

## A CASE OF GIANT RAPID EVOLVING BUSCHKE-LÖWENSTEIN TUMOR IN AN IMMUNOCOMPETENT PATIENT

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### ABSTRACT

Buschke-Löwenstein tumor (BLT) is a rare premalignant disorder, with a considerable potential of malignant transformation into squamous cell carcinoma; HPV infection (especially HPV 6 and HPV 11) have an important role in the etiopathogeny of the disease, along with immunosuppression- usually caused by HIV virus, a frequently encountered association. We report on the case of a 47 year old male patient who addresses our clinic for the occurrence of a giant tumoral lesion located in the intergluteal cleft, which had rapidly evolved despite the repeatedly negative HIV testing. The histopathologic examination confirms the clinical diagnosis of BLT; wide surgical excision of the tumor with safety margins was not followed by recurrence, during a follow-up period that exceeded 12 months. The case is distinguished through the large dimensions of the tumor, the extremely rare anatomical situation and the rapid evolution, despite the absence of HIV immunosuppression.

**Key words:** Giant condyloma acuminata, Buschke-Löwenstein tumor,  
human papillomavirus, squamous cell carcinoma

Giant Condylomata Acuminata of Buschke and Lowenstein is a rare, slowly growing, infiltrating, destructive form of verrucous carcinoma affecting the anogenital region. The condition is more frequently encountered in men and immunosuppressed patients (1,2). Some of the hallmarks of the disease are the high rate of recurrence and the elevated risk of malignant transformation towards squamous cell carcinoma (3). Human papillomavirus (HPV) has been identified as an important contributory factor in the tumoral development, and so did immunosuppression. DNA corresponding to 6 and 11 HPV subtypes has been frequently identified in typical cauliflower-like lesions, suggesting the etiopathogenic role of the virus in the initiation and progression of the tumor (4,5). The histology of the Buschke-Löwenstein tumor can appear benign, resembling common condyloma acuminata, though

there may exist multiple foci of malignant transformation occurring either spontaneous or secondary to X-radiation exposure. A proper biopsy must be wide and deep enough to accurately determine the extension of tumoral infiltration and the possible presence of a squamous cell carcinoma.

### CASE PRESENTATION

We report on the case of a 47 years-old male patient from the rural area, who addresses our clinic for a tumoral lesion that had occurred in the intergluteal perianal region 18 months beforehand and had been rapidly evolving for about 9 months, during which time the patient has postponed the medical consultation. The general clinical examination fails to reveal any pathologic findings, while local dermatological examination reveals a giant,

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exophytic, cauliflower-like tumoral lesion, modifying the normal local anatomy and infiltrating through the underlying tissue, with multiple fistulae opening bilaterally in the gluteal region (Fig. 1). The lesion is accompanied by alteration of the sphincter functionality, as the patient presents atrocious pain during defecation and anal incontinence manifesting as spontaneous elimination of semi-liquid stools, symptoms that had decisively contributed to the patients' presentation for a medical consult. The superficial lymph nodes were not palpable and showed no local signs of tumor infiltration. Laboratory findings were within normal range. Repeated HIV testing have also been negative.

The lesion has been excised in a department of general surgery, and the bioptic specimen sent for histopathologic examination has confirmed the clinical diagnosis of Buschke-Lowenstein tumor (BLT). Taking into consideration the high recurrence rate and the elevated risk of malignant transformation, the patient was followed up periodically after the procedure.



**FIGURE 1.** Giant, exophytic, cauliflower-like tumoral lesion situated in the intergluteal cleft, causing a considerable alteration of the local anatomy; multiple fistulae are also present, as well as peritumoral ulcerated areas

## DISCUSSION

Until recently, it was considered that the first to describe and nominate giant condyloma acuminata as a separate nosological entity were the German dermatologists Abraham Buschke and Ludwig Lowenstein, in 1925, who observed a penile lesion that clinically resembled both common condyloma acuminata (venereal warts) and squamous cell carcinoma, but differing from both of them regarding the biological behaviour and the histopathological appearance (6). Buschke and Lowenstein were credited to having been the first to describe

the lesion up until recently, when Marx and Karenberg showed in an article published in 2012 in the British Journal of Dermatology that the first to describe a case of giant condyloma acuminata was Wilhel Fabry, the parent of German surgery, in 1614, and for this reason they consider that the proper name of this affliction should be changed to Fabry-Buschke-Lowenstein, according to the historical reality (7).

Along with epithelioma cuniculatum (Ackerman tumor), oral florid papillomatosis and papillomatosis cutis calcinoides Gottron-Eisenlohr, Buschke Lowenstein tumor (BLT) is traditionally considered a variant of verrucous carcinoma, a group of premalignant nosological entities characterised by slow evolution and aggressive behaviour, with a considerable potential of malignant transformation into squamous cell carcinoma (8). Some authors tend to consider BLT as an intermediary condition between the common form of condyloma acuminata and the invasive squamous cell carcinoma (9).

BLT is a rare disorder; its exact prevalence is difficult to estimate due to the very similar appearance to common venereal warts and the fact that most literature data approaches only singular cases or even rarely-small series of cases, therefore explaining the lack of prevalence data for wide populations; however, it has been estimated that BLT represent between 5 and 24% of total penile tumors. Location in sites other than the penis (vulva, vagina, cervix, and scrotum) is even rarer (1), including the perianal situation, like that encountered in our patient. The alteration of the anal continence, also encountered in our patient, is rare, with only a few cases described in the medical literature on this topic (10).

BLT usually affects men more than women, with a M/F ratio in patients under 50 years old being of approximately 3.5:1; the mean age of male patients at lesion occurrence is 43 years (11); from these points of view, the patient presented hereby fits in the general pattern of the disease.

The clinical appearance of BLT is characteristic; usually it presents as a unique, cauliflower-like tumoral lesion developing in the external genitalia or the perianal area. The tumor slowly increases and in patients postponing medical help it may reach or exceed diameters of 10-15 cm. As a consequence of both precarious hygiene and maceration associated with bacterial superinfection, the lesions emanate a fetid odour. The presented case is particular due to the considerable dimensions of the tumor, hallmark of a late presentation to the hospital.

The typical evolution period of the tumor is situated in the range of a few years; Chu et al. observe, in a systematic review including 42 BLT cases, the largest study in the medical literature on this topic, an evolution period ranging from 2.8 to 9.6 years; in the case we are presenting, the lesions had only appeared 18 months before presentation and the tumoral growth was more aggressive in the second half of the time period, this proving an unusually high growth rate of the tumor; while usually the tumor progression parallels the extent of the immunosuppression (3,12), in our patient the elevated rate of tumor volume reduplication – in spite of repeated negative HIV testing that ruled out HIV infection – contributes to the particularity of the case.

Many of the BLT cases develop in immunosuppressed patients. Although there are cases of rapidly evolving BLT occurring as a consequence of physiologically reduced immunity during pregnancy (13), usually BLT is associated with HIV-related immunosuppression (14,15,16); these cases are distinguished through higher malignant transformation rates and increased therapy resistance (2). Moreover, HAART (highly active antiretroviral therapy) administered for HIV suppression fails to inhibit BLT tumoral development (17). In our patient, the repeatedly negative HIV testing rules out an HIV infection.

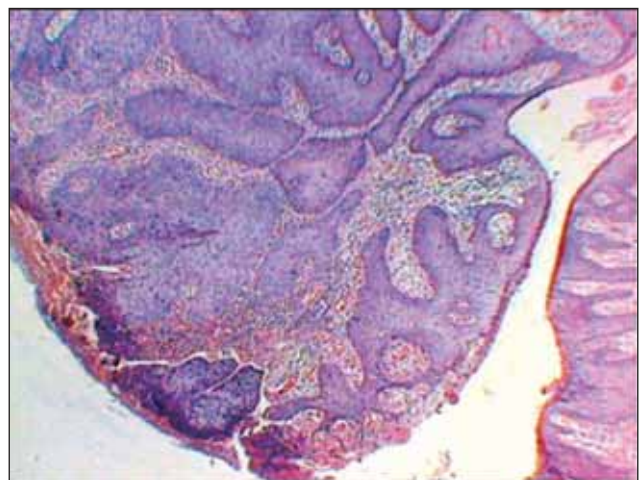
Receptive anal sex is also involved in BLT development (16); however, the anamnesis in our patient failed to identify this type of sexual intercourse in the patient history.

HPV plays a very important etiological role in development of BLT. Several types of HPV have been detected in BLT lesions, in particular HPV6 and HPV11 (5). The E6 gene product of the human papillomavirus induces rapid proteasomal degradation of p53 tumor suppressor protein, consequently abolishing the possibility of the infected tumor cells to arrest cell cycle progression or to induce apoptosis, the programmed cell death within these cells (1). Another mechanism through which HPV blocks infected cell apoptosis and determines the deviation of cell cycle towards tumor progression includes the blockage of the p73 protein function (18). The mechanistic aspects of cell proliferation and apoptosis blockage are not completely elucidated, many aspects of the mechanisms still being subject to controversy. Thomas and Banks proved that the HPV-11 E6 protein can bind to the Bak protein, a member of the Bcl-2 proapoptotic protein class, deactivating it and blocking the apoptosis activation of the intrinsic mitochondrial pathway, a critical aspect that could explain, inter alia, the

oncogenic potential of the virus (19). On the other hand, some authors assert the contrary, postulating that HPV could trigger apoptosis by p53 sequestration within the cytosol, where it would interact with the Bak protein on the mitochondrial surface, determining its oligomerization and causing the cytosolic release of pro-apoptotic mitochondrial factors (20).

Suggestive aspects pertaining to the presence of HPV infection were also revealed by the histopathological examination of the excised specimen; microscopic examination showed multiple exophytic projections with hyperparakeratosis, pronounced acanthosis and papillomatosis of the malpighian layer, with considerable thickening and elongation of the interpapillary ridges penetrating deep within the dermis; anastomoses of the interpapillary ridges are also observed, delimiting areas of various dimensions with circular appearance. The squamous layer cells partially present perinuclear vacuoles with hyperchromatic nuclei.

Atypical mitoses are rare, in disagreement with the relatively high rate of tumor growth. An intact basal membrane separates the epithelial proliferation masses from the underlying dermis; its integrity distinguishes BLT from squamous cell carcinoma. The dermis is oedematous, with lymphoplasmocytic inflammatory infiltrate and dilated capillaries. All these aspects of the anatomopathological examination of the bioptic specimen (Fig. 2-4) confirm the clinical diagnosis of Buschke Lowenstein tumor and succeed in ruling out the malignant transformation of the tumor, an extremely important aspect which contributed to choosing the appropriate subsequent therapy.

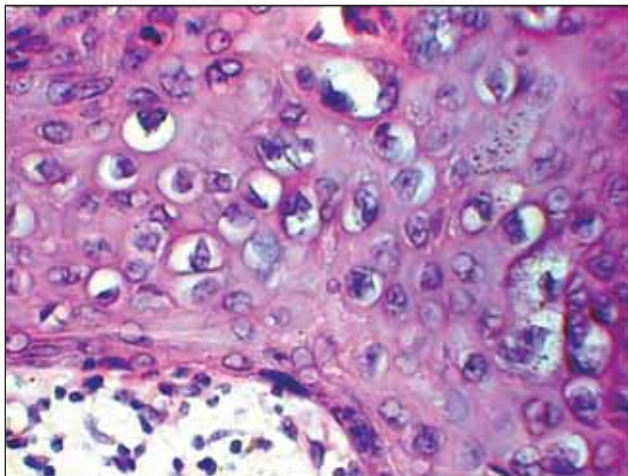


**FIGURE 2.** *Condyloma acuminata, Hemalaun-Eosin stained section (HE), 10X ob. – hyperkeratosis; exophytic projections with massive epidermal proliferation, elongated interpapillary ridges penetrating deeply within the edematous dermis*





**FIGURE 3.** *Condyloma acuminata*, HE staining, 20x magnification – hyperkeratosis with parakeratosis, papillomatosis, squamous layer thickening, elongated and thickened interpapillary ridges, which deeply penetrate within the paucifibrillar edematous dermis, with abundant inflammatory infiltrate. The clear demarcation between epithelial proliferations and underlying dermis areas which appear as circular areas can also be observed.



**FIGURE 4.** *Condyloma acuminata*, HE staining, 40X - characteristic appearance: numerous vacuolated cells with hyperchromic nuclei; mitotic figures and rare atypical mitoses; edematous dermis, with very well represented lymphoplasmocytic inflammatory infiltrate.

Since the disorder is extremely rare, there are no large studies that would allow an evidence-based therapeutic approach. Taking into account the considerable squamous cell carcinoma transformation potential, the mainstay of treatment for Buschke-Lowenstein tumor is extensive surgical excision within safety margins, advancing into the healthy surrounding tissue. The cases associated with massive tissue infiltration or already transformed into aggressive squamous cell carcinoma require an interdisciplinary approach, with the participation of the general surgeon (21). Other methods that could be used for removal of the tumor,

depending on the clinical-evolutive characteristics, are topical imiquimod 5% or podophylin, cryotherapy, electrotherapy or CO<sub>2</sub> laser excision, radiotherapy, Mohs microsurgery and chemotherapy (4), all of the above being less efficient when it comes to controlling the progression of the disorder and the frequency of the relapses (22). Interferon administration is also useful, but expensive and associated with high rates of tumor recurrences (23). Recently, a combined systemic approach consisting of the simultaneous administration of oral retinoids and intramuscular interferon  $\gamma$  was tested, with good results, but its application is limited by the high expenses (24). Other authors also reported the usefulness of systemic retinoids in the treatment of BLT: Mavrogianni et al. describe, in May 2012, a case of perianal BLT treated with radio-frequency excision followed by systemic acitretin administration, with good results (25). However, in this case the retinoid administration as an adjuvant therapy is contraindicated due to the hypertriglyceridemia. We chose the extensive surgical excision associated with every 3 months periodic follow-ups in order to detect any potential malignant transformation. In the 12 months following the intervention, no local recurrences were observed, while the mean time period for relapse occurrence seems to be 10 months, as cited in the literature (3); after the 12 months follow-up period, the frequency of the patients visits was reduced to one every 6 months.

The transformation rate into squamous cell carcinoma is about 40-60% (3,10); in the absence of malignant transformation BLT has a benign biological behaviour, provided that the presence of BLT is not accompanied by metastases (3). The prognosis of the disease depends mainly on the dimensions of the tumor at the moment of presentation, the promptitude of treatment administration and the patients' background, especially the presence of immunosuppression, with all these factors directly influencing the transformation rate towards squamous cell carcinoma. Cases of extremely aggressive evolution with fatal ending have also been described (26); the mortality rate can reach 20%, with all of the lethal cases occurring in patients with relapses (3). In the case we are presenting – despite the large dimensions of the tumors at the presentation – the promptly administration of an adequate treatment, the above mentioned benign histopathological features revealed by microscopic examination and the absence of immunosuppression are factors of good prognosis; however, the periodic post-therapeutic follow-up is mandatory, considering the high

recurrence risk and the possibility of squamous cell carcinoma transformation. The risk of relapse after surgical excision remains substantial; according to literature data, the recurrence occurs in 66% of the patients and is more frequently encountered in patients with delayed presentation; in this respect, the post-therapeutic follow-up of the patients with BLT has a paramount importance (3).

## CONCLUSIONS

The particularities of this case consist in the gigantic dimension of the tumor, the rapid pro-

gression of the lesion in a HIV-negative patient and the late presentation to the medical services, in an advanced stage of the disease. The early presentation, as well as the recognition of the lesion by the dermatologist, infectionist or the general practitioner can contribute to the prompt administration of the adequate therapy; surgical excision within safety limits and the periodic post-therapeutic follow-up in order to discover potential recurrences or the malignant transformation to squamous cell carcinoma are extremely important in the management of patients with BLT.

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