

Large Benign Condyloma Acuminatum: Successful Treatment with Isotretinoin and Interferon Alpha

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Condylomata acuminata are fleshy exophytic cutaneous lesions most commonly occurring in the anogenital region that are caused by the mostly sexually transmitted human papilloma virus (HPV). Benign condylomata are usually caused by HPV types 6 and 11, whereas HPV types 16, 18, 31 and 33 are often found in lesions with neoplastic transformation (1). A vast variety of therapeutic approaches has been used for years in the management of condylomata acuminata; however, no form of therapy has yielded consistently effective results. In particular, in large and extensive lesions, conventional topical therapy is ineffective, whereas a wide and sometimes mutilating surgical excision is, in many cases, necessary. We describe here a case of a large benign vulvar condyloma acuminatum treated successfully with combined systemic administration of isotretinoin and interferon (IFN- α).

CASE REPORT

A 19-year-old HIV-negative woman presented with a 6-month history of multiple small condylomata acuminata on the vulva, which had been treated with electrocauterization. Three months thereafter, the patient observed the recurrence of confluent condylomatous lesions in the same region and the development of a rapidly growing large exophytic mass. Approximately one month prior to the relapse of the vulvar condylomata she had been treated with high doses of systemic glucocorticoids over a period of 2 weeks because of recurrent severe anaphylactic reactions. She had no history or evidence of systemic infectious, autoimmune or neoplastic disorders. Physical examination revealed a large, soft, cauliflower-like, pale pink mass in the vulvar region (Fig. 1A). Routine laboratory tests including a complete blood count, blood chemistry, urinalysis, immunological (immunophenotype of peripheral lymphocytic subsets and serum immunoglobulins) and serological investigations (tests for syphilis, herpes simplex virus (HSV) 1&2, HIV 1 & 2, hepatitis A, B and C, Epstein-Barr virus and cytomegalovirus) were either negative or within normal limits. Chest X-ray investigations and electrocardiography were unremarkable. Colposcopy and proctoscopy did not detect any HPV lesions. Histological examination of skin biopsy specimens obtained from 3 different sites of the lesions revealed a hyper- and

parakeratotic epidermis with marked acanthosis and focal occurrence of koilocytes at the upper cell layers; there was an excessive papillomatosis, but no evidence of cellular atypia or stromal invasion. Based on these histological findings and the clinical features of the lesion, the diagnosis of large benign condyloma acuminatum was made. *In situ* hybridization using biotinylated HPV-DNA probes revealed the presence of HPV types from 6/11 group in the nuclei of keratinocytes at the upper epidermal layers.

Since the patient refused any form of surgical therapy, we decided to start a combined treatment with oral isotretinoin and subcutaneous IFN- α . The patient gave a written consent and was orally treated with 1 mg/kg/day isotretinoin (Roaccutan, Roche Hellas, Athens, Greece), whereas a dose of 3×10^6 IU IFN- α (Roferon, Roche Hellas, Athens, Greece) was subcutaneously injected three times/week. Two months after onset of treatment there was an impressive regression of the lesions (Fig. 1B), which revealed a complete remission after 4 months of continuous treatment (Fig. 1C). During the first 3 months of treatment the patient experienced occasional fever, chills, myalgias and leukopenia subsequent to the injection of IFN- α , whereas isotretinoin-associated adverse reactions, such as moderate cheilitis and dryness of mucosae, were observed throughout the treatment period. She has presently completed a 3.5-year follow-up after discontinuation of combined IFN- α and isotretinoin treatment and has experienced no recurrences of large benign condyloma acuminatum being completely free of any lesions.

DISCUSSION

Classification and nomenclature of large and extensive condylomata acuminata remain controversial. Those without atypia or locally invasive growth are classified by some authors as “giant condylomata” (2) and by others as “giant-sized condylomata” if they measure more than 2.5 cm in diameter (3). On the other hand, many authors use the term “giant condylomata” as a synonym of the so-called Buschke-Löwenstein tumours (BLT) (4). These HPV-induced tumours represent a rare maximal variant of condylomata acuminata, are mostly localized in the anogenital region, have a locally aggressive course, show a tendency to recur, and are regarded by some authors as a type of verrucous carcinoma. In our



Fig. 1. Clinical aspect of large benign condyloma acuminatum in the vulvar region, (A) prior to the onset of treatment, (B) after 2 months, and (C) after 4 months of combined therapy with subcutaneously applied interferon alpha and oral isotretinoin.

opinion, the term “giant condylomata” should be used exclusively to describe BLT, whereas the term “large benign condylomata acuminata” (LBCA) should be applied only to those lacking invasion or destruction of the underlying tissues. Nevertheless, in some cases LBCA, if left untreated, can transform into BLT, which can in turn evolve into verrucous carcinomas in approximately 30–50% of cases (5).

Olsen et al. (6) evaluated the effectiveness of systemic IFN- α vs. isotretinoin in the treatment of condylomata acuminata. After 6 weeks of therapy 56% of the patients treated with IFN- α alone had an objective clinical response, whereas no patient responded to isotretinoin alone. Nevertheless, a more prolonged administration of this retinoid might have positively influenced the therapeutic response. When IFN- α -treated patients with incomplete clearing additionally received isotretinoin there was an additive therapeutic effect. Our group reported that a 12-week treatment of 56 patients with refractory condylomata acuminata with isotretinoin alone, led to a complete response in 39.6% and to a partial response in 13.2%. Interestingly, a complete resolution was seen in 77.7% of the patients who had lesions of small size and short duration (7). IFN- α alone reveals an excellent therapeutic efficacy, not only in condylomata acuminata irrespective of size and duration, but also in giant condylomata (BLT) (8, 9).

The efficacy of the combined IFN- α and isotretinoin administration vs. isotretinoin alone in the treatment of condylomata acuminata has been evaluated in two separate studies (10, 11). In the first study it was found that combination therapy led to higher remission rates, compared with isotretinoin alone, whereas in the second study the achieved remission rates were similar. In both studies the duration of treatment required for remission was significantly shorter in the group of patients receiving the combination therapy.

To the best of our knowledge, this is the first time that combined IFN- α and isotretinoin administration is successfully applied in the management of LBCA. The exact mechanisms underlying the observed impressive therapeutic response and the complete remission of LBCA in our patient within 4 months of treatment are presently unknown. IFN- α is capable of reducing viral replication and epithelial growth and exerts distinct immunomodulatory effects (12). Isotretinoin, apart from being also a potent immunomodulator, dramatically affects epithelial differentiation and proliferation and induces apoptosis in HPV-affected cells (13). Since HPV replication is related to the state of keratinocyte differentiation, it is possible that isotretinoin may inhibit the DNA replication and assembly of HPV within the affected cells (14). Furthermore, a synergistic inhibitory effect of IFN- α and isotretinoin on HPV-induced angiogenesis has been detected subsequent to a 5-day intra-peritoneal administration of both compounds to experimental animals (15). Further

controlled studies are now required on the efficacy and safety of this combination therapy for LBCA.

The authors declare no conflict of interest.

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