Published in final edited form as:

Sex Transm Infect. 2009 August ; 85(4): 261–263. doi:10.1136/sti.2008.034959.

Rapid progression of an anal Buschke–Löwenstein tumour into a metastasising squamous cell carcinoma in an HIV-infected patient

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Abstract

Background—Buschke–Löwenstein tumour (BLT) of the anogenitalia is a locally invasive, destructively growing verrucous carcinoma that does not metastasise. Histologically BLT resembles benign condylomata acuminata. Nevertheless, the tumour grows relentlessly and may rarely progress into squamous cell cancer (SCC).

Results—A human immunodeficiency virus (HIV)-infected immunosuppressed patient developed (peri)anal warts accompanied by recurrent abscesses and fistulae. Histology revealed condylomata acuminata, and low-risk genital human papillomavirus (HPV) type 11b was detected. Six months later, the tumour had progressed into an ulcerated SCC that destroyed the rectum and perineum, with metastases to the inguinal lymph nodes. Whereas highly active antiretroviral therapy (HAART) effectively suppressed HIV replication, radiochemotherapy plus anti-EGFR antibody did not halt tumour progression, and the patient died from tumour-cachexia.

Discussion—As far as is known, this is the first report demonstrating rapid progression of a BLT into a metastasising SCC in an HIV-infected patient.

A 45-year-old HIV-infected patient had several years' history of recurrent anal and perianal warts with repeated surgical interventions. Recurrent abscesses and fistulae developed, both typical complications of Buschke–Löwenstein tumours (BLT). Histology was consistent with condylomata acuminata. In addition, focal intraepithelial dysplasias grade 2 had evolved. Human papillomavirus (HPV) typing of paraffin-embedded sections, performed by broad-spectrum polymerase chain reaction (PCR) with primers GP5/GP6¹ followed by DNA sequencing, identified low-risk mucosal HPV11b, but no high-risk types. In situ hybridisations (ISH) were positive with probes specific for low-risk HPV6/11 but negative

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Contributors: AH, AR, GS and RK were involved in the clinical care of this patient. AH and CS collected data; AH and RK prepared the manuscript and carried out the literature review; RK and GS reviewed the manuscript before submission; AH and RK revised the manuscript for resubmission; AS supplied the biopsies; ZB-H supplied the histopathology; AB supplied the radiographs.

Competing interests: None.

Patient consent: Obtained.

with probes specific for high-risk HPV16/18 or 31/33 (not shown). Taken together, a diagnosis of BLT was established.

Six months later, the patient presented with an exophytic, papillomatous, ulcerated tumour of the anus and perineum that infiltrated into the surrounding tissues (fig 1A). The anal sphincter apparatus was destroyed, causing faecal incontinence. Multiple fistulae openings draining malodorous, purulent fluid and bilateral inguinal lymphadenopathy were observed.

Computed tomography (CT) and MRI revealed tumour invasion deeply into the surrounding tissues including the anus, the basis of the penis and the prostate. The regional mesenteric, paraaortic and inguinal lymph nodes were enlarged. Cytology of swabs taken from the anal canal showed high-grade dysplastic cells. Due to its far progressed status, the tumour was only partially resected. Histology revealed a mid-differentiated invasive SCC (fig 1B) with bilateral metastases to the inguinal lymph nodes.

For detection of HPV replication, ISH was performed on histological sections of the anal SCC. Numerous tumour cells stained positive with probes specific for low-risk HPV6/11 (fig 1C) but were negative for high-risk HPV16/18 or 31/33 (not shown). To corroborate these findings, samples from the SCC were HPV-typed by PCR and sequencing, revealing low-risk HPV11b genomic DNA. Of note, the lymph node metastases were negative for HPV DNA by both ISH and PCR detection methods.

At a CD4⁺ T cell count (nadir) of 43 cells/mm³, highly active antiretroviral therapy (HAART) was initiated with a combination of tenofovir/emtricitabine and lopinavir/ritonavir. This regimen led to a rapid reduction in HIV viral load and a slow increase in CD4⁺ T cell counts.

Following palliative surgery, the patient received two cycles of combined radiochemotherapy (60 Gy X-irradiation, 10 mg/m² mitomycin C and capecitabine 1650 mg/m²) over 6 weeks. However, after completion, staging by CT revealed no significant reduction in tumour size. The majority of tumour cells (approximately 80%) expressed the epithelial growth factor receptor (EGFR) by immunohistochemistry (data not shown). Thus, cetuximab, an anti-EGFR monoclonal antibody with efficacy against colorectal and anal carcinoma,² was administered intravenously in an initial dose of 400 mg/m², followed by weekly doses of 250 mg/m² for a total of 6 weeks. However, a subsequent MRI demonstrated tumour progression, and the patient died from cachexia 14 months after diagnosis of the anal BLT.

DISCUSSION

Buschke–Löwenstein tumour is a highly differentiated verrucous carcinoma of the anogenital region and is regarded a distinct entity between condylomata acuminata and SCC.³ Similar to benign condylomata acuminata, BLT is caused by low-risk mucosal HPV6 or 11 that generally is not associated with malignant progression.⁴⁵ It differs from benign condylomata by deep infiltrative and destructive growth into adjacent tissues, although histologically these two entities may appear remarkably similar.⁶ In contrast to SCC, BLT lacks malignant histopathological features such as penetration of the basement membrane, abundance of mitotic figures and loss of epithelial stratification. Further hallmarks are extensive fistulation, abscesses and a high recurrence rate up to 66% following surgical ablation. Eventually, BLT may transform focally into SCC.⁷⁸ Although a main risk factor for progression of genital squamous intraepithelial lesions appears infection with high-risk HPV, transformed foci in BLT do not contain high-risk HPV.⁹ In fact, no high-risk HPV types were detected in our patient's tumour by two sensitive molecular biological methods. To the best of our knowledge, there exists only one report, in a renal transplant recipient, of

SCC with regional and distant metastases, that developed from low-risk HPV associated BLT.¹⁰ Interestingly, in our patient, metastases developed rapidly within months, thus resembling traditional anal cancers caused mostly by high-risk HPV infection. The presence of low-risk HPV in both cases suggests that continuous viral gene expression was required for further progression to the malignant phenotype.

HIV-induced immunosuppression may have had the greatest impact on tumour progression. The inability to mount an effective cytotoxic immune response against HPV-infected cells may allow increased viral genome amplification and gene expression, thus increasing the oncogenicity of lower-risk HPV types. This report also supports and extends previous observations that effective suppression of HIV replication by HAART may not improve concomitant HPV-associated cervical, anal or digital disease.^{11–15}

Acknowledgments

We thank D Lowy for critical reading of the manuscript and helpful discussion. We are grateful to S Drexler and C Nava for excellent technical assistance.

Funding: Supported by a grant to RK from the Austrian Science Foundation (FWF; P18990-B13).

REFERENCES

1. Snijders PJ, van den Brule AJ, Schrijnemakers HF, et al. The use of general primers in the polymerase chain reaction permits the detection of a broad spectrum of human papillomavirus genotypes. *J Gen Virol.* 1990; 71:173–81.
2. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med.* 2004; 351:337–45. [PubMed: 15269313]
3. Grussendorf-Conen EI. Anogenital premalignant and malignant tumors (including Buschke-Löwenstein Tumors). *Clin Dermatol.* 1997; 15:377–88.
4. Lehn H, Ernst TM, Sauer G. Transcription of episomal papillomavirus DNA in human condylomata acuminata and Buschke-Löwenstein Tumors. *J Gen Virol.* 1984; 65:2003–10.
5. Gissmann L, deVilliers EM, zur Hausen H. Analysis of human genital warts (condylomata acuminata) and other genital tumors for human papillomavirus type 6 DNA. *Int J Cancer.* 1982; 29:143–6.
6. Kirnbauer, R.; Lenz, P.; Okun, MM. Human papillomavirus. In: Bologna, JL.; Jorizzo, JL.; Rapini, RP., editors. *Dermatology.* 2nd ed.. Mosby; London: 2008. p. 1183–98.
7. Creasman C, Haas PA, Fos TA Jr, et al. Malignant transformation of anorectal giant condyloma acuminatum (Buschke-Löwenstein Tumor). *Dis Colon Rectum.* 1989; 32:481–7. [PubMed: 2791784]
8. Bjorck A, Athlin L, Lundskog B. Giant condyloma acuminatum (Buschke-Löwenstein tumour) of the anorectum with malignant transformation. *Eur J Surg.* 1995; 161:691–4.
9. Haycox CL, Kuypers J, Krieger JN. Role of human papillomavirus typing in diagnosis and clinical decision making for a giant verrucous genital lesion. *Urology.* 1999; 53:627–30.
10. Manias DA, Ostrow RS, McGlennen RC, et al. Characterization of integrated human papillomavirus type 11 DNA in primary and metastatic tumors from a renal transplant recipient. *Cancer Res.* 1989; 49:2514–19.
11. Chin-Hong PV, Palefsky JM. Natural history and clinical management of anal human papillomavirus disease in men and women infected with human immunodeficiency virus. *Clin Infect Dis.* 2002; 35:1127–34.
12. Handisurya A, Rieger A, Bankier A, et al. Human papillomavirus type 26 infection causing multiple invasive squamous cell carcinomas of the fingernails in an AIDS patient under highly active antiretroviral therapy. *Br J Dermatol.* 2007; 157:788–94.

13. Chin-Hong PV, Palefsky JM. Human papillomavirus anogenital disease in HIV-infected individuals. *Dermatol Ther.* 2005; 18:67–76. [PubMed: 15842614]
14. Hagensee ME, Cameron JE, Leigh JE, et al. Human papillomavirus infection and disease in HIV-infected individuals. *Am J Med Sci.* 2004; 328:57–63.
15. Piketty C, Darragh TM, Heard I, et al. High prevalence of anal squamous intraepithelial lesions in HIV-positive men despite the use of highly active antiretroviral therapy. *Sex Transm Dis.* 2004; 31:96–9. [PubMed: 14743072]

Key messages

- ▶ Buschke–Löwenstein tumour (BLT) is a rare, highly differentiated verrucous carcinoma that grows locally but usually does not metastasise.
- ▶ Low-risk genital human papillomavirus (HPV) 6 or 11, which usually causes benign condylomata acuminata, is regularly detected in BLT. In severe immunosuppression, BLT has been shown twice (including this report) to progress to a metastasising squamous cell carcinoma.
- ▶ Effective suppression of HIV replication by highly active antiretroviral therapy (HAART) may not improve concomitant HPV-associated disease.

Figure 1.

(A) Massive, exoendophytic, ulcerated tumour deeply infiltrating the rectum, perineum and surrounding tissues. Multiple fistulae openings exude purulent fluid. (B) Haematoxylin–eosin stained section of the anal cancer (magnification $\times 100$). Acanthosis and multiple koilocytes are present. (C) In situ hybridisation of the anal cancer. Low-risk HPV6/11-positive tumour cells are present throughout the lesion (magnification $\times 40$).