Regression of Deeply Infiltrating Giant Condyloma (Buschke-Löwenstein Tumor) Following Long-term Intralesional Interferon Alfa Therapy

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

In 1995, a 40-year-old heterosexual man developed a perianal tumor that rapidly increased in size. Following a clinical and histologic diagnosis of a large condyloma acuminatum (CA), the tumor was partially resected in a primary care hospital. Subsequently, recurrent perianal fistulae and abscesses required several surgical interventions, and the patient underwent a transverse colostomy to allow subsequent complete resection of the condyloma.

At the patient’s first visit in our clinic in 1996, physical examination demonstrated a smooth, exophytic, cauliflower-like perianal verrucous tumor extending toward the perineum, scrotum, and buttocks (Figure 1, left). A magnetic resonance imaging scan revealed that the tumor infiltrated deeply into the right side of the pelvis, including the ischiorectal fossa, internal obturator muscle, anal sphincter, perineum, and penile root (Figure 2, top).

Histologic reevaluation of a previously obtained biopsy specimen showed a large papillomatous tumor infiltrating deeply into the underlying tissues, without penetration of the basement membrane (Figure 3, top). The epithelium was acanthotic with blunt rete ridges, well stratified without apparent cellular atypia, and contained few mitoses and koilocytes (Figure 3, bottom). There was no evidence of areas of malignant degeneration or squamous cell carcinoma (SCC). DNA was extracted from the biopsy specimen and analyzed for human papillomavirus (HPV) DNA by hybrid capture assay.
The sample was positive for low-risk HPV type(s) and identified as HPV-6b by consensus primer polymerase chain reaction, followed by DNA sequencing of the amplimer (data not shown). Taken together, these findings were consistent with the diagnosis of giant condyloma (GC), or Buschke-Löwenstein tumor. The results of routine laboratory examinations were normal; serologic tests were negative for syphilis and human immunodeficiency virus; and lymphocyte subpopulations were normal.

**THERAPEUTIC CHALLENGE**

The primary therapeutic option of GC is radical surgery with or without adjunctive chemotherapy. Owing to the large extent of tumor invasion in this case, curative surgery would have been achieved only by hemipelvectomy and limb amputation. This severe mutilation was refused by the patient. Thus, alternative strategies had to be considered.

**SOLUTION**

Systemic or intralesional treatment with interferon resulted in complete remission in 2 previously described cases of Buschke-Löwenstein tumor, but failed to result in improvement in others. Because of the cases that showed remission, treatment with intralesional injections with interferon alfa-2b (Intron A; Schering Corp, Kenilworth, NJ) was initiated. The injections were well tolerated, without significant adverse effects, and the dosage was increased rapidly to 10 million units 3 times a week and continued on an outpatient basis. During the next few months, the tumor did not change clinically. However, about 6 months after the interferon therapy was initiated, the tumor slowly decreased in size. After 9 months of continuous treatment, clinical examination and magnetic resonance imaging revealed dramatic tumor regression, which appeared to be complete after approximately 12 months, leaving a deep defect in the right ischiorectal fossa (Figure 1, right, and Figure 2, bottom). To ensure sustained remission, treatment (10 million units 3 times a week) was continued for an additional 16 months and was then discontinued. Currently, after 28 months of treatment and 4 months of observation, no recurrence could be seen on magnetic resonance imaging scans. The absence of tumor was best demonstrated in short-time inversion recovery sequences, in which tumor tissue is displayed brightly against a dark background, allowing differentiation between active (with increased water content) and healed lesions.

A second biopsy specimen, which was obtained 12 months after the interferon alfa-2b therapy was initiated, revealed the absence of residual tumor tissue. Strikingly, a dense bandlike mononuclear cell infiltrate was seen closely attached to and invading into the epithelium, as is seen in lichen planus (Figure 4). The majority of the cells were CD3- and CD4-positive T lymphocytes; a minority of the cells were CD8-positive T cells; and a few CD68-positive macrophages were present. Single cells in the basal epithelial layers displayed discrete staining with an antibody to perforin. Also, a significant number of epithelial cells were positive for CD54 (intercellular adhesion molecule 1) and/or HLA-DR, molecules that are important for the initiation of immune responses. A DNA extract was negative for HPV by hybrid capture test and polymerase chain reaction.

**COMMENT**

Giant condylomata were first described by Buschke and Löwenstein in 1925 as "carcinomalike condylomata acu-
minata of the penis. The GC, or Buschke-Lo¨wenstein tumor, is a semimalignant neoplasm of the external genitalia and the perianal region. In contrast to CA, GC is characterized by locally invasive growth, resulting in local complications. Initially, it may be misdiagnosed as benign CA or malignant SCC. The tumor has a tendency to recur and to form abscesses and fistulae when it is present in a perianal area. The GC is part of a group of tumors designated verrucous carcinomas, which include florid oral papillomatosis of Ackerman (oropharyngeal), epithelioma cuniculatum (palmoplantar), and papillomatosis cutis carcinoides of Gottron (cutaneous). It is a rare condition, and its pathogenesis and natural history are not well understood. It has been proposed that GC represents an intermediate state between CA and SCC. Presumably, for unknown reasons, a very small subset of long-lasting CA eventually evolves into slowly invading tumors and then, if left untreated, into large papillomatous proliferations that penetrate deeply into the underlying tissue. A characteristic of GC is its benign-appearing histologic appearance, which resembles that of CA. It may be difficult to distinguish between these 2 conditions, particularly at an early stage of the disease. A large representative biopsy specimen is crucial to judge the architecture of the lesion in order to establish the diagnosis and to rule out foci of SCC. Giant condylomata invade by expansion rather than by infiltration, leaving the basement membrane intact, and show a well-stratified epithelium with minimal cellular dysplasia, mitoses, or atypical cells. The tumor does not metastasize initially and is thus considered a low-grade SCC. However, we have observed foci of SCC in a perianal GC of short duration and small extension, and 30% to 50% of GC will transform into SCC later in the course of the disease. Human papillomavirus type 6 or 11 DNA is regularly found in verrucous carcinomas, strongly suggesting a pathogenic role in tumor development. These low-risk HPV types normally lack malignant potential, as they are found in benign CA but not in anogenital cancers, which usually contain DNA of high-risk HPV, mainly types 16 or 18. It remains unknown which viral or host risk factors, such as increased viral gene expression or inability to mount a cytotoxic immune response, may change the oncogenic potential of HPV types 6 or 11, causing progression of benign CA to the invasive GC phenotype.

The literature about GC, which consists mainly of case reports, lacks controlled studies; therefore, treatment guidelines have not been established. An analysis based on 42 published cases concluded that the only consistently effective therapy is wide surgical excision of the tumor with clear margins, with or without adjunct chemotherapy. Other reported treatments include topical podophyllum resin, topical and systemic chemotherapy with fluorouracil, systemic bleomycin therapy in combination with cisplatin and methotrexate, laser excision, and tumor destruction using cryotherapy or electrocautery. Radiotherapy has been used in severe cases of verrucous carcinoma and remains controversial, as progression to SCC with metastases has been reported. Regardless of the treatment modality, there is a high rate of local recurrence, resulting in an overall mortality rate of 20%. For the treatment of benign genital or laryngeal warts, which are caused by low-risk HPV-6/11, systemic, intraleisional, or local application of interferon has demonstrated limited efficacy, mainly as adjunct to other established therapies, in decreasing the recurrence rate. Possible effector mechanisms include antiviral or antiproliferative effects on HPV-infected cells and immunomodulatory activities. Interestingly, 2 case reports have previously described successful interferon monotherapy for GC. Systemically applied recombinant interferon alfa-2a (1.8 million units 5 days a week) in a woman with GC infiltrating the vagina, cervix, and bladder resulted in complete regression of the tumor after 6 months, but the long-term outcome was not reported. Intraleisional injection of human recombinant interferon alfa-2b (9 million units 3 times a week) led to complete resolution of a GC after 5 months of continuous treatment, but lack of infiltration in that case makes the distinction from a large benign CA difficult.

A cell-mediated immune response plays an important role in the natural control of HPV infection. This is supported by the highly increased incidence of HPV-induced lesions in patients with iatrogenic or acquired cellular immunodeficiency, but not in those with humoral immune defects. CD4-positive lymphocytes and monocytes/macrophages dominate the cellular infiltrate in regressing genital warts, and there is a significant induction of the immune-accessory molecules HLA-DR and intercellular adhesion molecule 1 on keratinocytes. However, the viral or cellular determinants recognized in wart regression are unknown. In our patient, after the clinical regression of the GC, a biopsy specimen from residual tissue showed a delayed-type hypersensitivity-like dense mononuclear cell infiltrate attached to and invading the overlying epithelium. Immunohistochemical analysis revealed a pattern dominated by CD3/CD4-positive cells. It has been suggested that major histocompatibility complex class I–restricted cytotoxic T cells are the principal effectors of protective immunity to noncytopathic viruses and tumors and that important mechanisms in the clearance of virus-induced lesions include the secretion of perforin and certain granzymes by cytotoxic cells. Also, our results corroborate the hypothesis that CD4-positive lymphocytes restricted by major histocompatibility complex class II elements may also exert cytotoxic function in recovery from viral infection.

Because spontaneous regression of GC has not been reported to our knowledge, we can speculate that the long-term local injection of interferon had an immunostimulatory effect, possibly by inducing afferent, antigen presentation, as well as efferent, cytotoxic, immune mechanisms. Also, direct antiviral and antiproliferative effects of interferon may have contributed to tumor regression. In our patient, malignant transformation was not observed in a large excisional biopsy specimen. Although we cannot formally exclude the initial presence of malignant foci elsewhere, this fact might have contributed to the favorable outcome.
Previously reported failures of interferon to induce regression of GCs or to prevent recurrences may be explained by host-specific factors, lower interferon dosages, or shorter treatment periods, as we have not observed tumor regression before 6 months of continuous therapy. Regression was complete after 12 months of treatment and has continued for a total of 28 months to date.

Controlled studies are required to determine whether interferon alfa as a monotherapy or as an adjunct to surgery is an effective treatment compared with surgery alone and to ascertain its potential in reducing the high incidence of tumor recurrence.

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REFERENCES


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