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Primary mucinous carcinoma of the vulva with signet ring cells deriving from the cloaca

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Summary

Vulvar neoplasias are rarely encountered lesions at female genital tract, regardless if they are primary or metastatic. Presence of signet ring cells in a tumour at female genito-urinary tract is highly suggestive of a metastatic lesion particularly from a gastrointestinal tumour. Here the authors present a case of vulvar carcinoma with signet ring cells with an undetermined primary site possibly originating from embryonic cloaca.

Key words: Signet ring cell; Vulvar tumour; Primary vulvar cancer; Cloaca.

Introduction

Vulvar tumours constitute 3-5% of gynaecologic malignancies and compose < 1% of all malignancies in women [1]. Majority of the vulvar tumours are squamous carcinomas. Vulvar mucinous adenocarcinomas are extremely rare regardless of being primary or metastatic. Primary mucinous tumours of vulva may arise from Bartholin's glands, sweat glands, sebaceous glands, mesonephric remnants, ectopic breast tissue or in association with entero-cutaneous fistulas [2, 3]. Presence of signet ring cells in a tumour at genito-urinary site is highly suggestive for a metastatic lesion possibly from a gastro-intestinal origin [4, 5]. Here the authors present a case of signet ring cell mucinous adnenocarcinoma of the vulva with an undetermined primary origin.

Case Report

A 62-years-old woman presented with spotting and with a history of two vaginal births. Her medical history was unremarkable except for total abdominal hysterectomy and bilateral salpingo-oophorectomy performed in 2001 due to uterine fibroids. Her physical examination revealed an irregularly contoured rough nodule with a diameter of three centimetres on the medial side of right labium major. Speculum examination revealed a normal appearing vaginal vault. Transvaginal ultrasonography did not demonstrate a pelvic pathology. Pap smear was normal and tumour markers including CA 125, CA 19-9, CA 15-3, CA 72-4, and CEA were within normal limits (4.4 U/ml, 3 U/ml, 16.5 U/ml, 2.28 U/ml, and 0.38 ng/ml respectively). An excisional biopsy was performed. Pathologic examination revealed a mucinous adenocarcinoma with signet ring cells. The tumour was observed to invade dermis, extending trough the epidermis, and causing micro-ulcerations on stratified squamous epithelium of vulvar skin (Figure 1). Signet ring cells observed within the mucinous lakes (Figure 2A), stained positive for mucicarmine. Surgical margins of the resected specimen were free from tumoral cells. Immunohistochemical staining was performed. Tumour cells were extensively stained with CK20 (Figure 2B), CDx2, MUC2. Focal areas of staining were observed with CK7 and MUC5AC. MUC1 GCDFP-15 stains were negative for the specimen. Further investigations were performed to detect the possible primary site of the tumour considering the staining pattern, particularly for a gastrointestinal site tumour. Colonoscopic and gastro-duedonoscopic examinations were normal. Mammography did not demonstrate any suspicious lesions. PET-CT was unremarkable except for a mildly increased uptake compatible for inflammatory response (SUV max: 1.9) at the site of vulvar biopsy. Toraco-abdomino-pelvic CT did not demonstrate any pathologic lesions but a haemangioma with a diameter of 11 mm within liver.

A decision was made to perform expectant management. Monitoring included systemic physical examination, pelvic examination, vaginal vault smear, serum tumour marker level assessment, mammography, colonoscopy, and gastro-duedonoscopy. After two years of uneventful follow-up, patient presented with erythematous swelling at right thigh and pain on right aspect of pelvis. Pelvic examination revealed a rough reddish nodule with irregular contours measuring approximately 3×4 cm. Lower extremity venous Doppler examination did not reveal any signs of deep venous thrombosis or venous insufficiency. Serum levels of CA125, CA 19-9, and CEA were found within normal range. Pelvic MRI revealed irregularly contoured mass originating from right labium major, extending to distal portion of urethra and vaginal orifice, and infiltrating through pelvic floor muscles. Right para-iliac and inguinal lympadenopathy with subcutaneous edema in favour of extra-capsular lymphatic spread and nodular lesions at right iliac bone and right lateral side of sacral bone indicating metastasis were also demonstrated by pelvic MRI. These findings were considered as a recurrence of previously diagnosed malignancy and chemotherapy regimen consisting in carboplatin and paclitaxel was started. After six cycles of chemotherapy, PET-CT imaging demonstrated a physiological spread of F-18 FDG throughout the body. Colonoscopic, gastro-duedonoscopic examinations, mammography, and serum tumour marker levels were normal as well. The pa-

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Figure 1. — Infiltration of tumour cells in stratified squamous epithelium causing ulceration.

tient is disease-free at 41 months after the diagnosis and 12 months after completion of the chemotherapic regimen.

Discussion

Metastatic tumours of the vulva constitute only 5-8% of all vulvar malignancies. Vulvar metastases generally indicate a widespread primary disease and are usually considered as a preterminal event. The duration of survival changes in cases with metastatic vulvar lesions is in respect of the primary malignancy. Majority of these cases are reported to have disseminated diseases when diagnosed to have vulvar metastases. The overall mean survival rate of the women that have malignancies with vulvar metastases was estimated as 35.6 months subsequent to the diagnosis of metastatic vulvar lesions [1]. Most common extra-genital primary sites of vulvar metastasis were reported as breast carcinoma and gastro-intestinal system tumours [6]. In this case, any possible primary site of vulvar tumour was unable to be demonstrated despite all attempts. Systemic physical examinations, pelvic examinations, serum tumour marker levels, vaginal vault smears, PET-CT, mammographies, colonoscopies, and gastro-duedonoscopies were all normal at initial investigation, as well as the follow-up visits even at the time of recurrence that was occurred two years after the local excision.

Primary mucinous carcinomas of the vulva may arise from ectopic breast tissue, Bartholin's glands, sweat glands, sebaceous glands, mesonephric remnants or in association with entero-cutaneous fistulas [2,3].

Normally vulva includes some mammary-like tissue as a derivative of milk-lines. However, there are few number of reported adenocarcinoma cases derived from this ectopic mammary tissue. These usually form glandular structures and exhibit oestrogen or progesterone receptor positivity [7-10]. Although signet ring cells could be seen in breast cancer in rare cases [11] immunohistochemical features of the present case were not consistent with a carcinoma derived from breast tissue.

Primary carcinoma of Bartholin's gland constitutes 2-7% of all vulvar malignancies and adenocarcinomas comprise nearly 40% of Bartholin's gland carcinomas [12]. There are some criteria described for the definitive diagnosis of Bartholin gland carcinoma, such as demonstration of transition from normal Bartholin gland tissue to neoplastic tissue, histologically compatible localization of tumour with the origin of Bartholin's gland, and no evidence of other primary tumour [13]. In the present case there was no transition observed between normal Bartholin gland tissue and neoplastic tissue. Tumour margins were not connected with Bartholin's gland.

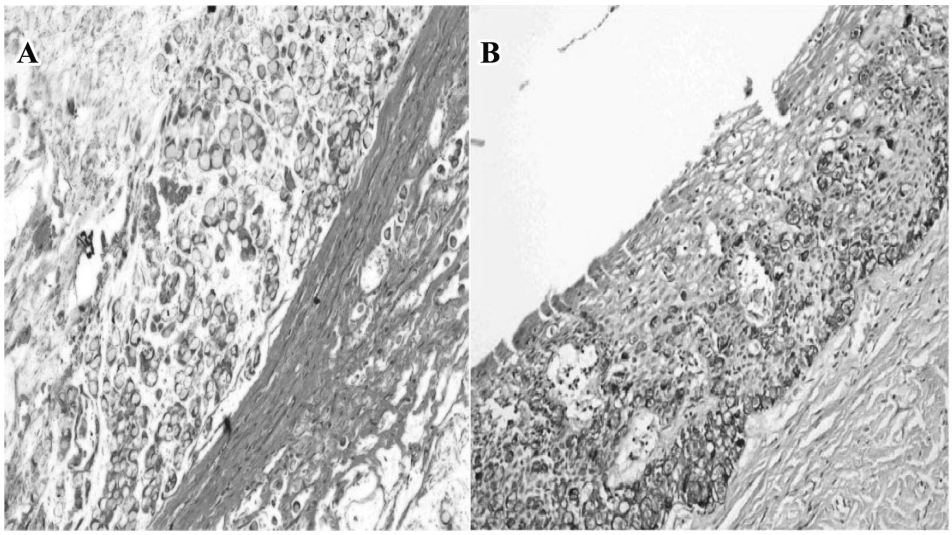

Figure 2. — A) Epithelial cells appearing as signet ring cells within the mucinous lakes. B) Staining of tumour cells with CK20 reside within the mucinous lakes and spread through the epidermis.

Table 1. — *Summary of the clinical presentation, management, and outcomes of reported vulvar adenocarcinoma cases with cloacogenic origin*

Author	Age (years)	Vulvar lesion	Other clinical findings	Treatment	Inguinal-femoral LNM	Distant metastasis	Prognosis
Tiltman et al. [15]	50	NA	NA	Modified RV+ BL IFLND	Yes	No	12 months DFF
Kennedy *et al.* [16]	Case 1: 54 Case 2: 63	NA	NA	Case 1: RV+BIFLND Case 2: Wide LE	No	No	Case1: 120 months Case 2: 48 months DFF
Ghamande *et al.* [2]	67	1.2 cm	No	RV+BIFLND	No	No	17 months DFF
Willen *et al.* [17]	57	1 cm	No	Wide LE	No	No	26 months DFF
Zaidi *et al.* [18]	43	4 cm	No	Modified RV+BILND	No	No	18 months DFF
Rodriguez *et al.* [19]	69	1,5 cm	No	Wide LE	-	No	36 months DFF
Liu *et al.* [20]	49	1.8 cm	Inguinal LAP	Wide LE+ BILND	No	No	24 months DFF
Dubé *et al.* [21]	58	2 cm	No	RHV+ ULIFLND	No	No	16 months DFF
Cormio *et al.* [22]	Case 1: 58 Case 2: 42	NA	NA	Case 1: RHV+BLIFLND Case 2: RV+BLIFLND	No	No	Case 1: metastatic colon cancer 36 months after treatment Case 2: 39 months DFF + dysplastic polyp in sigmoid colon
Karkouche *et al.* [23]	31	NR	NR	LE (recurrence after 6 months) LE for recurrence	-	-	15 months DFF
Chibbar *et al.* [24]	49	1 cm (multiple)	Inguinal LAP+ lower vaginal involvement+ lung metastasis	Chemo-radiation Punch biopsy+BLIFLND	Yes	Yes	DOD 27 months later
Musella *et al.* [25]	57	5 cm	Inguinal LAP+ Lower vaginal involvement	Neoadjuvant CT Radical vulvectomy+ ULIFLND	Yes	No	4 months DFF
Present case	62	3 cm	No	Wide LE	-	No	Recurrence after 24 months
		Recurrence: 4 cm	Recurrence: extensive spread	Recurrence: chemotherapy	Recurrence: yes	Recurrence: yes	12 months DFF after recurrence

RV: radical vulvectomy; RHV: radical hemivulvectomy; LE: local excision; LAP: lymphadenopathy; LNM: lymph node metastasis; BIFLND: bilateral inguinal-femoral lymph node dissection; ULIFLND: unilateral inguinal-femoral lymph node dissection; BILND: bilateral inguinal lymph node dissection; DFF: disease-free follow-up; DOD: died of disease; NA: not available; NR: not reported.

Immunohistochemical staining features of the tumour indicated that this tumour may not be derived from glandular heterotopias. In glandular heterotopias of vulva, cells stain positively for CK7, CD-X2 and CEA, but negatively for CK20 [14]. Extensive staining with CK20 in the setting of focal staining with CK7 in the present case strongly suggests that a glandular heterotopia is unlikely and the lesion might be secondary to metastasis, possibly from gastrointestinal system. Moreover tumour cells have not stained with GCDFP 15, excluding the possibility of extra-mammary Paget disease.

Primary vulvar carcinomas originating from cloacal remnants have been published in a handful of reports that are summarized at Table 1 [2, 15-25]. These tumours are known to have glandular structures, could be continuous with epidermis and may cause focal ulcerations. Signet ring cells could be observed in the tumours derived from cloacal origin, however a primary mucinous tumour of the vulva with signet ring cells derived from cloacal remnants is an exceptionally rare occurrence and has not been reported before.

The tumour in the present case might be derived from embryonic remnants of cloaca at vulvar region. On the other hand, the present patient has a history of two vaginal births with right mediolateral episiotomy and rectal mucosa could be involved in the course of episiotomy repair. In any case, origin of this tumour deemed to be closely related with cloaca.

Limited number of reports about this issue indicates a relatively indolent course and favourable prognosis in these types of tumours [24]. Less aggressive surgeries like local wide excision instead of radical vulvectomy could be curative in these tumours, particularly in the cases with negative surgical margins [16, 17] and in the absence of any clinical suspicion for metastasis to regional lymph nodes or distant sites.

Cormio *et al.* [22] reported two cases of vulvar cancer with cloacogenic origin. One of these cases was found to have disseminated colon cancer 36 months after surgical treatment of vulvar disease and the other case was found to have a dysplastic polyp at colon 39 months after vulvar surgery. The present authors have performed colonoscopy and gastro-duedonoscopy at follow-up visits. In their opinion, dissimilar with other types of vulvar cancer, performing colonoscopy and gastro-duedonoscopy in primary cloacogenic vulvar tumor follow-up, seems reasonable unless otherwise proven by future studies.

In the present case, the malignancy had relapsed after two years. Invasion of pelvic floor muscles, involvement of lymph nodes with extra-capsular spread and pelvic bone metastasis were detected. These factors indicate an unfavourable prognosis. This recurrence could be classified as FIGO Stage IVA if considered to be a primary vulvar tumour. However, despite these unfavourable prognostic factors, the disease seems to respond unpredictably well to carboplatin-paclitaxel regimen, similar to the case reported by Musella *et al.* [25]. A vulvar tumour with > two cm diameter and confined to the vulva or perineum was classified as $T_{1b}N_0M_0$ according to TNM classification and all patients with tumours larger than two cm require a thorough inguinal-femoral lymphadenectomy [26]. However a thorough inguinal-femoral lymphadenectomy is associated with long-term morbidities and should be avoided whenever the survival will not be compromised by omission of this procedure. Depending on the scarce data about this rare occurrence, considering the indolent course of this tumour, and the probable susceptibility to chemotherapy as indicated by limited number of reports in literature, future treatment of these patients might include more limited surgeries (for example to avoid the possible long-term morbidities associated with the groin dissection), if efficiency of a narrow surgery in preventing relapses is demonstrated to be similarly successful to wide surgeries in reliable studies that will be conducted for this aspect. However, without doubt, this issue should be clarified by studies with large number of cases prior shifting to a more conservative surgical approach and without support of reliable evidence limited surgeries should not be considered as safe and effective.

In conclusion, although the current evidence is not sufficient to reliably recommend a modality of treatment due to rarity of this kind of tumours, primary mucinous tumors of the vulva with a cloacal origin could have relatively good prognosis even if they include signet ring cells and might respond well to chemotherapy regimens comprising carbopatin and paclitaxel.

References

[1] Neto A.G., Deavers M.T., Silva E.G., Malpica A.: "Metastatic tumors of the vulva: a clinicopathologic study of 66 cases". *Am. J. Surg. Pathol.*, 2003, *27*, 799.

[2] Ghamande S.A., Kasznica J., Griffiths C.T., Finkler N.J., Hamid A.M.: "Mucinous adenocarcinomas of the vulva". *Gynecol. Oncol.*, 1995, *57*, 117.

[3] Matsuo K., Chi D.S., Eno M.L., Im D.D., Rosenshein N.B.: "Vulvar mucinous adenocarcinoma associated with Crohn's disease: report of two cases". *Gynecol. Obstet. Invest*., 2009, *68*, 276.

[4] Sarro R., Fiche M., Bisig B., Ketterer N., Benhattar J., Achtari C., de Leval L.: "An unusualuterine tumor with signet ring cell features". *Int. J. Gynecol. Pathol.*, 2012, *31*, 236.

[5] Giordano G., Pizzi S., Berretta R., D'Adda T.: "A new case of primary signet-ring cell carcinoma of the cervix with prominent endometrial and myometrial involvement: Immunohistochemical and molecular studies and review of the literature". *World J. Surg. Oncol.*, 2012, *10*, 7.

[6] Mazur M.T., Hsueh S., Gersell D.J.: "Metastases to the female genital tract: analysis of 325 cases". *Cancer*, 1984, *53*, 1978.

[7] Simon K.E., Dutcher J.P., Runowicz C.D., Wiernik P.H.: "Adenocarcinoma arising in vulvar breast tissue". *Cancer,* 1988, *62*, 2234.

[8] Greene H.J.: "Adenocarcinoma of supernumerary breasts of the labia majora in a case of epidermoid carcinoma". *Am. J. Obstet. Gynecol.,* 1936, *31*, 660.

[9] Cho D., Buscema J., Rosehein N.B., Woodruff J.D.: "Primary breast cancer of the vulva". *Obstet. Gynecol.,* 1985, *66*, 79.

[10] Yin C., Chapman J., Tawfik O.: "Invasivemucinous (colloid) adenocarcinoma of ectopicbreasttissue in the vulva: a case report". *Breast J.*, 2003, *9*, 113.

[11] Sandhu J., Dubey V.K., Makkar M., Suri V.: "Pure primary signetring cell carcinoma breast: a rare cytological diagnosis". *J. Cytol.*, 2013, *30*, 204.

[12] Stolen M.H., Mills S.E., Frierson H.F.: "The vulva and vagina". *In:* Mills S.E., Carter D., Greenson J.K., Reuter V.K., Stoler M.S. (eds). *Sternberg's Diagnostic Surgical Pathology*. 4th ed. Philadelphia: Lippincott, 2004, 2579.

[13] Chamlian D.L., Taylor H.B.: "Primary carcinoma of the Bartholin's gland: a report of 24 patients". *Obstet. Gynecol.,* 1972, *39*, 489.

[14] Horn L.C., Bauerfeind U.K., Strau H.G., Karbe I.: "Vulvalintestinal/entericheterotopia with a 10-yrfollow-up: a casereport and review of the literature". *Int. J. Gynecol. Pathol.*, 2014, *33*, 258.

[15] Tiltman A.J., Knutzen V.K.: "Primary adenocarcinoma of the vulva originating in misplaced cloacal tissue". *Obstet. Gynecol.*, 1978, *51*, 30.

[16] Kennedy J.C., Majmudar B.: "Primary adenocarcinoma of the vulva, possibly cloacogenic. A report of two cases". *J. Reprod. Med.*, 1993, *38*, 113.

[17] Willén R., Békássy, Carlén B., Bozoky B., Cajander S.: "Cloacogenicadenocarcinoma of the vulva". *Gynecol. Oncol.*, 1999, *74*, 298.

[18] Zaidi S.N., Conner M.G.: "Primaryvulvaradenocarcinoma of cloacogenicorigin". *South Med. J.*, 2001, *94*, 744.

[19] Rodriguez A., Isaac M.A., Hidalgo E., Márquez B., Nogales F.F.: "Villoglandular adenocarcinoma of the vulva". *Gynecol. Oncol.*, 2001, *83*, 409.

[20] Liu S.H., Ho C.M., Huang S.H., Shih B.Y., Lee F.K.: "Cloacogenic adenocarcinoma of the vulva presenting as recurrent Bartholin's gland infection". *J. Formos. Med. Assoc.*, 2003, *102*, 49.

[21] Dubé V., Veilleux C., Plante M., Têtu B.: "Primary villoglandular adenocarcinoma of cloacogenic origin of the vulva". *Hum. Pathol.*, 2004, *35*, 377.

[22] Cormio G., Carriero C., Loizzi V., Gissi F., Leone L., Putignano G., Resta L., Selvaggi L.: "Intestinal-type" mucinous adenocarcinoma of the vulva: a report of two cases". *Eur. J. Gynaecol. Oncol.*, 2012, *33*, 433.

[23] Karkouche R., Ansart F., Terris B., Lavenu M.C., Plantier F.: "Multiple tubulovillous adenomas of the vulva". *Am. J. Dermatopathol.*, 2012, *34*, 321.

[24] Chibbar R.,Wood K.A.,Giede C.K., Agrawal A.: "Unusually aggressive primary cloacogenic carcinoma of the vulva: a case report and literature review". *Case Reports in Clinical Medicine (CRCM)*, 2013, *2*, 302.

[25] Musella A., Marchetti C., Salerno L., Vertechy L., Iadarola R., Pecorella I., Panici P.B.: "An unexpected complete remission of advanced intestinal-type vulvar adenocarcinoma after neoadjuvant chemotherapy: a case report and a literature review". *Case Rep. Obstet. Gynecol.*, 2013, *2013*, 427141.

[26] Berek J.S.: Berek and Novak's Gynecology" 15th ed. Philadelphia: Lippincott Williams & Wilkins, 2012.

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