

Cervical intraepithelial neoplasia and squamous cell carcinoma of the anus in sexually active women

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Summary: Twenty-five patients with squamous cell carcinoma (SCC) of the anus have presented over an 8 year period; 18 were female. Six of 9 patients aged under 50 years were female. Five of these women had been treated for a previous cervical malignancy (2 invasive) and 4 practised anal intercourse; human papillomavirus (HPV) type 16 DNAs were isolated from their cervical anal/cervical paraffin sections. Signals were confined to the nuclei of the invasive anal SCC cells and the transformation zone of the cervix. HPV 6, 11 and 18 DNAs were not identified. Young women with cervical intraepithelial (CIN) III or invasive cervical SCC found in association with HPV infection are at risk of developing anal SCC ($P < 0.001$; Fisher's exact).

Introduction

Carcinomas arising within the anal canal and its margins are rare, accounting for only 2% of all carcinomas of the colon, rectum and anus, or about 330 cases a year in England and Wales.¹ Because of this, the number of cases presenting to individual surgeons will be very small and consequently the natural history becomes difficult to access. Recently it has been suggested that anal squamous cell carcinoma (SCC) may be related to the sexual transmission of the human papillomavirus.² In examining our experience of anal SCC we have defined a group of patients that seems to be at particular risk of developing this uncommon malignancy.

Patients and methods

The case notes of all 25 patients with anal SCC that presented to two health districts over an 8-year period (1980–1988) were studied and the histology reviewed. Five women with metachronous anal and cervical SCCs were identified. These women were reviewed as outpatients and a sexual history obtained. Formol-saline fixed, paraffin wax embedded archive material from these 5 female patients was then examined for HPV-6, 11, 16 and 18 DNAs using both *in situ* hybridization and Southern blot analysis.³ DNA studies were not performed on the remaining 20 patients.

Results

The median age at presentation of the 25 patients with anal SCC was 68 years (range 30–79); all but 7 were female. Only 9 patients were under 50 years of age at presentation, 6 of these being female (range 30–50 years). The commonest presenting symptoms were bleeding, pain, pruritus ani and the sensation of an anal swelling. One male patient had coexisting condyloma accuminatum.

Five of the female patients aged below 50 reported a past medical history of a previously treated cervical malignancy (Table I). Cervical malignancies predated the anal SCCs by between 4 and 13 years. The two patients with invasive cervical SCCs (stage I) had been treated by a Wertheim's hysterectomy followed by radiotherapy. The three *in situ* carcinomas (CIN III) were treated by abdominal hysterectomy after an initial cone biopsy. One patient, a prostitute had also been treated for rectal gonorrhoea; she later had an area of Bowen's disease excised from her perineum. Four of these women admitted to practising anal intercourse. Only one of these women, the prostitute, had attended a genitourinary clinic in the past. Three of the anal SCCs were suitable for treatment by local excision followed by radiotherapy, three required an abdominoperineal resection.

Human papillomavirus DNA hybridization studies and Southern blot analysis,³ on formol-saline fixed paraffin wax embedded archive material taken from the sub-group of 5 women, failed to identify HPV 6, 11 or 18 DNAs; the metachronous carcinomas did, however, contain active HPV 16 DNA infection. The HPV 16 positive cells were

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Table I Summary of 5 patients with anal squamous cell carcinoma and previous cervical malignancy

Age of anal SCC presentation	50	34	43	42	35
Tumour differentiation	G2	G2	G3	G2	G2
Treatment	APR	LEx & RT	APR	LEx & RT	LEx & RT
Time since cervical malignancy (years)	5	8	13	4	6
Cervical lesion and its treatment	Stage I RT & WH	CIN III H	CIN III H	Stage I RT	CIN III H
HPV 16 DNAs					
Anal	+	+	+	+	+
Cervical	+	+	+	+	+
Bowen's	-	+	-	-	-

APR = abdominoperineal resection; LEx = local excision; RT = radiotherapy; WH = Wertheim's hysterectomy; H = abdominal hysterectomy; G = Grade; 2 = moderate; 3 = poor; CIN = cervical intraepithelial neoplasia.

confined to the squamous epithelium of the cervical transformation zone and the nuclei of the invasive tumours cells within the anal mucosa. HPV 16 signals were only observed within the invasive/pre-invasive carcinoma cells and not in the surrounding stroma or control tissue sections (genital condylomas, palatine tonsil). The same HPV 16 signal was also obtained from the Bowen's diseased skin excised from one patient's perineum.

In 1981 the prevalence of *in situ* cervical carcinoma in Leicestershire was 5.6 per 1,000; the rate of one anal cancer arising within the population free of cervical cancer at 8 years is calculated at 0.09 per 1,000. It is thus very unlikely that the two malignancies are chance associations; Fisher's exact test $P < 0.001$.

Discussion

Anal SCC is a rare disease and most surgeons encounter only a few cases sporadically. An aetiological association between anal cancer and a sexually transmissible agent was first suggested from epidemiological data by Cooper in 1979.⁴ Other studies have supported this hypothesis, Austin reporting an association between male homosexuality and anal cancer.⁵ Recent reports² have suggested an association between anal SCC and human papillomavirus type 16 (HPV 16), the same HPV sub-type as is associated with invasive and intraepithelial cervical neoplasia.⁶ In a study that looked at human papillomavirus infection and multifocal intraepithelial neoplasia arising within the female lower genital tract,⁷ two cases of intraepithelial neoplasia (AIN) were seen in biopsies taken from near Hilton's line; no significance was attached to this finding. Anal intraepithelial neoplasia (AIN) had been considered rare until the findings of a recent study that looked at patients

presenting to a department of genitourinary medicine.⁸ AIN was found in 28% of patients that had coexisting anal human papillomavirus infection (HPV), the prevalence of AIN being highest in male homosexuals. When female patients with active anal HPV infection were examined, 35% had evidence of low-grade cervical intraepithelial neoplasia (CIN); 17% had evidence of both AIN and CIN.

Our study supports these findings and suggests that within a normal surgical practice outside of a London genitourinary clinic, the prevalence of CIN III/invasive cervical cancer found in association with anal SCC is surprisingly high. Although this is a small retrospective series the findings cautiously suggest that high-grade AIN found in association with HPV 16 infection needs appropriate therapy. Young sexually active women with active genital HPV 16 DNA infection associated with cervical malignancy seem to be at particular risk of developing this rare malignancy. We would suggest that, for gynaecologists treating these patients, a regional concept of disease needs to be considered, if not anticipated, particularly as the carcinogenic stimuli is likely to persist. The observation that CIN/invasive cervical carcinomas precede anal carcinomas suggests that these women had been exposed more frequently to a sexually transmissible agent, possibly acting as a cofactor; although all 5 women had admitted to anal intercourse this was infrequent. The most sexually active of our patients, a prostitute, also developed perineal Bowen's disease, again in association with active HPV 16 DNA infection.

In attempting to define the size of the problem and its natural history, we are currently applying colposcopy techniques to the examination of the anal canal⁸ in a series of 80 sexually active young women currently under follow-up for CIN II and III associated with active HPV 16 infection.

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