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Recalcitrant warts, associated with natural killer cell dysfunction, treated with systemic IFN- α

To the Editor:

Natural killer (NK) cells are large granular lymphocytes that are part of the innate immune system and are important in killing certain tumor cells as well as virally infected cells.¹ NK cell deficiency is rare, but has been associated with severe viral infections, particularly herpesviruses and human papillomavirus (HPV).^{1,2} NK cell dysfunction can be a result of either the absence of NK cells or defective cytotoxic activity.¹⁻³ Phenotypically, NK cells are characterized as CD3⁻CD56⁺. The intensity of CD56 expression on the surface of NK cells differentiates 2 subsets: (1) CD56^{dim}, which mediates cytotoxicity and represents the majority of NK cells in normal individuals, usually accounting for 85% to 90% of all NK cells; and (2) CD56^{bright}, which cannot mediate killing but secretes large amounts of cytokines and accounts for 5% to 10% of all NK cells.⁴ NK cells augment their cytotoxicity in response to several cytokines, including IL-2, IFN- α , and IFN- γ .^{4,5} Here we report a patient with recurrent warts, a decreased CD56^{dim} subset, and decreased NK killing activity who responded favorably to systemic IFN- α therapy.

A 51-year-old white female was referred by dermatology for recalcitrant periungual warts. The patient gave a history of persistent warts, with occasional exacerbations, on her fingers and under the fingernails that had been present for more than 5 years, but had worsened over the last 2 years. She did not have warts anywhere else, including the genital or anal areas. She failed to respond to several therapeutic modalities, including cryotherapy, cantharidin, laser therapies (CO₂ and pulsed-dye), intralesional IFN injections (specific IFN agent not specified), topical imiquimod, topical 5-fluorouracil, low potency topical corticosteroid, topical formalin 10%, diphencyprone 1%, and topical salicylic acid. In addition, she had

a significant problem with cold sores throughout her life but with no history of genital herpes. Interestingly, the cold sores seemed to develop before an exacerbation of her warts and would last for about 2 weeks. Past medical history was positive for a recent community-acquired pneumonia diagnosed by chest x-ray; she also had a history of recurrent and chronic sinusitis. Previous laboratory data included negative results for HIV and hepatitis C. Family history was positive for unspecified fungal infections; otherwise, there was no family history of immunodeficiency or autoimmune disorders. On physical examination, she had extensive periungual verrucous papules, with interruption of dermatoglyphics, loss of several nail plates, and surrounding erosion of the skin (Fig 1, A-C). Immune evaluation included immunophenotyping, which revealed normal distribution of CD3, CD4, CD8, CD19, and CD3⁻CD56⁺ (NK) cells. Her lymphocytes proliferated normally in response to concanavalin-A, phytohemagglutinin, pokeweed mitogen, IL-2, immobilized anti-CD3 antibody, mumps, and tetanus. Her immunoglobulin levels were as follows: IgG 1027 mg/dL (694-1618), IgA 183 mg/dL (68-378), and IgM 58 mg/dL (60-263). IgG subclasses were normal except for IgG3, which was slightly depressed at 11 mg/dL (21-134). Pre-Pneumovax and post-Pneumovax (Merck & Co, Whitehouse Station, NJ) immunization showed a 4-fold increase in titer to 4 of the 14 serotypes tested. By flow cytometry, 13.3% of her lymphocytes were CD3⁻CD56^{bright}, but only 0.83% were CD3⁻CD56^{dim} (Fig 2, A). Functional testing of NK cells revealed a markedly decreased killing activity on at least 3 occasions. The patient was started on a trial of recombinant IFN- α -2b (Intron-A; Schering-Plough Corporation, Kenilworth, NJ), 3 million IU subcutaneously 3 times a week. After an initial dramatic response, the patient had to decrease the frequency of her injections because of financial issues, with slowing of the response rate. Nevertheless, she had a significant resolution of the warts after 9 months (Fig 1, D-F). NK cell killing activity improved markedly and persistently after IFN therapy (Fig 2, B). Repeat flow cytometry examination revealed restoration of the CD56^{dim} subset and a decrease of the CD56^{bright} subset (data not shown).

We and others have reported NK cell dysfunction in patients with HPV-associated diseases.^{2,6-8} However, strategies at augmenting NK cell activity have not been examined in these patients. Our patient had a dramatic response to systemic IFN therapy. We believe that this response was a result of the increased NK cell cytotoxic activity induced by IFN- α . It is possible that IFN- α had a direct antiviral effect on the HPV-infected cells, but we believe this to be unlikely because the patient failed to respond to a trial of intralesional IFN injection as well as topical imiquimod, which induces local IFN- α secretion. A more likely scenario is that IFN- α acted directly on NK cells to augment their cytotoxic activity. IFN- α may trigger an autonomous feedback activation loop by causing NK cells to secrete IFN- γ , which then can further activate NK cell activity in an autocrine fashion. If this were the case, one would expect the patient's NK cell



FIG 1. A-C, Before IFN therapy. D-F, After IFN therapy.

activity to remain elevated after cessation of IFN therapy. Indeed, the patient's NK cell activity has remained normal after stopping IFN (data not shown), although she is using imiquimod, which may be maintaining the NK cell activation. It is also possible that IFN- α induced NK cells to secrete IFN- γ , which then activated HPV-specific T-cell responses that may have been the effector cells that induced remission. If this were the case, then one can argue that the abnormality in this patient is the inability of the CD56^{bright} cells to secrete IFN- γ until they received an activation signal from IFN- α . Such a scenario would suggest that the CD56^{bright} cells might play an important role in the development or function of the CD56^{dim} subset.

It remains unclear why the patient's CD56^{dim} NK cells were decreased. Indeed, little is known about the mechanisms that regulate the homeostasis of these 2 NK subsets. It is known, however, that IFN- α is very potent at inducing NK cytotoxic activity.⁹ It is possible, therefore, that the patient's deficit is a suboptimal secretion of IFN- α by dendritic cells. Another possibility is that the patient's

NK cells do not express the appropriate killer Ig-like receptor (KIR) needed for killing of HPV-infected cells by NK cells.^{1,3} Carrington et al¹⁰ have suggested that resistance to HPV-associated cervical neoplasia was dependent on the expression of specific inhibitory KIR/HLA ligand pairs. We have not examined the patient's KIR repertoire as of yet.

In summary, this patient suggests that the clinical phenotype of NK cell dysfunction may be subtle and that modulation of NK cell function *in vivo* can result in a dramatic therapeutic benefit.

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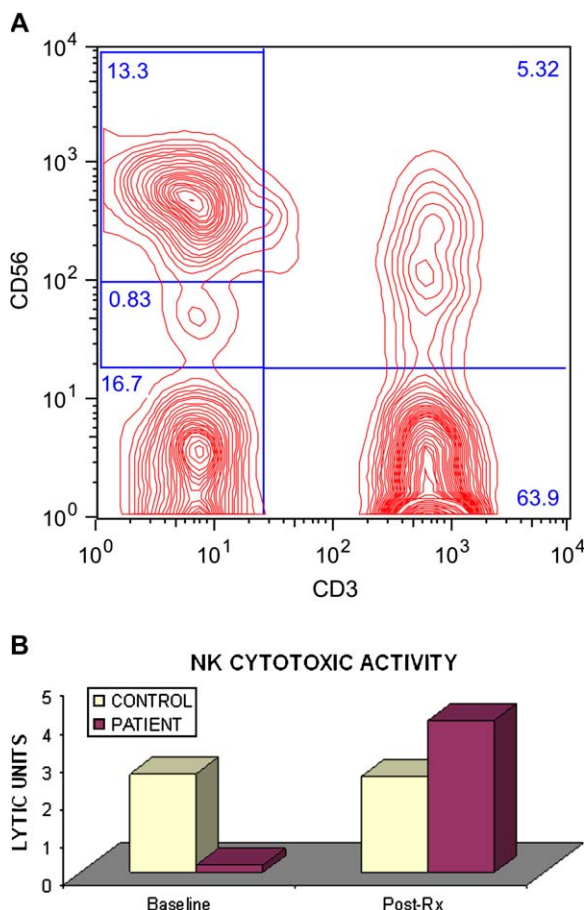


FIG 2. NK evaluation. **A**, Flow cytometry assessment of CD56^{bright} and CD56^{dim} NK subsets at presentation. **B**, NK cytotoxic activity: PBMCs were obtained and used, at various effector:target cell ratios in a 4-hour ^{51}Cr -release assay against K562, the standard NK cell tumor target. Percent specific lysis was calculated and linearized by the least-squared method. Lytic units were calculated with 1 lytic unit defined as the number of mononuclear cells needed to effect 30% specific lysis. The data presented are lytic units per 1,000,000 mononuclear cells.⁶ The data are representative values at each time point.

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Food intolerance and wheezing in young South Asian and white children: Prevalence and clinical significance

To the Editor:

In the United Kingdom (UK), prevalence of asthma has been reported to be lower in South Asian compared with white children, while hospitalizations and use of health services were more common.¹ Food intolerance has been associated with severe and persistent asthma²⁻⁶ in children. Hospital-based patient surveys in the UK backed up by objective laboratory testing suggest that food and drink more commonly trigger asthma in South Asian than in white children.⁷ A higher prevalence of food allergy in South Asians could therefore help to explain ethnic differences between prevalence and severity. Population-based data confirming these findings are lacking. We therefore assessed the prevalence and predictive value of reported food-related wheeze in a population-based cohort study of South Asian and white preschool children.

We studied a population-based cohort of 6100 white and 2600 South Asian (ethnic origin self-defined as Indian, Pakistani, or Bangladeshi) preschool children born between 1993 and 1997 in Leicestershire, UK, whose parents filled in postal respiratory questionnaires in 1998 and 2003.⁸ In 1998, questionnaires were returned for 4986 (84% of those with a valid address) white and 1825 (72%) South Asian children aged 1 to 4 years, and in 2003 for 3195 (56%) and 1039 (42%) children aged 6 to 9 years, respectively. Questionnaires from both surveys were available for 2962 white and 911 South Asian children. We asked core questions from the International Study on Asthma and Allergy in Childhood, plus detailed questions on frequency and severity of wheeze, triggers of wheezing episodes, environmental exposures, and socio-demographic variables. Food-related wheeze was assessed as one of several answers to the question on triggers: "Did any of the following things cause wheezing in your child? Food or drinks (yes/no/don't know)." We compared the prevalence of food-induced wheeze between South Asian and white children in 1998 and in 2003, assessed clinical features of children reporting food-induced wheeze, and determined whether food-induced wheeze in 1998 predicted persistence of wheeze 5 years later, using multi-variable logistic regression.

The overall prevalence of wheezing was lower in South Asian than white children in 1998 at age 1 to 4 years