

SHORT COMMUNICATION

Recurrent High-risk Human Papillomavirus-induced Anogenital Dysplasia in Chronic Idiopathic CD4⁺ T LymphocytopeniaAlexander Kreuter¹, Ulrike Wieland² and Monika Hampf³¹Department of Dermatology, Venereology and Allergology, Ruhr-University Bochum, Gudrunstr. 56, DE-44791 Bochum, ²Institute of Virology, National Reference Centre for Papilloma- and Polyomaviruses, University of Cologne, Cologne, and ³Department of Gynaecology and Obstetrics, Heinrich Heine University, Duesseldorf, Germany. E-mail: a.kreuter@derma.de

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Chronic idiopathic CD4⁺ T lymphocytopenia is a rare syndrome characterized by pronounced CD4⁺ T-cell depletion in the absence of HIV infection. Based on the Centers for Disease Control and Prevention diagnostic criteria, patients present decreased circulating T lymphocytes (<300 μ l or <20% of peripheral lymphocytes) on at least 2 occasions, a low CD4/CD8 ratio, absence of HIV infection, and no history of other immunodeficiencies or immunosuppressive drugs (1). Patients with chronic idiopathic CD4⁺ T lymphocytopenia may exhibit a broad spectrum of opportunistic and unusual fungal, bacterial, protozoal, and viral infections (2). We report here 2 women with chronic idiopathic CD4⁺ T lymphocytopenia diagnosed following longstanding and recurrent human papillomavirus (HPV)-induced high-grade anogenital dysplasia.

CASE REPORTS

Case 1. A 35-year-old Caucasian woman presented at our institution for the first time in 2001. Clinical examination revealed widespread, irregularly shaped leukoplakic lesions located at the perianal area and vulva (Fig. 1A). Histopathological analysis of 8 punch biopsies obtained from both areas showed high-grade anal intraepithelial neoplasia (AIN) and vulvar intraepithelial neoplasia (VIN), with strong expression of the cellular proliferation marker Ki67 as well as p16^{ink4A}, an indirect marker of HPV oncogene expression (Figs 1B and C). HPV-typing was performed with an alpha-HPV group-specific PCR followed by bead-based hybridization with 38 HPV-probes and demonstrated exclusively HPV16 in 17 lesional biopsies collected between 2001 and 2008. Furthermore, the patient

had a history of pulmonary tuberculosis and recurrent genital herpes simplex infection. Lymphocyte subpopulation analysis using fluorescence-activated cell sorting revealed significantly decreased CD4⁺ cells of 99/ μ l (normal range 410–1,590/ μ l) and a decreased CD4/CD8-ratio of 0.9 (normal range 2–3). HIV testing was repeatedly negative, and there was no history of other immunodeficiencies or immunosuppressive drugs (Table I). Based on these findings, a diagnosis of chronic idiopathic CD4⁺ T lymphocytopenia was made. The patient received numerous topical and ablative treatments, including 5-fluorouracil cream, imiquimod 5% cream, surgical curettage and electrocautery, and CO₂-laser therapy. However, recurrences occurred within a few months following all of these treatment modalities. The current treatment is topical 85% trichloroacetic acid.

Case 2. In 1986, a 24-year-old Caucasian woman presented for the first time with widespread anogenital condylomata acuminata. Histopathological analysis showed typical benign acanthomas with no further signs of dysplasia. She presented at our outpatient clinic 7 years later in 1993 with extensive high-grade VIN and AIN, as well as low-grade cervical intraepithelial neoplasia (CIN) and low-grade vaginal intraepithelial neoplasia (VAIN). Virological analysis demonstrated an HPV16 mono-infection in all of the lesions. After her first laser-surgical intervention in 1993, she presented annually with recurrent multifocal AIN, VIN, VAIN, and CIN, necessitating multiple surgical treatments. Additional treatment with subcutaneous interferon alpha was initiated, but the patient never remained free of recurrent lesions for longer than 12 months. Her HIV test was repeatedly negative, but she had recurrent *chlamydia trachomatis* and genital herpes simplex infections. In 2004, after more than 15 laser-surgical interventions, but still persisting high-grade AIN and VIN, she received a skinning vulvectomy with anal skin resection and coverage of the defect with 2 lateral transposition flaps. Since that time, she had 2 small VIN lesions at the vulvar scar in 2005 and recurrent high-grade AIN in 2008, which were surgically removed. In 2007, the patient received the quadrivalent

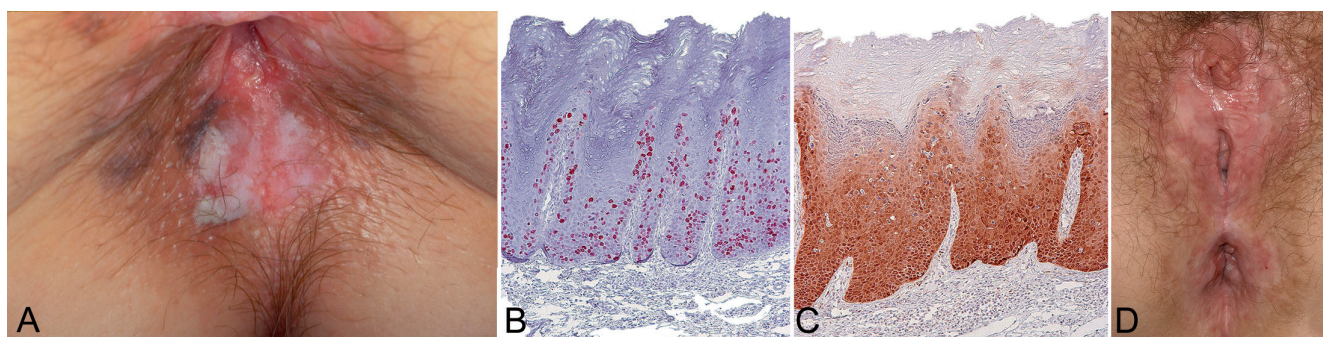


Fig. 1. (A) Clinical presentation of case 1: a multifocal, irregularly shaped, flat lesion is present, ranging into the anal canal. (B) Histopathological analysis of the perianal lesion of patient 1. Strong Ki67-immunoreactivity is present, with Ki67-positive cells reaching up into the upper epidermis (original magnification \times 200). (C) Immunohistochemical analysis using an anti-p16 monoclonal antibody demonstrates a strong and diffuse immunoreactivity for p16^{ink4A} in both the nuclei and cytoplasm, affecting the entire epidermis. These findings are consistent with high-grade anal dysplasia (AIN III) (original magnification \times 200). (D) Clinical presentation of case 2: widespread perianal and vulvar leukoplakia.

Table I. Clinical and laboratory characteristics of 2 female patients with chronic idiopathic CD4⁺ T lymphocytopenia

	Patient 1	Patient 2
Age at first diagnosis, years	35	24
HPV-associated disease, highest histopathological grade	AIN III, CIN III, VIN III	AIN III, CIN III, OIN I, VIN III, VAIN III
Lesional HPV-types	HPV16	HPV16
Recurrent HPV-associated disease, years	13.5	36
Circulating CD4 ⁺ cells (absolute ^a , relative ^b)	99/μl, 28%	20/μl, 2%
CD4/CD8 ratio	0.9	0.04
HIV serostatus	Negative	Negative
History of other immunodeficiencies or immunosuppressive drugs	None	None
History of other infectious diseases	Pulmonary tuberculosis, recurrent GHS	Chlamydia trachomatis, GHS
Smoking	No	No

^aAbsolute CD4⁺ cell counts (normal range 410–1,590/μl); ^brelative CD4⁺ cell counts (normal range 31–60%).

HPV: human papillomavirus; AIN: anal intraepithelial neoplasia, CIN: cervical intraepithelial neoplasia, OIN: oral intraepithelial neoplasia, VAIN: vaginal intraepithelial neoplasia, VIN: vulvar intraepithelial neoplasia; GHS: genital herpes simplex.

HPV vaccine to protect her against HPV6, 11, 16, and 18. In the same year, she presented with a wart-like lesion in her mouth that was found to be HPV16-induced oral intraepithelial neoplasia. A few weeks later, she complained about generalized muscle and joint pain, as well as fever and weight loss, and was therefore transferred to the clinic of haemato-oncology for further evaluation and exclusion of a malignancy. At that time, she was diagnosed with chronic idiopathic CD4⁺ T lymphocytopenia. Lymphocyte subpopulation analysis demonstrated a marked decrease of CD4⁺ cells of 20/μl and a decreased CD4/CD8-ratio of 0.04. She stayed in a stable condition until 2011, when she developed a stroke due to a cranial arterial malformation with aneurysm, and was therefore operated in the department of neurosurgery. She recovered completely without any neurological defect. In 2012, new peri- and intra-anal condylomata acuminata developed and were removed with electrocautery. Her current treatment is 5% imiquimod cream.

DISCUSSION

Rare, widespread, and recalcitrant fungal, bacterial, protozoal, or viral infections are a possible indicator of immunosuppression. Immunocompromised individuals are well known to be highly susceptible for persistent infections with HPV. To date, several cases of HPV-induced lesions in chronic idiopathic CD4⁺ T lymphocytopenia have been reported in the literature, with the majority presenting as common cutaneous warts. Most of these reports did not include HPV analysis. In those that included HPV typing, HPV2, 3, 6, and 49 were detected in the cutaneous lesions (2, 3). In contrast, mucosal HPV-induced disease has only been reported occasionally in patients with chronic idiopathic CD4⁺ T lymphocytopenia. Pasic et al. (4) reported a case of chronic idiopathic CD4⁺ T lymphocytopenia in a 3-year-old boy with juvenile laryngeal papillomatosis. Surgical ablation and interferon-alpha therapy were only partially effective, and the patient eventually died due to disseminated *Mycobacterium avium* infection. Park et al. (5) reported a 52-year-old woman with chronic idiopathic CD4⁺ T lymphocytopenia with HPV16-positive VIN and CIN. Six unsuccessful laser ablations were performed in this patient before wide local excision for her persistent VIN. Recently, Tomson et al. (6) reported a postmenopausal woman in her mid-50s with chronic idiopathic CD4⁺ T lymphocytopenia and

HPV16-positive AIN and VIN grade 3. She was unable to tolerate topical treatment with 5% imiquimod and cidofovir 1% as well as systemic treatment with acitretin 20 mg. CO₂ laser ablation produced little improvement. One year later, the patient developed an invasive anal margin carcinoma and was treated with combined radiochemotherapy. In line with these reports, both of our patients had longstanding and recurrent anogenital dysplasia. None of the 2 patients had a history of high-risk sexual behaviour. Interestingly, only HPV16 was detected in all analysed lesional biopsies, supporting the particular oncogenic potential of this HPV-type. In general practice, physicians should consider chronic idiopathic CD4⁺ T lymphocytopenia as an underlying condition in HIV-negative patients with extensive and chronic HPV-associated disease. Moreover, closely follow-up examinations are mandatory in these patients because progression to high-grade dysplasia or even invasive disease might occur rapidly.

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