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SHORT COMMUNICATION

Unresectable Perineal Cuniculatum Carcinoma: Partial Remission Using Systemic Isotretinoin and Interferon-α2a Therapy

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Carcinoma cuniculatum (CC) is a rare variant of verruciform squamous cell carcinoma (SCC) without metastatic potential. Curative treatment usually requires large surgical resection. We describe here a case of perineal CC complicating giant condyloma in an HIV-infected patient treated with combined systemic isotretinoin and interferon therapy when surgery, radiotherapy or chemotherapy could not be used.

CASE REPORT

A 42-year-old man was referred to our department with an abscessed perineal mass that had been evolving for 5 years without improvement after several antibiotic treatments. The patient had been co-infected with HIV and hepatitis B virus for 17 years and had a medical history of condylomas of the anal margin. With highly active antiretroviral therapy, HIV viral load was undetectable (T-lymphocytes $CD4^+$ count: 340/mm^3). His overall health condition was good, despite recurrent well-tolerated acute fevers. A smooth, cauliflower-like verrucous mass involved the right buttock and extended toward the anal margin, the scrotum and the opposite buttock (Fig. 1A). Multiple fistulas surrounded the mass and drained pus from which multi-resistant *Pseudomonas aeruginosa* was isolated. Magnetic resonance imaging (MRI) showed a subcutaneous mass of the right gluteal region infiltrating the underlying muscles, containing small collections of necrosis and several fistulas (Fig. S1A[1]). Pathological re-examination of a surgical biopsy specimen obtained 2 years previously showed a neoplastic epidermal proliferation, the architecture of which consisted in deep endophytic invaginations into a fibro-inflammatory tissue (Fig. S2A[1]), the invasive component presenting CC features (Fig. S2B[1]). There was no area of usual-type SCC. Human papillomavirus (HPV) 6 was identified by PCR. A diagnosis of CC complicating giant condyloma/Buschke-Löwenstein tumour (BLT) was finally rendered.

Owing to the large extent of tumour invasion with involvement of gluteal muscles and the proximity of the pelvic bones, curative surgery was rejected as well as radiotherapy and chemotherapy because of an expected increased risk of sepsis. Interferon (IFN)-α2a (3MUI subcutaneously once a day) and isotretinoin (1 mg/kg per day *per os*) were initiated, as well as adequate antibiotics and daily drainage of the collected masses. Cidofovir (5 mg/kg intravenously on weeks 0, 1, 3 and 5) was also started, but discontinued after the third administration due to moderate renal failure. Clinical and radiological reassessment after 4 weeks of therapy showed a 50% tumour collapse (Fig. 1B and Fig. S1B[1]). At that time, the occurrence of a major depressive syndrome led us to interrupt interferon treatment. Isotretinoin was maintained alone at the same dosage (Fig. S3[1]). In the 20th week, tumour regression was ongoing. The patient's psychological symptoms recovered and allowed the resumption of interferon. Pelvic radiotherapy (62 Grays) combined with oral chemotherapy (capecitabine 1.5 g twice a day) was then administered during 2 months with a continuous tumoural shrinkage (Figs 1C and S1C[1]). Fifteen months after the patient was initially referred, he still received the combined isotretinoin-interferon therapy with ongoing clinical (Fig. 1D) and radiological improvement (Fig. S1D[1]).

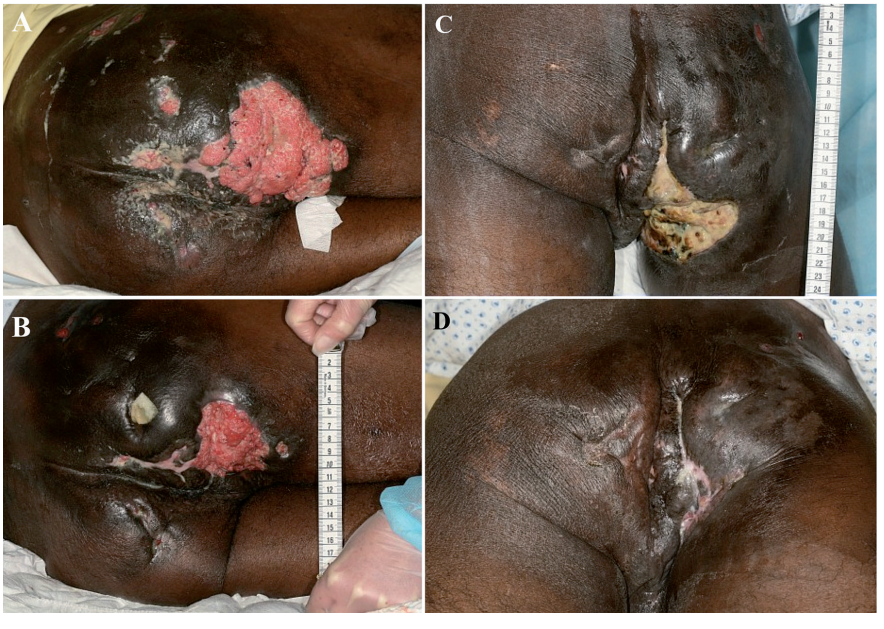

Fig. 1. Clinical presentation and evolution of a perineal carcinoma cuniculatum complicating giant condyloma under combined systemic isotretinoin and interferon-α2a therapy. (A) Smooth, exophytic, cauliflower-like, abscessed mass at the time of diagnosis. (B) Fifty percent tumour collapse at week 4. (C) Complete regression of the exophytic mass (month 9). (D) Almost complete healing (month 15).

DISCUSSION

Classification of CC has not always been uniform within the literature since the first description by Aird

et al. in 1954 (1). Recently, Chaux et al. (2) provided an update on verruciform tumours, which are defined by an exophytic growth pattern. They are well-differentiated SCC with increased survival compared with usual-type SCC. Verruciform SCC include warty, papillary, verrucous carcinoma and rare tumours, such as CC and BLT. The hallmark is papillomatosis and an endophytic labyrinthine growth pattern simulating rabbits' burrows often accompanied with fistula formation. CC has been described in many anatomical sites: the oral cavity, pharynx, oesophagus, penis and the sole of the foot where it was originally reported. No metastatic potential has been documented so far (3). The role of HPV in CC is equivocal, since no systematic association has been found (4). Interestingly, del Pino et al. (5) showed, by testing a spectrum of verrucous lesions for HPV, that 1/13 verrucous carcinoma, 1/5 verrucous hyperplasia and 3/3 BLT were positive for HPV. These results support the causal role of HPV in the development of BLT in a clearer way than in other verrucous lesions. In our case, clinical history, histological and viral analyses were in favour of CC complicating pre-existing BLT in an HIV-positive patient. CC developing on BLT seems to be extremely rare (6) and may be explained in our patient by the long diagnostic delay, since HPV6 is considered as a low-risk virus. In our case, the patient underwent 5 biopsies, including 2 surgical biopsies, before diagnosis could be established. CC pathological diagnosis requires large deep surgical biopsy specimens, so that the architecture can be appreciated. Moreover, chronic abscesses complicating the tumour can contribute to diagnostic delay.

Whenever possible, curative treatment of CC requires large surgical resection. No standard treatment is established for advanced unresectable tumours. Imiquimod (7), carbon dioxide laser, radiotherapy and conventional chemotherapy (8) (5-fluorouracil, bleomycin, cisplatin, methotrexate) are the most reported strategies, with an inconsistent efficiency. Currently, no data is available about the use of the epidermal growth factor inhibitor cetuximab in such tumours.

Based on the literature data, we discussed whether a combined systemic therapy with 13-cis-retinoic acid, IFN-α2a and cidofovir could be applied in our patient. Indeed, retinoids and IFN-α have synergistic effects in modulating cell proliferation, differentiation and apoptosis *in vitro* and clinical activity *in vivo* (9), particularly in patients with advanced cutaneous SCC (10–12). Lippman et al. (10) and Shin et al. (11) showed in 2 phase II trials, that this combined therapy gave a 68% and 34% overall response rate, respectively, in unresectable advanced cutaneous SCC. Another phase II study in 16 penile carcinomas (12) revealed a lower efficacy with a unique, but complete, response. In addition, cidofovir is an antiviral drug licensed for the treatment of cytomegalovirus retinitis in HIV patients. It has been shown to reduce the metastatic properties of HPV-positive tumour cells (13) and to be effective in anogenital condyloma, cervical (14) and vulvar intra-epithelial neoplasia (15). In our patient, partial response was obtained after 4 weeks of combined therapy and allowed the addition of conventional radio-chemotherapy. The premature discontinuation of cidofovir does not allow any conclusion about its possible synergistic role in healing the tumour.

The authors declare no conflicts of interest.

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