

原文題目(出處)：	WHIM syndrome and oral squamous cell carcinoma(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:105-8
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### Introduction

WHIM is the acronymic designation for a rare autosomal dominant syndrome characterized by warts, hypogammaglobulinemia, infections, and retention of mature neutrophils in the bone marrow (myelokathexis).

The first case was described, in 1964, in a 10-year-old girl with granulocytopenia and infections. Since then, <40 cases have been reported.

An increased susceptibility to human papillomavirus (HPV) results in multiple, often disfiguring, cutaneous warts and, in women, susceptibility to HPV-related cervical dysplasia or carcinoma.

Leukopenia with hypogammaglobulinemia renders patients susceptible to infections, especially bacterial infections of the respiratory tract, e.g., otitis, sinusitis, pneumonia, and cellulitis.

Not only are peripheral granulocyte counts low, but some neutrophils and eosinophils show abnormal morphology, including hypersegmented nuclei and vacuolated cytoplasm. Long-term antibiotic prophylaxis is often used.

We report the occurrence of HPV-related oral squamous carcinoma in 2 siblings with documented WHIM syndrome.

### Materials and Methods

Tissue samples for histopathologic study were formalin fixed, decalcified as required, and embedded in paraffin in accordance with generally practiced laboratory procedures. Immunostaining for p16INK4A (Biocare Medical, Concord, CA) was also done in a routine fashion using a Ventana automatic stainer. In situ hybridization for HPV used 2 cocktails (Ventana Medical Systems, Tucson, AZ) for low-risk (HPV 6 and 11) and high-risk (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 66) viruses.

### Case histories

The index patient is a 46-year-old woman with a history of WHIM syndrome clinically recognized since the age of 7 years, manifesting as cutaneous warts granulocytopenia, hypogammaglobulinemia, and recurrent infections including otitis,

sinusitis, pneumonia, and cellulitis. She has had several cutaneous basal cell carcinomas, as well as vulvar carcinoma in situ for which she underwent skinning vulvectomy at an outside institution.

She presented to her periodontist in June 2008 with 2 discolored gingival lesions adjacent to her maxillary incisors.

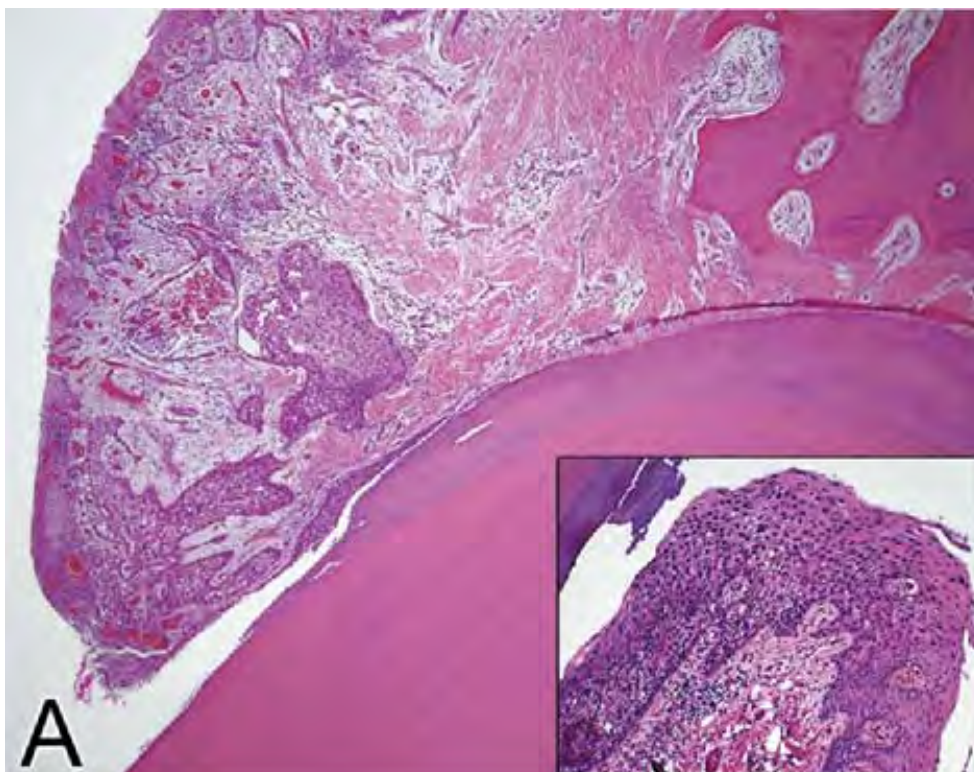
She is a nonsmoker and reports only occasional use of alcoholic beverages.

A biopsy of one of the gingival lesions showed invasive squamous cell carcinoma and was followed by resection of the upper alveolar ridge, consisting of the 4 upper incisors and adjacent maxilla.

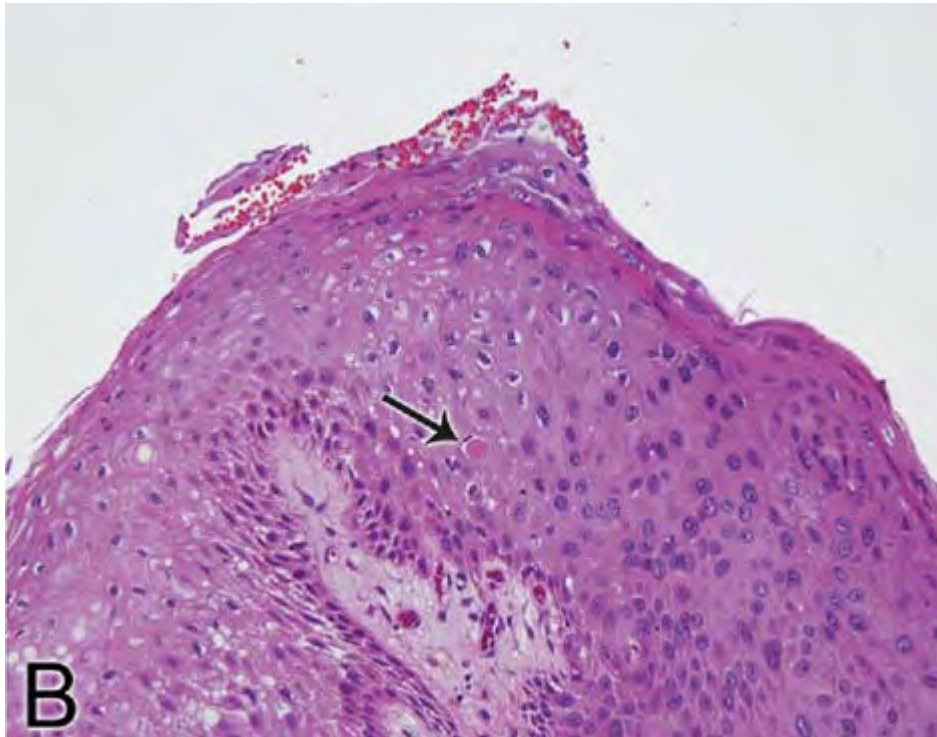


The anterior gingival surface demonstrated 2 ulcerated lesions.

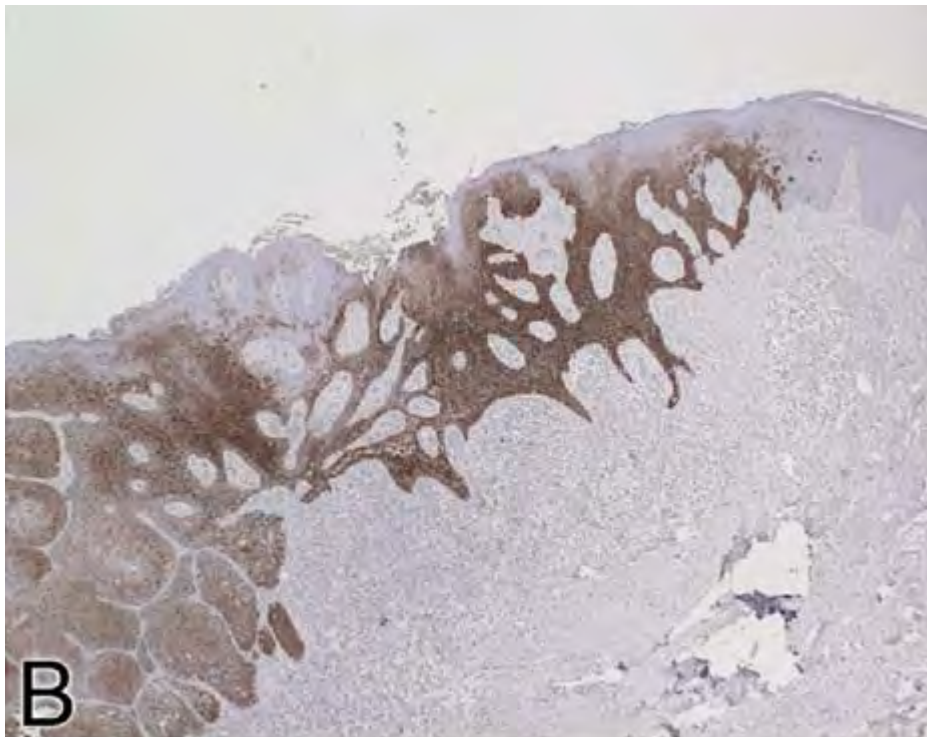
Both lesions demonstrated in situ and invasive nonkeratinizing squamous cell carcinoma, extending into the respective gingival sulci.



The surface epithelium demonstrated koilocytosis with nuclear pyknosis and focal binucleation, indicative of HPV infection.

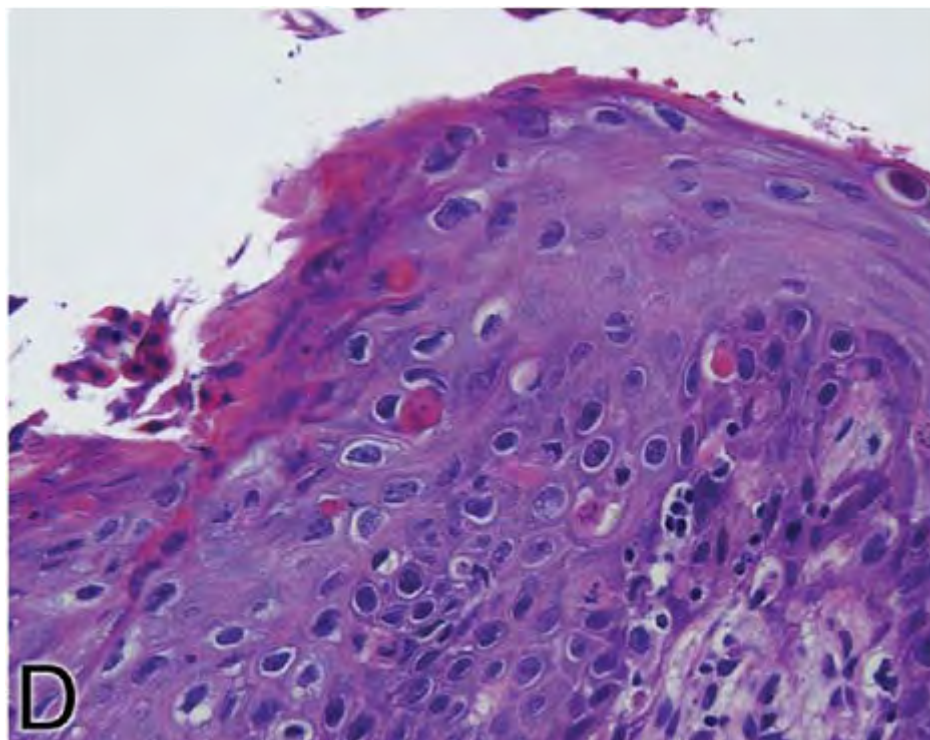
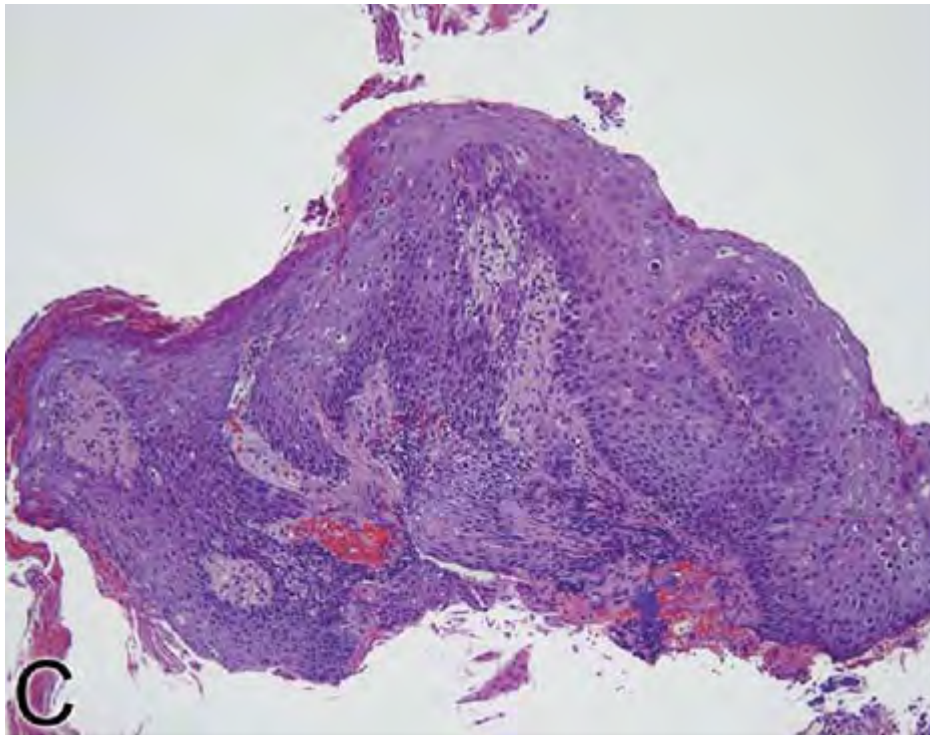


The p16 immunohistochemical stain was strongly positive.

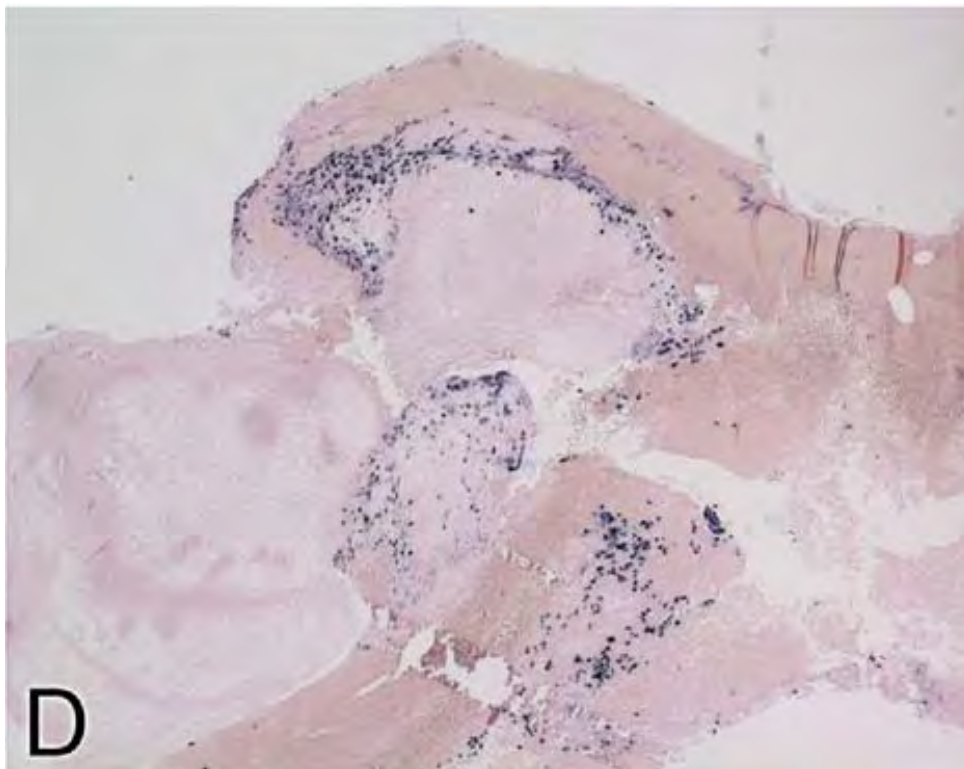
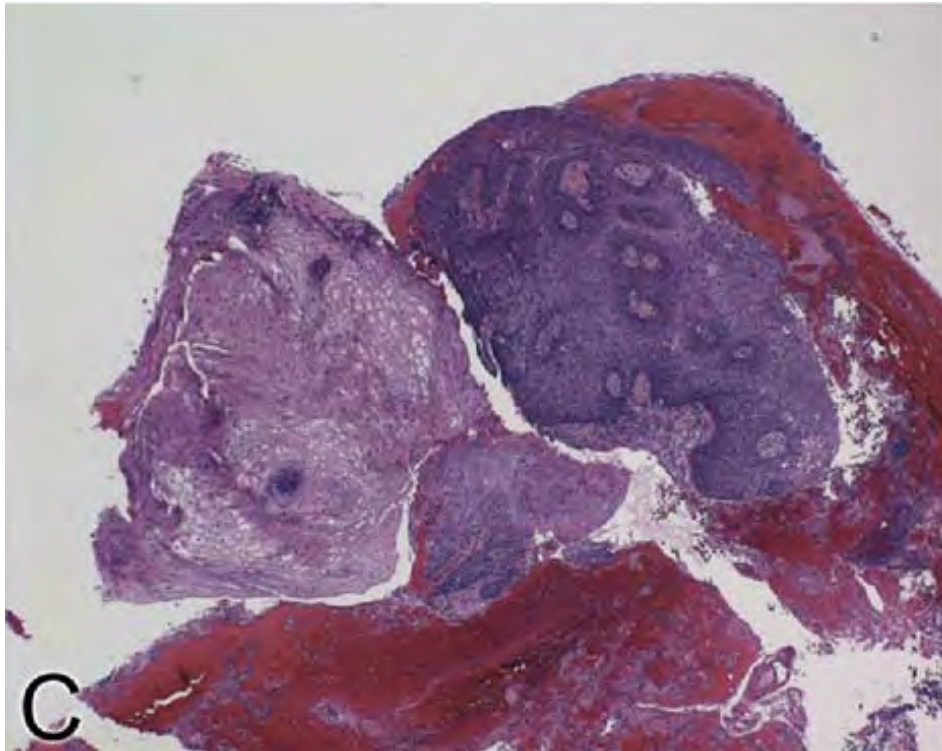


The patient's 40-year-old brother also suffered from WHIM syndrome. He had a history of Epstein-Barr virus-related B-cell lymphoma as well as squamous cell carcinoma of the maxillary sinus, diagnosed and treated by maxillectomy at an

outside institution. He did not have a history of tobacco or alcohol use. New oral lesions were noted, and biopsies showed in situ and invasive squamous cell carcinoma with evidence of surface viral change, similar to that seen in his sister.



In situ hybridization for high- In situ hybridization for high-risk HPV was focally present.



## DISCUSSION

The immune basis for WHIM syndrome may be related to a mutation in the chemokine receptor CXCR4, a 7-transmembrane protein expressed in a variety of stem and progenitor cells, including hematopoietic, neural and liver stem cells, primordial germ cells, and skeletal muscle and retinal progenitor cells.

The gene is located on chromosome 2q21, and a number of mutations causing truncation of the intracytoplasmic tail domain have been identified. The receptor's only ligand is CXCL12, and the CXCR4-CXCL12 complex affects:

- 1) Hematopoiesis of myeloid and lymphopoiesis of B cells.
- 2) Organogenesis of cardiac and neural systems.
- 3) Gastrointestinal angiogenesis.
- 4) Oncogenesis and metastasis of a variety of human neoplasms, including breast and prostate carcinomas, small cell lung cancers, myeloid neoplasms, and pediatric sarcomas.
- 5) Human immunodeficiency virus infection, as a coreceptor for the virus.
- 6) Chemotaxis of hemato/lymphopoietic cells to lymphoid organs (bone marrow, spleen, and lymph nodes).

The CXCR4 receptor can be turned off permanently or temporarily by internalization into vesicles, whence it can be either degraded or recycled back to the surface. Cells with a gain of function mutation of CXCR4 demonstrate decreased internalization in response to CXCL12, which results in increased intracellular signaling, increased chemotaxis toward CXCL12 in bone marrow, a mechanical inability to exit the bone marrow, and consequent peripheral neutropenia or leukopenia.

Unfortunately, CXCR4's role in HPV infection is not well characterized. HPV is associated with 80%-90% of cervical and anogenital carcinomas, and the female patient reported here did have a history of in situ squamous carcinoma of the vulva. HPV in head and neck squamous cell carcinoma may have an overall association of 25%-50%, depending on the method of viral identification (Southern blot vs. in situ hybridization vs. polymerase chain reaction [PCR]).

In both of the patients described here, microscopic examination of new oral lesions demonstrated surface viral changes associated with squamous carcinoma. One was positive for p16 oncoprotein, and the other demonstrated HPV by in situ hybridization. The lack of viral reactivity in the sister's lesion may be due to the acid involved in decalcifying the resection specimen.

In a recent evaluation of 41 cases of high-grade squamous dysplasia, 100% of cases (6 out of 6) with p16 positivity demonstrated HPV by PCR. Furthermore, PCR was negative in the p16-negative cases. In a second study comparing p16 expression to HPV in situ hybridization, 9 out of 10 cases with diffuse p16 staining demonstrated positive HPV in situ hybridization.

The identification of high-risk HPV and p16 oncoprotein in these cases suggests but cannot prove an etiologic role for the virus in carcinogenesis, because not

all lesions with HPV progress to carcinoma. Some studies suggest that concurrent use of tobacco or alcohol might increase the risk for carcinoma in patients who are already HPV positive. In light of such a “2-hit” hypothesis, the immune dysfunction precipitated by WHIM syndrome might serve as the second hit in patients with oral HPV, further increasing their risk for squamous carcinoma.

題號	題目
1	The immune basis for WHIM syndrome may affects followings, except: (A) Hematopoiesis of myeloid and lymphopoiesis of T cells. (B) Organogenesis of cardiac and neural systems. (C) Gastrointestinal angiogenesis. (D) Human immunodeficiency virus infection, as a coreceptor for the virus.
答案(A)	出處：Hematopoiesis of myeloid and lymphopoiesis of B cells.
題號	題目
2	In which organ of HPV is MORE associated with the malignancy of the female patient ? (A) Vulva (B) Cervical (C) Ovary (D) Uterus
答案(B)	出處：HPV is associated with 80%-90% of cervical and anogenital carcinomas, and the female patient reported here did have a history of in situ squamous carcinoma of the vulva. HPV in head and neck squamous cell carcinoma may have an overall association of 25%-50%.