Bowenoid papulosis (BP), Bowen’s disease (BD) and erythroplasia of Queyrat (EQ) are distinct clinical entities with similar histological findings of intraepithelial neoplasia, but with different clinical behaviour and different risks of progression to invasive squamous cell carcinoma (SCC). In the anogenital region, BP presents grey-brown or skin-coloured elevated papules with a maximum diameter of 1 cm, BD shows larger well-demarcated plaques, and EQ appears as a well-margined erythematous velvety patch or plaque, mainly on the glans penis (1). BP is rarely invasive and may even regress spontaneously, thus conservative treatments are often adequate. In contrast BD and especially EQ, should be treated relatively more aggressively. Human papillomavirus infection (HPV) may play a causative critical role, with variable risk of progression to invasive SCC (2, 3). It has been suggested that the management of high-risk HPV-associated lesions is best if tailor-made with a multidisciplinary approach. We report here the case of a sexually active woman affected by a dramatic and disabling HPV16-related anogenital BP and BD, with focal progression into invasive SCC.

CASE REPORT
A 42-year-old Caucasian woman was referred to our Dermatology Department with a 20-year history of asymptomatic, smooth, brownish, velvety surface macules and plaques in the anogenital region, labia minora and majora, fourchette, perianal region and groin. Lymphocyte count, including total CD3, CD4 and CD8, natural killer (NK)-cell and B-cell counts, as well as serum immunoglobulins were all within normal ranges. Tests for HIV-1, HIV-2, HTLV-1 and HTLV-2 were negative and she had no history of immunodepression or immunosuppressant drugs intake. She had smoked 40 cigarettes a day for 14 years. Her gynaecological and obstetric history included menarche at the age of 13 years with regular menstrual cycles and sexarche at the age of 18 years with several sexual partners. At the age of 20 years, she was surgically treated for grade 3 cervical intraepithelial neoplasia and performed an unspecified ablative technique for vulvar condylomata acuminata, followed by a 6-month period of interferon-γ (3,000,000 IU subcutaneously, 3 times a week). The patient was disease-free for approximately 10 years and then developed new vulvar lesions, which were treated surgically. At the age of 30 years she had a pregnancy without difficulties. Five years ago, she was referred to the gynaecology department for multiple vulvar lesions, clinically featuring as BP and histologically classified as vulvar intraepithelial lesions (VIN) III, treated by multiple surgical excisions. Imiquimod therapy was started, but the patient was not motivated to continue the treatment because of several local side-effects, such as severe irritation and burning. In the last year, we were consulted as dermatologists for the first time on how to achieve clinical remission of persisting BP papules in the groin and buttocks and BD plaques in the labial and perianal region (Fig. 1A). Four lesions had the appearance of clinically typical BP lesions (Fig. 1B, white arrowhead), one, within the lesion suspicious for BD, appeared clinically as a warty verrucous nodule clearly suspicious for a SCC (Fig. 1B, black arrowheads). All 5 lesions were surgically removed. Cervical cytological screening, colposcopy and pelvic ultrasound gave normal results. Histological findings of the papules and plaques (Fig. 1C) showed a variable extent of hyperkeratosis, irregular acanthosis, papillomatosis and cytological atypia. The warty nodule (Fig. 1D, E), measuring 1.9 cm in diameter, was a well-differentiated invasive SCC, 1.8 cm deep (fb International Federation of Gynecology and Obstetrics (FIGO) staging). For HPV DNA amplification, serial paraffin tissue sections from lesions clinically suspicious for SCC and BP, respectively, were accurately collected in sterile microtubes and successively purified using the commercial QIAamp DNA Mini Kit (Qiagen, Qiagen GmbH, Hilden, Germany). DNA quality was verified by human β-globin and HLA-DPB1 gene polymerase chain reaction (PCR). The presence of HPV DNA was detected using the SPF10-PCR and HPV Genotyping by using the Inno-Lipa HPV Extra Kit (Innogenetics Immunogenetics NV, Gent, Belgium) according to the manufacturer’s protocol. In both samples, the DNA test revealed the presence of high-risk HPV, type 16 (Fig. 1F). Since the distance of the nodular invasive SCC from the vulvar median line was greater than 1 cm, the patient was firstly submitted to a non-mutilating sectorial radical vulvectomy with total monolateral inguino-femoral node dissection. After obtaining signed informed consent and assuring contraceptive measures, we proposed the following combined protocol: selective dermatological β-irradiation brachtherapy and oral isotretinoin (0.5 mg/kg/day). In the last 3 months the patient underwent four cycles of brachtherapy in the absence of significant local or systemic adverse effects. She is now disease-free and still taking oral isotretinoin.

DISCUSSION
The carcinogenetic role of high-risk HPVs, which are often integrated in VIN/SCC, is still not fully understood (4–6). Especially younger women tend to have SCC and VIN associated with HPV infection (7). Beside the high-risk HPV16 infection detected in our patient, an additional risk factor which might have influenced her clinical course is smoking. It has been shown that women who are heavy smokers are more likely to have multicentric disease. According to some studies, women who continue to smoke after treatment are 30 times more likely to have persistent vulvar disease (7).

Surgical excision, electrocoagulation, cryotherapy, CO2 laser therapy, and photodynamic therapy, are recommended treatment modalities, but they are not always completely successful, because of the multifocal distribution of the BP lesions (10). Alternatives are chemotherapeutics including 5-fluorouracil, podophyllin, cidofovir, imiquimod, and either systemic or local...
HPV genotyping positive for HPV16.

Fig. 1. (A) Multiple smooth, brownish, velvety-surface papules and plaques in the genital and perianal area. (B) Close-up of the papules (white arrowheads) and of the verrucous pinkish nodule at the level of the right labia majus (black arrowhead). (C) Microscopic examination of one papule exhibiting typical bowenoid papulosis (BP) features and of the nodule (D) showing a well-differentiated squamous cell carcinoma (SCC). (E) At higher magnification atypical squamous cell nests invading the dermis (C–E: haematoxylin-eosin stain, original magnification: C and E: ×100; D: ×40). (F) Left: Reverse transcriptase PCR for detection of human papillomavirus (HPV) infection (lane 1: negative control; lane 2: positive control; lane 3: BP; lane 4: SCC). Right: HPV genotyping positive for HPV16.

retinoids (10, 11). A randomized placebo-controlled trial has demonstrated the role of oral isotretinoin in the treatment of recalcitrant cervix condylomata (12). Several pathways have been proposed to explain how retinoids can control viral replication. They can down-regulate the expression of HPV messenger-RNA or indirectly induce transforming growth factor-β, which inhibits cell proliferation and transcription of E6/E7 genes in cervical epithelial cells (13, 14).

Brachytherapy is a recently patented skin-focused superficial and selective form of radiotherapy, demonstrated to be effective in non-melanoma skin cancers (15). A synthetic resin containing a radioactive β-emitting isotope is applied to the lesion to perform a selective β-irradiation treatment, reducing the radiation exposure of the surrounding healthy tissues. We speculated that brachytherapy in combination with isotretinoin could cooperate to clear the bowenoid field and prevent recurrences, and in our patient this was accentually the case.

In conclusion, this case emphasizes the insidious evolution of high-risk, HPV-related anogenital lesions, featuring as BP, BD and invasive SCC, in a young sexually active patient, and describes a successful therapy able to achieve healing of the lesions, chemoprevention and improvement in quality of life.

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REFERENCES