

VERRUCOUS CARCINOMA OF THE VULVA: ABOUT 3 CASES

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ABSTRACT

verrucous carcinoma (VC) of the Vulva is extremely rare, accounting for less than 1% of vulvar cancer. Effectively, it is characterization by a slow growing, no metastasis or lymph node involvement. The aim of this study was to report our experience with this disease. Three patients with VC who were treated at National Institute of Oncology between 2013 and 2018. Clinicopathological characteristics, treatment and follow-up were extracted from the medical records. The average age at diagnosis was 66 years. The average time from the onset of symptoms to diagnosis was 21 months. All patients complained of a vulvar mass or nodule, accompanied by vulvar pruritus and/or pain, which was main reasons for consultation. A preliminary pathological diagnosis of squamous cell carcinoma was made in two cases. Surgical treatment included partial vulvectomy or radical vulvectomy with uni- or bilateral lymph node dissection in the groin. Tumor size ranged from 50 to 105 mm. In the final histology, we concluded VC of the vulva staged IB (2 cases) and staged III (1 case) with marginal limits in two cases. Concurrent radiochemotherapy was performed in one case, exclusive radiotherapy in one case and only surgery in one case. Radiotherapy approaches toxicity observed were grade 2 proctitis and radiodermatitis in all cases with renal toxicity in concurrent radiochemotherapy. The mean follow-up was 43 months with no recurrence. Only one patient observed after 1-year follow-up, lichen which was resected with wide local excision. **Conclusion:** Vulvar VC is a distinct type of slow-growing, tumor with unclear etiology. Surgery is the most effective treatment. Radiotherapy approaches are considered depending on disease stage and risk factors.

KEYWORDS: Verrucous carcinoma, treatment, surgery, radiotherapy.

INTRODUCTION

Vulvar verrucous carcinoma (VC) is a very rare variant of squamous cell carcinoma (SCC) that accounts for less than 1% of vulvar carcinoma.^[1] It is a locally invasive tumor that present as fungating, ulcerative masses. It is histologically often well differentiated and have no distant metastasis and a low incidence of lymph nodes involvement^[2], and is presented as an exophytic-appearing growth^[3] and impressive, with often locally destructive. Its dissemination through the lymph nodes or metastases are unusual. Pathogenesis is controversial, but some studies evocated the role for human papilloma virus (HPV) in the etiology.^[4] The treatment remains unclear, it's still a matter of discussion.

We report three cases of verrucous carcinoma of the vulva, treated at the National Institute of Oncology Rabat (INO), reflecting the clinical and therapeutic characteristics of this pathology.

MATERIALS AND METHODS

Our study is a retrospective analysis of three cases of vulvar VC collected at the at National Institute of Oncology between 2013 and 2018. We analyzed clinicopathological characteristics, treatment and follow-up which were extracted from the data of medical records.

RESULTS

The average age at diagnosis was 66 years (range to 55 and 74 years). The three patients are postmenopausal. The average time from the onset of symptoms to diagnosis was 21 months. (Table 1)

All patients complained of a vulvar mass or nodule, accompanied by vulvar pruritus and/or pain, which was the reason for consultation. Biopsy of the vulvar lesion revealed well differentiation squamous carcinoma in two cases and verrucous squamous carcinoma (case 3). In one case differentiated VIN is associated (case 1). On

clinical examination, our three patients presented with an exophytic tumor. And tumor was involving only the right major labia (case 1), fourchette vulvar (case2) and in one case (case 3), it involved Clitoris, fourchette vulvar, bilateral minor and major labia and inferior vagina without urethra and posterior commissure involvement. The CT-scan is performed for all three patients. It found a suspicious inguinal lymph node measured 10 mm of small axis in one case (case1). (Table 2)

Our three patient underwent surgical treatment. It consists in two cases to radical vulvectomy with bilateral inguinal lymph node dissection and one case to partial vulvectomy with unilateral inguinal lymph node dissection. In case 3, the surgery was enlarged to the inferior third part of the vagina. Pathological examination of the specimen confirmed the verrucous squamous carcinoma measured between 50 mm to 105 mm with no vessel and perineural invasion. In two cases, the margins are closed (3 mm in case 1 and < 1 mm in

case 3) and in one case, margins are negative (case 2). After final histology, the patients are staged with the FIGO 2009 classification. Two patients are stage IB and one patients stage III (case 3).

Two patients underwent adjuvant treatment. The case 1 had exclusive radiotherapy with 56 Gy (28 fractions of daily 2 Gy). Concurrent chemoradiotherapy was performed in case 3 with 70 Gy in 35 fractions of daily 2 Gy (46 Gy on the vulva and a boost of 24 Gy to the tumor bed and four daily cycles of cisplatin (40mg/m²). Regarding toxicity after two radiotherapy approaches we had observed grade 2 proctitis and grade 2 radiodermatitis in all cases with renal toxicity (clairance 42.2ml/mn) in case who received concurrent chemoradiotherapy which limited the continuation of concurrent chemotherapy. (table 3)

The mean follow-up was 43 months with no recurrence in all cases.

Case	Age (year)	Menopausal statut	Consultation period
Case 1	70	postmenopausal	24 months
Case 2	55	postmenopausal	22 months
Case 3	65	postmenopausal	17 months

Cases	symptoms	Tumor aspect	location	clinical Tumor size	Biopsy
Case 1	Pruritus + Bleeding + Pain + mass	exophytic	Right major labia + vulvar fourchette + clitoris	8 cm	Well differentiation squamous carcinoma with differentiated VIN
Case 2	Pruritus + purulent leucorrhoea + mass	exophytic	Right major labia	5cm	Well differentiation infiltrative squamous carcinoma
Case 3	Pruritus + Pain + Bleeding + mass	exophytic	Clitoris + vulvar fourchette + Bilateral minor and major labia	10 cm	verrucous squamous carcinoma

Case	Type of surgery	Pathological examination of specimen	stage (FIGO 2009)	Adjuvant therapy	Toxicity	Follow-up	Status
Case 1	Radical vulvectomy + bilateral inguinal lymph node dissection	Verrucous Carcinoma 6.5×4×3 cm + closed margins (deep margin 3mm and lateral margin 4mm) + no lymph nodes involved (0/13). + No vessel and perineural invasion.	Stage IB	Adjuvant Radiotherapy 56Gy (2Gy /fraction)	Radiodermatitis + Proctitis	53 months	No signs of recurrence
Case 2	Partial vulvectomy + unilateral inguinal lymph node dissection	Verrucous Carcinoma 5 cm + negative margins (deep margin 15mm and lateral margin 12mm) + No lymph nodes involved (0/11).	Stage IB	No adjuvant therapy	No	53 months	No signs of recurrence

		+ No vessel invasion.					
Case 3	Radical vulvectomy Enlarged to 1/3 vaginal inferior + bilateral inguinal lymph node dissection	Verrucous Carcinoma 10.5x3x4.5cm + closed margins (deep margin < 1mm and lateral margin 2mm) + No lymph nodes involved (0/20). + No vessel invasion.	Stage III	Adjuvant concomitant chemoradiotherapy 70Gy (2Gy /fraction) plus 4 cycles cisplatin (40mg/m ² weekly)	Radiodermatitis + Proctitis + renal toxicity	38 months	No signs of recurrence (lichen at 1 year managed with local excision)

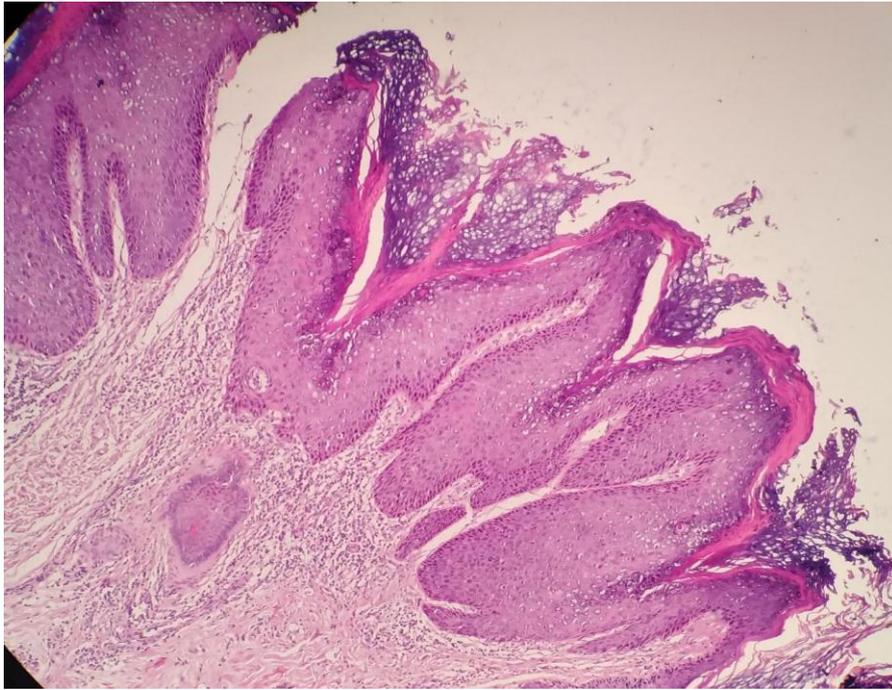


Fig 1: Prolifération tumorale carcinomateuse d'architecture verruqueuse avec hyperkératose (HE x 100).

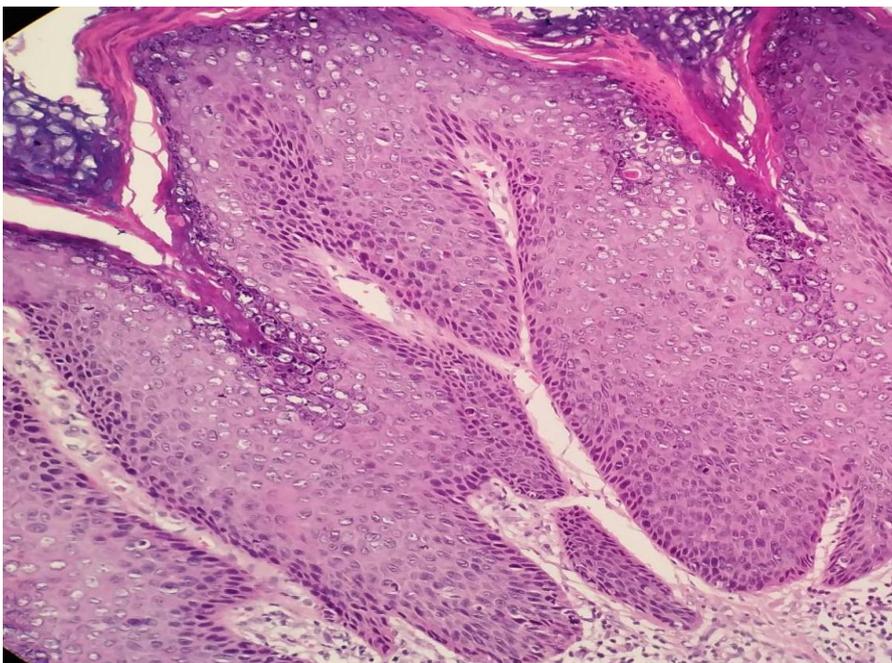


Fig 2: Atypies cytonucléaires modérées avec quelques figures de mitose (HE x 200).

DISCUSSION

The verrucous carcinoma is a distinct and peculiar entity in vulvar carcinoma classification. It is a rare histological variant of squamous carcinoma (<1% of vulvar cancer).^[1] VC of the vulva has particular comportment; its extensibility is uncertain and wayward: it is characterized as being locally invasive, the condition is not associated with metastatic spreading at distant organs and in lymph node.^[5]

This variant was first described in 1945 by Ackerman, who reported an uncommon variant of squamous cell carcinoma.^[6] VC can be founded in the oropharynx, perianal, cervix, female external genitalia, vagina, penis, scrotum, bladder, and anorectal regions.^[2,7,8] The most frequently affected site is the oral cavity.^[9]

Most cases occur in elderly postmenopausal women, who are nevertheless younger than those affected by squamous cell carcinoma.^[10] Nonetheless recently an increase incidence of this tumor in younger women has been observed. In our cases, all patients are postmenopausal women and one case was associated with vulvar intraepithelial neoplasia (VIN). In the study published in 2003, Louis-Sylvestre and al founded a remarkable coexistence of other vulvar lesions such invasive squamous carcinoma, VIN or lichen.^[11] Histology of the specimens verified the coexistence of verrucous and squamous carcinomas in four of the five cases in the Haidopoulos study.^[12] In a report published by Liu G (1), 15% (10/67) of VC coexisted with well-differentiated squamous cell carcinoma. In two patients of our cases, initial biopsy revealed squamous cell carcinoma. In fact, this well-differentiated form of squamous cell carcinoma is linked to viral infection by HPV, which explains the frequent association of verrucous carcinoma of the vulva with other lesions of vulva. The diagnosis, also, may be difficult to perform. For this reason, establishment of correct preoperative diagnosis by a large and sufficient deep vulvar biopsy as well as the meticulous assessment of the specimen by the pathologist is essential to separate genuine VC from coexistent verrucous and squamous tumors. it is convenient to avoid misdiagnosis and inadequate treatment. Histopathologic criteria for VC diagnosis include the following: verruciform growth pattern, a blunt interface between the neoplastic epithelium and the underlying submucosal stroma, minimal nuclear atypia and hyperkeratotic areas on the surface of the tumor with little keratin formation inside the tumor and diffuse chronic inflammation of the stroma. (fig 1 and fig 2) Histologically, it presents minimal cellular atypia and very mitotic figures compared with well differentiated squamous cell carcinoma.^[13]

Usually, the course of Vulvar VC is long; it progresses slowly and does not easily arouse the patient's attention. So The majority of patients presented tumors with voluminous sizes which often may be mistaken for vulvar condylomata. In our study, the main course time

from the diagnosis was 21 months which is consistent with some studies. In retrospective study at Tianjin Medical University General Hospital, six cases of vulvar VC were identified, and the mean time was 26 months and the longest time was 10 years.^[14] The main reasons for women with verrucous carcinoma such as those observing in our patients are pruritus, pain, and the presence of a mass in the external genitalia. An exophytic growth tumor with giant size was often presented, and the tumor often diffusely spread on the vulvar with both minor or major labia and mons or clitoris.

Verrucous carcinoma of the vulva may be difficult to treat. treatment is not well codified and is still a topic of debate. It differs from that proposed for squamous cell carcinoma.^[11] In literature, most surgeons recommend only a local excision as the best treatment without any lymph nodes removal. However, Haidopoulos and al. suggested that if coexist with SCC is confirmed, further lymphadenectomy is needed after tumor dissection.^[12] Because they believed that there were no reports of lymph node involvement in genuine VC in the literature because a large number of patients diagnosed with lymph node disease were found to have foci of invasive squamous cell carcinomas. Japaze and al. proposed node sampling in selected cases of vulvar VC with enlarged inguino-femoral nodes. Surgical procedure should be prioritized, and would depend on lesion size and location.^[2] All patients in our study, received surgery consisted to radical vulvectomy with bilateral inguinal lymph node dissection (cases 1 and 3) or partial vulvectomy with homolateral inguinal lymph node dissection (case 2). All excised lymph nodes were free of disease. In a retrospective study, 24 cases underwent unilateral or bilateral groin dissection or sampling and no lymph node involvement was detected.^[2] Surgery can be associated with local recurrences, especially when the tumor has been resected with inadequately limits.^[4,15] A free surgical margin of at least 1cm should be used in order to avoid recurrences.^[5]

The lesion is mainly invasive with imprecise boundaries; hence it is often difficult to perform resection with good quality edges. And the resumption of surgery can be difficult. Surgical margins are in healthy tissue with 12 mm minimal margin in one case of our study which received only surgical cure (case 2). The other patients had closed margins (3 mm and < 1 mm), and adjuvant treatment was performed. One patient had exclusive radiotherapy only. Concurrent chemoradiotherapy was performed in another woman with 70 Gy and four weekly cycles of concurrent cisplatin. After median 48 months of follow-up (range 38 to 53 months), our patients have no recurrence. Only the patient which received adjuvant chemoradiotherapy developed one year after his treatment a lichen which was managed by wide local excision. In a series of 4 VC cases reported by Boujoual which received initial total vulvectomy with inguinal dissection, 3 were completed by external

radiotherapy justified by the advanced stage of the disease and the edges of excision affected or limits. No local, locoregional or general recurrence was noted during 24 months.^[16]

Several authors suggest that VC are resistant to radiotherapy and sometimes may undergo transformation to squamous cell carcinoma. In some cases, radiation may cause anaplastic transformation, nevertheless this way of thinking is controversial and not furthermore comprehensive acquired.^[17-20]

Given the fact that treatment was not clearly defined and the good progress of our patients, radiotherapy can be considered in the event of closed margins if the resumption of surgery is not possible. However, large data are needed to corroborate this approach.

CONCLUSION

Vulvar VC is a distinct type of slow-growing, no metastatic tumor with unclear etiology. Surgery is considered the most appropriate treatment. Local recurrence was usually associated with inadequate resection. Radiotherapy approach can be considered in case with closed margins.

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