

Buschke-Löwenstein tumors: A series of 7 case reports

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Abstract. Giant condyloma acuminatum (GCA), or Buschke-Löwenstein tumor (BLT), represents an infrequent sexually transmitted disease (STD), caused by human papillomavirus (HPV), especially genotype 6 or 11. There are numerous risk factors for HPV, such as multiple sexual partners, homosexuality, prostitution, chronic genital infections, as well as the lack of proper hygiene. HPV infection is a field infection, where large areas of cells at a tissue surface are affected by the HPV virus; therefore, once the GCA is excised, treatment of the whole affected genital area needs to be undertaken. The treatment is classified into topical therapy (podophyllin, 5-FU, radiotherapy, topical photodynamic therapy), excisional therapy (CO₂ laser, cryotherapy, electrotherapy, surgery) and immunotherapy (imiquimod). However, the 'gold standard' therapy is represented by wide surgical excision without grafting, since it is considered that healing *per secundam* is an improved approach, because there is no risk of recurrences on fibrotic tissue. A total of 7 cases of the BLT with comorbidities and particularities are presented and it is recommended that it be taken into consideration that the incidence of the disease is increasing, emphasizing the importance of an early diagnosis, as well as an adequate treatment.

Introduction

Giant condyloma acuminatum (GCA), also known as Buschke-Löwenstein tumor (BLT), represents an infrequent sexually transmitted disease (STD) triggered most frequently

by HPV (human papilloma virus) 6 and 11 (1), and exceptionally 16 and 18 (2,3), having common risk factors with condyloma acuminatum (including multiple partners, prostitution, men having sex with men, poor hygiene as well as other STDs) (1,4,5).

BLT is always preceded by condyloma acuminatum, with certain authors considering that it is the midway between condyloma acuminatum and squamous cell carcinoma, and the malignant transformation risk is 40-60% (4,6). It is associated with the immunosuppressive status: Congenital or acquired immunodeficiencies, diabetes mellitus, alcoholism, chemotherapy, immunosuppressive therapy (7).

BLT may occur at any age, particularly after puberty. Men are more affected than women, usually between 30 and 50 years old, with a male/female sex ratio of 3:1. The general incidence in the US is 0.1%, similar with the one from the developed countries in Europe (4). It is considered that almost everyone will manifest a minimum of one HPV infection during their lifetime, often asymptomatic, transient, spontaneously resolved, without being aware of it and 2% will develop condyloma acuminata (8).

Clinically, it presents as an exophytic, vegetative tumor, frequently cauliflower-like, white-yellowish, slowly or rapidly growing depending on the immune status of the patient, that may invade and destroy the surrounding tissue, without spontaneous resolution (1,9). The risk of distant metastases is low (6). In 81-94% of the cases, the lesion is located on the penis. The anorectal area is affected in 10-17% of the cases and the urethra in 5% of the cases. In females, the vulva is generally the most affected, in 90% of the cases, while the anorectal location is less frequent (4). From a histopathological perspective, the hyperplastic epithelium is well-differentiated, with hyperkeratosis, parakeratosis, koilocytes, a bulging granular layer, papillomatosis and minimal atypia (1,9).

The treatment is classified into topical therapy (podophyllin, 5-FU, radiotherapy), excisional therapy (CO₂ laser, cryotherapy, electrotherapy, surgery) and immunotherapy (imiquimod). A rather new therapy to be considered is the photodynamic therapy, that uses aminolevulinic acid hydrochloride; photosensitizers have been revealed to have antiviral action (1). The association with invasive genital carcinoma, as well as its aggressive character, require multidisciplinary collaboration, including colonoscopy for the rectal invasion (10). Selecting the right treatment option depends on the

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tumor characteristics and on the skills of the physician, with surgical treatment remaining as the first line therapy, with a lower recurrence risk (3,4). If the tumors are invasive, the patients could require a colostomy and nephrostomy (10).

Case reports

Case 1. A 39-year-old male patient with no notable medical history, smoker, and sexual intercourse debut at 15 years old, presented to the Department of Dermatology of Ponderas Academic Hospital for a large exophytic cauliflower-like verrucous tumor in the perianal area and smaller similar lesions localized in the genital, supra-penile, scrotal and crural areas. The patient was negative for STDs and the genotyping was positive for HPV 16. The colonoscopy revealed no rectal invasion and the patient refused a colostomy.

A reduction of the tumor volume was performed with radiosurgical excision under general anesthesia and all the smaller lesions were excised in 10 sessions of CO₂ laser under local anesthesia. The histopathological report revealed epidermal hyperplasia, hyperkeratosis, papillomatosis, koilocytes, HPV 6-positive intra-tissue and no signs of malignant transformation.

The healing occurred by secondary intention, in 60 days. The patient received systemic antibiotic therapy with levofloxacin (500 mg/day for 15 days), then cefuroxime (1 g twice a day for 3 weeks), local and intrarectal sinecatechins (twice a day for 4 months), nonspecific immune stimulation with inosine pranobex (3 tablets twice a day for 10 days per month), alternately with *Coriolus versicolor* (3 tablets twice a day for 4 months). The peniscopy and the microscopic examination of the anogenital region revealed residual subclinical lesions. They were excised with CO₂ laser, 3 sessions of fractional photodynamic therapy with 8% levulinic acid applied topically under occlusion for 2 h, then 20 min of 635-nm red light at 70 mJ/cm² fluency, followed by 10 min of 411-nm blue light at 80 mF/cm² fluency, and finally 10 min of 635-nm red light at 70 mJ/cm² fluency. A total of 3 doses of Gardasil vaccine were administered (months 0-2-6) (Figs. 1-7).

Case 2. A 26-year-old male homosexual patient, smoker, sexual intercourse debut at 15 years old, and multiple sexual partners, presented to the Department of Dermatology of Ponderas Academic Hospital for a large exophytic cauliflower-like verrucous tumor in the perianal area. The patient had asymptomatic urethral co-infection with *Haemophilus influenzae*, was negative for STDs and the intra-anal and intra-urethral genotyping was positive for HPV 6 and 16. The colonoscopy revealed no rectal invasion.

The peniscopy and the microscopic examination of the anogenital region revealed 30 subclinical genital, supra-penile and crural lesions, which were excised with CO₂ laser in 4 sessions under local anesthesia. The histopathological report revealed epidermal hyperplasia, hyperkeratosis, papillomatosis, koilocytes and HPV 6-positive intra-tissue.

The patient received local and intrarectal sinecatechins (twice a day for 4 months), inosine pranobex (3 tablets twice a day, 10 days per month) alternately with *Coriolus versicolor* (3 tablets twice a day for 4 months). The peniscopy and the microscopic examination of the anogenital region revealed



Figure 1. Case 1: Clinical image of Buschke-Löwenstein tumor. Large exophytic cauliflower-like verrucous tumors of the perianal area and smaller similar lesions localized in the genital, supra-penile, scrotal and crural areas.



Figure 2. Case 1: Clinical image of Buschke-Löwenstein tumor. Close-up of the lesions.

residual subclinical lesions that were excised with CO₂ laser, 3 sessions of fractional photodynamic therapy with 8% levulinic acid applied topically under occlusion for 2 h, then 20 min of 635-nm red light at 70 mJ/cm² fluency, followed by 10 min of 41-nm blue light at 80 mF/cm² fluency, and finally



Figure 3. Case 1: Clinical image of Buschke-Löwenstein tumor. Close-up of the perianal tumor showing the characteristic verrucous surface.

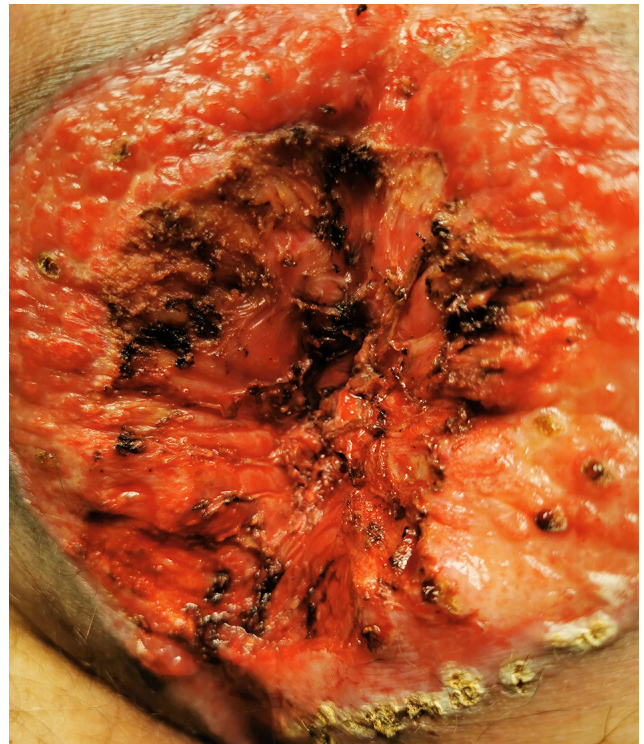


Figure 5. Case 1: Clinical image of the perianal lesion after radiosurgical excision.



Figure 4. Case 1: Clinical image of Buschke-Löwenstein tumors after CO₂ laser.

10 min of 635-nm red light at 70 mJ/cm² fluency. A total of 3 doses of Gardasil vaccine were administered (months 0-2-6) (Figs. 8-12).

Case 3. A 24-year-old male patient, smoker, and sexual intercourse debut at 14 years, consulted us at the Department of



Figure 6. Case 1: Clinical image of the scar tissue of the perianal area after excision at the follow-up visit.

Dermatology of Ponderas Academic Hospital for a vegetative, exophytic, intra-urethral tumor. The patient had asymptomatic urethral co-infection with *Ureaplasma urealyticum* and

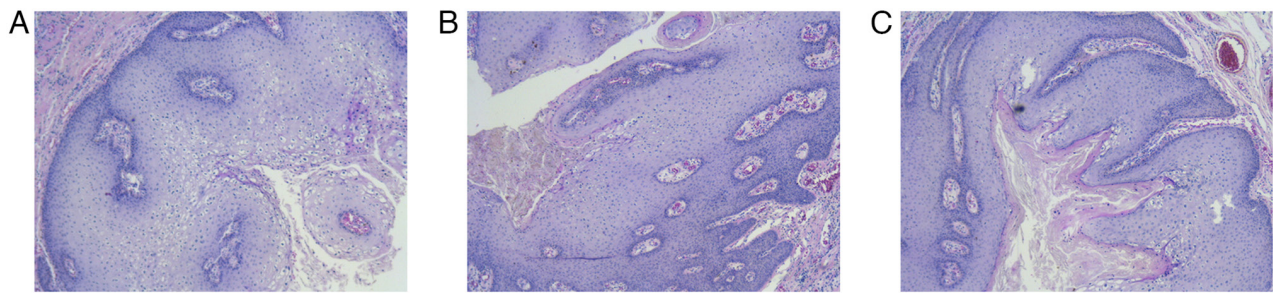


Figure 7. Case 1: Histopathology of Buschke-Löwenstein tumor revealing: (A) Acanthosis, endophytic growth and koilocytosis; (B) acanthosis, epidermal hyperplasia and prominent fibrovascular cores; and (C) acanthosis, papillomatosis, endophytic growth, koilocytosis, hyperkeratosis and parakeratosis.



Figure 8. Case 2: Clinical image of Buschke-Löwenstein tumor. Cauliflower-like verrucous tumor involving the perianal area.



Figure 9. Case 2: Clinical image of the lesion in the course of reepithelization after excision with CO₂ laser.

Klebsiella pneumoniae. The intra-urethral genotyping was positive for HPV 16 and 52.

The peniscopy and the microscopic examination of the anogenital region revealed 10 subclinical genital lesions and 15 subclinical lesions supra-penile and perigenital, which were excised in one session of CO₂ laser under local anesthesia.

The patient received systemic antibiotherapy with levofloxacin (500 mg/day for 30 days), meloxicam (15 mg/day for 30 days), Sunvert (1 tablet twice a day for 60 days), local and intrarectal sinecatechins (twice a day for 4 months), inosine pranobex (3 tablets twice a day for 10 days per month), alternately with *Coriolus versicolor* (3 tablets twice a day for 4 months). The peniscopy and the microscopic examination of the anogenital region revealed residual subclinical lesions, which were excised with CO₂ laser, 2 sessions of fractional photodynamic therapy with 8% levulinic acid applied topically under occlusion for 2 h, then 20 min of 635-nm red light at 70 mJ/cm² fluency, followed by 10 min of 411-nm blue light at 80 mF/cm² fluency, and finally 10 min of 635-nm red light

at 70 mJ/cm² fluency. A total of 3 doses of Gardasil vaccine were administered (months 0-2-6) (Fig. 13).

Case 4. A 32-year-old uncircumcised male patient presented to the Department of Dermatology of Ponderas Academic Hospital for multiple, giant flesh-colored, cauliflower-like growths involving the penis, the supra-penile and the right inguinal region. The patient denied experiencing pain, bleeding or dysuria. The patient had been sexually active since 16 years old and provided history of multiple sexual partners. Laboratory tests were performed in order to verify the status of the patient for STDs and the patient tested positive for an asymptomatic urethral coinfection with *Mycoplasma hominis*. The HPV genotyping revealed HPV 6, 11 and 54.

The treatment consisted of 5 sessions of CO₂ laser with local anesthesia, followed by 2 daily applications of sinecatechins ointment for 4 consecutive months in the affected areas. In addition, the patient was prescribed inosine pranobex



Figure 10. Case 2: Clinical image of the scar tissue after excision at the follow-up visit with a few recurrent HPV lesions at 1 o'clock.

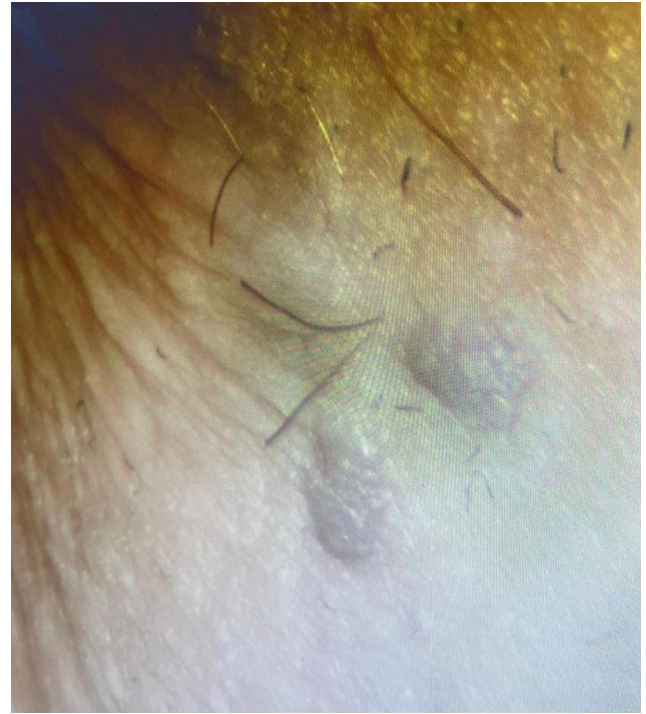


Figure 11. Case 2: Close-up of recurrent HPV lesions observed upon microscopic genital examination.

(500 mg x 6/day, 10 days/month for 4 months), alternating with *Coriolus versicolor* (6 cps/day 20 days/month for 4 months). The patient was advised to get vaccinated against HPV with 3 shots of Gardasil 9 vaccine.

At the follow-up visit, the microscopic analysis of the genital skin revealed certain persistent subclinical lesions, for which the patient underwent 2 sessions of topical photodynamic therapy. Briefly, 8% aminolevulinic acid (ALA) was applied and after 2 h, the dressing was removed and the lesions were irradiated using a red light for 20 min (the peak emission of 635 nm was used and the total dose was 70 mJ/cm²), then a blue light was used for another 10 min (80 mJ/cm²), followed again by a red light (635 nm, 70 mJ/cm²) (Figs. 14-16).

Case 5. An 18-year-old bisexual man presented to the Department of Dermatology of Ponderas Academic Hospital for a giant, indurated, flesh-colored, cauliflower-like tumor mass around the anus and certain other small lesions dispersed on the suprapubic area and around the penis. The patient had been recently diagnosed with HIV, and had been started on antiretroviral therapy. STD screening was positive for syphilis, *Ureaplasma urealyticum*, *Mycoplasma hominis* and *Candida*. The colonoscopy revealed no rectal invasion and the patient refused a colostomy.

The tumor was excised with radiosurgery under general anesthesia and all the smaller lesions were excised in 1 session of CO₂ laser under local anesthesia. A biopsy was sent to the pathologist.

The healing occurred by secondary intention, in 60 days. The patient received systemic antibiotic therapy with gentamicin (80 mg every 12 h), benzathine benzylpenicillin (2.4 MUI/week for 10 weeks) for the syphilitic infection, doxycycline (100 mg

2 tablets/day for 30 days), fluconazole (50 mg 1 tablet/day for 30 days), local and intrarectal sinecatechins (twice a day for 4 months), inosine pranobex (3 tablets twice a day, 10 days per month), alternately with *Coriolus versicolor* (3 tablets twice a day for 4 months) and was administered 3 doses of Gardasil 9 vaccine (months 0-2-6) (Figs. 17-19).

Case 6. A 34-year-old smoking woman presented to the Department of Dermatology of Ponderas Academic Hospital for a giant, indurated, flesh-colored, cauliflower-like tumor mass involving the vulvar area and certain verrucous papules distributed over the suprapubic area and buttocks. The medical history revealed that the patient had been HIV-positive for 23 years due to an erroneous blood transfusion (CD4 count, 750 cells/mm³). The patient tested positive for HPV 16, 18, 39, 6, 11 and 53 genotypes. The biopsy revealed poorly differentiated squamous cell carcinoma (T4N2MXV0L1). The patient underwent pelvicotomy with nephrostomy, followed by localized radiotherapy (Figs. 20 and 21).

Case 7. A 75-year-old female patient presented to the Department of Dermatology of Ponderas Academic Hospital for an indurated tumor mass located in the vulvar area. The lesion had been growing progressively for numerous years. The PCR test conducted on the vaginal brushing revealed the presence of HPV 6, 16 and 18. The tumor was excised with radiosurgery under general anesthesia. The biopsy of the lesion identified HPV 6 and 16 genotypes and revealed moderately differentiated squamous cell carcinoma. Therefore, the patient underwent pelvicotomy with nephrostomy, followed by radiotherapy (Fig. 22).

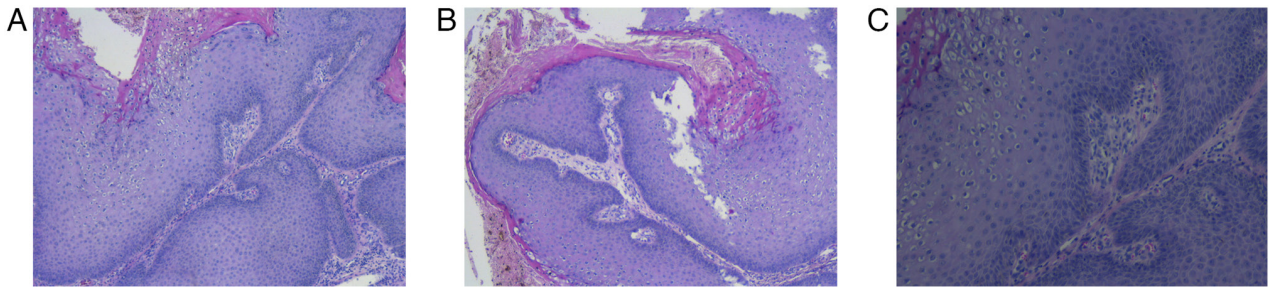


Figure 12. Case 2: Histopathology of Buschke-Löwenstein tumor displaying: (A) endophytic growth, koilocytosis and parakeratosis; (B) papillomatosis, koilocytosis and fibrovascular cores; and (C) koilocytosis and epidermal hyperplasia. No signs of malignant transformation.



Figure 13. Case 3: Clinical image of vegetative, exophytic intra-urethral Buschke-Löwenstein tumor.



Figure 14. Case 4: Clinical image of Buschke-Löwenstein tumor. Multiple, giant flesh-colored, cauliflower-like growths involving the right inguinal region.

Discussion

In 1925, Buschke and Löwenstein described BLT for the first time. They examined a penile lesion, which resembled both common condyloma acuminata and squamous cell carcinoma from a clinical point of view; however, it presented differences from both of these diseases concerning the biological behavior and the histopathological findings (9).

BLT represents an infrequent STD, caused by HPV, mostly genotype 6 or 11. There are numerous risk factors for HPV, such as multiple sexual partners, homosexuality, prostitution, chronic genital infections, as well as the lack of proper hygiene (4,9).

BLT is invariably preceded by condyloma acuminatum and it is more common in individuals with a suppressed immune system caused by AIDS, chemotherapy with immunosuppressive therapy alcoholism or diabetes. HPV screening for HIV-positive and immunocompromised patients should always be a priority in this category of patients (1,4).

A high prevalence of GCA has been reported in the homosexual and bisexual communities. Recurrent aggressive GCA has been reported in HIV-positive patients. BLT could occur at any age, particularly following puberty. However, the elderly should also be tested for HPV infection. Men are more affected than women, and the main affected areas are the penis, the anorectal area and the urethra in males, and the vulva in females (4,11).

From a clinical view, it presents as a voluminous cauliflower-like, flesh-colored tumor of papillomatous and irregular surface, ultimately surpassing 10 cm² in size (4).

From a histopathological point of view, BLT is characterized by papillomatosis and severe acanthosis. Generally, the hyperplastic epithelium is well-differentiated; nevertheless, the vacuolated epidermal cells reveal clear cytoplasm and hyperchromatic nuclei. The basal membrane is undamaged and there is a lymphohistiocytic inflammatory infiltrate present in the upper dermis. When a biopsy is performed, it should be deep enough to contain the whole tumor, particularly the epidermal/dermal interface (4).

The multiplication cycle of HPV needs stratified squamous epithelium (the junction between it and the columnar



Figure 15. Case 4: Clinical image of Buschke-Löwenstein tumor. Multiple, flesh-colored, verrucous lesions located on the penis.



Figure 17. Case 5: Clinical image of Buschke-Löwenstein tumor. Giant, indurated, skin-colored, papillomatous tumor mass around the anus.



Figure 16. Case 4: Clinical image of Buschke-Löwenstein tumor. Various skin-colored, cauliflower-like growths involving the penis and the suprapubic and the right inguinal areas.



Figure 18. Case 5: Clinical image of the lesion after radiosurgery.

or cuboid epithelium being the election site), explaining the HPV-associated cancers on the lips, oral cavity, cervix, prostate, penis, scrotum and rectum. The first structure infected is the basal keratinocyte nucleus and if the host defense mechanism is overcome, the virus multiplies and the DNA

copies, during cell division, are distributed to daughter cells, which are hard to identify if the viral gene expression is low. The risk of malignant transformation of infected cells is high if the infection persists more than 6 months; however, ~90% of the cases have a self-limited evolution of 2 years. There are numerous co-factors participating in HPV-related



Figure 19. Case 5: Clinical image of scar tissue and the reepithelization process after excision at the follow-up visit.



Figure 21. Case 6: Clinical image of Buschke-Löwenstein tumor. Close up of the vulvar lesion.



Figure 20. Case 6: Clinical image of Buschke-Löwenstein tumor. Gigantic, indurated, flesh-colored, papillomatous tumor mass involving the vulvar area and some verrucous papules scattered across the suprapubic area and buttocks.

carcinogenesis. The oncogenes E6 and E7 are the key viral oncogenes from HPV 16 and other high-risk HPVs that inactivate p53 and members of the retinoblastoma protein family leading to inhibition of apoptosis, progression of the cellular cycle and accumulation of genetic alterations, viral integration and uncontrolled cell proliferation. The tumor-induced inflammation promotes the proliferation, the survival of the malignant cells and the alteration of the response to chemotherapy. The HPV infection requires either intact skin tissue or wound healing and an active inflammatory process in the skin in order to multiply. This theory has a great



Figure 22. Case 7: Clinical image of Buschke-Löwenstein tumor. Indurated tumor mass located in the vulvar area.

impact on the treatment plan, healing *per secundam* being an improved approach in comparison with grafting after excision, since there is no risk for recurrences on fibrotic

tissue (as aforementioned HPV requires stratified squamous epithelium for replication) (12-14).

The main differential diagnoses include Bowen's disease (its dyskeratotic condylomatous form), squamous cell carcinoma, as well as keratotic pseudoepitheliomatous balanitis (4).

It is very difficult to differentiate between BLT and verrucous carcinoma. There are authors who consider these lesions to have numerous similarities. Nevertheless, other authors have strongly suggested that BLT is the midway lesion between condyloma acuminatum and verrucous carcinoma, considering it a condyloma-like precancerous lesion (4).

The most frequent complications of BLT include superinfection, fistulae or necrosis (15). Spontaneous regression is extremely rare, while recurrence following an incomplete excision is very frequent. In the case of GCA, histology does not reveal any evidence of malignancy, such as infiltration of the basement membrane, lymphatic invasion, angioinvasion or distant metastases. Bleeding, infiltration of the tumor basis or lymph node enlargement may lead to the suspicion of a malignant transformation into micro-invasive carcinoma or into well-differentiated squamous cell carcinoma, occurring in 30-50% of the cases (4,5,15).

The incidence of perianal GCA has slightly increased during the last few years, but it remains very hard to differentiate GCA from common condylomas or well-differentiated squamous cell carcinomas. There is a well-known association between HPV 16, 18, 31 and 33 and anogenital squamous cell carcinoma (5,16).

Numerous factors need to be considered when deciding on the most appropriate type of treatment, such as the size, the location of the giant condyloma, as well as previous therapies that have proven unsuccessful. The microscopic analysis of the genital skin for subclinical HPV lesions has a crucial role for an early detection of HPV lesions or recurrences and for selecting the best treatment plan (8).

The 'gold standard' therapy is represented by surgical treatment, which consists of full thickness excision and tumor-free margin control. According to the clinical condition of the patient, extensive abdominopelvic surgery may be recommended in cases of visceral involvement.

Preoperative imagistic investigations (CT and MRI) are required before surgery in order to assess the extensiveness of local and systemic disease, and to select the optimal treatment approach. Temporary colostomy followed by reintegration in cases of rectum involvement is also recommended. Despite the fact that numerous authors consider wide local excision followed by split-thickness skin grafts the mainstay of therapy, it is considered that healing *per secundam* is an improved approach, since grafting represents a risk factor for HPV (6-8).

HPV infection is a field infection, where large areas of cells at a tissue surface are affected by the HPV virus; therefore, once the GCA is excised, focus on treating the whole affected genital area is required. In literature, certain treatment methods for BLT are stated, but the risk of recurrence is very high (podophyllotoxin, usually used for common condyloma acuminata; 5-FU, with improved results for the intraurethral BLT; imiquimod, very aggressive therapy with numerous side effects; cryotherapy, CO₂ laser and sinecatechins, very effective with less side effects; and topical photodynamic therapy using both red and blue lights, which

was successfully used in our cases) (11,17). However, the best specific immunostimulation is the HPV vaccination with Gardasil 9. In case of verrucous carcinoma, chemotherapy needs to be added to the treatment plan. Radiotherapy, however, appears to be responsible for the alteration of BLT into anaplastic carcinoma (8,18).

In conclusion, despite the fact that numerous authors consider wide local excision followed by split-thickness skin grafts the mainstay of therapy, it is considered in the present study that healing *per secundam* is an improved approach, since there is no risk for recurrences on fibrotic tissue. For an improved understanding of this phenomenon, further studies are required.

Microscopic analysis of the genital skin for subclinical HPV lesions has a crucial role for an early detection of HPV lesions/recurrences and an improved outcome for the health and social life of the patient.

In case of BLT, there are cases that exceed the qualifications of the dermatologist; therefore, there may be a need for a multidisciplinary approach: Colonoscopy/proctoscopy for rectal invasion, cystoscopy and gynecological exam. The importance of gynecological examination and HPV screening for every female patient should not be overlooked, regardless of age (case 7), nor the importance of HPV screening for HIV-positive and immunocompromised patients (cases 5 and 6) (17,19).

Most importantly, a set of complete STD tests should be performed for all young male patients, as well as smokers and patients who have started their sexual activities early in life. In addition, non-specific immune stimulation and HPV vaccination with Gardasil 9 should be integrated in the treatment plan for every patient with an HPV infection.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

DBo performed the biopsies, the CO₂ laser excisions, the topical photodynamic therapy and participated in the therapeutic management of the cases. AC and DBr performed the photo documentation of the cases and performed critical review of the literature findings. NB performed the histopathologic examination. RC performed the wide local excision of the lesions. DBo and AC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

A written informed consent for clinical examination, surgery, treatment and obtaining images for publication was obtained from the patients.

Competing interests

The authors declare that they have no competing interests.

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