

HPV-ASSOCIATED BUSCHKE-LÖWENSTEIN TUMOURS IN A PATIENT WITH DISSEMINATED ANOGENITAL FORM OF CONDYLOMATA ACUMINATA – A DERMATOSURGICAL PROBLEM

G. Tchernev¹, J. Ananiev², M. Gulubova², I. Bakardzhiev³, G. Pehlivanov⁴,
M. Gonevski⁵, L. Zisova⁶ and J. C. Cardoso⁷

¹Polyclinic of Dermatology and Venerology, "Saint Kliment Ohridski University",
University Hospital "Lozenetz", Sofia, Bulgaria

²Department of General and Clinical Pathology, Medical Faculty, Trakia University, Stara Zagora, Bulgaria

³College of Medicine, Medical University of Varna

⁴University Clinic of Dermatology, Sofia

⁵St James's University Hospital, Leeds Teaching Hospitals, Clinic of Nephrology, UK

⁶Department of Dermatology and Venerology, Medical University, Plovdiv, Bulgaria

⁷Department of Dermatology, University Hospital of Coimbra, Portugal

Summary. Buschke-Löwenstein tumours are a relatively rare clinicopathological entity. However, due to their malignant potential and frequent association with some types of Human Papillomaviruses (HPV), their diagnosis should be promptly confirmed and appropriate management should be planned (according to the condition). In this article we present a middle-aged patient with long-standing tumoural lesions located in the anogenital area, which were confirmed clinically and histopathologically as well-differentiated squamous cell carcinomas of Buschke-Löwenstein type, in combination with disseminated anogenital condylomata acuminata. Histologically, large tumour nests of well-differentiated squamous cell carcinoma were observed, as well as a marked mononuclear cell infiltrate and conspicuous koilocytosis. Immunohistochemistry for Ki-67 revealed a relatively high proliferative index, and was strongly positive for HPV with a pan-HPV antibody (AK), confirming the presence of the virus in the tissue. Surgical removal of the various tumoural masses was performed by electrodesiccation, combined with shave-curettage under general anesthesia. Due to the excessive bleeding there was no possibility for complete removal of the perianal tumour formations and the therapeutic strategy was revised. Systemic therapy with interferon was planned with the purpose of reducing the tumour mass before further surgery.

Key words: *Buschke-Löwenstein tumour, HPV association, Ki-67, verrucous carcinoma*

INTRODUCTION

Buschke-Löwenstein tumours were first described by Buschke in 1925 [1]. In essence, they represent well-differentiated squamous cell carcinomas of verrucous type, localized in the anogenital area. Despite the fact that they have been described for nearly ninety years, Buschke-Löwenstein tumours are a relatively rare disease and rank in frequency only after the more common in-situ squamous cell carcinoma, basal cell carcinoma and malignant melanoma. It is important to note that among the suspected etiopathogenetic agents for their development are the human papilloma viruses (HPV), in particular (especially) types 6 and 11 [2, 3].

In most patients, the tumour presents as an exophytic bulky mass comparable to a mushroom or a cauliflower, sometimes reaching a large size. Despite its rapid growth this tumour rarely metastasizes. In order to determine an HPV association it is necessary to assess the morphological features and to use specific complementary methods [3].

We present the case of a middle-aged patient with the long-standing complaint of burgeoning tumour masses in the anogenital area, which were subsequently confirmed as well-differentiated squamous cell carcinomas of the Buschke-Löwenstein type, associated with disseminated condylomata acuminata.

CASE REPORT

A 39-year-old patient with over a ten-year duration of the symptoms, consisting of a gradually increasing tumorous formation in the genital area and anus, often accompanied by spontaneous bleeding and pruritus. This was associated with painful defecation. He did not report any risk factors such as sexually transmitted diseases, and he was not on any systemic medication.

CLINICAL FINDINGS

Clinical examination disclosed several tumorous formations with an exophytic growth pattern located in the perianal region. Some of them were cauliflower-like shaped, others were cherry-like, and had a variable degree of brown colour intensity. Some of these lesions were also involving the foreskin, frenulum and scrotum (Fig. 1-c).

Laboratory investigations did not reveal any abnormalities.

A metastatic lesion in the right inguinal area was suspected in the ultrasound examination but subsequent histopathological examination showed only a dermatopathic lymphadenopathy.

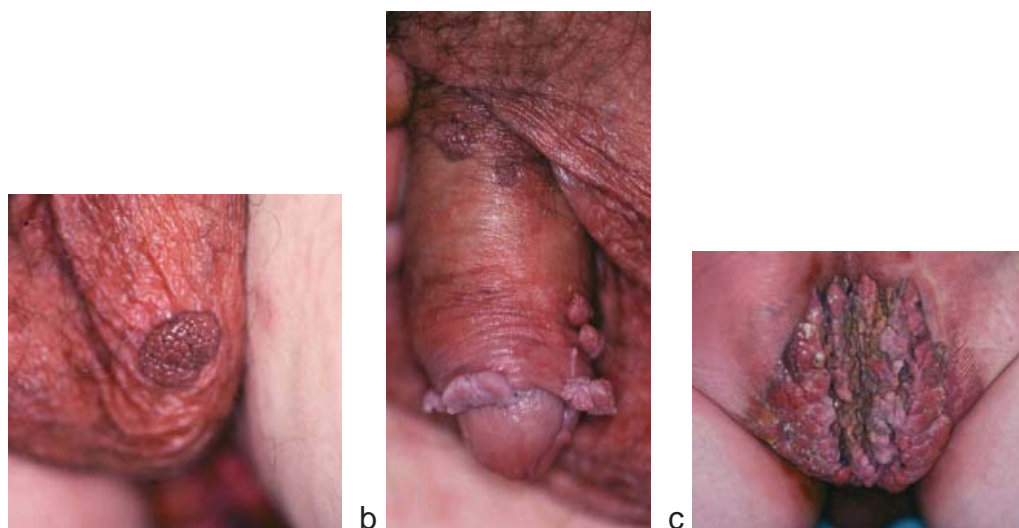


Fig. 1. a: Cherry-like tumour formation with a diameter of approximately 3 cm located on the left side of the scrotum – Buschke-Löwenstein tumour in the early stages of development; **b:** Multiple genital condylomas; so-called condyloma acuminata; **c:** Perianal tumour of Buschke-Löwenstein type with a tendency of infiltrative perianal growth

HISTOPATHOLOGY

The biopsy proved a verrucous and papillomatous tumour consisting of solid nests and lobules composed of atypical squamous epithelium associated with a heavy lymphoplasmacytic infiltrate (Fig. 2-c). Thorough studies of the large formation determined the presence of koilocytosis. Immunohistochemical analysis was performed to determine the proliferative index using Ki67 antibody and to detect the presence of HPV using the AK antibody against PAN-HPV. Ki-67 revealed a proliferative index of approximately 40%, which indirectly relates to the potential risk of transformation to a more aggressive squamous cell carcinoma in time.

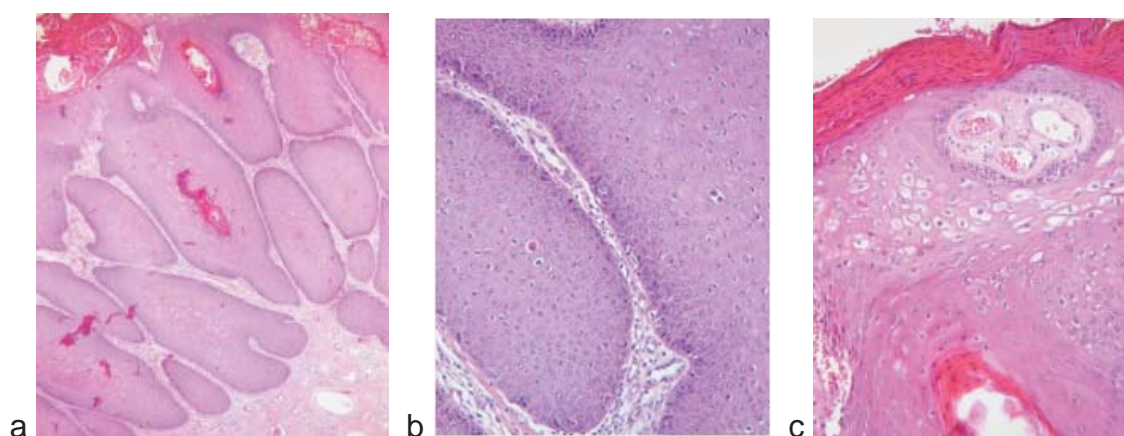


Fig. 2. a-c. Histopathological images of the tumour: **a)** Nests of well-differentiated squamous cell carcinoma; **b)** Mononuclear cell infiltrate surrounding tumour lobules; **c)** Koilocytosis, reflecting the possible presence of HPV in the tumour

These results helped to establish the diagnosis of a highly differentiated (G1) verrucous carcinoma of the anogenital region (Buschke-Löwenstein) with focal positive expression of HPV.

Histological examination of lymph nodes did not show the presence of metastases.

TREATMENT

After placing the patient under general anesthesia, an attempt to remove the lesion by electrodesiccation and curettage was made. Unfortunately, due to heavy bleeding associated with the perianal tumour, it was not possible to eradicate completely the tumoural tissue and the operation was discontinued. The remaining lesions in the genital area were removed by sharp curettage and fine scissors. No recurrences were observed.

DISCUSSION

There are different opinions in the literature about the malignant potential of Buschke-Löwenstein tumours. According to several authors, they are tumours that tend to have prominent local infiltrative and destructive growth. There is a serious risk of transition into squamous cell carcinoma over time if adequate therapeutic measures are not taken [2, 4]. According to our experience this period of transition is usually from 3 to 5 years. The tumour is an “intermediate” entity between perianal or anogenital warts of large size and a squamous cell carcinoma [2, 4]. In persistent lesions there is an increased risk of transformation into the more aggressive form of the disease, which metastasizes mainly to the regional lymph nodes. Such patients have generally had a significantly worse prognosis compared to patients with lesions that were completely eradicated in the early stages of the disease [2].

We present a case of a patient with a rare form of highly differentiated carcinoma as Buschke-Löwenstein tumours, diagnosed relatively late and treated surgically without a definitive cure for the anogenital lesion.

Based on the characteristics and natural progression, some authors have classified this disease as an intermediate between condyloma acuminata and squamous cell carcinoma [2, 4]. It is not a surprise, since the early stages of warts and tumours of Buschke-Löwenstein type have similar histopathologic features. Tumours at later stages of development have clinical features of cauliflower, white to yellowish colour and papillomatous, uneven surface. Histopathologically in most cases papillomatous formations with significant acanthosis and hyperplastic epithelium could be observed, composed of cells with pale cytoplasm and hyperchromatic nuclei while maintaining its basal membrane [5].

Special attention must be paid to the etiopathogenesis of this disease. It is known that HPV types 16 and 18 are among the most frequently blamed for the development of squamous cell carcinoma, and HPV types 6 and 11 most often for the development of verrucous carcinoma [2, 3, 7]. Moreover, there is evidence to justify routine methods such as immunohistochemistry or PCR testing for HPV, provided it is performed as required, for morphological confirmation in Buschke-Löwenstein tumours [7]. Tissue detection of human papillomaviruses can be done by PCR using tissue from the lesion, in situ hybridization or immunohistochemistry. Using immunohistochemical methods (HPV-PAN-AK) in the histological sections we proved the presence of HPV, which was localized mainly in the areas of koilocytosis. A more accurate classification of the different subtypes of HPV viruses was not conducted. We also determined immunohistochemically the proliferation index with Ki-67, which showed a strong positive reaction in approximately 40% of cell nuclei.

Upon this we can conclude that the diagnosis based on biopsies performed in time, with subsequent immunohistochemical phenotyping and association with HPV, are especially important for the correct and successful treatment of these patients. This is especially important considering the possible progression of Buschke-Löwenstein tumours to less favorable, poorly differentiated variants of squamous cell carcinoma with potential for lymph node metastases. Surgical excision is the treatment of choice. Topical therapy alone, such as with 5-fluorouracil, podophyllin, or interferon (IFN), is generally insufficient to control the disease or prevent progression of the giant lesions [8]. This kind of therapy may be effective only in early lesions of condylomata acuminata. Ablation with carbon dioxide laser has also been effective, with the advantage of permitting a bloodless field [9].

Inadequately treated Buschke-Löwenstein tumours have a relentless progression and can be fatal by direct spread to pelvic organs. By definition, adequately treated Buschke-Löwenstein tumours have low recurrence rate and, therefore, an excellent prognosis. However, one study of perianal/anogenital Buschke-Löwenstein tumours, with treatments ranging variously from podophyllin to pelvic exenteration, showed a 68% recurrence rate with a 21% mortality rate [9, 10].

In our patient we discussed the possibility of implementing systemic intravenous therapy with Cidofovir for a period of 2-3 weeks and a total of 2-3 months of subcutaneous therapy with interferon to reduce the tumour mass for subsequent surgery.

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✉ *Address for correspondence:*
 Assoc. Prof. Georgi Tchernev, MD, PhD
 University "St. Kliment Ohridski"
 Polyclinic of Dermatology and Venerology
 Univeristy Hospital Lozenetz,
 Medical Faculty
 1 Koziak str.
 1407 Sofia, Bulgaria