Verrucous carcinoma of the anus containing human papillomavirus type 16 DNA detected by in situ hybridisation: a case report

Fuji Chang, O Kosunen, V-M Kosma, S Syrjänen, J Lahtinen, K Syrjänen

Abstract
Verrucous carcinoma of the anus is a distinct and rare variant of well-differentiated squamous cell carcinoma. A case of anal verrucous carcinoma in a 35 year old man was studied by light microscopy and in situ DNA hybridization. Human papillomavirus (HPV) type 16 DNA sequences were demonstrated in the tumour cells, as well as in cells showing koilocytotic and dyskeratotic changes. The possible viral (HPV) aetiology of verrucous carcinoma is considered with a review of the previous literature.

Case report
A 35 year old man was submitted into Kuopio University Central Hospital in November 1989 with the complaint of an exophytic tumour in the anal region. The tumour had been in its place more than five years, but during the last few months, it had...
begun to grow and to cause pain. The tumour did not interfere with the patient's defecation, and there was no dysuria. So far, no data on patient's eventual homosexual behaviour or results of HIV test are available.

On gross examination, there was an exophytic mass involving the perianal skin, measuring $2 \times 3$ cm. The tumour was gray-white, rough surfaced and warty in appearance. Radical excision of the tumour was carried out, and the material was submitted for histopathological examination.

Histological sections were stained with haematoxylin and eosin. Microscopic examination revealed the morphological features consistent with a verrucous carcinoma. The tumour was composed of papillary fronds of well-differentiated squamous epithelium with extensive hyperkeratosis and parakeratosis (or superficial dyskeratosis) (fig 1). The epithelium was hyperplastic and penetrated into the underlying tissues in broad bulbous downgrowths, that is, was pushing rather than infiltrating. The cells in the superficial and intermediate layers showed extensive koilocytic changes morphologically identical to those of condylomatous lesions (fig 2). The tumour stroma was infiltrated by abundance of chronic inflammatory cells.

In situ hybridisation on paraffin-embedded sections using $35S$-labelled HPV DNA probes was performed as detailed previously. DNA probes of HPV types 6, 11, 16, and 18 were kindly provided by Professor H. zur Hausen (Deutsches Krebsforschungszentrum, Heidelberg, FRG). Abundant HPV 16 DNA sequences were demonstrated particularly in the superficial epithelium which correlated well with the presence of condylomatous lesions, as indicated by the black silver grains superimposed on nuclei of koilocytotic and dyskeratic cells. In addition, HPV 16 DNA sequences were found in the cancer cells as well (fig 3).

**Discussion**

Anal verrucous carcinoma is a rare disease, and the case reports published so far are much fewer than those related to oral, larynx and external genitalia. The clinical and morphological features of anal verrucous carcinomas are similar to those in the other anatomical sites. Clinically, it shows a slowly-growing course and a relatively favourable prognosis with little metastatic potential. The histopathological changes include a thickened papillary epithelium showing hyperkeratosis and parakeratosis in the upper layers, and acanthosis in the underlying layers. The epithelium is well-differentiated, and usually forms large bulbous rete ridges with well-demarcated borders pushing into the underlying stroma.

However, the diagnosis of verrucous carcinoma in the anogenital area may encounter problems both clinically and histologically. Differential diagnosis, including condylomata acuminata, giant condyloma acuminatum (also known as Buschke-Lowenstein tumour), pseudo-epitheliomatous hyperplasia as well as keratinising squamous cell carcinoma, has been thoroughly discussed by a number of previous authors. The aetiology of verrucous carcinoma is not generally agreed. In the oral cavity it has been previously related to cigarette smoking and tobacco chewing, to poor oral hygiene, or poor dentation. Penile lesions, on the other hand, have been linked with the presence of redundant prepuce, poor hygiene, or preexisting condylomata acuminata. Of particular interest is the possible viral aetiology of verrucous carcinoma. The histological appearance, that is, papillomatosis, koilocytosis, acanthosis and superficial dyskeratosis found in verrucous carcinoma, seems to bear a close resemblance to the cytopathic changes caused by HPV. Okagaki examined 12 of 27 cases of vulvar verrucous carcinoma by electron microscopy and found eight cases with intranuclear HPV-like particles in the superficial layer of the epithelium. Similar results...
were reported also in cervical\textsuperscript{18} vaginal\textsuperscript{11} and penile\textsuperscript{25} verrucous carcinomas. Recently, Blessing \textit{et al.}\textsuperscript{12} examined three cases of verrucous carcinoma (one perineal, one penile and one laryngeal); all of them showed HPV capsid proteins with immunoperoxidase technique. More recently, HPV type 6, 11 and 16 DNA sequences were demonstrated in verrucous carcinomas of the larynx,\textsuperscript{16} vagina\textsuperscript{20} and vulva.\textsuperscript{17} The presence of HPV 16 DNA sequences in the present case of anal verrucous carcinoma by in situ DNA hybridisation further supports the concept that verrucous carcinoma might share a common viral aetiology with condylomatous lesions.

It is noteworthy that strong evidence has been provided during the past few years implicating an important aetiological role of HPV infection in the development of anogenital intraepithelial neoplasia and squamous cell carcinoma.\textsuperscript{19,26-28} There have been many case reports of anogenital intraepithelial neoplasia and carcinoma in situ with condylomatous lesions in or in the adjacent mucosa. Similarly, numerous reports on malignant transformation of the anogenital condylomata and giant condylomas have been published.\textsuperscript{26-28} With histopathological assessment, Taxy \textit{et al.}\textsuperscript{29} found that 10 of 16 cases of anal squamous cell carcinoma were associated with condylomatous changes. Using Southern blot and dot blot hybridisation techniques, Palmer \textit{et al.}\textsuperscript{30} recently analysed a large group of anal squamous cell carcinoma. HPV 16 DNA sequences were detected in 23 of 41 and HPV 18 in 2 of 41 cases; no detectable HPV 6 or 11 DNA sequences were found in these malignancies. These findings have close parallels with genital squamous cell carcinomas and further support the concept of the involvement of HPV 16 and 18 in development of anal squamous cell carcinoma.

Therefore, the different morphological lesions, i.e. condylomata acuminata, giant condyloma acuminatum and verrucous carcinoma (and perhaps squamous cell carcinoma) could be interpreted as closely related entities, probably caused by HPV infection, and thus may represent a continuous spectrum of the same process, HPV-induced squamous cell carcinogenesis.
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