EDA/EDAR, including several with great importance to the immune system, they can result in immunodeficiency in addition to ED. Normally appropriate receptor-ligand interactions recruit the intact IKK complex, which includes the NEMO. Once assembled, the IKK can phosphorylate $I\kappa B$ allowing NF- κ B to dimerize and translocate into the nucleus to induce appropriate gene transcription.

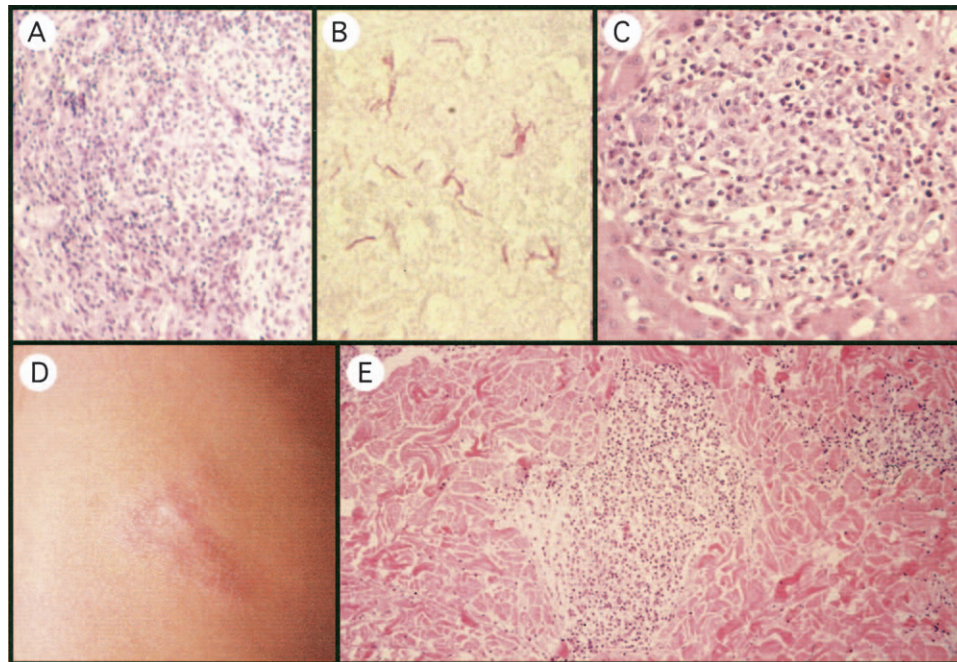


Fig 2. **A**, Granuloma within lymph node, patient No. 1b. **B**, Multiple bacilli within lymph node, patient 1b. (Acid-fast stain; original magnification: $\times 100$.) **C**, Well-defined noncaseating granuloma in hepatic parenchyma, patient 1b. **D**, Annular scaly infiltrated plaque on right side of back of patient 2. **E**, Ill-defined, noncaseating granulomas in dermis, patient 2. (**A**, **C**, and **E**, Hematoxylin-eosin stain; original magnifications: **A** and **C**, $\times 20$; **E**, $\times 10$.)

Table I. Genetic, clinical, and histopathologic characteristics of patients with nuclear factor- κ B essential modulator mutation and immunodeficiency and mycobacterial infection

Patient No.	1a	1b	2	3	4
Predicted NEMO mutation	394X	394X	Q403X	C417R	Exon 9 deletion
Ectodermal dysplasia	+	+	+	+	–
Age at mycobacterial infection	14 mo	22 mo	7 y	14 y	11 y
Mycobacterial infection	Disseminated	Disseminated	Cutaneous (initially) disseminated (9 mo later)	Osteomyelitis	Cutaneous
Culture site	Blood	Blood	Blood/skin	Bone	Skin
Culture result	MAI	MAI	MAI	<i>M abscessus</i>	<i>M bovis</i>
Cutaneous lesions	–	–	+	–	+
Cutaneous histopathology	NA	NA	Ill-defined, noncaseating granulomas	NA	Well-defined, noncaseating granulomas
Cutaneous acid fast bacilli stain	NA	NA	Positive	NA	Positive
Other end-organ disease	Colitis hepatitis	Colitis hepatitis	None	None	None
Treatment					
Multiple antibiotics	+	+	+	+	+
Duration of therapy	4 mo	11 mo	12 y	3 y	2 y
Intravenous immunoglobulin	+	+	+	+	+
Gamma-interferon	+	+	+	–	–
Outcome	Died at 21 mo	Died at 33 mo	Improved on therapy	Improved on therapy	Cleared after 2 y

MAI, *Mycobacterium avium-intracellulare*; NA, not applicable; NEMO, nuclear factor- κ B essential modulator.

from his blood and bone marrow. Patient 3 presented with back pain, which was attributed to vertebral osteomyelitis caused by infection with *M abscessus*. Patient 4 had a several-year history of skin lesions that were not associated with fever or other signs of systemic disease. Skin culture grew *M bovis*; he had previously received BCG immunization.

All patients received a multiple-drug regimen to treat their mycobacterial diseases, which included interferon gamma in those with dissemination (Table D). Patients 1a and 1b died from complications of their mycobacterial infections. Patients 2 and 3 have required continuous antimycobacterial medications and have not had major disease exacerbation while receiving multiple drugs directed at the sensitivities of the cultured organisms. Patient 2 is not still receiving interferon gamma because of presumed lack of clinical response to this drug. Only patient 4 has successfully stopped antimycobacterial therapy. He has been off of antibiotics and free of disease for 2 years.

DISCUSSION

The spectrum of mycobacterial disease for patients with NEMO-ID was variable but often severe. MAI was the most common species found in this series and caused disease similar to that found in patients with other immunodeficiencies.¹⁶ Interestingly, one boy presented with cutaneous MAI (patient 2) that disseminated more than 9 months later, which is more unusual in individuals with immunodeficiency as skin lesions are typically found in the context of dissemination.¹⁷ The lack of skin lesions in the other two boys with MAI suggests it was not caused by his dysplastic ectoderm.^{7,8}

Importantly, patient 4 had isolated cutaneous disease and grossly normal ectoderm. This limited presentation may have been a feature of his particular NEMO mutation (he was the only patient with an aberrant exon 9). Further immunologic and molecular studies to address this are in progress. In addition, although patient 3 had infection with *M abscessus*, which can cause skin disease in patients who are immunodeficient,¹⁸ his findings were limited to his vertebra. Taken together, the patterns of mycobacterial disease in patients with NEMO-ID suggest that cutaneous infection is probably less related to the dysplastic ectoderm and more reflective of the previously reported specific immune deficits, many of which are critical in antimycobacterial defense.⁷⁻⁹

This series demonstrates that patients with NEMO-ID are susceptible to a variety of mycobacterial diseases irrespective of ED. Patients with ED and signs of mycobacterial disease, and boys with com-

bined immunodeficiency and atypical mycobacterial infection, should be evaluated for NEMO-ID. Our data also strengthen previous recommendations to avoid BCG vaccination for patients with NEMO-ID.¹⁹ We would extend these recommendations to include male patients with ED until the genetic origin is proven to be unassociated with immunodeficiency.

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CORRECTION

Sansbury JC, Cocuroccia B, Jorizzo JL, Gubinelli E, Gisondi P, Girolomoni G. Treatment of recalcitrant scleromyxedema with thalidomide in 3 patients. *J Am Acad Dermatol* 2004;51:126-31 (July).

Fig 2, part D, showing the histologic characteristics of a papular lesion in a patient with scleromyxedema, was incorrect. The correct part D is shown below. We apologize for this error.

