



Case report

A rare malignancy: A case report of early progression of anal Buschke–Löwenstein tumor into squamous cell carcinoma in an immunocompetent patient

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ABSTRACT

Introduction and importance: Buschke–Löwenstein tumor (BLT) is a rare perianal lesion caused by low-risk mucosal HPV 6 or 11 but less frequently associated with high-risk HPV types. It is a large, exophytic, verrucous lesion of the anogenital region. BLT presents as a benign tumor but exhibits malignant clinical behavior and has a high rate of local recurrence and malignant transformation. The optimal treatment approach for BLT is still debated due to the lack of consensus. Various therapeutic modalities have been proposed, including topical agents, surgical excision, immunotherapy, chemo-radiotherapy, and electrocoagulation.

Case presentation: This case report presents a heterosexual, immunocompetent patient with anal pain, pruritus, and spontaneous bleeding. The physical examination revealed an exophytic, pedunculated verrucous lesion, which appeared to be a typical fibroepithelial lesion.

Clinical discussion: The patient underwent wide excision, followed by a re-excision due to a surgical margin issue. The tumor exhibited malignant transformation into a well-differentiated SCC. However, due to the tumor's stage, size, location, histological type, and the extended time interval between the two surgeries, postoperative radiotherapy was not performed. Follow-up examinations over 12 months revealed no evidence of recurrence in either the patient's clinical evaluation or pelvic MRI.

Conclusions: Although comprehensive research is lacking, wide local excision is considered the preferred first-line treatment for early-stage cases without evidence of local invasion. Furthermore, HPV immunization can prevent the development of Buschke–Löwenstein tumor, and early administration of the HPV vaccine is recommended to avoid acquiring HPV infection.

1. Introduction

Buschke–Löwenstein tumor (BLT), also known as giant condyloma acuminatum, is a rare perianal lesion typically found in immunocompetent individuals. It was originally described as a penile neoplasm by Buschke and Löwenstein in 1925 until the first case in the anal region was reported in 1963 by Knoblich and Failig. The incidence in the adult population is estimated to be approximately 0.1 %, with a recent increase in reported cases. While previously considered synonymous with verrucous carcinoma, recent studies and the World Health Organization (WHO) in 2019 have suggested that BLT and verrucous carcinoma are distinct entities [1–5].

Buschke–Löwenstein tumor is a large, exophytic, verrucous lesion of

the anogenital region caused by human papillomavirus (HPV) types 6 and 11, which are considered low-risk types. Risk factors associated with BLT include immunosuppression, pregnancy, alcohol and tobacco consumption, poor local hygiene, herpes simplex virus, and HIV infection. Histologically, it is a benign tumor with malignant clinical behavior, exhibiting a high tendency for local recurrence (66 %) and malignant degeneration but without lymphatic, vascular, or neuronal invasion. While exhibiting slow-growing behavior in immunocompetent individuals, it can grow rapidly in immunocompromised individuals. Some authors consider BLT to be an intermediate between condyloma acuminatum and squamous cell carcinoma (SCC). Buschke–Löwenstein tumor is histologically distinguished from condyloma acuminatum by extensive proliferation and deep penetration into local tissues. The

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critical feature distinguishing it from squamous cell carcinoma (SCC) is the preservation of the basement membrane and its lack of ability to metastasize. The risk of degeneration for squamous cell carcinoma ranges from 30 % to 56 %, while condyloma acuminatum has a risk of only 2 % [1,4-7,10].

There is no defined non-surgical treatment for BLT, but several therapeutic approaches have been proposed. These include topical medications (25 % podophyllin [2,5,9] and 5 % imiquimod [8] ointments), cryotherapy [5], photodynamic therapy [5,6], laser [6], electrocoagulation, immunotherapy [4,5], chemotherapy and radiotherapy [1-4,6,10]. Surgical excision is the preferred treatment when the tumor is resectable, especially when diagnosed at an early stage. However, surgical removal can present several complications, and in cases of anal sphincter invasion, an abdominoperineal resection of the rectum may be required [1-7,10].

2. Case report

A 73-year-old male patient resorted to surgical consultation because of anal pain, pruritus, and spontaneous bleeding. As the individual's medical records mentioned, a diagnosis of hemorrhoids had been documented in the patient's medical history. The patient had no clinically evident immunodeficiency and claimed not to have homosexual activity or promiscuity, but did have a history of heavy smoking for 40 years (more than 30 cigarettes a day) and regular alcohol consumption (40-70 g/day).

The physical examination revealed a 3 cm diameter exophytic,

pedunculated verrucous lesion located 2 cm away from the anal canal on the right side in the direction of the gluteal region. No inguinal lymph nodes were palpable on physical examination. Through mere visual inspection, the lesion appeared to be a typical fibroepithelial lesion. Furthermore, it has been observed that the tumor is in close proximity to the sphincter complex but does not appear to involve it at this time. As a result, it was decided to pursue primary resection as the initial therapeutic approach.

The surgical procedure involved a wide excision technique, which was employed to ensure macroscopically complete removal of the lesion without infiltration into the surrounding tissue. A Lonestar retractor was utilized intraoperatively to optimize the surgical field of view. The excision was performed utilizing a high-energy ultrasound dissection device as an alternative to bipolar electrocoagulation. The wound was closed with a simple surgical interrupted suture using an absorbable, braided polyglycolic acid (PGA) suturing material. The lesion's histological grade is G1, infiltrating the lamina propria without lymphovascular or perineural invasion. Based on the results of the immunohistochemical tests, it can be concluded that the p16 is positive, which is generally associated with the presence of the human papillomavirus (HPV). Additionally, the MIB1 was found to be low, while the p53 protein exhibited a wild-type pattern. The final pathological examination concluded a BLT with malignant transformation into a well-differentiated SCC (pT2) [Figs. 1-4].

The patient exhibited no postoperative complications and was discharged within 24 hours following the surgical procedure. The administration of postoperative analgesia and additional dressing changes was

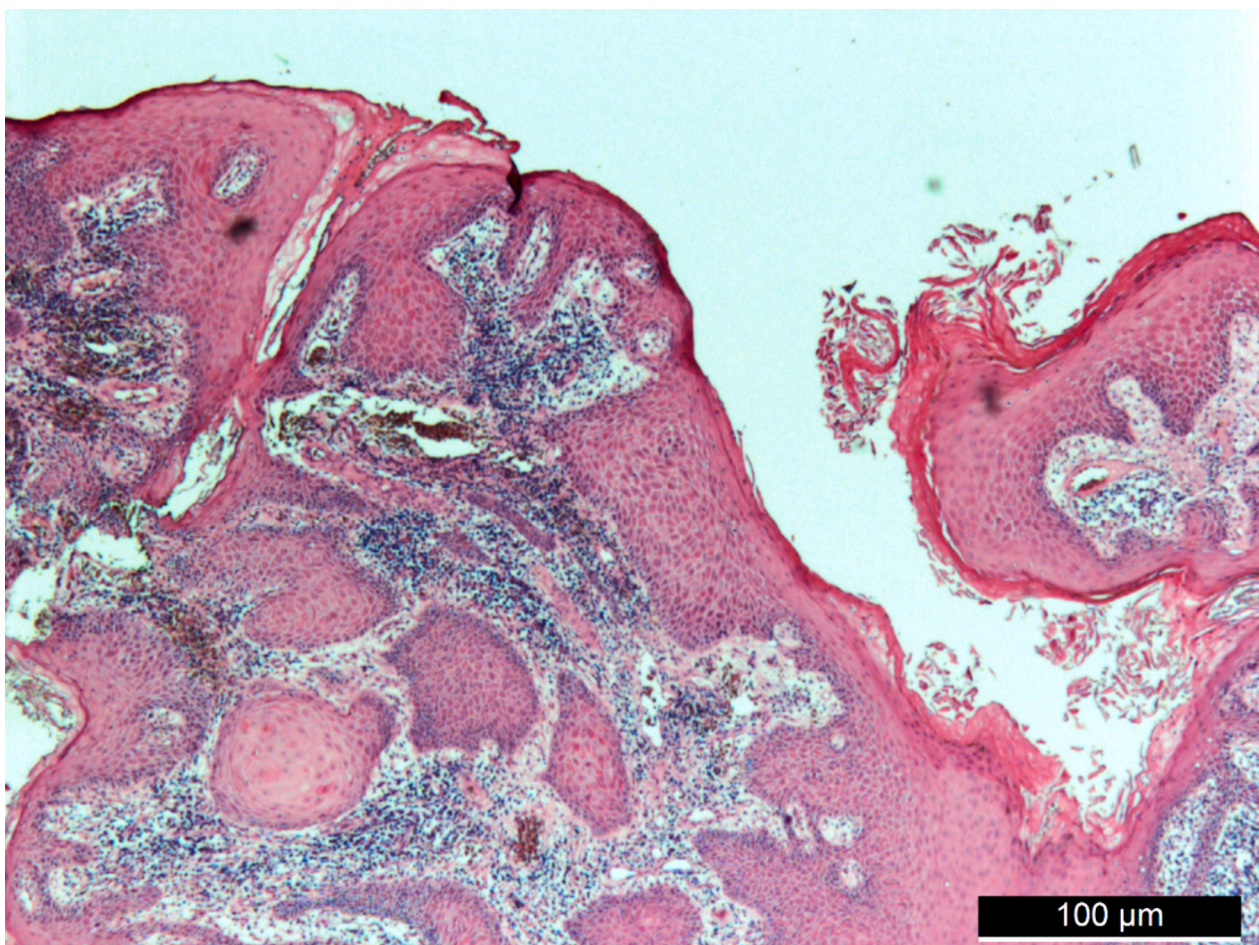


Fig. 1. Hematoxylin-eosin stained tissue sections I.

Hematoxylin-eosin stained tissue sections show exophytic papillary growth patterns with well-formed papillae, hyperkeratosis and parakeratosis, koilocytes, lymphocytic infiltration.

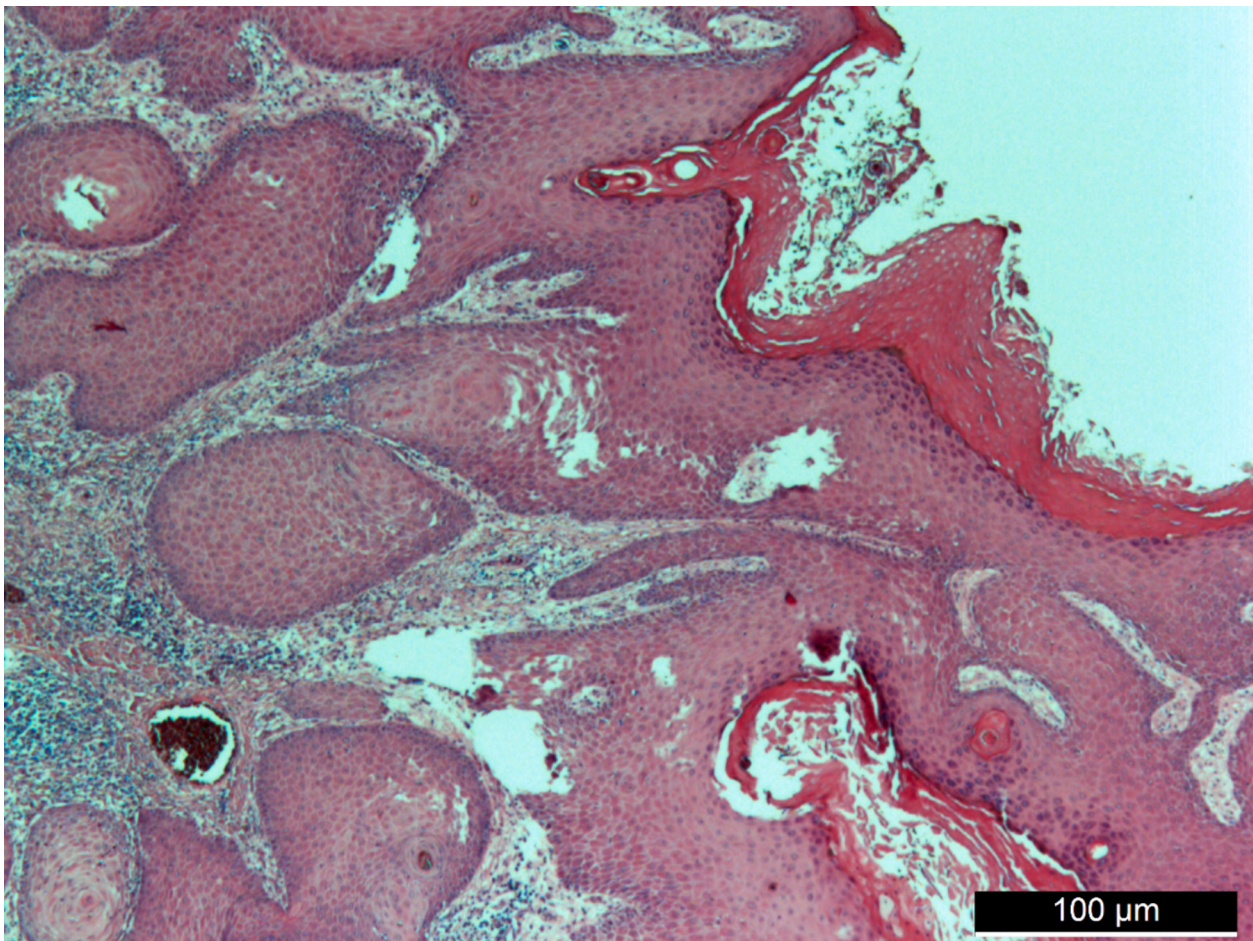


Fig. 2. Hematoxylin-eosin stained tissue section II.

Hematoxylin-eosin stained tissue sections show exophytic papillary growth patterns with well-formed papillae, hyperkeratosis and parakeratosis, koilocytes, lymphocytic infiltration.

not required. As part of the oncological staging in the postoperative phase, we conducted thoracic and abdominal CT and pelvic MRI scans. The diagnostic imaging tests, including CT and MRI, revealed no evidence of distant metastasis or local recurrence. The tumor was confirmed to be at the definitive stage of IIa (pT2N0M0). The results were presented to a multidisciplinary oncology team. Following their evaluation, a re-excision was recommended owing to the 1.5 mm surgical margin. Following the initial surgery, the patient was unable to undergo a second operation until six months later due to familial obligations. During the second surgery, a repeated wide excision was performed. The pathology report of the removed specimen revealed no residual tumor cells or recurrence. The patient's clinical course progressed without complications and resulted in complete recovery. The multidisciplinary oncology team was presented with the results once again. They conducted a comprehensive evaluation of the tumor's stage (IIa), size, location, histological type, and the extended time interval between the two surgeries. Based on their assessment, it was concluded that postoperative radiotherapy was unnecessary for the patient. In the subsequent patient management, the “watch and wait” strategy was employed.

Follow-up examinations conducted over 12 months revealed no symptoms or evidence of recurrence in either the patient's clinical evaluation or pelvic MRI.

3. Discussion

Buschke-Löwenstein tumor, also known as giant condyloma

acuminatum, is a rare and locally invasive tumor of the anogenital region. BLT has known risk factors such as immunosuppression, pregnancy, poor hygiene, HPV, herpes simplex virus, and HIV infection. Histologically, it presents as a benign tumor but exhibits malignant clinical behavior and has a high rate of local recurrence and malignant transformation. BLT is considered intermediate between condyloma acuminatum and squamous cell carcinoma. It is typically caused by low-risk mucosal HPV 6 or 11, which is generally associated with benign growth and is not considered a high-risk factor for malignant progression. Less frequently, BLT is associated with high-risk HPV 16 and 18, but HPV 16 infection is correlated with invasive BLT. However, unlike benign condyloma, it tends to grow invasively into local tissues, leading to extensive fistulation, abscesses, and high recurrence rates even after surgical ablation, sometimes up to 66%. Histologically, BLT can appear similar to benign condyloma. Still, it lacks malignant features such as penetration of the basal membrane, abundance of mitotic figures, and loss of epithelial stratification, which are characteristic of SCC. Interestingly, BLT may transform focally into SCC, and there have been reports of SCC with regional and distant metastases that developed from low-risk HPV-associated BLT. The risk of malignant transformation into SCC ranges from 30% to 56%, whereas condyloma acuminatum has a significantly lower risk of only 2% [1,4,5-7,10].

Human Papillomavirus (HPV) infection is primarily transmitted through sexual contact; however, the virus can also spread through horizontal and vertical pathways. Following HPV infection of basal keratinocytes, viral DNA persists in the episomal form. In most cases, the immune system eliminates the infected cells. However, occasionally, the

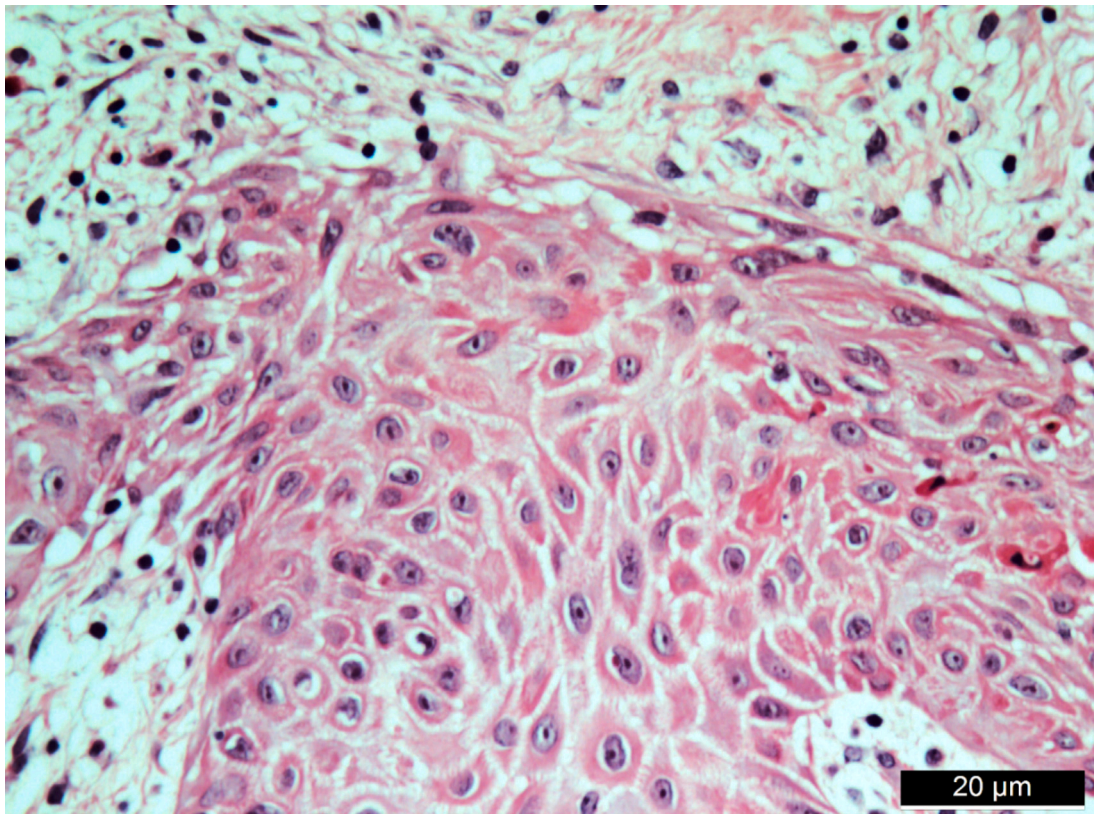


Fig. 3. Hematoxylin-eosin stained tissue section III.

Hematoxylin-eosin stained tissue sections show exophytic papillary growth patterns with well-formed papillae, hyperkeratosis and parakeratosis, koilocytes, lymphocytic infiltration.

elimination process fails, leading to the establishment of chronic HPV infection. Replication of HPV in dividing epithelial cells is accompanied by increased expression of the E6 and E7 oncoproteins, which are responsible for genomic instability, cell cycle disruption, cell proliferation, immortalization, and malignant transformation of HPV-infected cells. Additionally, E6 and E7 oncoproteins induce immunosuppression, which hinders the immune system's ability to detect HPV-infected and transformed cells. HPV integration into the host cell genome results in the upregulation of E6 and E7 expression, which contributes to HPV-associated malignancy. Prophylactic HPV vaccines can prevent over 80 % of HPV-associated anogenital cancers by eliciting an immune response that prevents initial infection with a given HPV type. However, these vaccines do not eliminate persistent viruses once the infection has occurred or prevent the development of HPV-associated neoplasms. Therefore, the development of therapeutic vaccines is necessary to treat chronic HPV infections and HPV-associated malignancies [11].

Because there is no consensus on the optimal treatment approach for BLT, the treatment algorithms are primarily based on case reports and small case series. Various therapeutic modalities have been proposed, including topical agents (such as podophyllin [2,5,9] and imiquimod [8]), cryotherapy [5], photodynamic therapy [5,6], immunotherapy [4,5], chemotherapy, radiotherapy [1-4,6,10], laser [6] and electrocoagulation. Wide local excision seems to be the first-line treatment, but sometimes, an abdominoperineal resection is mandatory to achieve an R0 resection because radicality is the cornerstone of the treatment. In situations where a negative-margin resection is not feasible, neo-adjuvant chemoradiation (chemotherapy: 5-fluorouracil, mitomycin-C, cisplatin; radiotherapy: 45 Gy in fractions \pm pelvic boost) should be offered to downsize the tumor. Chemoradiation alone may be indicated for patients who are not candidates for surgery or in cases where downsizing is unsuccessful. Additionally, adjuvant radiotherapy (45–66 Gy in fractions) should be considered when malignant transformation

towards squamous cell carcinoma (SCC) occurs [1-4,6-10].

The clinical presentation of the patient under discussion was characterized by the presence of exophytic, pedunculated verrucous lesions, along with pain, pruritus, and bleeding. The patient had no immunodeficiency and claimed not to have homosexual activity or multiple sexual partners but had a history of heavy smoking and regular alcohol consumption. Given the clinical findings, a wide excision was chosen as the primary therapeutic modality. The tumor exhibited BLT with malignant transformation into a well-differentiated SCC (pT2), and diagnostic imaging tests revealed no evidence of local spread or distant metastasis. The multidisciplinary oncology team recommended a re-excision due to a surgical margin issue. The second surgery was successful, with no signs of residual tumor cells or recurrence. According to the National Comprehensive Cancer Network (NCCN) Guidelines, adjuvant radiotherapy should be considered in malignant transformation into squamous cell carcinoma (SCC) cases. The primary goal of this treatment is to reduce the recurrence rate of cancer. Nevertheless, based on the tumor's stage (IIa), size, location, histological type, and the extended time interval between the two surgeries, it was determined that postoperative radiotherapy was not performed on this patient. Follow-up examinations conducted over 12 months revealed no symptoms or evidence of recurrence in either the patient's clinical evaluation or pelvic MRI.

4. Conclusion

Buschke-Löwenstein tumor is a rare, histologically benign, locally aggressive entity associated with human papillomavirus (HPV) types 6, 11, 16, and 18. The tumor has a high recurrence rate and malignant transformation towards a squamous cell carcinoma (SCC). HPV immunization can prevent the development of Buschke-Löwenstein tumor, and the early administration of the HPV vaccine is recommended to

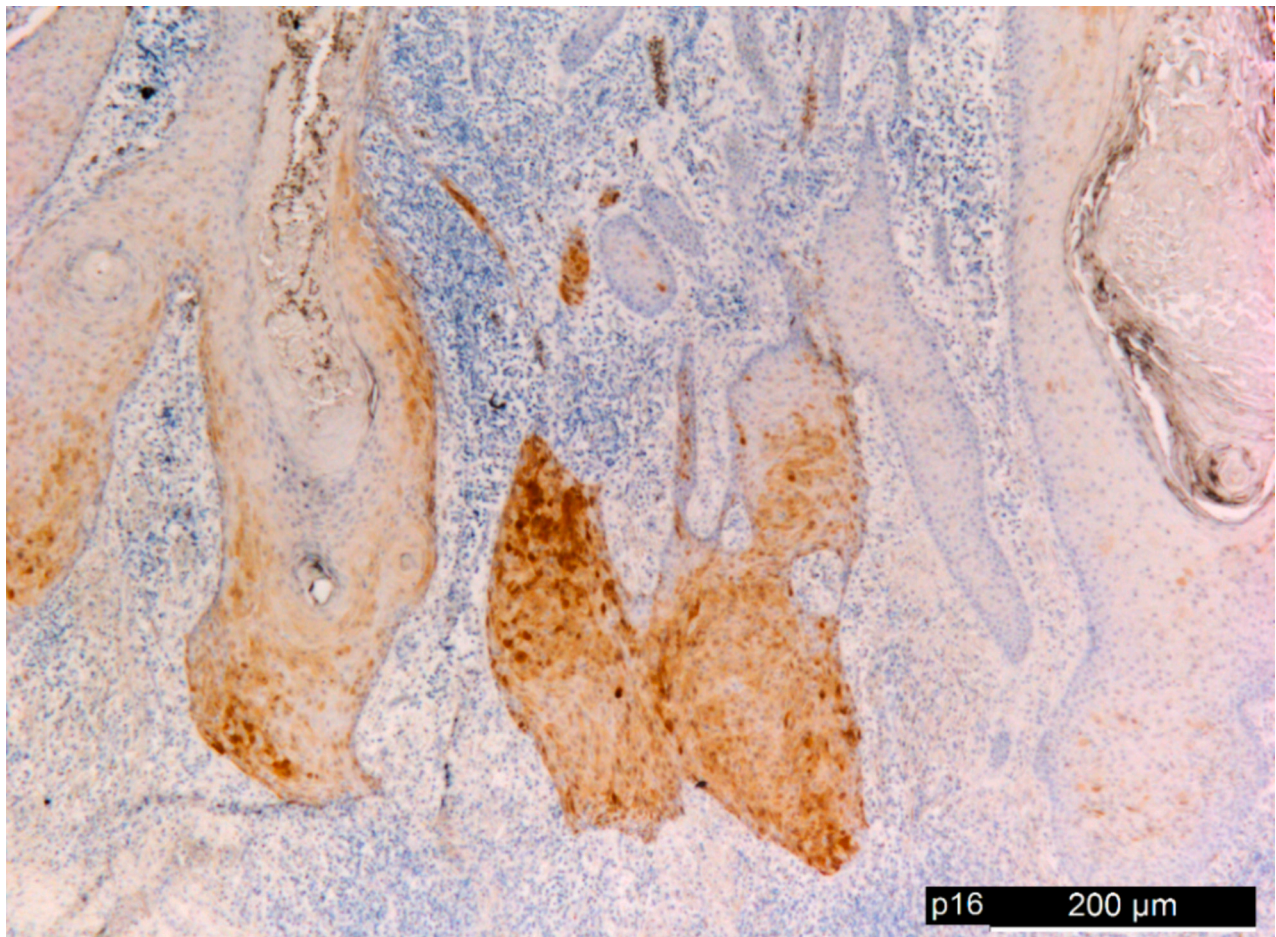


Fig. 4. P16 immunohistochemistry, which is generally associated with human papillomavirus (HPV), is positive.

avoid acquiring HPV infection.

There is a lack of consensus on the optimal treatment for this particular condition due to the absence of comprehensive research. However, after an extensive review of the literature, it has been found that radical surgical excision is the preferred first-line treatment, especially in cases where there is no evidence of local invasion and the condition is in its early stages. In cases where malignant transformation into SCC has occurred, wide local excision with clear margins is also the recommended primary therapeutic approach, supplemented with adjuvant radiotherapy based on the established guidelines.

List of abbreviations

BLT	Buschke-Löwenstein tumor
SCC	squamous cell carcinoma
HPV	human papillomavirus

Declarations

The work has been reported as being in line with the SCARE criteria.

Consent

Written informed consent was obtained from the patient, in their native language, for publication of non-identifying information, including accompanying intraoperative images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

The ethical committee approval was not required given the article type (case report), and the patient consented to the publication of the study, as the study does not contain data on the individual identification or ethnic identification of the patient.

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Author contribution

Norbert Balogh contribute to the publication (first author, corresponding author).

Péter Kolozsi contribute to the publication (data collection, data analysis, interpretation).

Dezső Tóth contribute to the publication (data collection, data analysis, interpretation).

Guarantor

The Guarantor is the corresponding author, Norbert Balogh.

Research registration number

Not applicable.

Conflict of interest statement

The authors declare that they have no conflicts of interest regarding the publication of this paper.

Data availability

All the datasets used in this report about the patient can be found in the digital register of the Surgical Department of the University of Debrecen. The patient gave written informed consent to the publication of this case report and accompanying images.

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