

Treatment of giant condyloma acuminatum of the anus.

State of the art



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Giant condyloma acuminatum (GCA) is a rare cauliflower-like lesion, also known as Buschke-Lewenstein tumor (BLT). Although characterized by benign histological features, the local behavior of GCA is extremely aggressive, showing progressive infiltration of the surrounding structures leading to tissue destruction by compression. As the correlation between HPV and GCA development grew stronger, the majority of the Authors came to the conclusion that HPV can not only cause CA but, associated with particular risk factors, it can lead to much more serious conditions such as BLT. Since the treatment of GCA is still not yet standardized, a very accurate pre-operative analysis of the lesions is required to plan the most suitable treatment approach. Based on current knowledge, macroscopic evaluation of local tumor invasion and extensive radical resection appear to be the only valid therapeutic approach, due to its association with long-term survival and minimal recurrence. Looking forward for new techniques and new tissue sparing treatments, at the moment, GCA can be safely treated with radical excision without immediate tissue reconstruction; long-term complications, such as stricture and stenosis, can be prevented by adequate wound healing and by a particularly intense and long-term follow-up program.

KEY WORDS: Anus, Giant condyloma acuminatum

Introduction

Giant condyloma acuminatum (GCA) is a rare cauliflower-like lesion, also known as Buschke-Lewenstein tumor (BLT). This clinical entity was reported by Buschke and Lewenstein as giant carcinoma-like genital warts. The first case of giant condyloma acuminatum localized in ano-rectal region was described in 1967 by Knoblich and Failing ¹.

Although characterized by benign histological features, the local behavior of GCA is extremely aggressive, showing progressive infiltration of the surrounding structures leading to tissue destruction by compression. Microscopically GCA shows thickened squamous epithelium, prominent papillomatosis, intact basement membrane and lack of anaplasia or invasion ².

Unlike the ordinary condiloma acuminata (CA), GCA can be characterized not only by its tendency to infiltrate deep adjacent layers, but also by a higher potential for malignant transformation (30-50%) and high recurrency rate (66%) ^{3,4}. BLT's typical growth is slow and its symptoms, as pain, bleeding, itching, fistulae and defecation issues, are due to a massive tissue inflammation and compression of the nearby structures. Moreover fistulas can develop bacterial infection, which may lead to severe sepsis, connected to a particularly high mortality rate (25-30%) for a rare benign tumor ^{5,6}.

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The etiology of GCA is still not clear. It has been a long time since the first correlations between this anal lesion and human papilloma virus (HPV) were made. In 1986 Bohschart et al. demonstrated the presence of HPV 6 and 11 in GCA's cells⁷. As the correlation between HPV and GCA development grew stronger, the majority of the Authors came to the conclusion that HPV can not only cause CA but, associated with particular risk factors, it can lead to much more serious conditions such as BLT. Little is known about the concomitant factors influencing the pathogenesis of GCA. Of interest, Human Immunodeficiency Virus (HIV) seems to play a role in this particular lesion's development. In fact, as largely demonstrated, immunocompromised people, such as those with HIV infection, have a higher incidence of HPV-related ano-genital affections and frequently show an adverse evolution of the disease⁸. Other minor risk factors have been associated to GCA development, like low socio-economic status, diabetes, smoking and oral contraception⁹. GCA treatment is still controversial. Many treatment strategies have been suggested during the years but, it is worth mentioning that most of the treatments described in literature are based on case reports or small series. Due to the rare occurrence of the disease, in fact, controlled studies are still missing, leading clinicians to base the treatment of these lesions on their personal experience.

Medical Treatment

Topic medications are often the first line of choice in the treatment of anal warts. The most commonly used therapeutic strategies are based on caustics (bi- or trichloroacetic acid, liquid nitrogen), cytostatics (podophyllin, 5-fluorouracil) or immuno-modulatory agents (interferon, imiquimod)¹⁰. However, they often show several limitations in GCA treatment.

Podophyllin applications, commonly used and proven effective on CA, should be avoided in GCA. Podophyllin, in fact, seems to induce histological changes mimicking in situ carcinomas making hard to microscopically discriminate these two entities¹¹.

In our best knowledge, interferon (INF- α) showed positive results in sporadic cases^{12,13} by modulating the cytokine activation, especially when associated to other agents like imiquimod and electrosurgical resection^{14,36}. Nevertheless in most cases interferon showed limited results, especially when used to treat large lesions¹⁵.

Imiquimod (1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4 amine) is an immune response modifier, with strong antiviral activity and has been expected to be successful where INF- α showed some kind of utility, meaning all those situations where the enhancement of cell-mediated immunity is needed¹⁶. Some encouraging therapeutic effects have been reached by using this drug, especially in pediatric patients, in which a chance of medical treat-

ment should be offered before considering an extensive surgical resection^{17,18} have been described. Van Egmond et al. described three cases of GCA successful treatment using imiquimod, therefore the Authors promote this therapeutic strategy in patients with small lesions or in patients unfit for surgery¹⁹. Recently this treatment has given satisfactory results in association with surgery.

Also radiotherapy plays a controversial role on treatment of GCA. Radiations, in fact, may contribute to the malignant transformation of BLT, and their effectiveness in the treatment of primary lesions, except for very small ones, is not yet confirmed.

At present, the main role of radiotherapy is synergic to surgery: incomplete surgically removed GCAs have been successfully treated using a combination of chemo-radiotherapy, while some other authors have published encouraging results about its role as neoadjuvant (to reduce mass dimensions) or adjuvant (to reduce recurrence rates) therapy^{20,21}.

Recently, the use of carbon dioxide (CO₂) laser therapy has been described. This technique is used to destroy surrounding tissues and to obtain hemostatic incisions, wound sterilization and reduction of lymphatic spread. In the literature, a relevant rate of healing have been reported with this new technique (about 75%)^{9,22,37}. It must be reminded though that, before using this technique, multiple biopsies should be taken to exclude an early invasive disease. Moreover, due to its special features, the depth of tissue destruction must not be inferior to 8 mm, since BLT deeply infiltrates the nearby structures²³.

Surgical Treatment

Wide local excision, achieving a disease free status (confirmed by negative resection margins), is at present the treatment of choice for BLT and for the prevention of its recurrence²⁴. These lesions are frequently characterized by huge dimensions and deep infiltration and major surgery such as pelvic exenteration or abdominoperineal amputation may be necessary. In fact an aggressive surgical approach is needed in case of malignant transformation or disease relapse.

Considering the wide excision often required, BLT's surgery is not free from complications. The first surgical issue is the blood loss. GCAs are usually large masses with a high risk of intraoperative bleeding. De-bulking of the mass via neoadjuvant chemo-radiotherapy could lead to a safer surgical treatment. Most recently, pre-operative angioembolization of the mass has been suggested by Holubar et al. with encouraging results²⁵. Since benefitting of an aggressive approach, GCA surgery often leads to severe perineal wounds of difficult management. GCA removal, such as anal surgery in general, is often burdened with the risk of anal stenosis, due to scar tissue, as widely described in literature. This is

an invalidating condition for patients, possibly leading to difficult evacuation, pain and bleeding^{26,27,32}.

To prevent this issue several types of plastic flap reconstruction have been proposed by many authors.

One of the most popular anal reconstruction technique, especially for anal stenosis treatment, is the "V-Y shaped flap"²⁸. It is an advancement flap performed by making a Y incision with the linear side of it in correspondence of the anal stenosis and the angulated part on the perianal skin. The angulated part of the incision, once adequately mobilized, is sutured to the linear side of it, determining a V shaped wound²⁹. The criticisms of the technique is represented by the risk of ischemic necrosis of the wound apex and by the lack of elastic tissue in the anal canal due to inadequate dimensions of the tip of the flap.

The bilateral rotational S-flap was first described by Ferguson as a treatment of anal stenosis following hemorrhoidectomy (Ferguson). Since its introduction it has been applied in different types of anal lesion repair but, due to the large incisions needed and to a long healing process it is only used in specific cases to repair wide anal defects³⁰. Some other reconstruction techniques commonly used are rotational flaps, free flaps and skin grafting³¹.

It is worth mentioning that these kind of major primary flap reconstruction plasties are characterized by a long time of healing and therefore by a much longer hospital stay. Moreover, such extensive kind of reconstructions are connected to a high risk of bleeding and infection which can ultimately lead, as a paradox, to a recurrence of anal stenosis.

At present many authors discourage plastic reconstruction after surgery and recommend an extensive removal of the lesion followed by second intention wound healing^{32,33}. In these authors' opinion the risk of stenosis with this procedure is low and it is overcome by long-term follow-up. Since the majority of scar tissue leading to stenosis development forms within the first three months after surgery and consolidates in about one year, the follow-up schedule must be particularly intense. These patients must be checked weekly for the first month, then every three and six months. To ensure a successful outcome periodic controls must be done for at least one year, advising local hygiene and self dilatations. Recently Balducci et al. promoted the use of V.A.C.® dressing in case of large perineal wounds to promote healing and prevent bacterial infection, as demonstrated by their single case experience³⁵.

Conclusion

Since the treatment of GCA is still not yet standardized, a very accurate pre-operative analysis of the lesions, based on accurate imaging (CT scan or MRI), is required to plan the most suitable treatment approach. Based on

current knowledge, macroscopic evaluation of local tumor invasion and extensive radical resection appear to be the only valid therapeutic approach, due to its association with long-term survival and minimal recurrence. Looking forward for new techniques and new tissue sparing treatments, at the moment, GCA can be safely treated with radical excision without immediate tissue reconstruction; long-term complications, such as stricture and stenosis, can be prevented by adequate wound healing and by a particularly intense and long-term follow-up program.

Riassunto

Il condiloma acuminato gigante (GCA) è una rara lesione simile a cavolfiore, nota anche come tumore di Buschke-Lewenstein (BLT). Sebbene sia caratterizzato da caratteristiche istologiche benigne, il comportamento locale del GCA può essere estremamente aggressivo, mostrando una progressiva infiltrazione delle strutture circostanti che portano alla distruzione del tessuto mediante compressione. Poiché la correlazione tra lo sviluppo di HPV e GCA è aumentata, la maggior parte degli Autori è giunta alla conclusione che l'HPV non solo può causare condilomatosi, ma, associato a particolari fattori di rischio, può portare a condizioni molto più gravi come BLT.

Poiché il trattamento della GCA non è ancora standardizzato, è necessaria un'analisi preoperatoria molto accurata delle lesioni per pianificare l'approccio terapeutico più adatto. Sulla base delle attuali conoscenze, la valutazione macroscopica dell'invasione locale del tumore e l'estesa resezione radicale sembrano essere l'unico approccio terapeutico valido. In attesa di nuove tecniche e nuovi trattamenti di risparmio tissutale, al momento, la GCA dovrebbe essere trattata con un'escissione radicale senza una ricostruzione tissutale immediata; complicazioni a lungo termine, come la stenosi, possono essere prevenute con un'adeguata guarigione delle ferite e con un programma di follow-up particolarmente intenso e a lungo termine.

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