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Buschke – Löwenstein Tumor: Presentation of a Case

***Correspondence:**

paololeonej@gmail.com

Address: Av. Pedro J. Menéndez Gilbert y Atahualpa Chávez (junto a la ciudadela Atarazana). Apt. Postal 090505. Departamento de dermatología. Instituto Oncológico Nacional "Dr. Juan Tanca Marengo", Sociedad de Lucha Contra el Cáncer, Solca, Guayaquil, Ecuador. Phone [593] (04) 371 8300 EXT. 2218.

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Paolo Leone Jimenez [1], Maria Fernanda Carvajal [1].

1. Department of Dermatology, National Oncology Institute "Dr. Juan Tanca Marengo," Society for the Fight Against Cancer, Solca, Guayaquil, Ecuador.

Abstract

Introduction: Buschke-Lowenstein tumor (BLT) is a sexually transmitted disease caused by human papillomavirus (HPV), described as an intermediate form between condyloma acuminata and squamous cell carcinoma. It mainly affects the genital and anorectal areas and has the capacity for malignant transformation and a high recurrence rate. Surgery is the first-line treatment.

Clinical case: We present the case of a 27-year-old male patient with warty lesions of progressive growth in the inguinal and genital areas. Through the clinical-pathological correlation, the diagnosis of BLT was reached. After discussion in a multidisciplinary committee, it was declared unresectable, and treatment with radiotherapy was resolved, in addition to therapeutic vaccination against HPV, both systemic and intralesional.

Conclusion: BLT is locally aggressive and challenging to treat, so prevention against HPV is essential. Therapeutic vaccination in conjunction with radiotherapy offered clinical improvement.

Keywords:
MESH: Buschke-Lowenstein Tumor, Condyloma Acuminata, Human Papillomavirus 6, Human Papillomavirus 11, Nonvalent Vaccine, Radiotherapy

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Introduction

Buschke – Löwenstein tumor was first described in 1925 by AbrahamBuschke and Ludwig Löwenstein as a neoplasm of the penis that resembled both condyloma acuminata and squamous cell carcinoma [1]. It is a highly aggressive locoregional tumor, which is why it is said to behave malignantly but with low metastatic activity. It mainly affects the genital area, although rare cases have been described in which it appears in the anorectal area [2].

Although it is considered histologically benign and is a rare entity, it has a potential for malignant transformation of 8.5–23.8% and reported mortality rates of 20–30% [3, 4]. The leading cause of this tumor is HPV, generally subtypes 6 and 11, which is considered a sexually transmitted disease [5].

TBL is a rare entity with no apparent therapeutic guidelines, although surgery is considered the first-line treatment. Next, we present a clinically advanced case where surgery was impossible, making it difficult to manage. Other therapeutic options that could be useful in similar cases were explored.

Clinical case

The patient is a 27-year-old male Hispanic, a man who has sex with men (MSM), who came to the consultation due to multiple warty lesions of 3 years of evolution, which began as small warty plaques on the glans and were treated with podophyllotoxin. Despite treatment, one year before the initial consultation, the lesions recurred and worsened, involving the entire glans, scrotum, and inguinal region.

As a personal history, the patient was HIV+ (human immunodeficiency virus +), diagnosed in September 2019, and was on antiretroviral treatment with lopinavir, ritonavir, atazanavir, tenofovir, and emtricitabine. In addition, he was diagnosed with KS in 2020, for which he received treatment with thalidomide and had a history of chylothorax due to tuberculosis.

The patient provided the report of a biopsy performed in a private center in January 2021 that indicated a viral wart with moderate dysplasia in an unspecified genital region lesion. In the pelvic region, a sizeable cauliflower-like tumor with a warty surface was observed, which compromised the entire scrotum and another that compromised the glans almost wholly, in addition to multiple satellite lesions. This tumor caused limitations in walking and was painful. Bilateral inguinal lymphadenopathies and bilateral edema in the lower extremities were observed and palpated.

Diagnostic workshop

In the laboratory tests performed, the following was found:

- Erythrocytosis (red blood cells - January 2021: 5.72 x 106/µL. Range: 4.00 – 5.50 x 106/uL)
- Thrombocytosis (Platelets - January 2021: 584.00 x 103/µL; July 2021: 466.00 x 103/µL. Range: 150.00 – 450.00 x 103/uL).
- HIV viral load was undetectable at the last check-up (August 24, 2021).
- The CD4 count was 298 cells per cubic millimeter (August 24, 2021).
- Report of a standard chest radiograph indicates subsegmental atelectasis bibasal, with bilateral obliteration of the costophrenic angles.

A new biopsy (Figure 1), genotyping, and a computed tomography (CT) scan of the abdomen, pelvis, and chest were performed. The histopathology report concluded that it was a giant condyloma acuminata and that there was no evidence of the malignant transformation of the tumor (Figure 1), while the molecular biology report indicated the detection of HPV genotype 11 deoxyribonucleic acid (DNA).

Abdominal and pelvic CT revealed an exophytic lesion at the level of the glans and scrotum throughout its extension and bilateral adenopathies with an infiltrative aspect in the inguinal region (right adenopathy of 10 mm in its greater axis and left of 16 x 10 mm, both accompanied by other smaller ones). Chest CT reported a left lamellar pleural effusion.

Fine-needle aspiration puncture (FNA) of inguinal lymph nodes was performed with the following result: atypical lymphoid cells of undetermined significance, for which the clinical

oncology service recommended performing a biopsy of one of the inguinal lymph nodes. A biopsy of a nodule in the right inguinal region was performed. The following results were obtained: Fibroadipose tissue with chronic inflammation and foreign body-type giant cellular granuloma; no lymph node or neoplastic cells were identified in the sample.

Clinical evolution

In the time that elapsed from the initial consultation to performing the biopsy of the inguinal adenopathy, a marked deterioration of the clinical picture was observed, highlighting the local aggressiveness of this entity (Figure 2).

The case was presented at a meeting of a clinical-surgical oncology committee (COCQ), and it was decided not to perform resection surgery due to the size of the lesion, so the patient was referred to the radiotherapy service for definitive treatment. He received 50 Gray (Gy) radiotherapy with a scheme of 1.8 Gy in a single fraction per day from L3 to the distal third of the femur.

Additionally, one month before radiotherapy treatment, treatment with therapeutic vaccination was started using both the systemic and intralesional 9-valent vaccine against HPV (Gardasil 9®). Initially, proposed as a systemic and intralesional guideline, the scheme was at 0, 1, and 4 months.

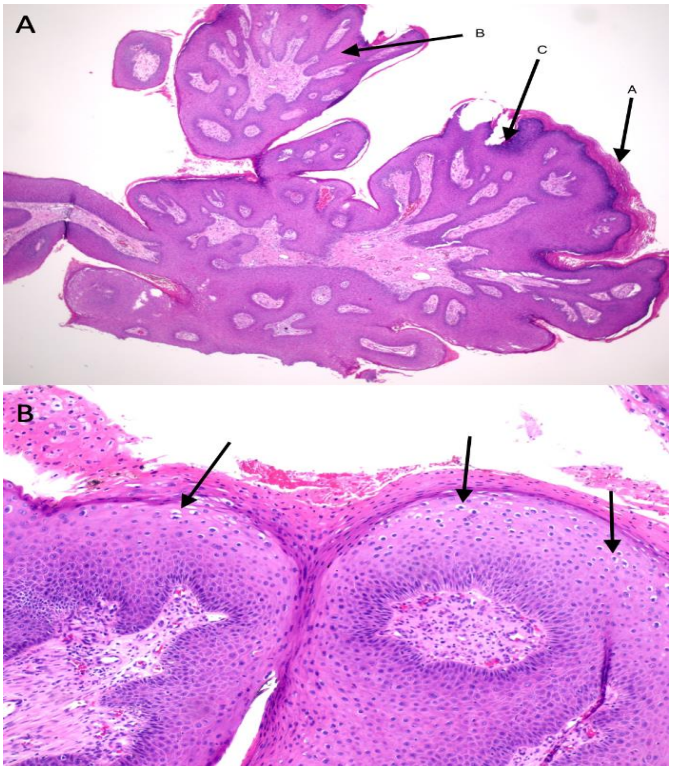

Figure 1. Hematoxylin and eosin-stained skin biopsy – low power. Hyperkeratosis (A), irregular acan-thosis with papillomatosis (B), and foci of hypergranulosis with atypical keratinocytes (C) are observed. B: Loss of standard architecture is observed; some keratinocytes present pyknotic nuclei with a whitish halo correspond-ing to koilocytes (arrows). Some keratinocytes show slight histological pleomorphism.

Due to the size of the lesion, in the initial regimen, the vaccine was injected into the balanopre-putial sulcus and into two satellite lesions, diluting 0.5 ml of the vaccine in 2.5 ml of saline solution (SS) and administering between 0.2 and 0.4 ml per injection. Injection site to assess the response to treatment (Figure 3). The patient improved in the clinical picture after the first regimen was decided to use, for the second regimen, 1 ml of the vaccine in 5 ml of saline solution, consistently administering between 0.2 and 0.4 ml per injection site (Figure 4).

At the time that elapsed from the second regimen to the following control (3 months), the lesions recurred on the glans and foreskin, despite having continued treatment with radiother-apy. For this reason, it was decided to increase an intralesional regimen four months after treatment, using 1 ml of a vaccine in 5 ml of SS.

As an adverse effect of the vaccination, he presented pain at the injection site. At the time of writing, 2 of the three systemic regimens (at 0 and 1 months) and 3 of 4 intralesional regi-mens (0, 1, and 4 months) were administered.

Discussion

TBL is a sexually transmitted disease that appears in 0.1% of the sexually active population and occurs mainly between the fourth and sixth decades of life [6]. It affects men more frequently (ratio of 2.7:1, some series indicate 4.4:1), but its appearance in women and children has been described in some cases. (7,8) It is very aggressive locally, with a high rate of recurrence (60% - 70%) and malignant potential (30% - 56%) [7]. The main risk factors for its development are HPV infection, smoking, and immunocompromised states (acquired immunodeficiency syndrome [AIDS], immunosuppressive therapy, alcoholism, diabetes, and chemotherapy) [8–10].

Infection with HPV subtypes 6 and 11, which are precisely the cause of 90% of condyloma acuminata [7, 11], is the cause of the disease.

Clinically, it presents as one or several large verrucous lesions with a cauliflower-like appearance that usually ulcerate and may form fistulas [7, 12]. It generally appears on the external genitalia, although in 10–17%, it can appear in the anorectal region [6]. Commonly presented symptoms are pain, discomfort, bleeding, the presence of a mass lesion, and discharge. A series of 38 cases reported that the average size and thickness of the tumors reviewed were between 2 – 14 cm and 0.2 – 2.5 cm, respectively, so we can consider that the case we present is rare, as it is more significant than average. [8].

The diagnosis is mainly clinical, where larger verrucous plaques will be observed than those observed in the case of condylomata acuminata. Histologically, it differs from a simple condyloma in that TBL exhibits increased mitotic activity, significant papillomatosis, thickened tumor margins, and a tendency to penetrate and infiltrate adjacent tissues [7].

In some series, TBLs that presented more invasion had more frequent keratosis, abnormal mitoses, and microabscesses. Neutrophils represent essential clues to predicting the presence of underlying invasive carcinoma when reviewing biopsy results [8]. Other essential data to differentiate a giant condyloma acuminata from a squamous cell carcinoma is that the basement membrane is intact in the former, and there is no lymphatic invasion or lymph node metastasis [13].

Due to the low incidence of this tumor, there are no established guidelines on its treatment yet, but several therapeutic options are described in the literature that must be chosen individually. Treatment currently focuses more on removing verrucous tissues rather than trying to eradicate the virus [11]. Surgical treatments include surgery with wide margins, and medical treatments such as therapeutic HPV vaccination, imiquimod 5% cream, sinecatechins/polyphenon E, podophyllotoxin, bleomycin, and peptides isolated from amphibians have been described [11, 14, 15].]. Some series suggest that these treatments be followed by physical or chemical ablation if they are large warts [16, 17].

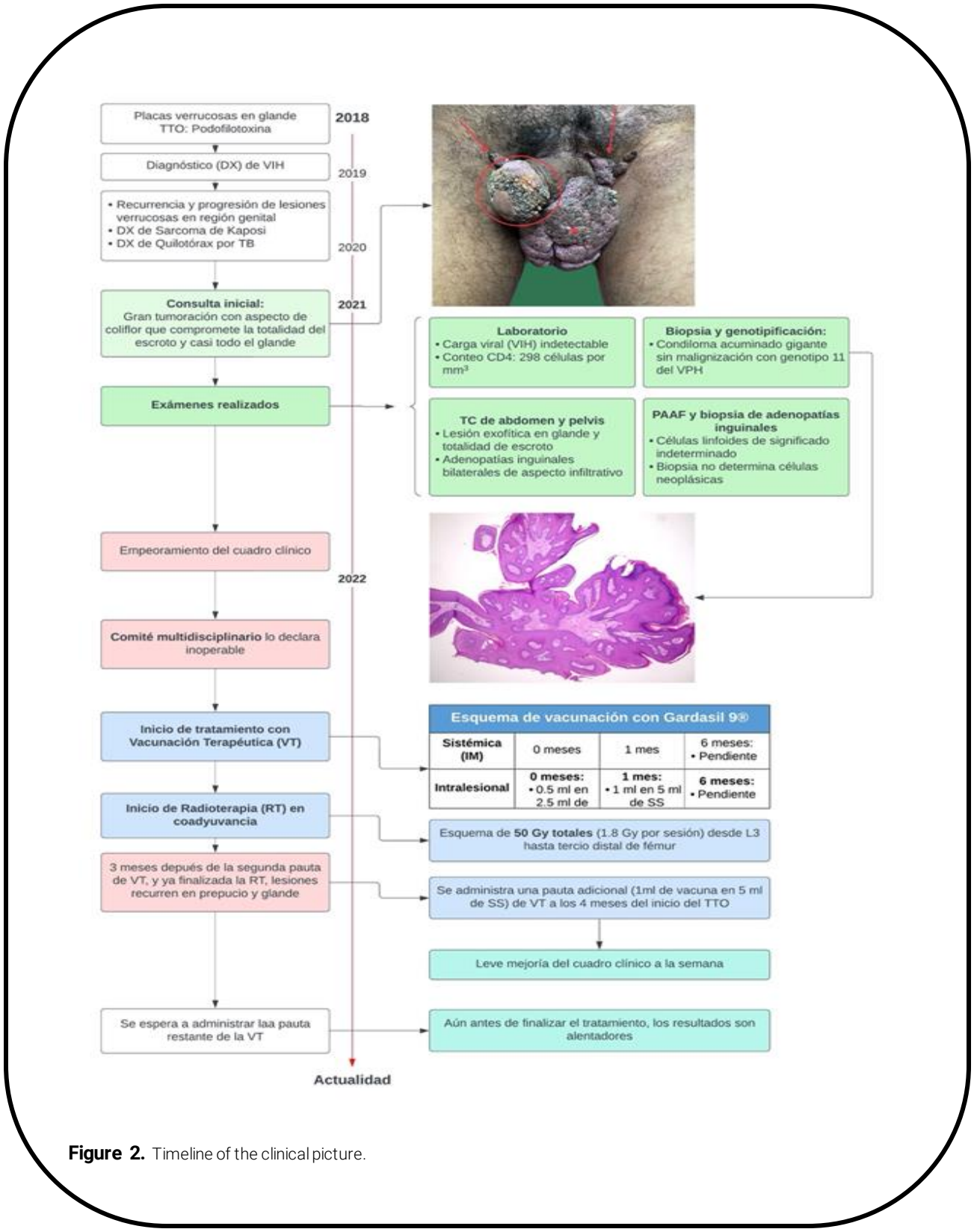

Figure 2. Timeline of the clinical picture.

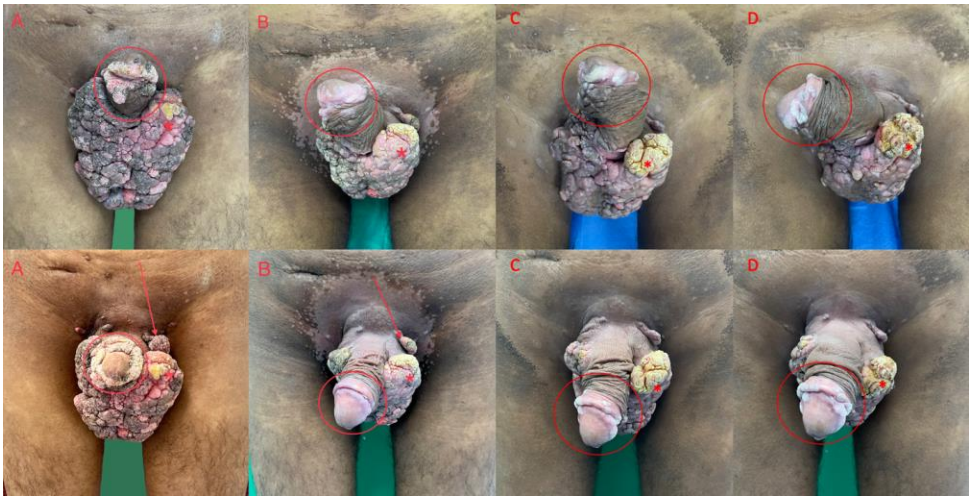

Figure 3. Comparative frontals of the clinical picture at 0 – 2 – 4 – 4.1 months. (A) Before starting treatment, (B) one month after administering the second dose of VT and 17 radiotherapy sessions, (C) one month after administering the second dose of VT, and (D) one week after administering a dose of additional intralesional VT. A decrease in the size of satellite lesions (arrows) of the lesions in the glans and balano-preputial sulcus (circle) was observed, but when more than one month passed without VT, the lesions recurred in the glans and foreskin, while the tumor mass that compromised the scrotum remained stable (*). Circled, arrowed, and asterisked areas injected with the HPV vaccine.

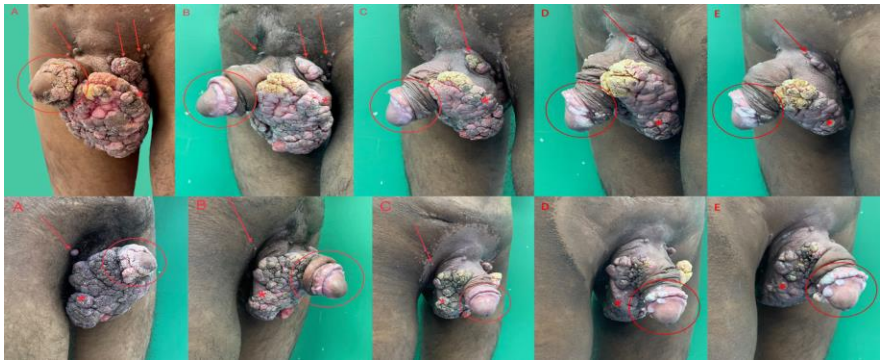

Figure 4. Comparative profiles of the clinical picture at 0 – 1 – 2 – 4 – 4.1 months. (A) Before starting treatment, (B) one month after administering the first dose of the vaccine, (C) one month after administering the second dose of the vaccine and 17 radiotherapy sessions, (D) at four months after starting treatment with VT and ending RT, and (E) at four months, one week after administering an additional intralesional dose of VT. A decrease in the size of satellite lesions (arrows) of the lesions in the glans penis and the balano-preputial sulcus (circle) was observed while the vaccination was monthly, and then the lesions recurred. The decrease in the tumor mass that compromises the scrotum was constant during the four months (*).

The management of this entity has proven to be complicated, so the focus on identifying risk factors and prevention through HPV vaccination is of the utmost importance. The previously exposed patient presented immunosuppression as a risk factor due to his HIV diagnosis, in addition to being MSM, which could have accelerated the growth of the lesions.

The difficulty of being unable to count on surgery due to tumor extension led to treatment with therapeutic vaccination. In the reviewed literature, only one other article mentions the use of this treatment with an excellent result [15] but taking into account that in that publication, the size of the lesion was significantly smaller (4 cm), in the said study, the bivalent vaccine against HPV systemically, in the present case the nonavalent was used.

Although the therapeutic vaccination was not completed at the time of writing, we noted that there was clinical improvement each time the therapeutic vaccination was administered, even when the additional regimen was administered after the glans and foreskin lesions recurred, for more than that the improvement was slight. Regarding radiotherapy, although a slight clinical improvement was observed during treatment, it was not as evident as that observed with vaccination, and once the prescribed regimen was completed, the lesions recurred.

In this case, therapeutic vaccination proved helpful and could be considered a first-line treatment in patients with not very advanced tumors or in unresectable tumors to reduce tumor size and evaluate complementary treatment. Aggressive treatment with a more adjusted VT scheme in large tumors seems necessary. TBL is generally associated with specific HPV subtypes (Table 1).

Table 1. Correlation of HPV subtypes and their respective diseases [18].

Illness	Associated HPV Type
plantar warts	1, 2, 4, 63
Myrmecia	60
common warts	1, 2, 4, 26, 27, 29, 41, 57, 65, 77
Common butcher warts	1, 2, 3, 4, 5, 10, 28
flat warts	3, 10, 27, 38, 41, 49, 75, 76
intermediate warts	10, 26, 28
condyloma acuminata	6, 11, 30, 42, 43, 44, 45, 51, 53, 54, 55, 70
Cervical carcinoma	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 66, 68, 70
laryngeal papillomas	6, 11
conjunctival papillomas	6, 11, 16
Buschke–Lowenstein tumor	6, 11, 16, 18, 52
intraepithelial neoplasms	Low grade: 6, 11, 16, 18, 31, 33, 35, 42, 43, 44, 45, 52, 52, 53, 74 High grade: 6, 11, 16, 18, 31, 33, 34, 35, 39, 42, 45, 51, 52, 56, 58, 66
Others	6, 11, 16, 30, 33, 36, 37, 38, 41, 48, 60, 72, 73

The vast majority of the literature reviewed suggests that the gold standard is surgery with wide margins [5, 6, 8, 19–23]. Preoperative imaging studies are required to assess the extent of the injury and choose the correct intervention. Despite being the therapy of choice, reinterventions are frequently necessary to complete the initial resection due to the high recurrence rate of this tumor [22]. A study with 38 cases reported a recurrence of 23.7% and a mortality of 2.6% at 23 months after undergoing radical surgery [8]. Due to the size of the lesions, their resection can result in extensive defects that may benefit from reconstruction using rotational flaps [1, 2]. Minimally invasive surgery, such as Mohs micrographic surgery, can be used in minor cases, as it has poor results and a high recurrence rate [22].

Regarding the specific treatment in TBL, imiquimod is an immunomodulator that directly activates the cells of innate immunity through Toll-like receptors [7]. It induces the secretion

of proinflammatory cytokines, including interferon-alpha [16]. It also provokes a tremendous inflammatory response by dendritic cells, Langerhans cells, and CD8+ T lymphocytes. It also facilitates the accumulation of CD8+ T lymphocytes in the genital tract, inhibiting tumor growth through gamma interferon. Imiquimod has been shown to induce apoptosis of tumor cells [11]. It is used three times a week for 16 weeks, and local erosions, erythema, and a burning sensation at the application site have been reported as adverse effects [16, 17, 20].

Interleukin 10 inhibitors are also used in treating TBL, a cytokine that exerts an anti-inflammatory action by suppressing the function of macrophages and dendritic cells and acting on T cells, decreasing their production of cytokines. [24]. Imiquimod enhances IL-10 secretion to prevent excessive immune responses and thus prevent autoimmune diseases. Using imiquimod in conjunction with an IL-10 inhibitor has increased efficacy when treating warts [11]. Attention should be given as high or dysregulated levels of IL-10 increase the risk of chronic infection [24].

In some isolated reports, there is treatment with natural peptides isolated from amphibians that are applied in gel form and have been shown to have antimicrobial and anticancer activity. Caerin 1.1 has an anticancer effect against several cancer cell lines in humans (leukemia, lung, colon, melanoma, prostate, ovary, and breast). Caerin 1.9 has broad-spectrum antimicrobial activity and has recently been shown to inhibit the growth of cancer cells in humans. Vitro [11, 16]. It was shown that when both peptides were used in combination with imiquimod, there was strong growth inhibition of HPV+ cells [11]. In addition, both peptides have been shown to have a cytotoxic effect on HPV 16 TC-1 cells and both attract T and NK cells to the tumor site [17].

Administration of the PNGVL4a-CRT/E7 DNA vaccine intralesionally has been shown to elicit a robust immune response by CD8+ T cells in HPV 16+ tumors [25]. In a recent study, a case was treated with systemic 2-valent (Cervarix) and intralesional 9-valent (Gardasil-9) vaccination, with clinical resolution of the condition 12 weeks after starting treatment [15].

Finally, several additional treatments have been described but used in specific situations. Among the local treatments, we found the use of trichloroacetic acid and radiotherapy. However, it can contribute to a malignant transformation of the LBT, for which its use is controversial, the use of $CO_{2\,laser}$, cryotherapy, and electrofulguration in small cases [7, 26]. Systemic therapy has also been used, among which we find the use of intramuscular or intralesional interferon (consensus interferon, interferon alfa-2a, interferon pegylated) for patients with unresectable tumors in monotherapy or as adjuvant therapy in conjunction with ribavirin, postoperative radiotherapy, 5-fluorouracil, cisplatin, mitomycin, methotrexate, and bleomycin as the most commonly used drugs [6, 7, 11, 26, 27].

Vaccination as a preventive measure is essential since HPV infection is the world's most common sexually transmitted disease [28]. Vaccination of male patients with the quadrivalent HPV vaccine that protects against subtypes 6, 11, 16, and 18 has been shown to significantly reduce the risk of anogenital HPV infection and thus could prevent TBL[7].

Editor's note

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Conclusions

Prevention with HPV vaccines in patients with warts is the most critical measure; once the case is advanced, the management of LBT is complex since it is a very aggressive tumor locally, with an easy invasion of neighboring tissues. Resection surgery is the gold standard, and

if it is early in the wrinkle or resectable tumor phase, it is the best therapeutic option. The treatment of cases considered unresectable is complicated, and therapeutic vaccination offers encouraging results as long as the vaccination schedule is adjusted and no more than two months elapse between intralesional doses.

Abbreviations

LBT: Buschke-Lowenstein tumor
HPV: Human papillomavirus
HIV: Human Immunodeficiency Virus
CT: Computed tomography
DNA: deoxyribonucleic acid
FNA: fine needle aspiration puncture
AIDS: Acquired immunodeficiency syndrome.

Administrative information

Additional Files

The authors declare none.

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Author contributions

1. Conceptualization: Paolo Leone Jiménez, María Fernanda Carvajal.
2. Formal analysis: Paolo Leone Jiménez.
3. Research: Paolo Leone Jiménez, María Fernanda Carvajal.
4. Methodology: Paolo Leone Jiménez.
5. Project administration: María Fernanda Carvajal.
6. Supervision: María Fernanda Carvajal.
7. Validation: Paolo Leone Jiménez.
8. Visualization: Paolo Leone Jiménez, María Fernanda Carvajal.
9. Writing - draft or original: María Fernanda Carvajal.
10. Writing - revision and edition: Paolo Leone Jiménez.

All authors read and approved the final version of the manuscript.

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Availability of data and materials

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Statements

Ethics committee approval

It does not apply to observational studies with a review of databases or medical records.

Consent to publication

The authors have permission for publication from the patient referred to in this case.

Conflicts of interest

The authors declare that they have no conflict of interest or competence.

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