

Association of natural killer cell dysfunction and recurrent Stevens-Johnson syndrome in a pediatric patient

Jason Casselman, D.O.,¹ John Venglarcik, M.D.,² Matt Bludorn, III, M.S.,³ Leah Chernin, D.O.,⁴ David Swender, D.O.,⁴ Hiag Tcheurekjian, M.D.,⁵ and Robert Hostoffer, D.O.⁴

ABSTRACT

Stevens-Johnson syndrome (SJS) is a debilitating condition involving the skin and mucous membranes. It is commonly the result of adverse drug reactions but can also be caused by infections. A predisposition to recurrent viral infections, such as in the case of natural killer (NK) cell dysfunction, may manifest with virally induced SJS. We present this case to suggest a possible association between NK cell dysfunction and recurrent SJS. An 11-year-old girl presents with recurring erythema, erosion, and ulceration of oral and vaginal mucosa. Small fluid-filled bumps would appear, leading to blistering and later sloughing of mucosal tissue, and bleeding would ensue. Seven separate episodes have occurred over an 8-year period, with each episode being preceded by symptoms of an upper respiratory infection. NK cell function assays were performed and NK cell phenotyping was ordered. NK cell assays showed decreased NK cell cytotoxicity at all ratios of K562 target cells. NK cell surface expression evaluation showed an immature phenotype but normal overall numbers of NK cells. NK cells are a pivotal part of the innate immune system, and, among other things, provide defense of viral infection. This case represents the manifestation of recurrent SJS as a result the lack of protection from viral illness, usually provided by NK cells in the healthy immune system.

(Allergy Rhinol 4:e25–e26, 2013; doi: 10.2500/ar.2013.4.0044)

Stevens-Johnson syndrome (SJS) is a debilitating condition involving the skin and mucous membranes.¹ Cutaneous eruptions often progress to areas of epidermal detachment and sloughing, represented by separation of tissue with mechanical pressure (positive Nikolsky sign).² Although medications such as antibiotics and anticonvulsants are the most common etiology of SJS, infections make up a significant proportion of the cases reported.² Infectious triggers are often viral upper respiratory infections; however, herpes simplex and human immunodeficiency virus have also been found to elicit the onset of SJS.³ Natural killer (NK) cells play a key role in the pathophysiology of SJS.⁴ NK cell degranulation products have been found in the blister of patients with SJS.⁴

The NK cell is a cytotoxic lymphocyte that acts by releasing cytoplasmic protein granules of perforin and granzyme, which subsequently cause cell death *via* apoptosis. The purpose of the NK cell in destroying the virus is thus fulfilled through this mechanism as virions within the infected cell are not released as with cell

lysis, but destroyed while *in vitro via* apoptosis.⁵ Any disruption of NK cell quantity and function will therefore lead to the propensity for recurrent viral infections in the absence of any therapeutic interventions.⁶ Additionally, disruption of NK cell function may alter the clinical presentation of immunologically mediated pathologies such as SJS.⁷

We describe an 11-year-old girl diagnosed with recurrent SJS. The patient's symptoms began in September 2003 1 week after recovering from a simple "head cold." The patient woke up to find two to three small bumps appearing on her hands and left foot. The following day small fluid-filled lesions were discovered inside the patient's mouth, mostly on the inside of her upper lip. The oral symptoms continued that evening, with increasing numbers of oral lesions, edema of the lips, and white lesions on the tongue, as well as halitosis. Over the course of several days the lesions in her oral cavity began to ulcerate and bleed, and the edema slowly decreased. Initial workup included cultures for herpes simplex virus and enterovirus, which were both found to be negative. Over the course of 8 years similar episodes have recurred on six separate occasions, with upper respiratory symptoms and fever preceding each. Mucosal involvement extended beyond the oral cavity to include the vaginal area during several disease flares. In addition, ocular symptoms continued with increasing inflammation and purulent discharge. Further questioning revealed a history of similar ocular symptoms in the patient's mother. Workup during the 8-year span included serologies for herpes simplex virus, cytomegalovirus, and Epstein-Barr virus, which

From the ¹Department of Medical Education, Pontiac Osteopathic Hospital, Pontiac, Michigan, ²Department of Pediatrics, North East Ohio College of Medicine, ³Department of Medical Education, Lake Erie College of Osteopathic Medicine, Erie, Pennsylvania, ⁴Department of Medical Education, Richmond Medical Center, University Hospitals, Richmond, Ohio, ⁵Department of Medical Education, Case Western Reserve University, Cleveland, Ohio

The authors have no conflicts of interest to declare pertaining to this article
Address correspondence and reprint requests to Jason Casselman D.O., Department of Medical Education, Pontiac Osteopathic Hospital, Pontiac, MI
E-mail address: jason.casselman@gmail.com

Published online April 4, 2013

Copyright © 2013, OceanSide Publications, Inc., U.S.A.

Table 1 Results of NK cell function tests

Test	Result	Units	Reference Range
NK% cytotoxicity at 50:1	11	%	≥ 20
NK% cytotoxicity at 25:1	4	%	≥ 10
NK% cytotoxicity at 12:1	2	%	≥ 5
NK% cytotoxicity at 6:1	1	%	≥ 1
NK lytic units	1.7	%	≥ 2.6
CD 16/56%	11	%	6–27

NK = natural killer.

were all found to be negative. Additional immunologic and autoimmune assessment included ESR, CRP, ANA, ANA panel, immunoglobulin levels, and lymphocyte enumeration and all proved to be negative. The suspicion of a possible *Mycoplasma pneumoniae* trigger was investigated and resulted in IgM titers positive for *Mycoplasma* in two of the episodes but negative in the remaining episodes. A biopsy of the mucosal lesion showed results consistent with SJS. A variety of treatment regimens were attempted throughout the disease course including antivirals, oral antibiotics, oral steroids, and i.v. immunoglobulin. The treatments did very little to change the course of the disease, with only the antiviral medications (acyclovir and valacyclovir) providing any relief of symptoms.

NK cell function assays were ordered to evaluate the function capacity of the patient's NK cells. At the time the NK cell assays were ordered, the patient was in a symptom-free interval of the disease. The results showed decreased NK cell function, with decreased cytotoxicity at all ratios of K562 target cells (Table 1).

NK cell surface expression evaluation showed an immature phenotype (decreased number of CD57⁺, ~6% of NK cells) but normal overall numbers of NK cells (CD3⁺, CD16⁺, and CD56⁺ 11% with absolute of 374). The patient's mother was also tested, with the results showing a similar NK cell defect.

This case shows that defects in the innate immune system, particularly NK cells, allow repetitively similar viral infections that subsequently produce repetitively similar clinical outcomes once an infectious/immunologic/clinical portal has been created in the host. These defects may also alter the course of immunologically mediated similar pathologies such as SJS or erythema multiforme major resulting in poor antibody responses to triggering pathogens and a clinical picture that may be skewed because of lack of pathological inflammatory response.

REFERENCES

1. Harr T, and French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. *Orphanet J Rare Dis* 5:39:1–12, 2010.
2. French LE. Toxic epidermal necrolysis and Stevens Johnson syndrome: Our current understanding. *Allergol Int* 55:9–16, 2006.
3. Gerull R, Nelle M, and Schaible T. Toxic epidermal necrolysis and Stevens-Johnson syndrome: A review. *Crit Care Med* 39:6: 1521–1532, 2011.
4. Tewary P, Yang D, de la Rosa G, et al. Oppenheim1. Granulysin activates antigen-presenting cells through TLR4 and acts as an immune alarmin. *Blood* 116:3465–3474, 2010.
5. Lanier L. Natural killer cells. In Samter's Immunological Diseases, 6th ed. Austen KF, et al. (Ed). Philadelphia, PA: Lippincott Williams & Wilkins, 166–168, 2001.
6. Rossi ME, Marranci S, De Marco A, et al. Reduced natural killer function in children with recurrent respiratory tract infections. *Pediatr Med Chir* 15:1–4, 1993.
7. Chung WH, and Hung SI. Genetic markers and danger signals in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Allergol Int* 59:325–332. (Epub Oct 25, 2010.) □