Case study

Sporadic case of warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis syndrome

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The term WHIM syndrome (WHIMS) is an acronym describing a rare primary immunodeficiency disorder characterized by warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis, the unusual association of neutropenia with bone marrow myeloid hypercellularity. WHIMS was recently associated with mutations in the gene encoding the chemokine receptor CXCR4 and as such is the first disease ascribed to abnormalities of chemokine signaling. We report a sporadic case of WHIMS in a woman presenting with recurrent infections and human papilloma virus–related genital dysplasia. (J Allergy Clin Immunol 2005;116:1101-5.)

Key words: *WHIM syndrome, myelokathexis, CXCR4, warts, combined immunodeficiency*

Abbreviations used
G-CSF: Granulocyte colony-stimulating factor
HPV: Human papilloma virus
HSV: Herpes simplex virus
WHIMS: Warts, hypogammaglobulinemia, bacterial infections, and myelokathexis syndrome

CASE PRESENTATION

After an episode of lobar pneumonia caused by *Streptococcus pneumoniae* with confirmed bacteremia, a 52-year-old white British woman was referred to the Outpatient Unit of the Department of Clinical Immunology at St Bartholomew's Hospital, London. She had a history of intractable human papilloma virus (HPV)–related dysplasia, having first presented at the age of 33 years with vulval dysplasia and grade III cervical intraepithelial neoplasia. Over a period of several years, severe multifocal dysplasia was managed by vulvectomy and total abdominal hysterectomy, together with bowel resection and formation of a stoma for grade III anal intraepithelial neoplasia. A selection of histopathological sections is presented in Fig 1.

Further questioning revealed a significant infection history. She reported frequent bouts of respiratory sepsis from an early age, which generally responded fully to oral antibiotics with no significant respiratory symptoms between exacerbations. During infancy, she presented with extensive cellulitis of the right leg, requiring urgent hospital admission for intravenous antibiotics and, ultimately, surgical debridement. At the age of 10 years, she developed warts affecting both hands; these proved refractory to treatment, but eventually went into spontaneous remission after a period of several months. At age 21 years, neutropenia was identified before a routine dilatation and curettage. Extensive investigation including a bone marrow aspirate and trephine was inconclusive. The etiology of her neutropenia remained unclear, and she was subsequently lost to hematology follow-up. More recently, she had been troubled by severe, recurrent perioral herpes simplex virus (HSV) infection, as well as a single episode of unidermatomal thoracic zoster.

She was born at term by spontaneous vaginal delivery, with no problems in the neonatal period. There was no history of opportunistic or mycobacterial infections, and childhood infections ran a benign course without apparent complications. She had tolerated vaccination with smallpox and BCG with no adverse sequelae. There was no other relevant past medical history, and apart from hormone replacement therapy, she was not taking any regular medication. Her parents, a single sibling, and her 2 children have remained free of significant infections, warts, and Pap smear abnormalities, and with the exception of one of her offspring who has not been tested, all immediate family members have normal blood films. She has never smoked cigarettes and drinks minimal alcohol.

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Disclosure of potential conflict of interest: H. Longhurst has acted as an advisor for Bioproducts Laboratory, Hertfordshire, United Kingdom, has participated in a clinical trial of 'Subgam' Immunoglobulin preparation, and has spoken by invitation for Baxter Healthcare, Berkshire, United Kingdom. Her department has received funds from various immunoglobulin manufacturers. The rest of the authors have none to disclose.

Received for publication May 6, 2005; revised August 2, 2005; accepted for publication August 23, 2005.

Available online October 10, 2005.

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0091-6749/$30.00

doi:10.1016/j.jaci.2005.08.040

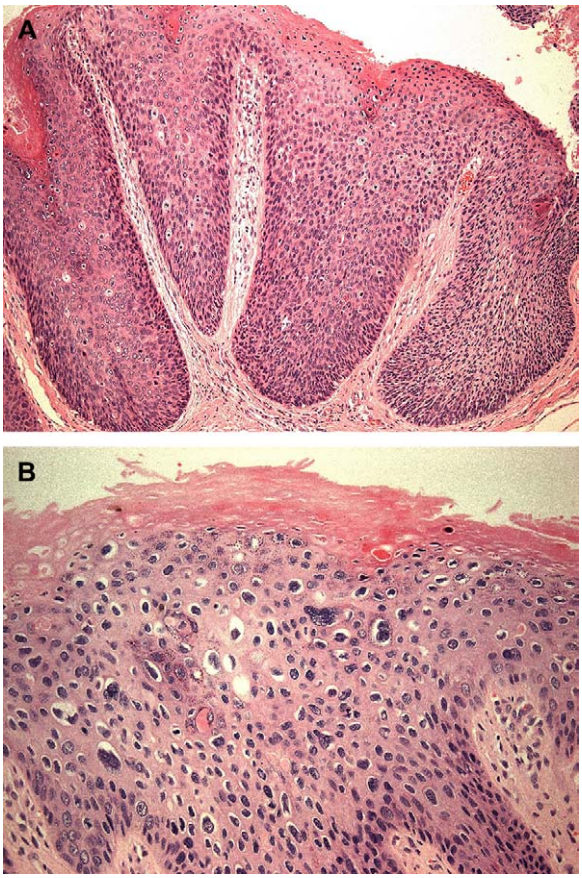

FIG 1. A, Vulval biopsy showing full-thickness epithelial dysplasia. There are numerous mitoses throughout the full thickness of the epithelium. **B,** Vulval biopsy from the same patient showing florid koilocytosis. Note perinuclear halos and large irregular nuclei (hematoxylin and eosin; original magnification ×200).

Physical examination was unremarkable, with no clinical evidence of bronchiectasis and no palpable lymph nodes. A blood film revealed lymphopenia and neutropenia, with further investigation demonstrating the latter to be noncyclical and in the severe to moderate range (absolute neutrophil count between 0.1 and 0.8×10^9/L). The results of routine immunological tests are summarized in Table I. Analysis of lymphocyte surface markers revealed severe panlymphopenia, with a CD4 count of just 69×10^6/L (normal range, 455-1320/L); however, lymphocyte proliferation assessed by thymidine incorporation after stimulation with recall antigens was satisfactory. Further investigation demonstrated IgG at the lower end of the normal range, with mild deficiency of IgA and IgM. Baseline antibody titers specific to *Haemophilus influenzae* and *S pneumoniae* were nonprotective, and after immunization, she mounted a poor specific antibody response to *H influenzae* and no response to *S pneumoniae*. Serum electrophoresis did not demonstrate paraproteinemia, and the urine was free of Bence-Jones proteins. Pulmonary function tests and plain chest radiography were unremarkable.

DIFFERENTIAL DIAGNOSIS

This patient's repeated respiratory sepsis raises the possibility of humoral immune deficiency, whereas a cellular component is suggested by intractable HPV-related dysplasia as well as zoster and recurrent HSV infection. The lifelong infection history indicates a primary immunodeficiency disorder. The history, clinical examination, and basic investigations (pulmonary function tests and plain radiography) are not suggestive of significant chronic respiratory disease, although definitive imaging by high-resolution computerized tomography was not performed initially given the possibility of immunodeficiency associated with an underlying DNA repair defect. Another aspect of her presentation is severe neutropenia, although notably (with the exception of cellulitis) the range of infections she has had are not particularly suggestive of neutropenic sepsis, and there was some evidence that in the past she had mounted a neutrophilia while unwell. The serum immunoglobulin levels are not markedly reduced, but the history together with poor vaccine response is supportive of significant humoral immunodeficiency.

CD40 deficiency[1] (hyperimmunoglobulin syndrome type 3, autosomal-recessive) is characterized by combined immunodeficiency and neutropenia, but is excluded by the immunoglobulin profile and relatively benign clinical course. Common variable immunodeficiency[2] is associated with predominantly humoral immunodeficiency, although in some cases, a degree of cellular immunodeficiency may coexist. Cytopenias, often autoimmune in nature, are not uncommon in common variable immunodeficiency. However, low IgG is characteristic of the condition. Certain DNA repair defect syndromes[3] may lead to a range of cellular and humoral immune deficiencies, sometimes associated with sensitivity to ionizing radiation. However, the condition that best fits her phenotype is warts, hypogammaglobulinemia, bacterial infections, and myelokathexis syndrome (WHIMS), a rare form of congenital neutropenia characterized by bacterial infections and marked susceptibility to HPV infection.

LABORATORY AND OTHER TESTING/PROCEDURES

A bone marrow aspirate was performed to investigate further the possibility of WHIMS. The erythroid and megakaryocytic lineages were normal and granulocytes and their precursors plentiful. However, there was vacuolation of mature neutrophils, polymorph nuclear hypersegmentation, and thin strands connecting the lobes, supporting the diagnosis (Fig 2).

With informed consent, a blood sample was drawn for isolation of DNA from peripheral leukocytes by using the Puregene kit (Gentra, Minneapolis, Minn). A PCR-RFLP assay was used to screen for the presence of the recurrent 1000C→T mutation as described.[4] Primer sequences are