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Buschke-Loewenstein tumour

A histologic and ultrastructural study of six cases

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Summary. Results on the light- and electron microscopic studies of six cases of Buschke-Loewenstein tumour are presented. The role of chronic irritation is emphasized in the aetiology of the tumour. Fistulas and abscesses arising in the tumour are dangerous as they give rise to chronic sepsis.

In two perianal tumours, in situ or invasive carcinoma developed.

Electron microscopy revealed varying degrees of differentiation of keratinocytes. As a result of the defective desmosomes, the tumour cell underwent segregation, with widened intercellular spaces containing oedema, erythrocytes and leucocytes. This phenomenon is probably responsible for frequent bleeding and fistula formation. The investigations disclosed that the Buschke-Loewenstein tumour is a special form of squamous carcinoma and therefore, radical surgical excision must be attempted even in case of a benign histological picture.

Key words: Buschke-Loewenstein tumour – Giant condyloma – Anogenital region – Electron microscopy

Buschke-Loewenstein tumour is a rare tumour affecting the penis, vulva, scrotum or the perianal region. Its macroscopic and microscopic appearance and biological behaviour suggest that it should be considered as an entity. The tumour is slow growing, painful, cauliflowerlike mass with a tendency to ulceration. Among the growths, deep fistulas may arise with exudation of foul-smelling fluid containing keratin and pus. The tumour generally involves large areas of the skin surface showing partly exophytic and partly endophytic growth. It does not produce either lymph node – or distant metastases (Alexander and Kaminsky 1979; Ananthakrisnan et al. 1981; Dawson et al. 1965; Harvey et al. 1983; Hornstein and Weidner 1969; Judge 1969; Kisbenedek and Szilágyi 1977; Machacek and Weakley 1960).

This bizarre tumour is characterized histologically by a seemingly benign epithelial proliferation. Due to discrepancies between the clinical appearance and the histological diagnosis, multiple excisions are usually performed. Recognizing the correct diagnosis and performing the adequate therapy are of great practical importance (Dawson et al. 1965). In some cases, the Buschke-Loewenstein tumour may transform into genuine in situ or invasive carcinoma (Dawson et al. 1965; Nasemann 1973; Sturm et al. 1975).

Differentiation from condyloma acuminatum can be difficult, because condyloma acuminatum tends to expand. In addition, several reports have apeared on malignant change in vulvar condyloma acuminatum (Blaustein 1982; Daling et al. 1984; Kovi et al. 1974; Lee et al. 1981; Lupulescu et al. 1977; Rastkar et al. 1982). According to Prasad and Abcarian (1980) perianal condylomata have a tendency to become malignant, particularly when associated with fistula. Intraepithelial carcinoma of the anus has occurred in a homosexual man (Croxson et al. 1984).

Some authors consider the Buschke-Loewenstein tumour to be identical with the Ackermann's verrucous carcinoma of the oral mucosa or of the skin (Kao et al. 1982; Klima et al. 1980; Kraus and Perez-Mesa 1966; Prioteau et al. 1980), while it is regarded as separate entity by others (Hull et al. 1981; Mostofi and Price 1973). Verrucous carcinoma is characterized by a benign histological

picture, slow growth and by absence of metastases (Lever 1983; Prioteau et al. 1980). Carcinoma cuniculatum of the sole also belongs to this group of tumours (Kao et al. 1982; Klima et al. 1980).

Electron microscopic studies of the Buschke-Loewenstein tumour have so far been published only by Hull et al. (1981) and by Orfanos (1972).

We present detailed light- and electron microscopic studies of six Buschke-Loewenstein tumours. In two perianal tumours, malignant transformation occurred. The electron microscopic study aimed at comparing the mature and dedifferentiated cells of the tumours.

Material and methods

From 1974–1984, six cases of Buschke-Loewenstein tumour were observed in our hospital. The clinical features of the patients are listed in Table 1. Patients ranged in age from 26 to 61 with a sex distribution of four men and two women. In one case the tumour was located in the glans penis, in one case in the inguinal region (Fig. 1) in one case in the vulvar and perianal regions and in three cases surrounding the anus. In the first case of tumour of the penis was associated with phymosis. In the fourth case, the perianal tumour had arisen around the orifice of the fistula of 20 years's standing. In the fifth case, the patient had been treated 20 years for ulcerative colitis.

The duration of the tumour varied from three months to ten years. In three cases, there were several recurrences after

Table 1

No.	Age (yr)	Sex	Location	Size (cm)	Duration	Treatment	Follow-up
1.	35	male	inguinal region	12 × 10 × 10	10 years	radical operation	free of recurrence after one year
2.	42	male	glans penis	5 × 4 × 4	3 months	amputation of penis	free of recurrence after half a year
3.	26	female	vulva, perianal, gluteal region	17 × 13 × 10	6 months	repeated excisions	died after 15 months
4.	43	male	perianal region	12 × 10 × 8	10 years	repeated excisions	free of recurrence after four years
5.	35	male	perianal region	15 × 10 × 2	2 years	radical operation	free of recurrence after two years
6.	61	female	perianal region	6 × 6 × 4	1 year	radical operation	free of recurrence after one year

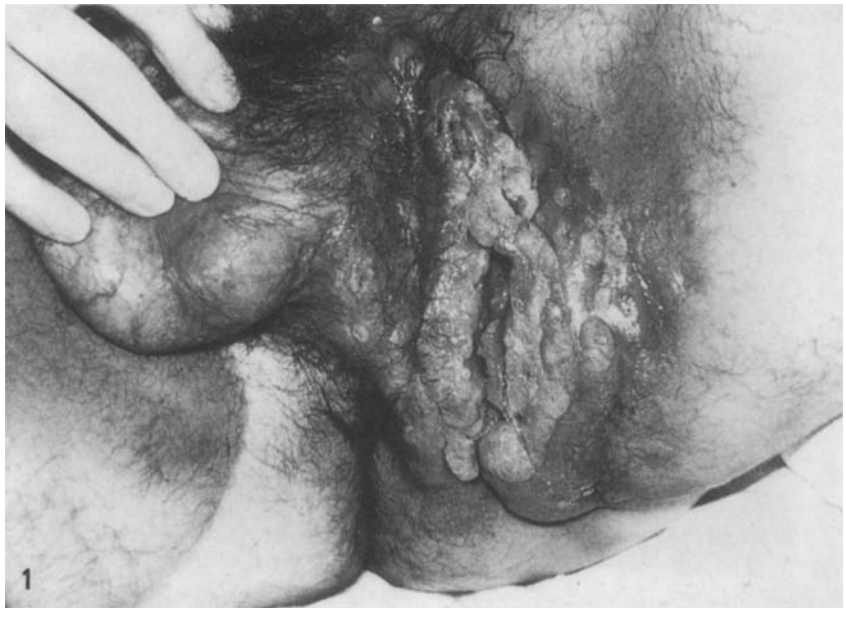


Fig. 1. Ulcerated Buschke-Loewenstein tumour in the inguinal region of a 35-year-old man (Case 1)

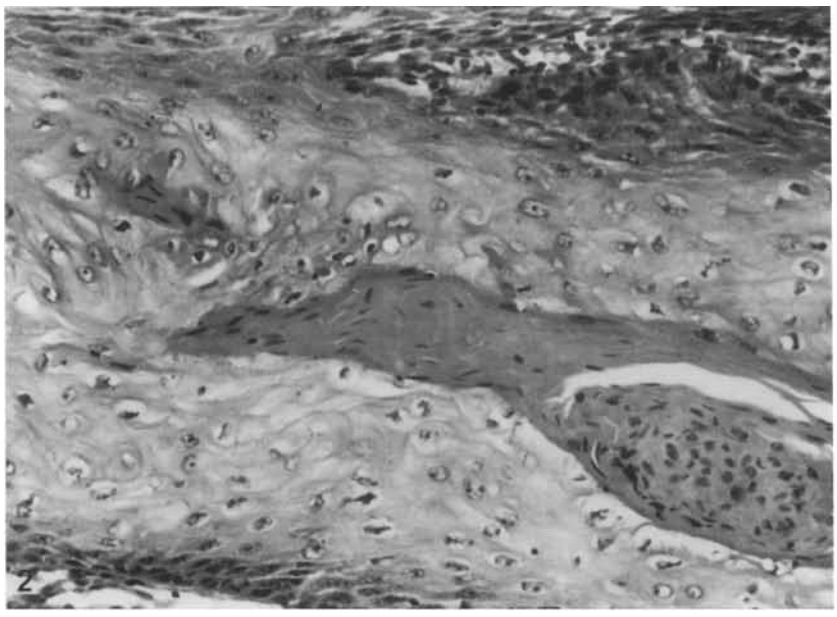


Fig. 2. Well-differentiated keratinizing squamous epithelium. (Case 2) H and E ×250

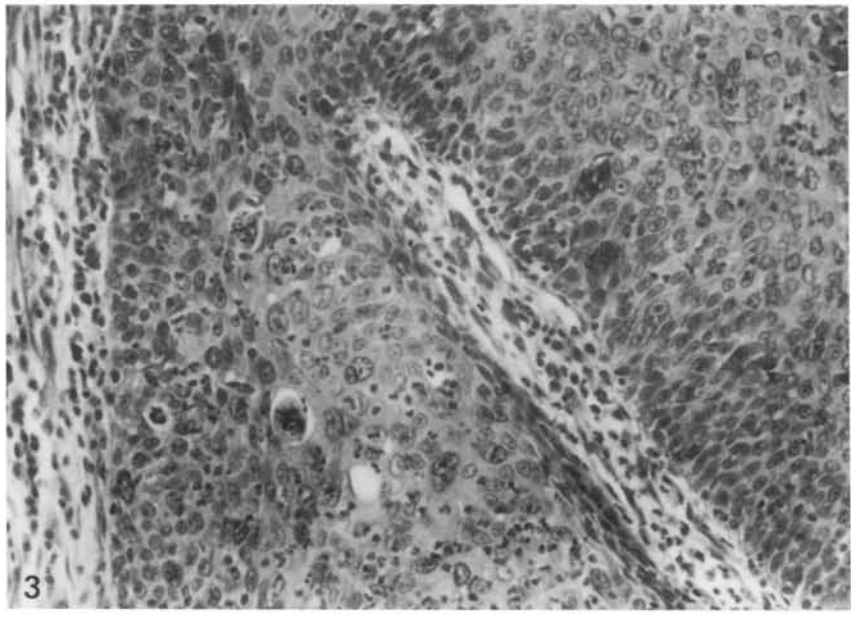


Fig. 3. In situ carcinoma with severe epithelial atypia, pleomorphism, anaplasia. (Case 5) H and E ×225

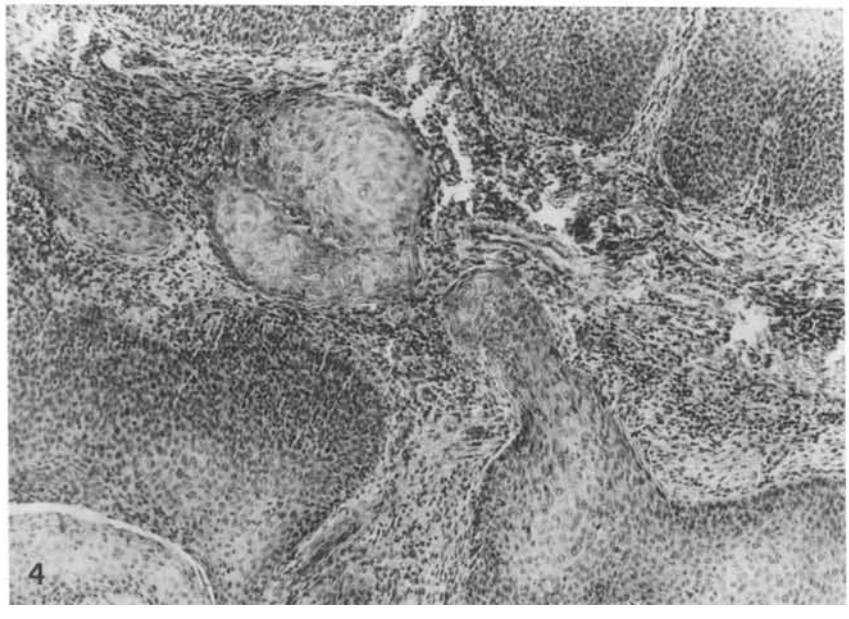


Fig. 4. In deep regions of the sixth tumour, invasive squamous cell carcinoma is present. H and E ×150

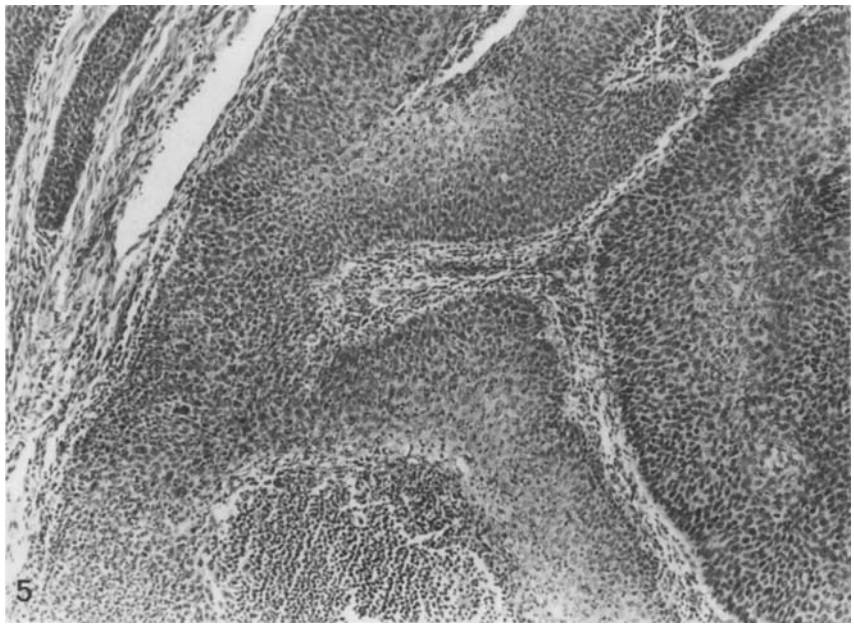


Fig. 5. Case 6: Intraepidermal microabscesses. H and E ×150

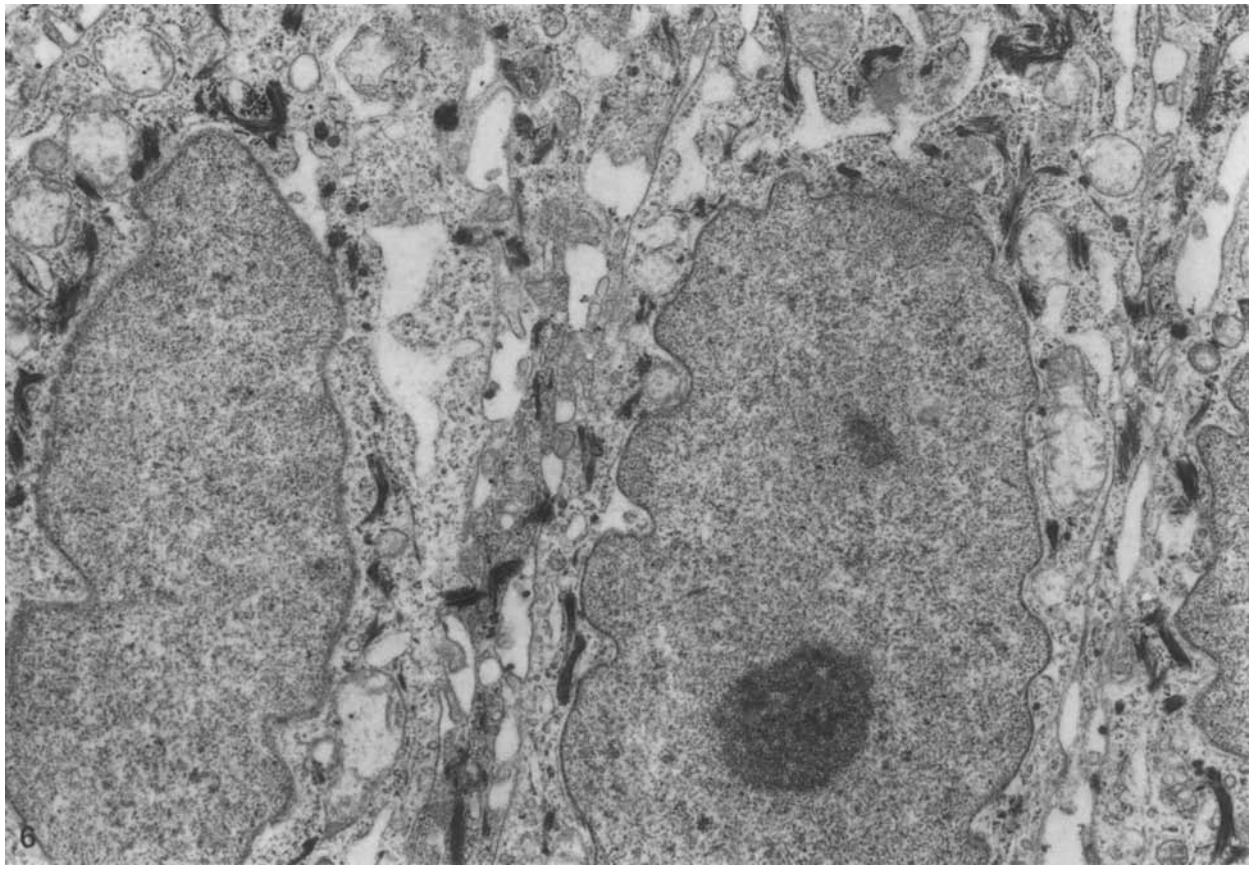
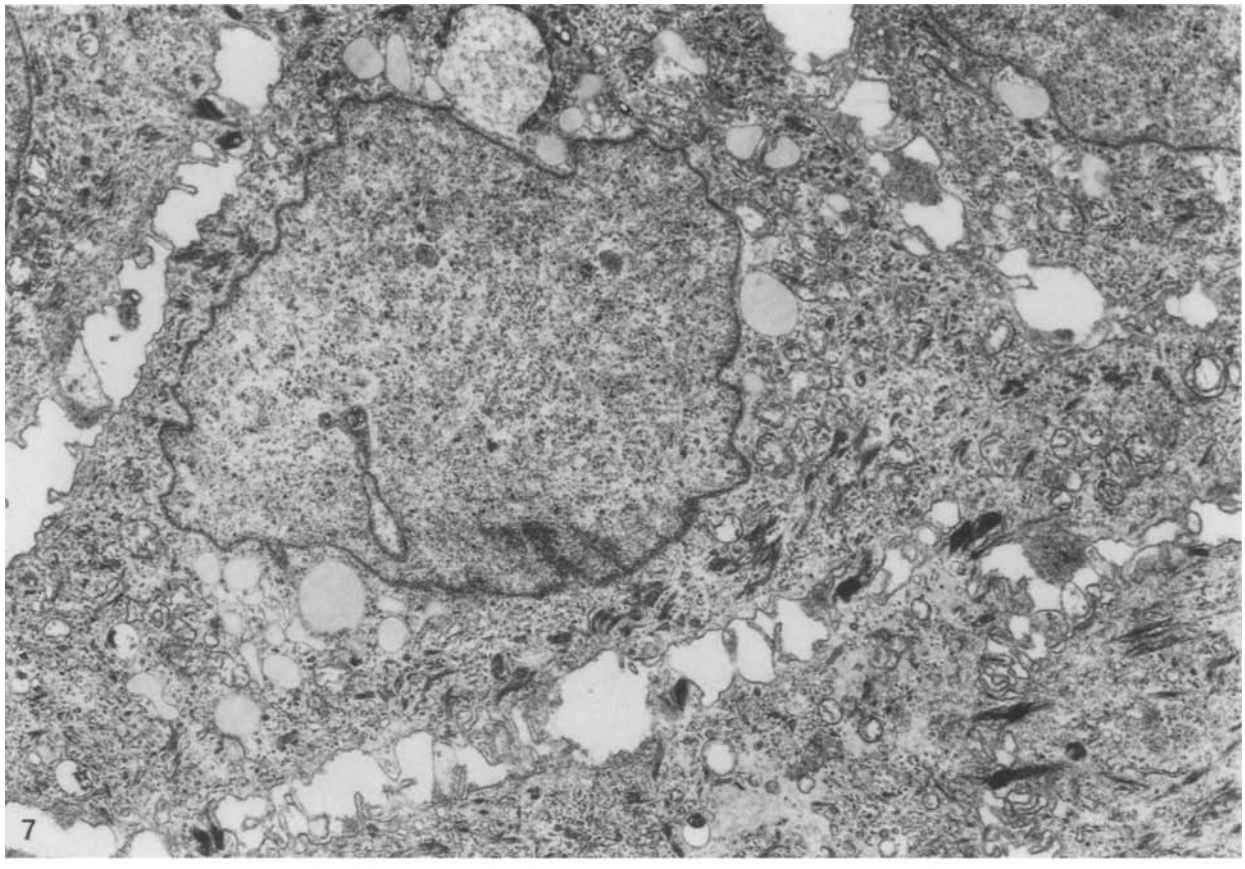


Fig. 6. Electron micrograph shows the tumour consisting of well differentiated keratinocytes. The number of tonofilaments is decreased. ×6,000

Fig. 7. The dedifferentiated keratinocyte contains irregular nucleus. The cytoplasmic organelles are reduced in number. The cells are connected by a small number of desmosomes. Tonofilaments are short and irregularly clumped. ×6,000

Fig. 8. On the lateral cell membrane, several processes are present with a large number of desmosomes. ×16,560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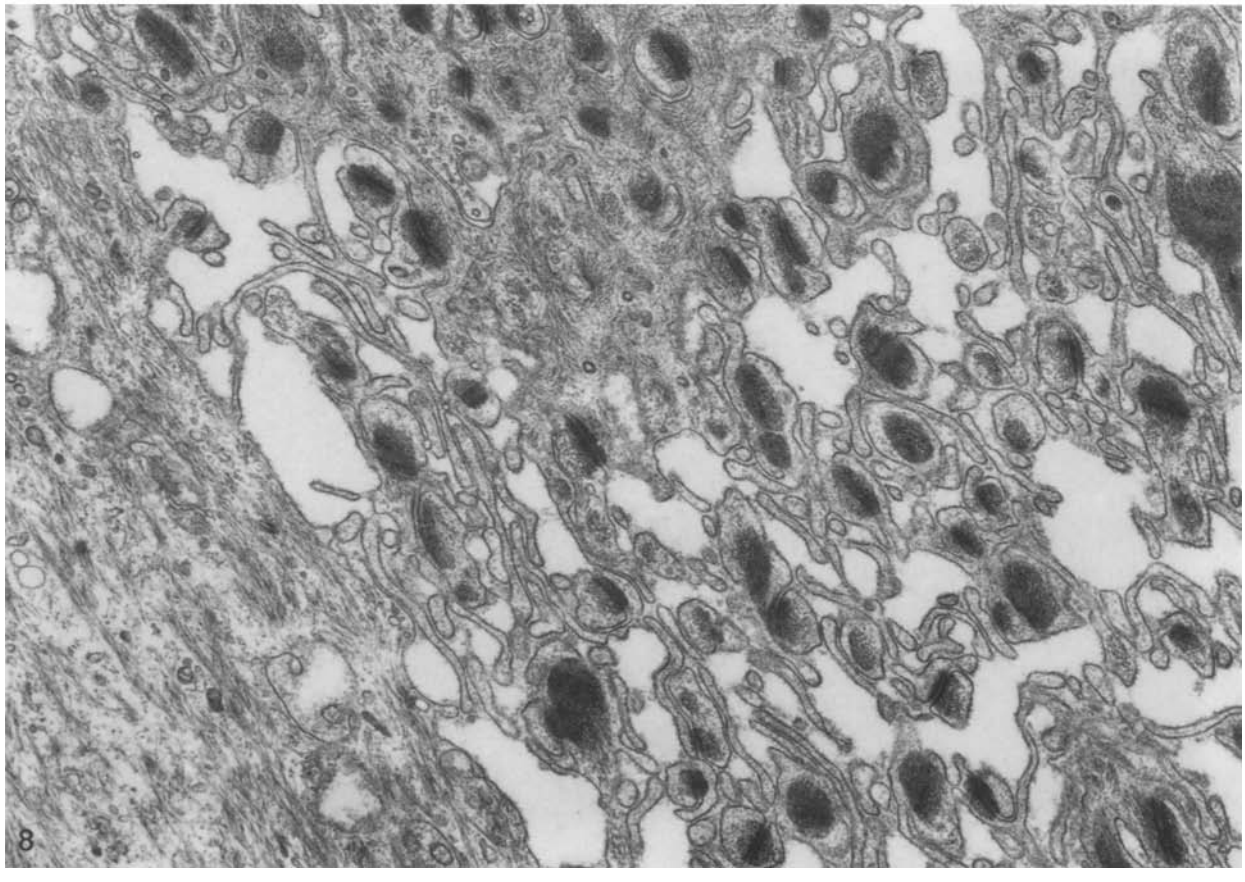
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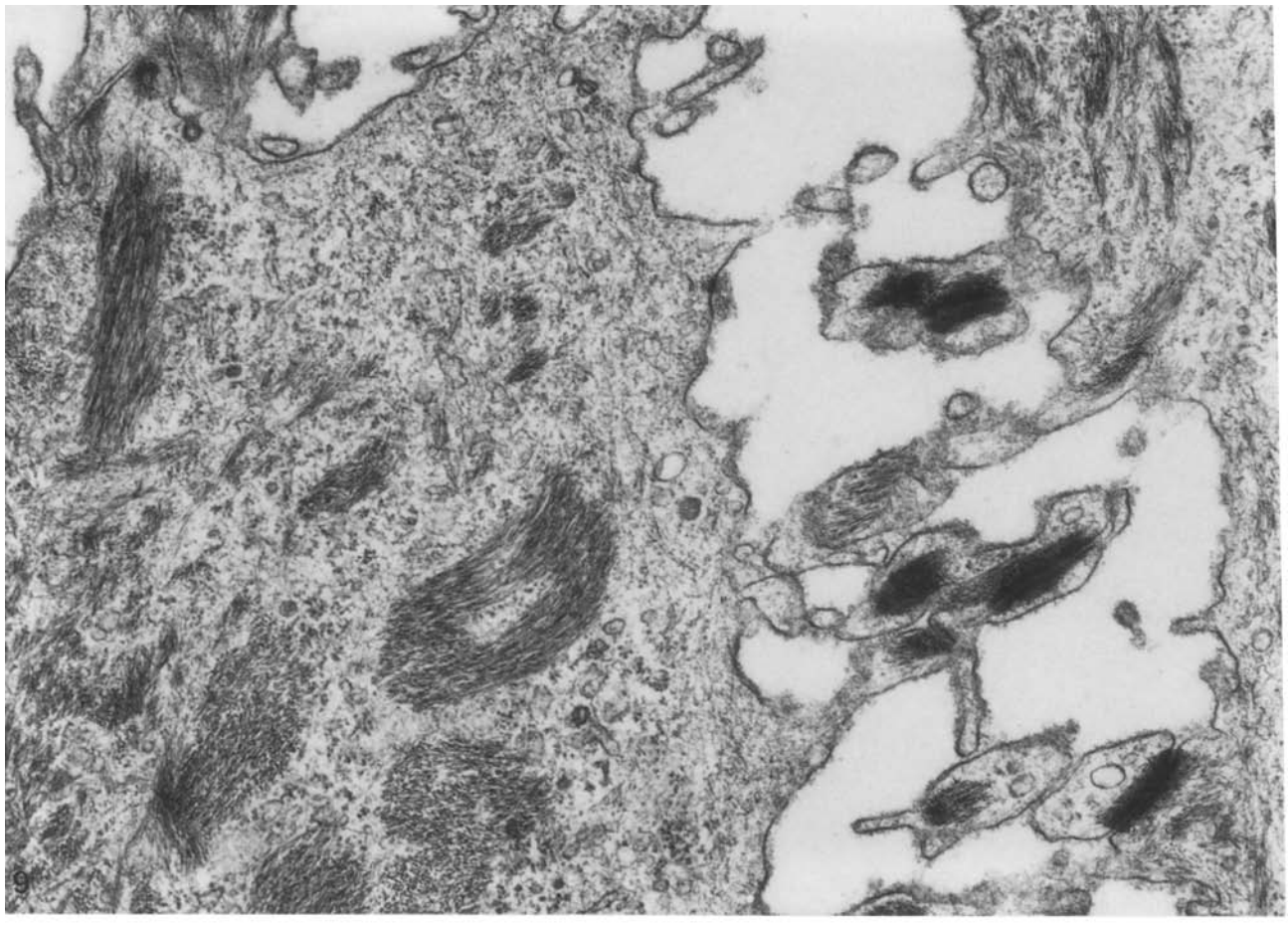

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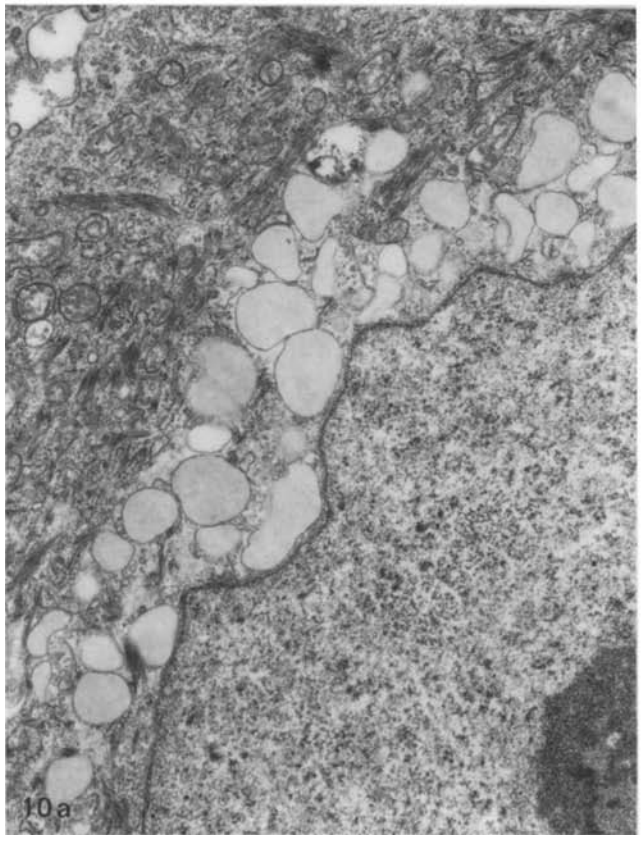

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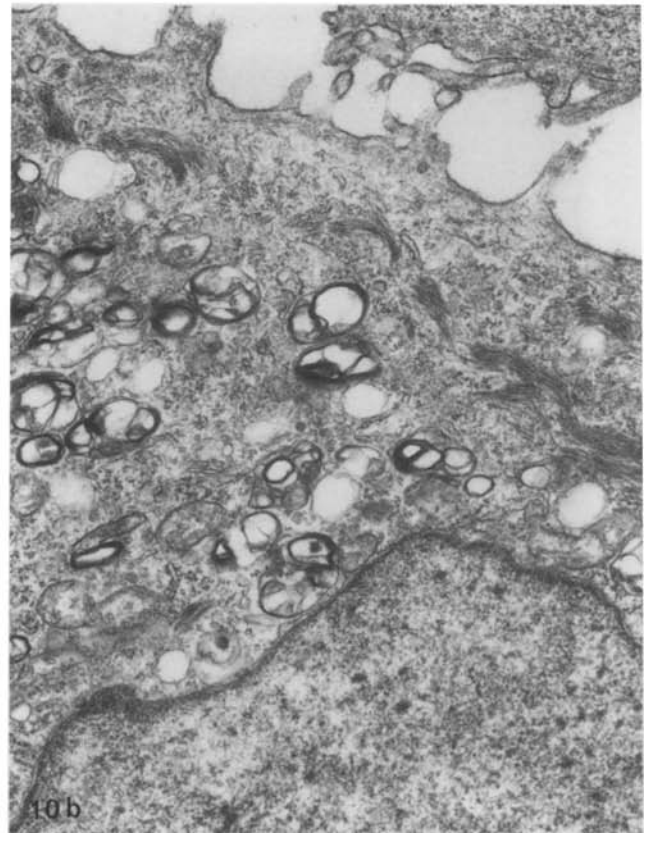

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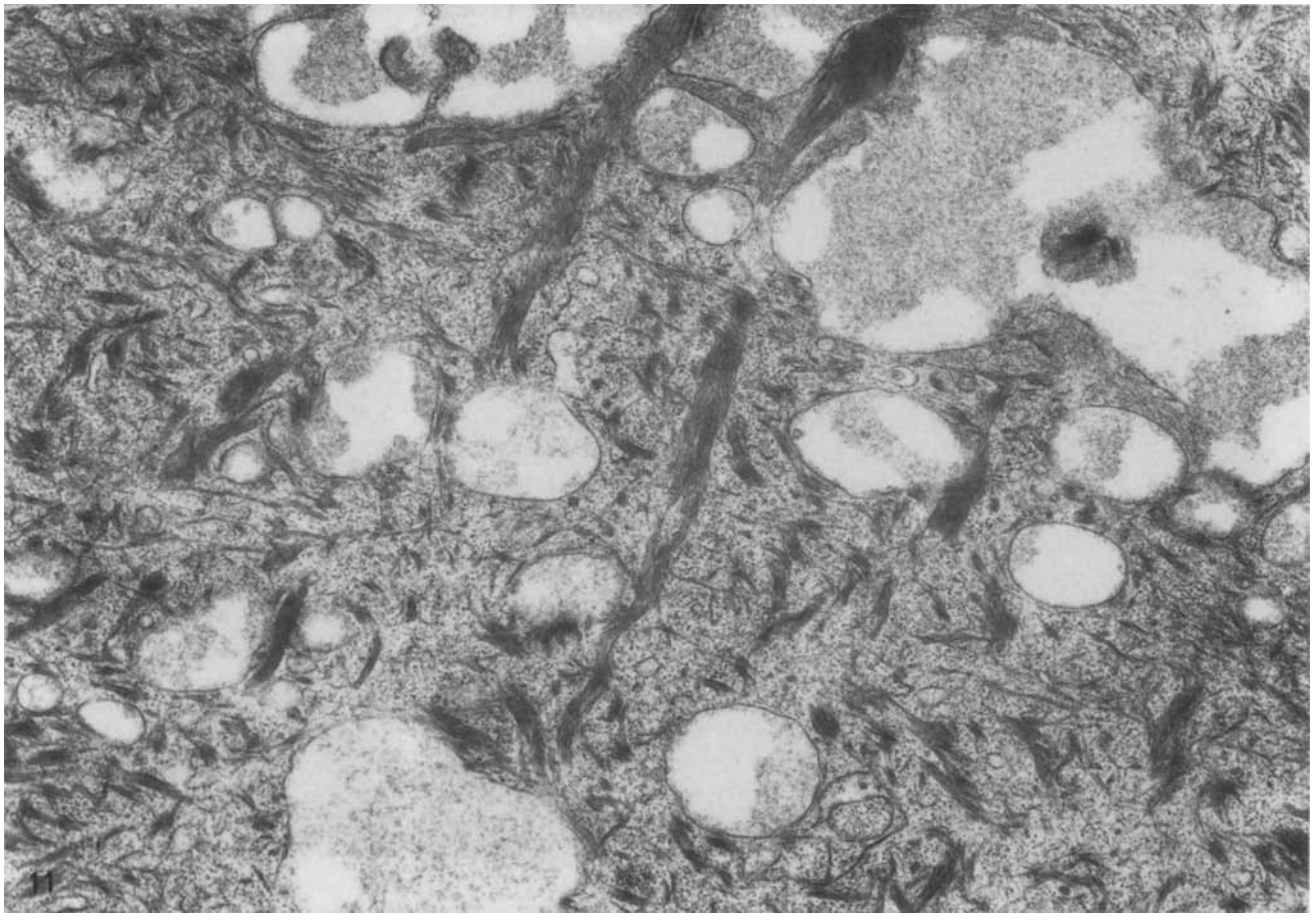

Fig. 11. The intercellular space is extraordinaryly widened, filled with granular material. Vacuoles are present in the cytoplasm containing similar granular material. × 25,000

surgical excisions. One patient (a 28-year-old woman, Case 3) died of cachexia 15 months after the first removal. Autopsy revealed only local infiltration, without metastases. The abscesses in the tumour gave rise to chronic sepsis, this may also have contributed to cachexia.

Gross findings. The neoplasms ranged from 5–17 cm in greatest dimension. The tumours presented as ulcerated, fungating masses. Sinus openings studded the surfaces and produced foul-smelling, grayish-white material when pressure was applied. On sagittal section of gross specimens, papillary tumour masses extended from the epidermal surface penetrating and destroying the dermis and subcutaneous tissue.

Light microscopic findings. The characteristic histological pattern showed both endophytic and exophytic growth with undulating papillomatosis of densely keratinized, well-differentiated squamous epithelium (Fig. 2). The keratinocytes were separated by thin stroma that were infiltrated with lymphocytes.

In the fifth case, i.e. the perianal tumour, intraepithelial carcinomatous foci were seen with a considerable degree of nuclear polymorphism and several mitotic figures (Fig. 3).

In the sixth case, in the deep regions of the tumour, invasive squamous carcinoma developed (Fig. 4). Intraepidermal microabscesses were frequent (Fig. 5).

Method of electron microscopic examinations

Specimens from different regions of the tumours (8–10 blocks) were selected, fixed in 2% Palade buffered osmium tetroxide for one hour. They were dehydrated in a graded series of ethanol and embedded in Araldite. The sections were prepared by Reichert's ultramicrotome and photographed by the JEM 100 CX electron microscope. For orientation semithin (0.5 micron) sections were stained with Toluidin blue.

For control, 4 specimens of normal skin were used, prepared according to the above method.

Fig. 9. The intercellular space is widened and the desmosomes are disconnected from the tonofilaments. × 25,000

Fig. 10. a In the perinuclear region, vacuoles can be seen. × 15,000; **b** Dense lamellar bodies in the cytoplasm of an anaplastic keratinocyte. × 16,500

Results of electron microscopy

In the differentiated regions of the tumours, the keratinocytes retained their connections. The nuclei were relatively large, containing prominent nucleoli. The cells were connected by mature desmosomes. The cytoplasm contained varying amounts of organelles and short tonofilaments (Fig. 6).

In the dedifferentiated regions, the shape of the nuclei became irregular with many invaginations. The cytoplasmic organelles were reduced in number (Fig. 7). The tonofilaments became fragmented. The cells were connected by a small number of desmosomes. On the lateral cell membrane, several processes were present. As a result of the serpiginous plasma membrane, the desmosomes came close to each other (Fig. 8). The intercellular spaces widened in other places and the desmosomes were disconnected from the tonofilaments (Fig. 9).

The dedifferentiation of the keratinocytes occurred in regions furthest away from the connective tissue septa.

The basal lamina was well preserved along the basal surface of the keratinocytes.

In tumours with malignant change, the cytoplasmic organelles were extensively destroyed, with accumulation of vacuoles (Fig. 10a) and dense lamellar bodies (Fig. 10b). The intercellular spaces were fairly widened with a width of 100–200 nm in some places. They contained granular material similar to that seen in vacuoles in the cytoplasm of the cells. The vacuoles appeared near the intercellular space (Fig. 11) but they were occasionally present in distant regions of the cytoplasm. Red cells were seen in the widened intercellular space, while elsewhere leucocytes appeared.

The presence of virus could not be demonstrated in spite of a thorough study.

Discussion

The Buschke-Loewenstein tumour (synonyms: giant condyloma, carcinoma-like condyloma) develops slowly. Some authors connect it with inadequate genital hygiene and chronic irritation (Hull et al. 1981; Klima et al. 1980). Ananthakrisnan et al. (1981) reported on 24 cases of Buschke-Loewenstein tumour of the penis from India, twenty of their patients had not been circumcised. In our second case, the tumour of the penis was preceeded by congenital phymosis. The importance of chronic irritation is also shown by our Case 4 having had a 20-year history of perianal fistula, as well as by Case 5 with a 20-year history of ulcerative colitis. Both patients had perianal tumours. In Case 3 regression of the vulvar and perianal tumour mass achieved by a preternatural anus, thus eliminating the irritation.

The possibility of a viral infection in the aetiology of the tumour is greatly discussed (Harvey et al. 1983; Rastkar et al. 1982). In our investigations, the presence of virus could not be demonstrated.

Our electron microscopical studies revealed varying degrees of differentiation of keratinocytes. In the adjacent areas of the connective tissue septa, the keratinocytes were more differentiated and arranged more closely to each other. In the regions farther away from the connective tissue septa, the intercellular spaces were fairly widened. They contained granular material which, enclosed in vacuoles was also found in the cytoplasm of the tumour cells. Presumably, the decreased cohesion of the epithelial cells altered fluid permeability and consequent intercellular oedema gave rise to severe destruction of the tumour cells.

Red blood cells and leucocytes were observed in the widened intercellular spaces. It is assumed that the frequent bleeding and foul-smelling fistulae are due to the separation of the tumour cells and their permeability to red blood cells and leucocytes.

In the well-differentiated regions of the tumours, the keratinocytes were similar to the normal keratinocytes (Allen and Potten 1975; Breathnach 1971; Lever 1983), however the number of desmosomes was less, the tonofilaments were short, fragmented, and irregularly clumped. The nuclei were large containing one or two prominent nucleoli. On the lateral surface of the cells, there were several irregular cytoplasmic processes indicating intense proliferation of the tumour cells (Beerens et al. 1975).

The process of dedifferentiation of the epithelial cells was studied by Sugár (1968) in early carcinoma of the skin and the laryngeal mucosa, by Sato and Seiji (1973) in leukoplakia and Bowen's disease and by Shingleton et al. (1968) in cervical carcinoma in situ. The electron microscopic characteristics of the malignant transformation of keratinocytes were similar to our material.

The electron microscopic features of keratinocytes of our Buschke-Loewenstein tumours did not differ from the verrucous carcinoma of the skin and oral mucosa (Kao et al. 1982; Prioteau et al. 1980). They also resembled the squamous carcinoma of the oesophagus (Toner et al. 1980), the oral mucosa (Fejerskov et al. 1980), the cervix uteri (Ferenczy and Fenoglio 1979), the lung (Green

et al. 1969), the nasopharynx (Lin et al. 1969) as well as the squamous carcinoma and keratoacanthoma of the skin (Bülow and Klingmüller 1971; Fisher et al. 1972).

On the basis of our electron microscopical examinations and of the published data, we consider the Buschke-Loewenstein tumour to be a special type of squamous carcinoma in which radical surgical excision is inevitable.

According to Hull et al. (1981) electron microscopic appearances are of diagnostic value. In our opinion, the macroscopic and light microscopic pictures of Buschke-Loewenstein tumour are so characteristic that no electron microscopic study is required. We agree with Fisher et al. (1985) that electron microscopy will provide important data concerning the degree of differentiation of the tumour cells.

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