

# Squamous carcinoma of the anus in young homosexual men with T helper cell depletion

LINDA C HOWARD,\* S PATERSON-BROWN,† J N WEBER,\* S T F CHAN,† J R W HARRIS,\* AND G GLAZER†

From the \*Praed Street Clinic and the †Department of Surgery, St Mary's Hospital, London

**SUMMARY** Two cases of squamous carcinoma of the anus in white homosexual men aged 36 and 47 years are reported, each with a short history of rapidly enlarging perianal lesions. Immunological studies showed that both men had pronounced T helper lymphocyte depletion, and antibody to human T cell lymphotropic virus type III (HTLV-III) was detected in both patients. In addition one patient had a long history of wart virus infection of the anal canal.

The diminished cellular immunity associated with HTLV-III may have been responsible for the development of the squamous carcinoma, either directly or by its association with human papilloma virus infection.

## Introduction

Carcinoma of the anus is a relatively rare tumour that generally presents in older people. Since 1979, however, there have been increasing reports of younger homosexual men developing this cancer.<sup>1-4</sup> In these reports the commonest histological pattern of the tumour was squamous, and the most recent papers noted a possible association with human papilloma virus (HPV) infection, lymphocyte abnormalities, the acquired immune deficiency syndrome (AIDS), and the AIDS related complex.<sup>3,4</sup>

We report here two further cases of squamous carcinoma of the anus in young homosexual men with evidence of T helper cell depletion, which further supports the theory that virally induced tumours may occur more commonly in this group of patients.

## Case reports

### CASE 1

A 36 year old homosexual man gave a six week history of perianal swellings, which initially resembled perianal warts, but then increased rapidly in size and bled on contact. He had lost one stone in weight but had no bowel symptoms. Apart from having had treatment for syphilis eight years previously and a long

history of perianal warts, his medical history was unremarkable.

On examination there was non-tender mobile lymphadenopathy in the cervical, axillary, and inguinal regions. The perianal lesions were raised, indurated, and exuded pus. Clinically they resembled large infected warts 4 × 3 cm on the left and 2 × 2 cm on the right of the anus, which extended into the anal canal almost to the dentate line.

Hepatitis B surface antibody (HBsAb) was detected by an enzyme linked immunosorbent assay (ELISA, Abbot). An ELISA (Organon) gave weakly positive results for antibody to human T-cell lymphotropic virus type III (HTLV-III), and the Venereal Disease Research Laboratory (VDRL) test gave strongly positive results for syphilis, at a titre of 1/256. The lymphocyte count was  $2.0 \times 10^9/l$ , T helper cells were 17% ( $0.34 \times 10^9/l$  (normal  $> 0.54 \times 10^9/l$ )), T suppressor cells were 45%, and the ratio of T helper to T suppressor cells was 0.4 (normal  $> 1.2$ ). (Lymphocyte subsets were measured by Ficoll-Hypaque separation and staining with monoclonal antibodies, Leu 2a and Leu 3a (Becton Dickinson)).

In view of the high VDRL titre, conventional treatment with intramuscular depot penicillin was started. The anal lesions progressed during antibiotic treatment, and a biopsy specimen showed a well differentiated invasive squamous cell carcinoma.

The lesions were completely excised locally with preservation of sphincter function. Bilateral inguinal lymph nodes were sampled and showed benign reactive hyperplasia only. Follow up at nine months

Address for reprints: Dr Linda C Howard, Department of Genitourinary Medicine, Westminster Hospital, Dean Ryle Street, London SW1P 2AP

showed a well healed anus, with no evidence of local or distant recurrence of tumour.

#### CASE 2

A 47 year old homosexual man gave a six week history of a discharging perianal lesion and the passage of stools streaked with blood and mucus. He had no history of either perianal warts or sexually transmitted disease, and had otherwise been fit and well.

On examination, he had a temperature of 38°C, but no lymphadenopathy. There was an infected indurated lesion to the right of the anal margin, which extended into the anal canal above the dentate line.

Syphilis serology tests gave positive results, with a VDRL titre of 1/128, *Neisseria gonorrhoeae* was isolated from a rectal swab, HBsAb was not present in the serum, but antibodies to HTLV-III were detected by ELISA (Organon). Immunological studies showed a lymphocyte count of  $1.2 \times 10^9/l$  with T helper cells  $0.4 \times 10^9/l$ , T suppressor cells  $0.6 \times 10^9/l$ , and a ratio of T helper to T suppressor cells of 0.6 (methods used were the same as in case 1). Anergy to three recall antigens, purified protein derivative of tuberculin (PPD) 1/1000, *Candida albicans*, and streptokinase or streptodornase, was seen at 48 hours.

The patient was treated with depot penicillin for his syphilis and spectinomycin for his rectal gonorrhoea, and a biopsy specimen of the anal lesion showed a moderately well differentiated squamous cell carcinoma of the anus. Abdominoperineal resection of the rectum was carried out, and the patient remained well for six months. He has recently been readmitted to hospital with a large pelvic recurrence and hepatic metastases.

#### Discussion

Carcinoma of the anus is relatively rare in the United Kingdom and less than 100 cases a year are reported by the Office for Population and Census Survey (OPCS) (table I), with no documented increase in the past five years. At this hospital, however, the number of patients with this tumour, though small, has risen since 1983, with four patients a year now presenting (table II). The tumour is also appearing in association with homosexuality.

This trend has been noted in various published reports about homosexual men.<sup>1-4</sup> Cooper *et al* reported four homosexual men (mean age 42 years) with cloacogenic carcinoma of the anus, three of which had squamous features.<sup>1</sup> Leach and Ellis reported two cases of adenocarcinoma of the rectum in homosexuals aged 36 and 39 years.<sup>2</sup> Frederick *et al* reported two squamous carcinomas in homosexual men aged 34 and 53, one of whom had a 30 year history of perianal warts.<sup>3</sup> Both these patients had normal lymphocyte counts at presentation, though one of them had a falling

TABLE I Data for 1979-84 from the Office for Population Census and Survey (OPCS) showing yearly incidence of squamous carcinoma of the anus in men and women

Year	Anus unspecified		Anal canal	
	Men	Women	Men	Women
1979	44	45	14	27
1980	40	52	18	27
1981	29	50	21	24
1982	34	52	25	25
1983	48	40	20	24
1984	37	58	21	32

lymphocyte count at follow up, but a normal distribution of T helper and T suppressor cells.

Crosson *et al* reported seven homosexual men with condylomata accuminata and squamous carcinoma-in-situ in adjacent anal mucosa.<sup>4</sup> On histological examination all the lesions displayed evidence of papillomavirus infection. Three of the patients had AIDS according to the Center for Disease Control (CDC) definition, and another had AIDS related symptoms.

The two patients reported here were both relatively young men, compared with men with this tumour reported by the OPCS (mean age at diagnosis 67 years). Their histories were extremely short, and in both cases the tumours appeared clinically to have an infectious rather than neoplastic aetiology (one warts and the other an abscess), and the biopsy results were unexpected. The positive syphilis serology results were thought to represent an anamnestic response, and no treponemes were found in either case despite specific staining of the biopsy specimens and dark ground examination of the lesions. The finding of a positive HTLV-III serology test result in one patient and a weakly positive reaction in the other, who also had generalised lymphadenopathy, suggests that HTLV-III infection may be implicated.

TABLE II Yearly incidence of squamous carcinoma of the anus at St Mary's Hospital, London, 1979-85. (Age at presentation (in years) in parentheses)

Year	Men	Women
1979	0	0
1980	1 (79)	
1981	0	0
1982	1 in-situ (40)	1 (70)
1983	0	2 (60 and 56)
1984	2 (48 and 74)	2 (83 and 64)
1985	3 (36, 47 and 70)	1 (69)

Both herpes simplex virus and HPV have been implicated in the pathogenesis of carcinoma of the cervix in women.<sup>5</sup> Cells of the transitional zone of the anorectal junction and the female cervix uteri have a common embryological origin, and Stern and Kaplan reported a series of 10 women with carcinoma of the cervix, in whom there was either coexistent or subsequent anal carcinoma.<sup>6</sup> Similar risk factors may therefore apply to carcinogenesis at these sites. There is also considerable evidence of squamous carcinoma and carcinoma-in-situ developing in longstanding condylomata accuminata.<sup>7-11</sup>

The series of seven homosexual men of Croxson *et al* suggested an association between HPV infection, HTLV-III infection, squamous carcinoma, and carcinoma-in-situ.<sup>4</sup> The aetiology of the anal cancer in one of the homosexual men that we have reported may well represent the effects of HPV infection in an HTLV-III affected person with a compromised immune system, as shown by T helper cell depletion and cutaneous anergy to recall antigens. It is not clear whether HTLV-III alone is carcinogenic, though this could be supported by the fact that the second patient did not apparently have a history of HPV infection. If the former interpretation (that combined infections are the cause) is correct, we may expect to see a rise in the incidence of squamous carcinoma of the anus in homosexual men, and possibly an increase of squamous carcinoma at other sites that HPV may infect, such as the tongue. Evidence for this is accumulating, and Daling *et al* have reported an increase in squamous carcinoma of the anus in unmarried men in New York with a history of syphilis; these men were assumed but not proved to be homosexual.<sup>12</sup> In addition, Shemen *et al* have shown an increasing incidence of carcinoma of the tongue in New York men.<sup>13</sup>

Homosexual men presenting with enlarging perianal lesions, with or without a history of anal warts, who may be at risk of HTLV-III infection, should undergo an early biopsy to exclude malignancy. This will also apply to patients with positive syphilis serology test results who have lesions resembling condylomata lata, if these lesions do not respond promptly to penicillin treatment.

Both our patients underwent surgical excision of their lesions, and though it is not the intention of this

report to discuss the alternative forms of treatment of squamous carcinoma of the anal canal, there is clearly a need for further documentation to assess the relative merits of surgery or radiotherapy, or both, with or without chemotherapy, in this group of "high risk" patients.

The oncological implications of HTLV-III infection may have to be extended to include more virally mediated tumours, particularly squamous carcinomas; this is analagous to the development of squamous malignancies in immunosuppressed patients who have had renal transplants.<sup>14</sup>

#### References

1. Cooper HS, Patchefsky AS, Marks G. Cloacogenic carcinoma of the anorectum in homosexual men: an observation of four cases. *Dis Colon Rectum* 1979;22:557-8.
2. Leach RD, Ellis H. Carcinoma of the rectum in male homosexuals. *J R Soc Med* 1981;74:490-1.
3. Frederick P, Osborn D, Cronin C. Anorectal squamous carcinoma in two homosexual men. *Lancet* 1982;ii:391.
4. Croxson T, Chasen A, Rorat E, Barash I. Intra-epithelial carcinoma of the anus in homosexual men. *Dis Colon Rectum* 1984;27:325-30.
5. zur Hausen H. Human genital cancer: synergism between two virus infections or synergism between a virus infection and initiating events? *Lancet* 1982;ii:1370-2.
6. Stern BD, Kaplan L. Multicentric foci of carcinomas arising in structures of cloacal origin. *Am J Obstet Gynecol* 1969;104:255-66.
7. Siegel A. Malignant transformation of condyloma accuminatum. Review of the literature and report of a case. *Am J Surg* 1962;103:613-7.
8. Friedberg MJ, Serlin O. Condyloma accuminatum: its association with malignancy. *Dis Colon Rectum* 1963;6:352-5.
9. Fitzgerald DM, Hamit HF. The variable significance of condylomata accuminata. *Ann Surg* 1974;179:328-31.
10. Lee SH, McGregor DH, Kuzioz MN. Malignant transformation of perianal condylomata. *Dis Colon Rectum* 1981;24:462-7.
11. Boxer R, Skinner D. Condylomata accuminata and squamous cell carcinoma. *Urology* 1977;9:72-8.
12. Daling JR, Weiss NS, Klopfentien LL, Cochran LE, Chow WH, Daufuku R. Correlates of homosexual behaviour and the incidence of anal cancer. *JAMA* 1982;247:1988-90.
13. Shemen LJ, Klotz J, Schottenfield D, Strong EW. Increase of tongue cancer in young men. *JAMA* 1984;252:1857.
14. Koranda SC, Dehmel EM, Kahn G, Penn I. Cutaneous complications in immunosuppressed renal homograft recipients. *JAMA* 1974;229:419-24.