

A 2-year-old girl with a recurrent vesicular rash

Mary K. Paul, M.D., and Christopher Chang, M.D., Ph.D.

ABSTRACT

Rashes related to viral infection are a relatively common occurrence in pediatrics. We present the unusual case of a 2-year-old girl referred for evaluation of recurrent rashes thought to be caused by Varicella zoster. She had no systemic symptoms of Varicella infection and otherwise had a benign immune history. The rashes were responsive to treatment with acyclovir. However, she did not have detectable IgG antibody to Varicella zoster. Relevant immunology labs were sent, which led to the diagnosis. The patient was started on prophylactic acyclovir and has since been doing well with only one minor recurrence of the rash. This case illustrates the importance of a detailed immune assessment in the evaluation of unusually severe, recurrent, or atypical pediatric exanthems.

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CASE PRESENTATION

Chief Complaint

Recurrent rash.

History of Present Illness

A 2-year-old girl presented to the emergency room at the age of 9 months for a rash on her left shoulder, upper back, and chest. She was diagnosed with shingles. However, her pediatrician attributed the rash to a primary *Varicella zoster* virus (VZV) infection because she had not been previously vaccinated. The rash was described as macular and vesicular in various stages of healing. No treatment was given and the rash resolved after 3 weeks. At 15 months of age she developed another rash in the same area, which again resolved spontaneously. Three months later, she developed another erythematous vesicular rash near the left axilla, was diagnosed with *V. zoster* and treated with acyclovir. The rash recurred at 22 and 23 months of age and she was again treated with acyclovir. No family members had a similar rash; however, her mother had a history of cold sores. Her infection history is otherwise notable only for recurrent otitis media. There is no family history of immunodeficiency. *Varicella* IgG lev-

els and a viral culture from an unroofed vesicle were obtained.

Physical Examination

Vital signs were normal. Her conjunctivae were clear. She had congested nares with clear rhinorrhea bilaterally and pale, enlarged turbinates. She had normal tonsils and cervical lymph nodes. Lungs were clear and cardiac exam was normal. Skin exam showed a cluster of small (<5 mm) hypopigmented macules near her left axilla, otherwise, no lesions were seen.

Diagnostic Studies

V. zoster IgG was 0.3 (<0.9 was considered negative). IgG was 865 mg/dL, IgA was <31 mg/dL, and IgM was 145 mg/dL.

QUESTION

What is the differential diagnosis?

- Functional natural killer (NK) cell deficiency
- Classic NK cell deficiency
- Molluscum contagiosum
- Nonspecific viral exanthem

Additional Studies

What additional diagnostic studies would be helpful in establishing the diagnosis?

Laboratory studies to consider: mitogen stimulation, flow cytometry, Toll-like receptor function, vaccine titers, and NK cell function.

Clinical Course

Flow cytometry revealed low NK cell numbers (49 cells/ μ L; normal, 130–720 cells/ μ L) and NK cell

From the Division of Allergy and Immunology, Thomas Jefferson University, A.I. duPont Hospital for Children, Wilmington, Delaware

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Address correspondence to Christopher Chang, M.D., Ph.D., Division of Allergy and Immunology, Thomas Jefferson University, A.I. duPont Hospital for Children, 1600 Rockland Road, Wilmington, DE 19803

E-mail address: cchang@nemours.org

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Table 1 Flow cytometry shows reduced numbers and percentage of CD16⁺56 cells on initial evaluation

Flow Cytometry	9/13	10/13*
CD45	2770	4245
CD3%	61%	43%
CD3	1698	1687
CD19%	35%	52% H
CD19	982	2115
CD16 ⁺ 56%	2% L (4%)	4%
CD16 ⁺ 56	49 L (130)	168
CD4%	43%	25% (28%)
CD4	1177	964
CD8%	15%	16%
CD8	416 L (490)	595
H/S	2.8	1.62

*Repeat testing performed 1 mo later showed improved cell numbers.

H = high; L = low; H/S = helper/suppressor ratio.

cytotoxicity assay showed decreased to absent NK cell function (Tables 1 and 2). Our patient was started on long-term prophylaxis with acyclovir for prevention of severe infection. Viral culture from an earlier lesion was positive for enterovirus. Her pneumococcal antibody response was suboptimal. T- and B-cell mitogen stimulation, Toll-like receptor functional assay, and tetanus and diphtheria titers were normal. At 1 month follow-up, she was doing well except for a vesicular rash on her feet that resolved within 1 week. She received Pneumovax (Merck, Summit, NJ) and had a good response. Repeat flow cytometry revealed normal NK cell numbers (168 cells/ μ L; normal, 130–720 cells/ μ L), but NK cytotoxicity assay again showed decreased NK cell function (Tables 1 and 2). *Herpes simplex* virus (HSV) 1 IgG was positive (IgM was not), but titers for cytomegalovirus (CMV) and Epstein–Barr virus (EBV) were negative. A third NK cell cytotoxicity assay again showed decreased NK cell function (Table 2). A fourth assay from another lab showed decreased NK lytic units and slightly decreased NK cells compared with control (Table 2). She remains on acyclovir prophylaxis and was doing well at her 4-month follow-up.

DISCUSSION

NK cells are large granular lymphocytes that play an essential role in innate immunity.¹ They do not require sensitization to be activated and their function is tightly integrated with other cells in the innate and adaptive immune systems.^{2,3} NK cells lyse target cells and secrete immunoregulatory cytokines.⁴ Their pri-

mary roles are defense against viral infections and tumor cell surveillance; however, they also participate in immunoregulation and modulation of autoreactivity.⁵ NK cells are found in cord blood, peripheral blood, bone marrow, and the spleen.⁶ Mature peripheral blood NK cells express low levels of CD56 as well as Fc γ RIIIA (CD16). NK cells that express high levels of CD56 without CD16 are a developmentally immature but functional NK cell subset.⁵

Recurrent herpesvirus infections may indicate an underlying immunodeficiency.⁷ In humans, NK cells are an intricate part of the host defense against herpesviruses and human papilloma virus (HPV).⁸ Once activated, NK cells mediate contact-dependent killing of target cells through mobilization of lytic granules. After a killing program is triggered in an NK cell, lytic granules, particularly perforin and granzymes, are sent to the interface formed with the target cell and their contents are dispersed. This cytotoxicity function can be antibody independent or occur through recognition of IgG-opsonized cells by CD16 to enable antibody-dependent cell-mediated cytotoxicity. NK cells thus play a role in adaptive immunity.⁵

Another function of NK cells is production of cytokines or chemokines that play a role in immune regulation, particularly type I interferons (IFNs), IL-12, IL-15, and IL-18.⁵ These cytokines are also produced by infected cells, activated dendritic cells, and macrophages. Type 1 IFNs directly activate NK cells to enhance cell-mediated cytotoxicity. They also induce secretion of IL-15, a cytokine capable of inducing NK cell proliferation. IL-12 activates NK cells to increase the production of IFN- γ , which recruits and activates cytotoxic T lymphocytes and CD4⁺ T-helper 1 cells. IL-18 induces IFN- γ production by NK cells, both independently and synergistically with IL-12. Both IL-12 and IL-18 are critical in priming the NK cell response to viral infection.⁸

The third function of NK cells is promotion of immunity through contact-dependent costimulatory and regulatory mechanisms. Activated NK cells express many important costimulatory and regulatory ligands and can home to key immunoregulatory sites, particularly secondary lymphoid tissues.⁵

NK cell deficiency represents a small but important subset of primary immunodeficiencies that increases susceptibility to viral pathogens, particularly HSV, CMV, VZV, and HPV.^{1,5} In 1989, Biron *et al.* first reported the case of a young girl who lacked functional NK cells and experienced recurrent herpesvirus infections during childhood and adolescence.⁹ More recently in 2005, Etzioni *et al.* described a 2-year-old girl with fatal *Varicella* and isolated NK cell deficiency found on autopsy.¹⁰ Several subsequent studies have evaluated other immunodeficiency syndromes, such as NEMO deficiency, Hermansky–Pudlik syndrome,

Table 2 NK cell cytotoxicity assays performed on three separate occasions consistently show decreased NK cell function

NK cell Cytotoxicity/Functional Assays	9/17/13	10/30/13	12/30/13	1/24/14*
NK % cytotoxicity at 50:1 (≥20)	3 L	7 L	5 L	
NK % cytotoxicity at 25:1 (≥10)	1 L	4 L	2 L	
NK % cytotoxicity at 12:1 (≥5)	1 L	1 L	1 L	
NK % cytotoxicity at 6:1 (≥1)	1	0 L	0 L	
NK Lytic Units (≥2.6)	0 L	0.6 L	0.2 L	
% CD16 ⁺ CD56 (NK Cells) (3–16%)	2 L	5	2 L	
Patient PBMC % NK cells				4.2 L (5–16%)
Patient LU20 NK				189.8 L (>316.2)
Control PBMC % NK cells				12.1 (5–16%)
Control LU20 NK				590.1 (>316.2)
Interpretation	Decreased to absent NK cell function	Decreased NK cell function	Decreased NK cell function	Decreased LU20 compared with control

*Functional NK assay showed decreased LU20 in the patient compared with control.
NK = natural killer; PBMC = peripheral blood mononuclear cell; L = low.

and mutations in FcγRIIIa that all cause varying degrees of NK cell impairment, resulting in increased susceptibility to viral infections.^{1,5}

A diagnosis of exclusion, NK cell deficiency, requires the impact on NK cells to be the major immunologic abnormality present. Although many diseases, infections, physiological states, and drugs can affect NK cell numbers and/or function, NK cell deficiency refers to abnormalities that are fixed over time and primary in nature.⁵ Classic NK cell deficiency (CNKD) is characterized by the absence of CD3⁺CD56⁺ NK cells and function. Functional NK cell deficiency (FNKD) is defined by normal numbers of NK cells with abnormal cytotoxicity. Functional analysis of NK cell activity should be performed using reliable and validated assays on at least three occasions a month apart.⁵

After Biron *et al.* published the original case of CNKD,⁹ the causative gene defect was identified in GATA2 and the disease was redesignated as CNKD1. At least 18 additional patients have been described. Within this group, 53% (10/19) had recurrent herpesvirus infections. VZV was the most common infection seen, followed by CMV, EBV, and HSV. Twenty-one percent developed malignancies, including HPV-related cancers, leukemia, and an EBV-associated smooth muscle tumor.⁵

A familial form of CNKD was discovered in 2006 among members of a large consanguineous Irish cohort with NK cell deficiency and susceptibility to viral infections. These patients also had adrenal insufficiency, growth retardation, and microcephaly. One patient developed an EBV-driven lymphoproliferative

disorder, and two others developed severe viral respiratory illnesses.¹¹ The cohort was evaluated genetically and the clinical phenotype was linked to the minichromosome maintenance 4 (*MCM4*) gene on chromosome 8 with an autosomal recessive inheritance. Two additional Irish families with similar phenotypes were found to have the same mutations in *MCM4*, leading to speculation that *MCM4* is required for immune function homeostasis. This familial form of NK cell deficiency has been designated CNKD2 and should be suspected in patients with decreased NK cell cytotoxicity, endocrine abnormalities, and/or growth abnormalities.⁵

Ornstein *et al.* evaluated patients with severe, recurrent herpesvirus infections and identified five patients with functional NK cell abnormalities.¹² The most common herpesvirus implicated was HSV1. Infections involving VZV, HPV, EBV, and respiratory viruses were also described.⁵ Only one gene defect has been identified to cause FNKD—a mutation in the *FCGR3A* gene encoding CD16. This rare mutation causing FNKD1 is autosomal recessive and prevents CD16 from being used as a costimulatory receptor when CD2 is ligated during spontaneous NK cell cytotoxicity.⁵

The role of antiviral agents in treatment is limited to anecdotal reports using prophylactic acyclovir or ganciclovir to decrease susceptibility to herpesvirus infections. Given the risk for HPV infection, all patients with NK cell deficiency should receive recombinant HPV vaccination. Other novel therapeutic trials in CNKD1 include the use of IFN-α and hematopoietic stem cell transplant.⁵

Final Diagnosis

The final diagnosis was functional NK cell deficiency.

CONCLUSION

Patients with recurrent and/or severe viral infections should be evaluated for NK cell deficiency. CNKD presents with abnormal NK cell numbers and FNKD presents with normal numbers but reduced cytotoxicity function. Further research is needed to determine if there is a role for prophylactic antiviral agents in the treatment of NK cell deficiency.

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