https://doi.org/10.22516/25007440.1258

Case report

Inverted-Growth Buschke-Löwenstein Tumor: A Case Report with Therapeutic Proposal

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Citation:
Márquez-Velásquez JR, Miranda-Ruiz LF, Mateus-Barbosa LM, Grisales-Ramírez S, Miranda-Ruiz CA, Tamayo JA. Inverted-Growth Buschke-Löwenstein Tumor: A Case Report with Therapeutic Proposal. Revista. colomb. Gastroenterol. 2025;40(2):252-259.
https://doi.org/10.22516/25007440.1258

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Received: 20/07/2024
Accepted: 27/01/2025

Abstract

The Buschke-Löwenstein tumor (BLT) is a type of giant epithelial tumor typically characterized by a broad base, infiltrative potential, and local tissue destruction. As a result, recurrences are common, which confers a certain degree of malignant potential. From a histopathological standpoint, it is composed of hyperplastic epithelium, minimal atypia, and well-differentiated tissue with hyperkeratosis, parakeratosis, and the presence of koilocytes. This finding is a hallmark of human papillomavirus (HPV) infection at the cellular level, along with granular changes and mitotic activity in the basal layer. This article describes a rare variant with inverted growth and infiltration of the anal and perianal tissues, associated with a clinical presentation of anal fissures and fistulas. A therapeutic proposal is also discussed. The case involves a 35-year-old male from Bello, Antioquia, who presented to our institution with a 4-year history of perianal openings with purulent discharge, pain, and bleeding. A contrast-enhanced pelvic MRI revealed infiltration of the anal, perianal, and adipose tissues by condylomatous lesions with displacement of adjacent structures. A medical management protocol developed at the Instituto de Coloproctología (ICO) in Medellín, Colombia, was implemented and complemented with surgical treatment.

Keywords

Condyloma acuminatum, human papillomavirus, verrucous carcinoma, anoscopy, anal cancer, anal neoplasms.

INTRODUCTION

Approximately 80% of sexually active individuals, regardless of sexual preference, will come into contact with human papillomavirus (HPV) at some point in their lives, though not all will develop secondary lesions[1,2]. Anal and perianal lesions have become increasingly common in heterosexual individuals of all ages due to the growing prevalence of anal sex. It is well-established that HPV causes 98% of genital cancers (anus, cervix, vagina, penis) as well as laryngeal cancers, and there is emerging speculation that it may even play a role in the development of esophageal and lung cancers[3,4].

It is estimated that out of the world's population of over 7 billion, approximately one million people are newly infected with HPV daily. According to the World Health Organization (WHO), around 290 million women were infected by 2018, making HPV the leading cause of sexua-

lly transmitted infections (STIs) worldwide and, consequently, a major public health concern.

Certain factors increase the risk of anal cancer associated with higher morbidity from HPV infection. Typically, the specific cellular and molecular damage caused by this virus is linked to the overproduction of genetic material and disruptions in the regulatory factors of cellular replication and apoptotic mechanisms. This leads to increased cell replication and the development of cellular dysplasia. Histopathology reveals enlarged nuclei, chromatin overproduction, or simply hypercellularity, while phenotypically, large warts with varied morphological formations develop. When these exceed 3 cm in diameter, they are classified as Buschke-Löwenstein tumors (BLT).

This case report describes an atypical growth pattern of BLT. Due to the loss of squamous epithelial continuity in the anal canal, verrucous infiltration into deep tissues occurred, with the potential to replace gluteal muscle. This infiltration colonized fistulous tracts, resulting in an inverted-growth BLT. A systematic review was conducted using five medical literature search engines (NCBI, BVS, Ovid, Trip Database, Google Scholar), which confirmed that no similar scientific records exist in the literature.

CASE REPORT

A 35-year-old male patient from Bello, Antioquia, who is HIV-positive (diagnosed in 2015), presented with a four-year clinical history of perianal orifices discharging mucopurulent fluid, bleeding, and pain. Initial conventional anoscopy identified a complex horseshoe perianal fistula with three secondary openings located in the right anterolateral, right lateral, and right posterolateral quadrants. The primary orifice could not be determined. Additionally, condylomatous lesions were observed, involving the entire length and 100% of the anal canal circumference. A biopsy of the lesions revealed a "low-grade squamous intraepithelial lesion (LSIL)."

The fistula and condylomas were surgically managed by a general surgery specialist at Clínica Las Américas in Medellín, Colombia. The patient returned in August 2020 due to the reappearance of new lesions and was subsequently evaluated at Instituto de Coloproctología (ICO). Physical examination identified five active fistulous tracts lined with condylomas, a non-mobile induration in the right gluteal region, and anal sphincter involvement with functional impairment (**Figure 1**).

A contrast-enhanced pelvic MRI was performed, reporting "gluteal infiltration by condylomas, with greater involvement on the right side and possible ipsilateral sphincter compromise" (**Figure 2**).

High-resolution anoscopy was also performed, confirming high-volume HPV-related disease. HPV genotyping tested positive for high-risk strains: 39, 52, and 68 (**Figure 3**).

Medical management was initiated using "*ICO seguro*" (ICO's Safe Protocol), which consisted of: Topical 5% 5-fluorouracil cream applied to perianal condylomatous lesions and inside the anal canal every 12 hours (5 consecutive days followed by 9 days of rest). Subcutaneous methotrexate (25 mg weekly) for 16 weeks. One month after completing therapy, a 50% reduction in disease burden was confirmed. However, subsequent follow-ups showed a plateau in response. Thus, in May 2021, surgical resection of the anal canal tumor was scheduled, with sphincter preser-

Figure 1. Macroscopic appearance of the inverted Buschke-Löwenstein tumor. Images property of Instituto de Coloproctología (ICO) S.A.S.

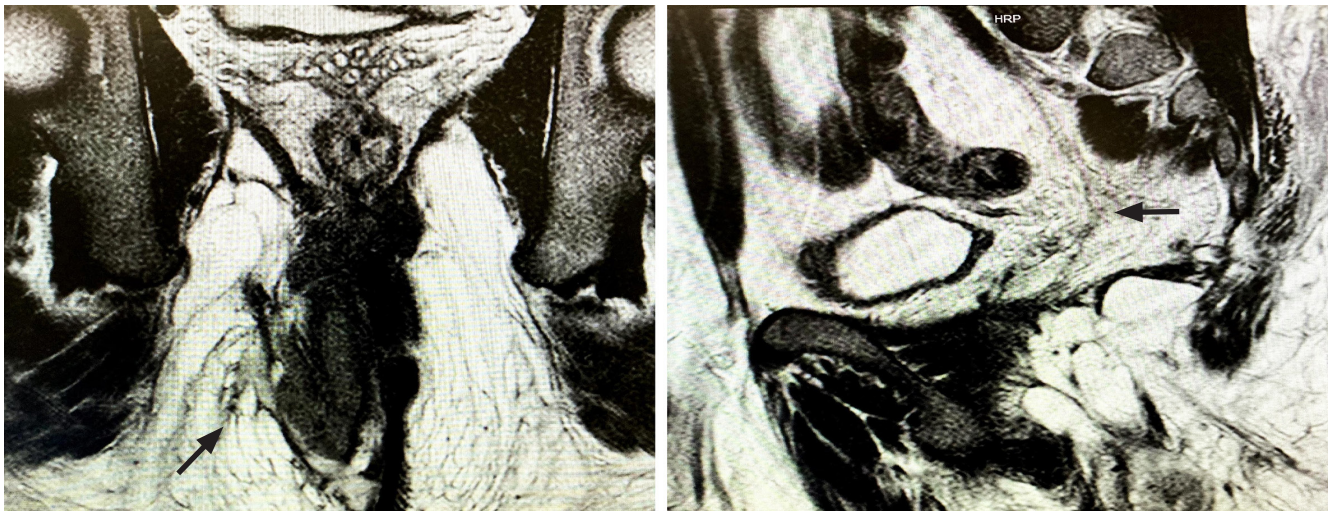

Figure 2. MRI of the inverted Buschke-Löwenstein tumor. Arrows indicate gluteal infiltration with predominant right-sided condyloma involvement and possible ipsilateral sphincter compromise. Images property of Instituto de Coloproctología (ICO) S.A.S.

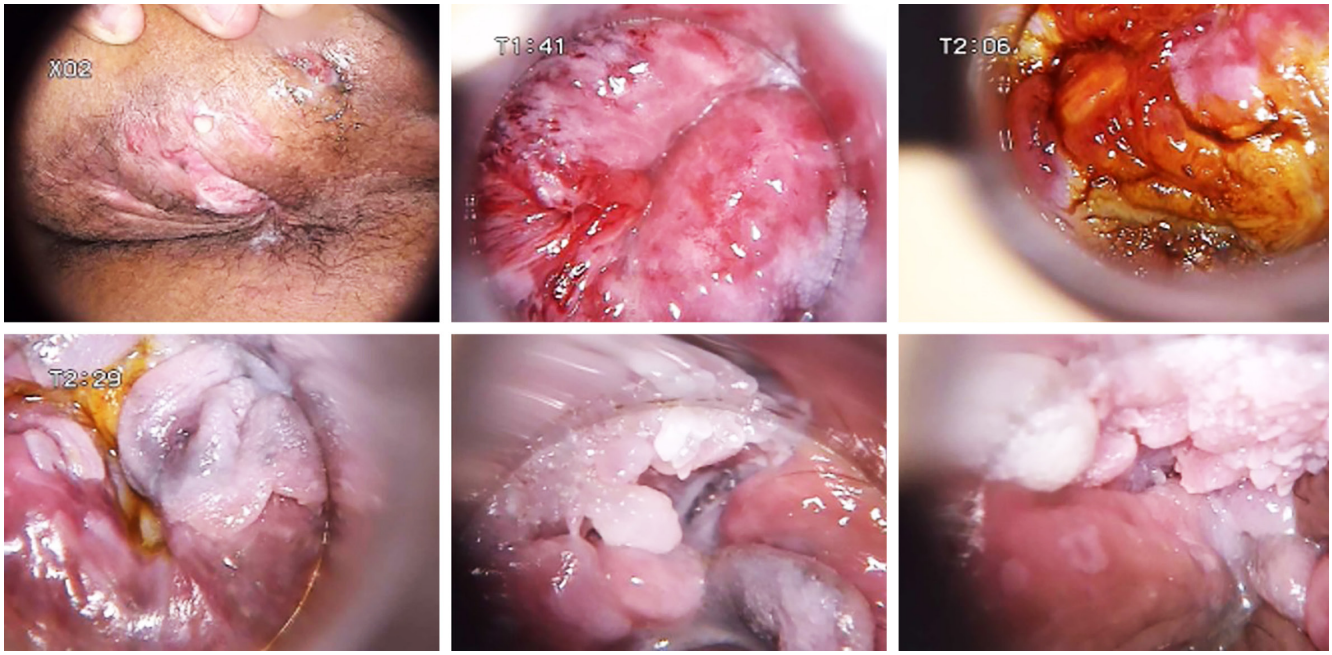

Figure 3. High-resolution anoscopy of the inverted Buschke-Löwenstein tumor. Images property of Instituto de Coloproctología (ICO) S.A.S.

vation and gluteal flap rotation to cover the defect (**Figure 4**). Histopathological analysis of the samples confirmed "condylomas with high-grade dysplasia."

One month postoperatively, follow-up examination showed 90% healing with no evidence of fistulas. A year later, on May 10, 2022, a control high-resolution anoscopy revealed HPV recurrence with high-volume disease involving 100% of the anal canal (**Figure 5**).

Medical therapy with 5-fluorouracil and methotrexate was reintroduced per the previous protocol. However, due to poor patient adherence, serial ablative therapy was initiated instead, achieving lesion resolution.

By July 2023, high-resolution anoscopy showed recurrent lesions affecting 50% of the anal canal. Repeat serial ablative therapy was performed, resolving active lesions (**Figure 6**) while preserving continence.

Figure 4. Surgical resection of the inverted Buschke-Löwenstein tumor with gluteal flap rotation and sphincter preservation. Images property of Instituto de Coloproctología (ICO) S.A.S.

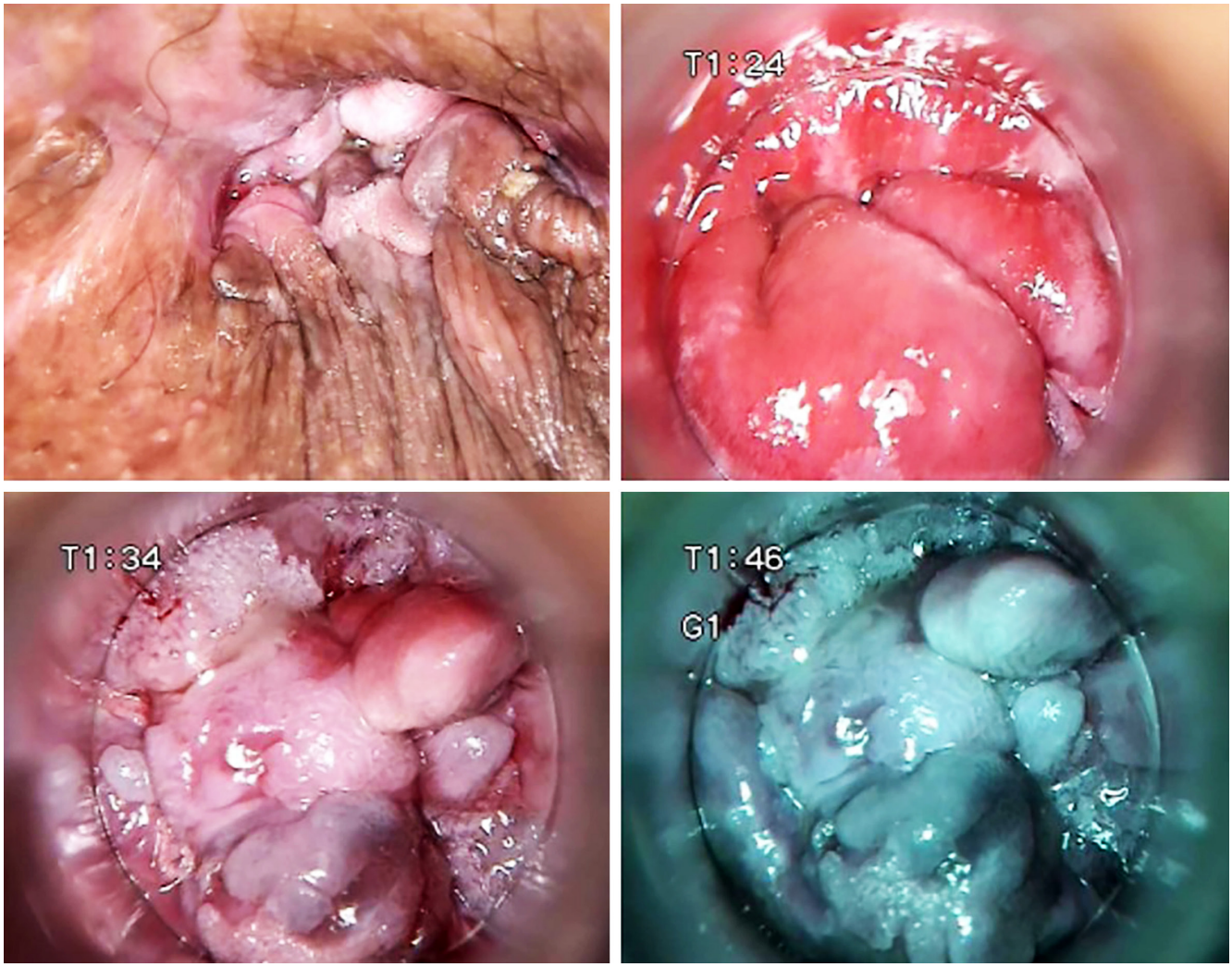

Figure 5. Recurrence of the inverted Buschke-Löwenstein tumor on high-resolution anoscopy one year after surgical resection. Images property of Instituto de Coloproctología (ICO) S.A.S.

Figure 6. Serial ablative therapy with resolution of active lesions in the inverted Buschke-Löwenstein tumor. Images property of Instituto de Coloproctología (ICO) S.A.S.

Currently, the patient's social circumstances have limited adherence to scheduled follow-ups. Nevertheless, he reports no recurrence of prior symptoms and feels confident about his current condition.

DISCUSSION

HPV is a small, non-enveloped, double-stranded DNA papovavirus, and its sexually transmitted infection is the most common human pathogen infection[5]. The main risk factors for HPV infection include sex with uncircumcised men, promiscuity, and early age of first sexual contact. Additionally, patients who have undergone solid organ transplantation (kidney, liver, etc.), those undergoing chemotherapy or radiotherapy (leukemia, lymphomas), or those on immunosuppressive treatment (biologic agents, chronic steroid use, diabetes, etc.) are at higher risk. Some studies, such as that by Nyitray et al., have reported anal carcinoma rates up to 10 times higher in kidney transplant patients compared to the general population[6].

Anal squamous cell carcinoma (ASCC) is a rare neoplasm, accounting for less than 5% of all gastrointestinal cancers. The current global incidence is estimated at 1.8 cases per 100,000 individuals, and both incidence and mortality rates have been increasing. Ninety percent of cases are associated with HPV infection. In fact, few physicians are aware that anal cancer is more common in women than in men. When analyzing high-risk groups—such as HIV-infected patients or men who have sex with men (MSM)—it is notable that anal cancer rates are exponentially higher in these populations than in the general population (1.8/100,000). Specifically, the incidence of anal cancer in HIV-negative MSM is 35/100,000, while in HIV-positive MSM, it rises to 131/100,000[7].

Currently, HPV infection is recognized as responsible for nearly all cervical cancers, 95% of anal cancers, 65% of vaginal cancers, 50% of vulvar cancers, 35% of penile cancers, and a significant proportion of head and neck cancers[8].

To date, nearly 450 HPV genotypes have been isolated and sequenced[9]. Of these, 40 subtypes infect through mucosal epithelial contact. Among high-risk types, strains 16, 18, 31, 33, 35, 52, and 45 stand out as the most significant carcinogenic agents, isolated in 91% of these tumors. However, types 16 and 18 alone account for 79% of anal canal cancers[10].

Giant condyloma acuminatum is also known as Buschke-Löwenstein tumor (BLT). It is a rare, locally invasive tumor arising from a preexisting wart-like lesion, often described as an exophytic, cauliflower-like growth. BLT was first reported in 1896 by Abraham Buschke in Neisser's *Atlas Stereoskopischer der Hautkrankheiten*. Later, in 1925, Abraham Buschke and his assistant Ludwig Löwenstein described BLT as a penile lesion clinically resembling both common condylomas and squamous cell carcinoma (SCC), but with distinct histological features and biological behavior[11,12].

Some authors consider BLT an intermediate condition between condyloma and squamous cell carcinoma[13]. Histologically, the tumor appears benign, with papillomatosis, epithelial hyperplasia, and koilocytosis; however, clinically, it can behave aggressively with extensive infiltration. Other distinguishing clinical features include extensive fistulation, abscess formation, and high local recurrence rates after surgical resection[14].

Focally, these tumors may also transform into invasive squamous cell carcinoma in approximately 30% to 50% of patients, with an overall mortality rate of 20%[15]. Metastasis is rare, and growth rates typically range from two to 10 years in immunocompetent individuals[15], though rapid progression may occur in immunocompromised patients.

This condition is more prevalent in men than women, with a ratio of 2.7:1[16]. Commonly affected sites include the penis, perianal region, vulva, vagina, rectum, scrotum, perineum, and bladder[17].

BLTs contain low-risk HPV, particularly strains 6 and 11, which appear central to the pathogenesis of this neoplasm. However, the cause of the transformation from benign condylomas to locally invasive BLT remains unknown[14,18]. Highly active antiretroviral therapy (HAART) does not affect concomitant HPV-related disease and has no efficacy against BLT[14].

Routine imaging studies—such as contrast-enhanced pelvic CT and MRI—are recommended to assess local and

regional extension, which is crucial for determining optimal treatment[19].

Traditionally, wide-margin surgical resection, with or without reconstructive surgery, has been the gold standard for treatment[12]. However, the high recurrence rates (66%) associated with this approach suggest the need to shift current paradigms, as mutilating surgery—which often sacrifices sphincter function while offering such low cure rates—does not represent the optimal solution.

In 2019, the authors developed an innovative medical treatment called *ICO-Seguro*—a low-morbidity, non-invasive approach with higher response rates compared to surgical resection for managing HPV-related anal pathology. This method significantly improves quality of life. However, it is crucial to acknowledge that the proposed therapy is still far from curative.

Among the 7,100 patients evaluated to date using high-resolution anoscopy and trained specialists, 17% (n=1,207) were found to have high-volume disease (i.e., prominent perianal tumors). The remaining cohort included 30% (n=2,130) healthy patients and 53% (n=3,763) with minor lesions. The latter group underwent outpatient cauterization under local anesthesia and anoscopic guidance. This procedure required no bowel prep, enemas, fasting, surgical intervention, or accompaniment, and caused no significant pain, tissue damage, or bleeding.

For high-volume disease, treatment combined 5-fluorouracil (5-FU) and methotrexate: Topical 5-FU acts as a local chemotherapeutic agent, disrupting DNA synthesis and mildly inhibiting RNA formation, inducing metabolic imbalance that triggers cell death. It targets rapidly proliferating and abnormal cells in actinic keratoses and basal cell carcinoma. Methotrexate slows disordered cellular growth.

Post-treatment follow-up under the *ICO-Seguro* protocol includes: (1) High-resolution anoscopy at 6 months. (2) If no lesions are detected, annual monitoring for two consecutive years, transitioning to anal cytology screenings thereafter.

Lastly, quadrivalent and nonavalent HPV vaccines (Gardasil) significantly reduce genital warts incidence. While no studies have measured their impact on BLT rates, these vaccines likely lower BLT risk since they target HPV strains 6 and 11—the primary drivers of BLT growth. Some authors also suggest therapeutic potential, citing cases of giant condyloma acuminatum regression post-vaccination[12].

CONCLUSION

The Buschke-Löwenstein tumor (BLT) in the anal and perianal region is a rare but dramatic lesion, presenting significant management challenges. With evolving sexual behaviors and preferences, cultural openness, and the growing number of immunocompromised yet sexually active individuals, the incidence of this condition is expected to rise—particularly as the anus becomes an increasingly explored erogenous zone.

The prognosis of BLT likely depends on its size, local recurrence, transformation to squamous cell carcinoma (SCC), secondary infections, and associated immunodeficiencies.

The traditional management approach has been surgical resection. However, the primary issue lies in the fact that this intervention often leads to varying degrees of scarring, which may result in fibrosis, anal stenosis, or even fecal incontinence—all without guaranteeing complete cure.

Instituto de Coloproctología (ICO) is the only institution in the region dedicated to early detection and comprehensive management of anal HPV infection. Since 2019, it has evaluated over 7,000 patients, establishing itself as the national leader in case registries and research in this field. ICO has developed an innovative, non-invasive, low-morbidity medical treatment program that demonstrates better response rates than surgical resection. While promising, it is important to acknowledge that these treatments are not yet curative.

Early diagnosis and appropriate aggressive treatment can reduce both medical and surgical morbidity, as well as overall mortality.

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