Gynecologic Oncology Reports 47 (2023) 101193

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Review article

Primary intestinal-type adenocarcinoma of the vulva. A case report and review of the literature

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ARTICLE INFO

Keywords:
Vulvar cancer
Intestinal-type adenocarcinoma
Primary vulvar adenocarcinoma
Cloacogenic vulvar adenocarcinoma
Goblet cell
Signet-ring cell

ABSTRACT

Background: Primary non-squamous cell carcinomas of the vulva are rare entities including various tumor types. Among these, primary vulvar intestinal-type adenocarcinoma (vPITA) is extremely rare. Until 2021, less than twenty-five cases have been reported in the literature.

Case presentation: We report a case of vPITA in a 63 years old woman with a histopathological diagnosis of signet-ring cell intestinal type adenocarcinoma at vulvar biopsy. Accurate clinical and pathological work-up excluded secondary metastatic localization, and vPITA was diagnosed. The patient was treated with radical vulvectomy and bilateral inguinofemoral dissection. Adjuvant chemo-radiotherapy was performed because of a positive lymph node. At 20 months follow-up the patient was alive and free of disease.

Conclusion: The prognosis of this very rare disease is unclear and optimal treatment is not well established. About 40% of clinical early-stage diseases reported in literature had positive inguinal nodes, more than in vulvar squamous cell carcinomas. A proper histopathologic and clinical diagnosis is mandatory to exclude secondary disease and to recommend an adequate treatment.

1. Introduction

Vulvar cancer is a rare malignancy, representing the 0.65% of all female cancers (Siegel et al., 2021). More than 90% of invasive vulvar cancers are squamous-cell cancers (vSCC); the majority of them are not HPV-related, arising via differentiated Vulvar Intraepithelial Neoplasia (Singh and Gilks, 2020) and may be associated with chronic inflammation or lichen sclerosus (Pouwer and DEN Einden, 2020). Only about 30% of vSCCs are HPV-related (Hinten et al., 2018). All the other histological types (e.g. vulvar melanoma and primary vulvar adenocarcinoma arising from Bartolino's glands (Weinberg and Gomez-Martinez, 2019) account for about 10% of primitive vulvar cancers.

Among primary adenocarcinomas of the vulva, intestinal-type adenocarcinomas are extremely rare, with only few cases reported in the literature (Willén, 1999; Tiltman and Knutzen, 1978; Kennedy and Majmudar, 1993; Ghamande et al., 1995; Zaidi and Conner, 2001; Rodriguez et al., 2001; Liu et al., 2003; Dubé et al., 2004; Cormio et al., 2012; Karkouche et al., 2012; Musella et al., 2013; Chibbar et al., 2013; Sui et al., 2016; Tepeoğlu et al., 2018; Lee et al., 2017; Matsuzaki et al., 2017; He et al., 2017; Esmaeili et al., 2018; Kurita et al., 2019; Kaltenecker et al., 2019; Moscoso et al., 2021). The diagnosis is based on morphological characteristics and immunohistochemical phenotype resembling intestinal-type adenocarcinoma (Willén, 1999).

Because of the exiguity of cases, the prognosis of the disease is not well known, and different therapeutic approaches have been used. There are no specific guidelines and the optimal management of this condition is still debated.

2. Case presentation

A 63-year-old woman presented with a history of vulvar itch in the previous 4 months with a vulvar small boil persisting in the last weeks.

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https://doi.org/10.1016/j.gore.2023.101193
Received 12 March 2023; Received in revised form 13 April 2023; Accepted 15 April 2023
Available online 21 April 2023

She was nulliparous, not a tobacco user and did not use oral contraceptive in the past. Surgical menopause occurred at 55 years old, when she underwent hysterectomy and bilateral salpingo-oophorectomy for uterine leiomyomas with abnormal uterine bleeding and concomitant ovarian cysts; histology was negative for preneoplastic or neoplastic lesions. In the same year, she was diagnosed with ductal breast cancer and underwent a right-side mastectomy with sentinel node assessment - final stage pTis pN0(s) -, followed by adjuvant radiotherapy. The subsequent follow-up was negative for recurrent disease. During her life, she had regular screening for FIT (fecal immunochemical test), regular gynecological examinations and regular cervical smears according to the Italian national cervical cancer screening programme. No vulvar lesions or symptoms were previously reported.

When the patient referred to our Institution, a complete gynecological examination was performed. The vulva presented with a mild postmenopausal atrophy. A single 10 mm nodular lesion of the lower third of the right labia minora was found, at less than 2 cm from vulvar midline. The lesion appeared velvety, raised on the vulvar surface, and reddish, with central, easily bleeding, ulceration. The lesion was not painful and mobile on the deep tissue. No other vulvar, perineal or perianal lesions were noted; no suspect nodes in the inguinofemoral regions were found.

The routine pelvic examination revealed a normal vagina and a regular vaginal vault; at vaginal/rectal examination the rectovaginal septum was regular, with no pelvic masses detected. At the routine transvaginal ultrasound, no abnormality was found.

A wide local excision with 1 cm clear peripheral margins was performed in outpatient setting, with local anesthesia, removing the whole lesion with macroscopic clear margins. The histological examination revealed an invasive, moderately differentiated, mucinous intestinal type adenocarcinoma with signet-ring cells (Fig. 1). The depth of invasion was 4 mm, and no lymph-vascular nor perineural space invasion was observed. Immunohistochemically the tumor cells were positive for MUC5AC (Fig. 2A), MUC2 (Fig. 2B), CEA (Fig. 2C), CK20 (Fig. 2D), CDX2 (Fig. 2E); focal and weak positive for CK7 (Fig. 2F) and negative for estrogen and progesterone receptors, CD56, chromogranin A, synaptophysin, HER2, p16, Ca125, GCDFP-1, WT1, Villin, MUC6. Ki67 positivity was 60%.

The lesion was close to the deep surgical resection margin (less than1mm).

Blood routine examination was regular; the serological evaluation for HBV, HCV, and HIV was negative. Plasma levels of tumor markers SCCAg, CA-125, CA15.3, CA19.9, and CEA were negative as well.

After surgical excision of the lesion, the patient underwent a thorax and abdominal-pelvic CT scan with contrast, and a PET-CT, without evidence of suspicious findings and with normal-sized retroperitoneal lymph nodes. Gastroscopy and colonoscopy, with biopsies, were also both negative for neoplasia. Therefore, a primary signet-ring cell intestinal-type adenocarcinoma of the vulva, FIGO stage 1B (pT1 cN0 Mx, G2) was finally diagnosed.

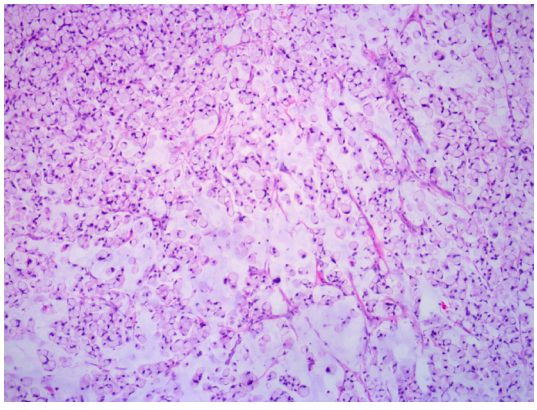

Fig 1. Signet-ring cell, intestinal type adenocarcinoma of the vulva. H/E original magnification 200x.

Considering the histopathological diagnosis, the clinical stage of the neoplasia, the "close" deep surgical margin status and the localization at less than 2 cm from the vulvar midline, the patient was treated with radical vulvectomy and bilateral inguinofemoral lymph node dissection according to the surgical technique described by Micheletti et al. (Micheletti et al., 2005).

After surgery, the patient had a regular postoperative course, and was discharged on day 9. The pathological examination of the surgical specimens showed no residual disease in the vulvar region. Twelve lymph nodes were examined (seven removed from the left groin, five from the right one), with a single 4 mm metastasis without extracapsular neoplastic spread observed in one node from the left groin.

The final pathological diagnosis was a primary signet-cell, intestinal-type adenocarcinoma of the vulva, with groin node metastasis, stage IIIA according to FIGO stage 2021. (pT1B N1 M0 according to TNM VIII Ed) (Olawaite et al., 2021). Tumor immunohistochemistry, positive for CEA, MUC2, MUC5AC, CDX2, CK20, and CK7 (weak) was consistent with intestinal phenotype.

The case was then discussed in a multidisciplinary tumor board meeting and an adjuvant treatment was proposed. Two months after surgery, the patient started helical intensity modulated radiation therapy (Tomotherapy) and concurrent chemotherapy with adjuvant purposes. 1.8 Gy daily fractions to a cumulative dose of 45 Gy were delivered. The target volume enclosed the vulvar surgical bed, distal vagina, bilateral inguinofemoral, obturator, and internal and external iliac nodes. A concomitant boost of up to 50 Gy was delivered to the vulvar surgical bed. Weekly cisplatin and daily capecitabine were administered along the radiation therapy (RT) course at the following dosage regimen: 30 mg/sqm/week and 1650 mg/mq/day, respectively, for 5 weeks. After completing adjuvant treatment a close follow-up was scheduled, with gynecological examination, *trans*-vaginal ultrasound, vulvoscopy, and evaluation of serum level of CEA every 3 months. A thorax and abdominopelvic CT scan with contrast were performed 6 and 12 months after surgery. After 20 months of follow up no recurrence emerged and the patient was alive and free of disease.

Informed consent was obtained by the patient for clinical data collection and case description.

3. Discussion

Primary vulvar adenocarcinomas are rare. Among them, primary intestinal-type adenocarcinomas are extremely rare, with only a few cases described, therefore no standardized diagnostic or therapeutic strategies are available.

We searched the PubMed/MEDLINE and SCOPUS databases using the keywords "adenocarcinoma vulva'', "goblet cell", "signet cell", "intestinal type", and "mucinous" and found 21 reports describing a total of 23 cases of vPITA until December 10, 2022 (Table 1).

The pathogenesis of vPITA is unclear: the most likely hypothesis is the persistence of cloacal remnants in adult life outside the gastrointestinal tract. During the embryo development, the labia majora originate from labioscrotal folds, while the labia minora from the urethral folds; both of them are closely associated with cloacal development and may undergo malignant transformation (Tiltman and Knutzen, 1978; Kennedy and Majmudar, 1993; Lee et al., 2017). Another hypothesis is that the vestibular region may derive from cloacogenic tissue; the presence of this tissue may be a normal feature and not secondary to an aberrant tissue (Willén, 1999).

Other Authors hypothesized that it may be secondary to a repair process of an iatrogenic secondary lesion, reporting a case of a woman with a previous history of fourth-grade perineal laceration and subsequent development of the neoplasia in the same site (Ghamande et al., 1995).

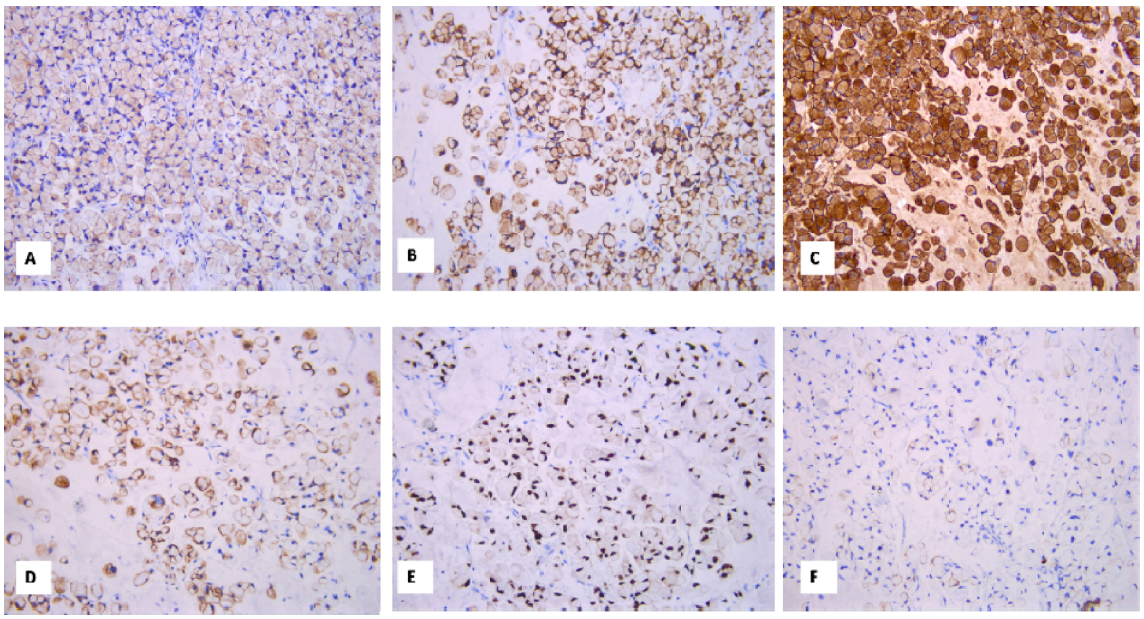

Fig 2. Immunohistochemical staining with: MUC5AC (A), MUC2 (B), CEA (C), CK20 (D), CDX2 (E), CK7 (F). HIC original magnification 200x.

Table 1
Cases of primary intestinal type vulvar adenocarcinoma in the literature.

Author	Age	Surgery	LN Status	Adjuvant treatment	Immunohistochemical pattern	FU months	status
Tilman, 1978	50	modified RV + LND	pos	no	*NR*	12	NR
Kennedy, 1993	54	RV + LND	neg	no	*CK+*	120	ned
Kennedy, 1993	63	WLE	neg	no	*CEA-*	48	ned
Ghamande, 1995	67	RV + LND	neg	no	*CEA+*	NR	
Willen, 1999	57	WLE	neg	no	*CK17+, broad CK+, polyclonal CEA+-, chromogranin A +-*	26	ned
Zandi, 2001	43	modified RV + LND	pos	no	*CEA+, broad CK+, p53+, ras10 +-, ER-, PR-, bcl2-, c-Erb2-*	18	ned
Rodriguez, 2001	69	WLE	neg	no	*CK20+-, CK7+, CEA apical, OC125 apical, OC19,9 apical*	36	ned
Liu, 2003	49	WLE + LND	neg	no	*NR*	24	ned
Dube, 2004	58	WLE	pos	no	*CK20+-, CK7+, ER-, PR-*	16	ned
Cormio, 2012	59	RV + LND	pos	CT	*CK7+*	54	dod
Cormio, 2012	42	RV + LND	neg	no	*CK20+-*	39	ned
Karkouche, 2012	31	WLE	neg	no	*CK20+, CK7-*	15	ned
Musella, 2013	57	NACT + WLE + LND	neg	no	*CK20+, CK7-, CEA+, CDX2 + focal, p16+, Ca125 +-, ER-, vimentin-*	17	ned
Chibbar, 2013	49	NACT + LND	pos	CT** + RT	*CK20+, CK7-, CEA+, CDX2+, p53+, ER-, PR-, WT1-*	27	dod
Sui, 2016	43	WLE	neg	CT*	*CK20-, CK7+, PAS+, AB+, CAM 5.2+, p16 + focal, ER-, PR-, GCDFP15-, CA125-, villin-, CA19.9-, TTF1-, napsinA-*	24	ned
Tepeoglu, 2016	40	WLE + LND	pos	no	*CK20+, CK7 + focal, polyclonal CEA+, CDX2+, WT1-, GCDFP15-*	38	ned
Lee, 2017	64	WLE	neg	no	*CK20+, CK7+, CEA+, CDX2+, p53+, p16+*	12	ned
Matsuzaki, 2017	68	WLE	neg	no	*CK20+, CK7-, CDX2+, MUC2+, MUC6-, MIB1+*	60	ned
He, 2017	63	WLE	neg	no	*CK20+, CK7 focal+, CDX2+, ER-, PR-, p53-*	26	ned
Esmaeili, 2018	67	WLE	neg	no	*CK20+, CK7+, CEA+, CDX2-, p53+, PR+, ER-*	8	ned
Kurita, 2019	63	WLE + LND	neg	RT	*CK20+, CK7-, CDX2+, GCDFP15-*	12	ned
Kaltenecker, 2019	53	biopsy	pos	CT* + RT	*CD20+, CK7-, Mcea+, vimentin-, p53+*	12	dod
Moscoso, 2021	66	WLE + LND	neg	no	*CK20+, CK7-, CEA+, CDX2+, p16+, WT1+, MUC4+, CD10+, chromogranin A weak focal*	NR	
Present case, 2022	63	WLE + LND	pos	CT* + RT	*CK20+, CK7 + focal, CEA+, CDX2+, p53+, Ki67+ (60%), ER-, PR-, CD56-, chromogranin A -, synaptophysin -*	20	ned

FU: follow-up; NR: non reported; dod: death of disease; ned: no evidence of disease; WLE: wide local excision; RV: radical vulvectomy; LND: lymphnode dissection; NACT: neoadjuvant chemotherapy; LN: Lymphnode; CT: chemotherapy; RT radiotherapy; * Carboplatine and taxol; ** Folfiri; ^not specified.

The natural history of vPITA is also poorly understood, so the metastatic potential of the tumor and its metastatic pattern of spread are not well defined. It is assumed that, similarly to vSCC and other adenocarcinoma arising in the vulvar region, the metastatic process first involves the inguinofemoral lymph nodes, on one or both sides depending on the localization of the tumor. In women affected by clinical early-stage vSCC, positive pathological nodes are reported up to 28% of patients (Hermann et al., 2021). Among the 23 cases of vPITA reported in the literature, 2 were treated with neoadjuvant chemotherapy followed by surgery; 1 with definitive radiochemotherapy; 9 with surgery and

clinical/instrumental assessment of groin lymph nodes status; 11 with vulvar surgery and regional lymph node dissection. Among these, pathological examination of inguinal lymph nodes is reported in 10 cases, with 40% of them (4/10) showing nodal metastasis. Adding our case, in which we found a single positive inguinofemoral node, the frequency of groin lymph nodes metastases in early-stage disease rise to 45.5% (5/11), which is more than reported for early-stage vSCC.

The management of vPITA is still debated, there are no guidelines and no consensus about optimal surgical strategy. However, considering the high incidence of groin lymph node metastases, in our opinion a complete inguinofemoral nodes or sentinel node dissection (ipsilateral or bilateral according to the location of the lesion) is advisable (Sopracordevole et al., 2018).

The role of adjuvant treatment in women with groin nodes metastasis is debated as well. In three cases (Tiltman and Knutzen, 1978; Zaidi and Conner, 2001; Tepeoğlu et al., 2018) no adjuvant therapy was performed, without relapse after 12, 18, and 38 months. In our case, because of the IIIA1 stage of the tumor, even considering the small amount of data available in the literature, we opted for adjuvant radiotherapy and concomitant chemotherapy. To choose the correct chemotherapy, we looked at similar cases described in the literature (Cormio et al., 2012; Sui et al., 2016) and our experience in gastrointestinal tumors, so we opted for cisplatin and capecitabine association. Twenty months after initial treatment the patient was still free of recurrence. In most of the cases described in the literature, a good prognosis is reported and the disease seems to be rather indolent. However, recurrences are reported also many months after primary surgery. Unfortunately, only a short follow-up is available in most of the cases (less than two years in 12/23 cases).

We have to consider that the disease, differently from what happens for vSCC, affects middle-aged women: the mean age of cases reported in this review is 55.75 years, ranging from 31 to 69. They are relatively young women, and we have to give them the best diagnostic and therapeutic approach in this rare condition.

4. Conclusion

vPITA is a rare entity. An accurate diagnostic process and staging are mandatory to rule out secondary disease and to confirm the vulvar primitivity anytime an intestinal-type tumor is found in the vulva. The proper management is still debated. A radical vulvectomy (or radical excision) with a concomitant appropriate surgical assessment of inguinofemoral lymph nodes (ipsilateral or bilateral according to the location of the lesion) should be performed, with adjuvant therapy in high-risk patients (lymph node positivity or close resection margins). A close and long term follow-up is mandatory.

CRediT authorship contribution statement

Francesco Sopracordevole: Conceptualization, Writing – review & editing. **Giulia Azzalini:** Writing – original draft, Investigation. **Nicolò Clemente:** Writing – review & editing, Conceptualization. **Anna Del Fabro:** Investigation. **Giorgio Giorda:** Supervision. **Mariasole Fichera:** Writing – original draft, Investigation. **Marco Gigante:** Supervision. **Giorgio Bogani:** Writing – review & editing. **Vincenzo Canzonieri:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Italian Ministry of Health – Ricerca corrente – for publication funding.

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