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

Alexandra Geusau, MD; Gertraud Heinz-Peer, MD; Beatrix Volc-Platzer, MD; Georg Stingl, MD; Reinhard Kirnbauer, MD; University of Vienna Medical School, Vienna, Austria

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-Loewenstein 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-Loewenstein 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 epidermis, 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 Loewenstein in 1925 as “carcinomolike condylomata acu-
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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