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Primary adenocarcinomas of the vulva and related structures: An enigmatic and diverse group of tumors☆

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ABSTRACT

Approximately half of adenocarcinomas that involve the vulva are secondary, either through direct extension or metastases from elsewhere. Primary vulvar adenocarcinomas are rare and encompass a diverse array of neoplasms that are nominally classified based on the presumed tissue or organ of origin, the tumoral phenotype, or both. In this review, we summarize the clinicopathologic features of adenocarcinomas that originate from the vulva and related structures, including the terminal urethra. Adenocarcinomas of this region encompass lesions that are defined by their primary site (such as adenocarcinomas of the Bartholin gland, which by definition must be in the region of the Bartholin gland), histomorphology and immunophenotype (such as clear cell carcinoma and adenocarcinoma of intestinal [cloacogenic] type), or both (such as adenocarcinoma of skene gland origin, which is associated with that specific organ but which also displays a distinctive phenotype that is similar to the phenotype of high grade prostatic adenocarcinoma). Other types, such as mammary-type adenocarcinomas, are presumed to originate from the putative mammary-like glands of the vulva and display a spectrum of pathologic features that are similar to their mammary counterparts. Similarly, vulvar carcinomas of sweat gland origin are pathologically similar to their counterparts in the non-vulvar skin and include a variety of cutaneous adnexal-type malignancies such as apocrine adenocarcinoma and eccrine adenocarcinoma. Some tumors, such as adenoid cystic carcinoma, may represent a Bartholin gland adenocarcinoma, a carcinoma of sweat gland origin, or a carcinoma arising from extramammary Paget disease (EMPD), depending on the context. Invasive carcinomas of various types have been reported in 7–12.7% of EMPD, and these are likely the most common primary glandular malignancy of the vulva. Occasional vulvar adenocarcinomas have been reported to be HPV-associated, although this association has not been established for the broader group of vulvar adenocarcinomas. Rare adenocarcinomas are not classifiable by the aforementioned nosologic scheme, and are designated as vulvar adenocarcinoma NOS.

Introduction

By a substantial margin, the most common malignant tumors of the vulva are squamous cell carcinomas. Other primary tumors, including melanomas, sarcomas and other histotypes of carcinoma constitute a minority of the lesions. Glandular malignancies are notably rare, with an estimated incidence rate of 0.9–2.5 per 1000,000 women per year, based on a population-based analysis from the Netherlands.[1] This analysis also showed that 45% of adenocarcinomas that involve the vulva are secondary, either through direct extension or metastases from elsewhere. This observation is in keeping with our own experiences that approximately half of glandular malignancies that involve the vulva are secondary, and clearly necessitates that the possibility of a secondary adenocarcinoma should be excluded before a diagnosis of a primary vulvar adenocarcinoma is made.[2]

The 2020 College of American Pathologists (CAP) cancer protocol[3] listed 1) adenocarcinoma, NOS; 2) adenocarcinoma, mammary gland type; 3) adenocarcinoma, skene gland type; 4) adenocarcinoma, sweat gland type; 5) adenocarcinoma, intestinal type; and 6) adenocarcinoma, with associated Paget disease as non-exhaustive histologic types of

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primary vulvar adenocarcinomas. The 2014 World Health Organization (WHO) classification listed 1) Paget disease, 2) adenocarcinoma of Bartholin gland 3) adenocarcinoma, mammary gland type 4) adenocarcinoma, skene gland origin, 5) "phyllodes tumor, malignant", 6) adenocarcinoma, sweat gland type and 7) adenocarcinoma, intestinal type, as primary vulvar malignant tumors of glandular type.[4] In the aforementioned study, which was based on the PALGA "Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief" database, a nationwide network and pathology registry in the Netherlands, the four most common histotypes identified were invasive carcinoma arising from Paget disease (30%), adenocarcinoma NOS (22%), tumor of the skin appendages (19%) and adenoid cystic carcinoma (10%).[1]

In this review, we describe the clinicopathologic features of adenocarcinomas that are primary to the vulva and related structures. Adenocarcinomas in this region encompass lesions that are defined by their primary site (such as carcinomas arising from the Bartholin gland) ,[5] histomorphology and line of differentiation (such as clear cell carcinoma[6, 7] and adenocarcinoma of intestinal (cloacogenic) type,[8] or both (such as adenocarcinoma of skene gland origin that are associated with a specific organ and have a distinctive phenotype[9]). Other types, such as mammary-type adenocarcinoma are presumed to originate from the putative mammary-like glands,[10] whereas carcinomas of sweat gland origin show lines of differentiation and possibly a histogenesis that are similar to their counterparts in the non-vulvar skin.[11-13] Some tumors, such as adenoid cystic carcinoma, may represent a Bartholin gland adenocarcinoma, a carcinoma of sweat gland origin, or a carcinoma arising from extramammary Paget disease (EMPD), depending on the context.[14] Due to the frequent presentation of the terminal urethral adenocarcinoma as a vulvar mass,[15] they will be also included in this review. EMPD will be briefly discussed since since it is covered in more detail in another contribution from this issue as well as elsewhere.[10, 16-19] We focus herein more on the issue of invasive disease arising in EMPD. The rare biphasic malignancies that may occur in this setting, such as malignant "phyllodes tumor", are not discussed in this review, as they are not purely glandular malignancies. Rare lesions, including human papilloma virus (HPV)-associated primary vulvar adenocarcinomas and carcinomas of sweat gland origin, are only briefly mentioned in this review, and the reader is referred to other treatises on these subjects.[11-13]

Anatomy of the vulva

Knowledge of the basic anatomy of the vulva, with special emphasis on the location of normal glandular structures, is important to accurately diagnose the various adenocarcinoma types. The vulva is a skin bearing organ covered with squamous epithelium in all anatomic compartments except the vestibule.[20] The vestibule is bounded anteriorly by the frenulum of the clitoris, medially by the external part of the hymenal ring and posteriorly by the line of Hart. Sebaceous glands are abundant in the lateral aspects of the labia majora and the perineum area. They are associated with hair follicles and their ducts open directly to the surface of the skin and medially toward the vestibule. The labia minora are devoid of glandular elements except sebaceous glands. The clitoris is also devoid of glandular structures. The adnexal glands e.g. apocrine and the eccrine sweet glands are present in the labia majora, prepuce and perineal bodies and like adnexal glands anywhere in the skin could be the primary source of adenocarcinoma (will be briefly discussed in this review) .[21]

The squamous epithelium of the vulva merges with the transitional epithelium of the terminal urethra and the epithelium of the para-urethral (Skene) glands (homologue of the prostate in males) which is located anteriorly (mons pubis side) and composed of pseudostratified mucous secreting cells. The ducts of the Skene glands are lined with transitional epithelium and open directly to the outer surface of the vulva as well as to the posterior and the lateral aspects of the urethra.[22]

The major Bartholin (vestibular) glands are located posterolateral

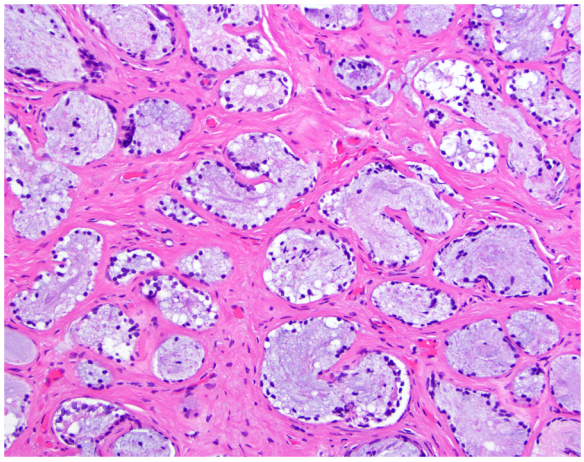

Fig. 1. Bartholin (vestibular) glands formed of simple mucous secreting columnar epithelium.

(toward the perineum) and as that of the Skene glands are formed of simple (not stratified) mucous secreting columnar epithelium [Fig. 1]. The Bartholin ducts are lined by three types of epithelium 1) simple columnar epithelium toward the acini, 2) squamous epithelium toward the duct openings and 3) transitional epithelium in-between. The minor Bartholin glands are scattered within a few millimeters from the superficial epithelium and are composed of simple columnar epithelium.[21]

The mammary-like glands are specialized anogenital sweet glands located in the sulcus between the labia majora and labia minora as well as in the perineum.[12] The ducts of the mammary-like glands are long, relatively wide and coiled from which may sprout acini, diverticula, and short branches; the glands and the ducts are lined by simple columnar epithelium with apical snouts similar to apocrine metaplasia of the breast which are surrounded by outer myoepithelial layer.[23]

The vulva (except the clitoris) drains to the inguinal and femoral lymph nodes (regional lymph nodes). The clitoris drains to the internal iliac, obturator and external iliac lymph nodes, which makes knowledge of the exact location of the malignant tumor crucial in determining the expected first station lymph node metastasis and consequently the most optimal operative procedure to perform.[24] It should be noted that internal iliac/hypogastric, external iliac, and common iliac lymph nodes are not considered regional lymph nodes for all vulvar tumors, including tumors arising from the clitoris, and any metastasis in these lymph nodes are staged as distant metastasis (pM1) in the 2020 CAP cancer protocol for malignant vulvar tumors.[3]

Adenocarcinoma of bartholin gland

Definition

Invasive adenocarcinoma arising in the area of the Bartholin gland (deep in the labia majora) mostly with transitional areas from benign to malignant tumor on histologic examination, and that display no evidence that it originated from elsewhere.[5, 25] As a practical matter, tumors that are large may not be able to fulfill these criteria, including transitional areas to benign Bartholin gland. Nonetheless, a minimal requirement is that the tumors be in the region of the Bartholin gland.

Epidemiology and clinical presentation

Bartholin gland malignant tumors represent 7.7% of all vulvar cancers and adenocarcinoma represent 12% of Bartholin malignant neoplasms, which makes this entity approximately 1–2% of all vulvar malignant tumors.[25-27] Less than 100 patients have been reported. They range in age from 23 to 92, with an average of 56 years. The patients

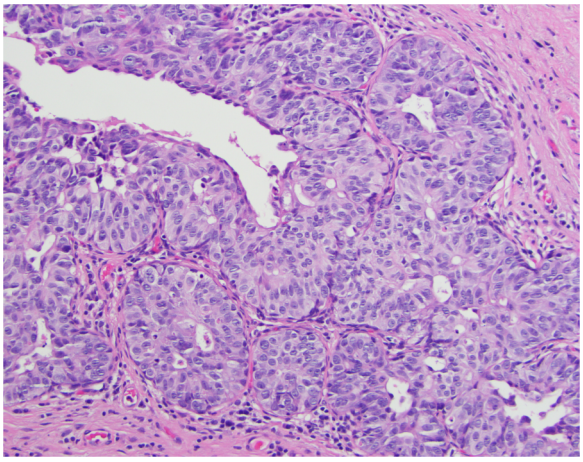

Fig. 2. Adenocarcinoma of Bartholin gland. The tumor exhibits nested and solid growth pattern.

usually present with painless mass in the posterior vulva. Other rare presenting symptoms are itching, bleeding, ulceration and pain.[28]

Macroscopy

The tumors are usually well circumscribed, unencapsulated, gray white to yellow with solid to cystic cut surfaces.[27, 29]

Histopathology

The tumors arise from the mucin secreting columnar epithelium of the gland acini with multiple architectural and growth patterns [Fig. 2]. The tumors are usually mucinous adenocarcinomas.[27] Other architectural patterns reported are papillary, nested solid, and glandular. An enteric or signet ring phenotype may be present and may mimic gynecologic-type CCC.[29-32] The tumors may show salivary gland carcinoma-type morphology (including features reminiscent of adenoid cystic carcinoma, myoepithelial carcinoma, and epithelial–myoepithelial carcinoma). Some cases maybe associated with or represent the invasive component of vulvar EMPD. Transition from benign mucin secreting acini to malignant glands is usually present in most cases and indeed has been proposed as a requirement for diagnosing primary Bartholin gland adenocarcinoma.[5, 30, 31, 33, 34] However, many cases in which the tumor entirely replaces the Bartholin gland have been reported.[29, 32, 35, 36]

An adenocarcinoma in situ may arise in the major or minor vestibular glands [Fig. 3]. In the latter, the surface squamous epithelium is replaced with glands and solid nests of atypical columnar epithelium with frequent mitotic and apoptotic figures. In the reported case, the columnar epithelium was positive for mucin histochemical stain, focally positive for CK20, positive for CK7 and p16 (HPV18 detected by ISH). No stromal invasion was identified. Normal minor vestibular glands are identified.[37]

Table 1 summarizes the clinicopathologic features of representative published cases in the English literature of Bartholin gland adenocarcinomas.

Immunohistochemistry

The rare CCCs arising from the Bartholin gland are immunophenotypically similar to the CCC arising in other sites of the gynecologic tract, namely NapsinA+, CK7+, PAX8+, Vimentin+, ER-, PR-, calretinin-, CD10-, CEA-, p16-, P53 (wild type) and p63[35]-. Adenocarcinoma, NOS is usually ER+, PR+, B72.3+, P16-, CAM5.2+, CEA+, EMA+. [34] The enteric pattern is immunophynotypically similar to colorectal adenocarcinomas: CK7+, CK20+, CDX2+, CEA+, CA19–9+, PAX8-, ER-, PR-, CA125-, and GATA3[32]-. In-situ carcinoma arising from the minor vestibular glands are CK7+, P16+, CK20 focally positive, ER-, PR-, GATA3-, CDX2-, uroplakin -, PSA[37]-.

Prognosis and clinical outcome

Most patients with Bartholin gland adenocarcinoma present at an advanced stage with the tumor already extending to adjacent structures or to the lymph nodes.[30, 36] The prognosis is dependent on tumor size, tumordifferentiation (grade) and lymph node metastasis.[25, 27]

Key diagnostic points: adenocarcinoma of Bartholin glands

- Most commonly, mucin secreting adenocarcinoma, NOS
- Architectural patterns include papillary, nested solid, glandular. An enteric or signet ring phenotype may be present, as may salivary gland-type carcinomas and conventional gynecologic tract CCC
- Adjacent benign mucin secreting glands usually present

Immunophenotype

Positive: ER, PR, CAM5.2+, CEA+, EMA+
Negative: P16, P53 (wild type)

Adenocarcinoma, skene gland origin

Definition

Invasive adenocarcinoma of primary Skene gland origin that is morphologically similar to prostatic adenocarcinoma. It may or may not be positive for prostatic markers e.g. PSA in tissue section and/or elevated serum PSA[9] (IHC or serum levels are not required for diagnosis).

Epidemiology and clinical presentation

The disease is extremely rare with an approximately 14 reported patients that ranged in age from 46 to 88, with an average of 71 years. The patients present clinically with mass lesions around the urethral opening or anterior vagina, hematuria, urinary retention, stress incontinence and urethritis[9] (Table 2).

Macroscopy

The reported tumors ranged in size from 0.9–3.5 cm with an average diameter of 2 cm[9]. The tumors were firm, solid and yellow tan nodules.[38]

Histopathology

Some authors propose that at least a fraction of adenocarcinomas of the distal female urethra are of Skene gland origin.[15, 39-43] Others consider only adenocarcinomas that are morphologically similar to prostatic adenocarcinoma (with or without immunoreactivity for prostate markers) in tissue sections to be classifiable as Skene gland adenocarcinoma.[9, 38, 44-51] We adopt the latter approach in the current review. The presence of residual benign Skene gland or the growth of the tumor in the lumen of a Skene gland are helpful clues that may demonstrate the origin of a tumor in this region to be the Skene gland. Morphologically, the tumors are similar to prostatic adenocarcinoma of predominant Gleason pattern 4 + 4 = 8, with cribriform architecture

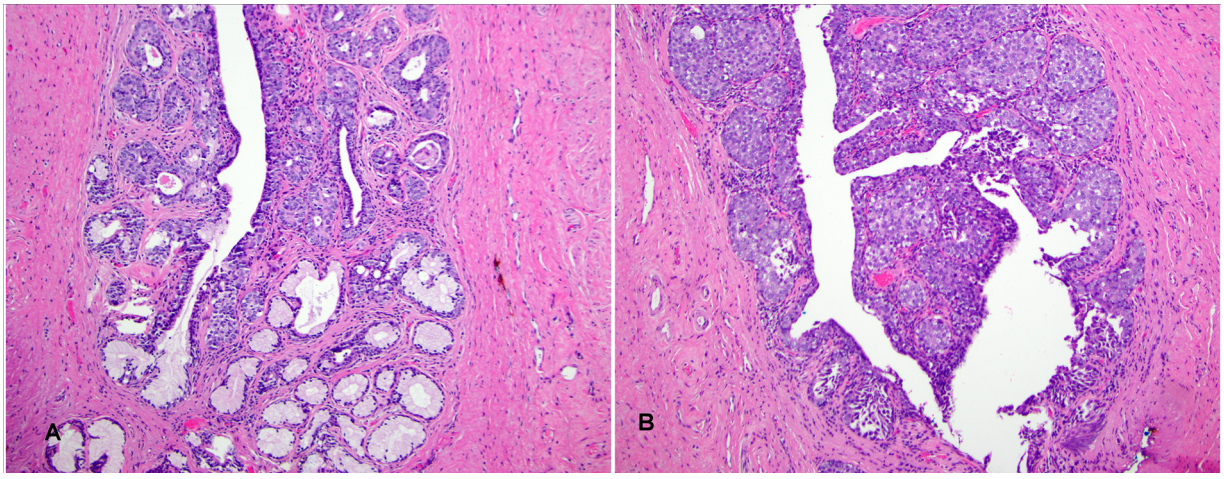

Fig. 3. Adenocarcinoma in situ arising in Bartholin gland. Note the transition of the benign Bartholin gland epithelium with atypical adenocarcinoma cells with no stomal invasion in A and groups and nests of adenocarcinoma cells entirely replaced the gland epithelium with no stromal invasion in B. B) Adenocarcinoma in situ arising in Bartholin gland. Groups and nests of adenocarcinoma cells entirely replaced the gland epithelium with no stomal invasion.

(majority of cases), poorly formed and fused glands, solid, cystic and papillary patterns with focal signet ring or intestinal features (Table 3).

Tables 2-4 summarize the clinicopathologic features of published cases of adenocarcinomas of Skene gland origin that fulfil thediagnostic criteria adopted in this review.[38, 44-51]

Tumor grading

Due to the rarity of the tumor, there is no consensus on a grading system. The CAP cancer protocol[3] recommends using a three-tier grading system for all vulvar malignant tumors (well, moderately and poorly differentiated). It is not known if the Gleason grading system used for prostatic adenocarcinoma applies for cases that are morphologically and immunophenotypically identical to prostatic adenocarcinoma.[9]

Prognosis and clinical outcome

The few cases reported appear to behave indolently with most patients were alive at a variety of follow up intervals. Due to the rarity of cases, there is no consensus on a treatment strategy.[9] Serum PSA levels may potentially be used for monitoring patients after surgery.[38, 45] (Table 4)

Key diagnostic points: adenocarcinoma, Skene gland type

- Similar to prostatic acinar adenocarcinoma of Gleason 4 + 4 = 8
- Cribriform (majority of cases), poorly formed and fused glands

Immunophenotype

Positive: PSA, PSAP, P501S, NKX3.1, AMACR
Negative: HMWCK, P63

Adenocarcinoma, intestinal (cloacogenic) type

Definition

Primary vulvar adenocarcinoma that typically displays villoglandular architecture, mucinous type epithelium, and intestinal differentiation arising superficially in relation to the surface squamous epithelium and not arising from specific glandular (e.g. Bartholin or Skene gland) or vulvar structure, and diagnosed after the clinicopathologic exclusion of a metastatic disease.[52-54]

Epidemiology and clinical presentation

Vulvar adenocarcinoma of intestinal type is very rare with only a few cases published.[52, 55, 56] The reported patients ranged in age from 31 to 69, with an average of 56 years. The patients presented clinically with painless mass, dyspareunia, bleeding, pain, discharge, discomfort and pruritis.[8, 53, 56-60]

Macroscopy

The lesions have been described as papillary, exophytic mass, nodule(s), polyp-like, red velvety, nodule with central cyst with or without surface ulceration. The reported lesions ranged in size from 0.7–3.5 cm with an average size of 2 cm[52, 54–56].

Histopathology

A heterogenous group of tumors that are generally morphologically similar to intestinal adenocarcinoma. The predominant morphology may be an adenocarcinoma, NOS, or mucinous, signet ring or villoglandular cytoarchitecture. Glands are lined by well to moderately atypical columnar cells with frequent mitotic and apoptotic figures and intracellular and extracellular mucin production [Fig. 4 and 5] .[8, 55, 57-64] One case was described as displaying anaplastic and spindle cell carcinomatous components and heterologous chondrosarcomatous and osteosarcomatous elements, thereby classifiable as a (carcinosarcoma) .[65] An in-situ lesion has also been described in the hymen with

TABLE 1
Clinicopathologic characteristics of representative cases of vulvar Bartholin gland adenocarcinoma reported.

Reference	Age (y)	Symptoms	size (cm)	Benign Bartholin gland	Architecture	Immunophenotype	Lymph node/ distant metastases	Treatment	follow up (months)	outcome
Lulenski and Naji[27]	74	Mass, bleeding	10	yes	Branching and arborizing, columnar cells, intra and extracellular mucin.	none	no	Surgery	9	Alive/NED
Chamlian and Taylar[5]	80	Mass	3	yes	Mucin producing adenocarcinoma with papillary formation		inguinal	chemotherapy	12	DOD
	42		3.5	yes			no	Surgery	44	Alive/NED
	41		1.5	yes			no		31	Alive/NED
	39		2	yes			no		24	Alive/NED
	83		3	yes			no		7	Alive/NED
	53		9	yes			inguinal		42	DOD
	67		2.3	yes			no		144	Alive/NED
	70		3.5	yes			no		86	Alive/NED
Mossler et al[25]	50	Mass	3		Moderately differentiated mucinous adenocarcinoma		multiple		40	DOD
	64		2				One		14	Alive/NED
	47		6				one		156	Alive/NED
	34		NA		Poorly differentiated adenocarcinoma with solid and papillary growth patterns	ER+, PR+	multiple		5	DOD
	15		8			none	multiple		2	DOD
Copeland et al[33]	Median (57) Range 23–86	Mass Pain Discharge Bleeding	8	N/A	Mucosal villous hyperplasia x2 Conventional colonic adenocarcinoma x3 Mucinous carcinoma x3 All cases are moderately differentiated with mucin production	none	yes	Surgery and radiotherapy	51	DOD
			2	yes			no	Surgery	69	DND
			6				na	Surgery	180	Alive/NED
			7				no	Surgery and radiotherapy	138	DOD
			2				no	Surgery	89	Alive/NED
			4				no	Surgery	48	Alive/NED
Felix et al[34]	na	nodule	na	yes	Adenocarcinoma NOS	CEA+, ER+, CAM5.2+, PR+, EMA+ P16-,	na	na	na	na
Ohno et al[36]	92		5	no	Mucinous adenocarcinoma with signet ring cells	CA19.9+, CEA+, P53+, HPV-	inguinal	Radiotherapy	10	DOD
Herghelegiu et al[35]	54	mass	1.5	no	CCC, solid pattern	CK7+, PAX8+, Napsin-*A*+, Vimentin+, ER-, PR-, CD10-, CEA-, p16-, P53-, p63-.	LN/distant	Surgery and chemoradiotherapy		na
Nazeran et al[30]	72			yes	nested architecture with solid and glandular growth	P16-, Her2-, ER-, PR-	distant	Surgery and radiotherapy	52	DOD
Lim et al[29]	46	Painless lump	4	No	Papillary and glandular patterns, clear cytoplasm, hobnail nuclei	n/a	no	Surgery	9	Alive/NED
Robinson et al[32]	55			no	villoglandular mucinous adenocarcinoma, columnar cells floating in mucin, goblet cells	CK7+, CK20+, CDX2+, CEA+, CA19–9+, ER-, PR-, PAX8-, CA125-		Surgery and radiotherapy	30	Alive/NED
Chatzistamatiou et al[31]	49	Mass	NA		CCC					

NED, no evidence of disease; DOD, dead of disease; CCC, clear cell carcinoma.

Table 2
Clinical characteristics of reported cases of adenocarcinoma of Skene gland origin.

Reference	Age (years)	Symptoms	size (cm)	Site	Treatment
Tregnago and Epstein[9]	63	NA	1.5	periurethral	surgical
	87	Nodule	2	periurethral	surgical
	87	Bleeding, urethral polyp	1	periurethral	surgical
	61	Urethral polyp	1.5	periurethral	surgical
Dodson et al[38]	70	flat tumor	2	periurethral	surgical
Kyriazis et al[44]	71	Urethral mass	0.9	urethra	surgical
Zaviacic et al[45]	70	flat tumor	1.5	vagina	None
Muto et al[46]	69	periurethral mass	NA	periurethral	NA
Svanholm et al[47]	72	polypoid mass	1	urethra	surgical
Sloboda et al[48]	46	incontinence & hematuria	3.5	periurethral	surgical
Murphy et al[49]	NA	NA	NA	NA	NA
Pongtippan et al[50]	88	hematuria	3	periurethral	Radiotherapy
Korytko et al[51]	71	incontinence & hematuria	3	bladder neck	Radiotherapy

NA: Not available.

villoglandular growth pattern confined to the surface squamous epithelium with no stromal invasion identified. The cells are mildly atypical columnar epithelium with mucin secretion and interspersed goblet cells.[53]

Tubulovillous adenomas analogous to their colonic counterparts have been reported in the vulva.[66, 67] An intramucosal carcinoma with moderate to severe atypia has been described in one of these lesions[66] and an invasive carcinoma has been described in another case.[55, 61]

Immunohistochemistry

Intestinal type adenocarcinomas are mostly positive for CDX2, CK20, CEA-p [Fig. 5], CK7, CK17, villin, are mostly negative for ER, PR, BCL2, HER2/neu, and display a wild-type phenotype for p53[8, 54, 58–61, 68].

Prognosis and clinical outcome

Most patients with vulvar intestinal type adenocarcinoma have a protracted indolent course and are alive with no evidence of disease on follow up.[8, 55, 57, 59-61, 68] A few reported cases were associated with an aggressive course and death of disease.[52, 56, 69]

Table 5 summarizes the clinicopathologic features of representative published cases of primary vulvar adenocarcinoma, intestinal type.

Key diagnostic points: adenocarcinoma, intestinal type

- Similar to colonic adenocarcinomas
- Villoglandular, cribriform, papillary, mucinous and signet ring features.
- Nuclei with mild to moderate atypia
- Eosinophilic cytoplasm with intra and extracellular mucin

Immunophenotype

Positive: CEA, CDX2, CK20, CK7, villin
Negative: ER, PR, p53, BCL2

Adenocarcinoma of the terminal urethra

Definition

An adenocarcinoma of primary urethral origin presenting as vulvar lesion and morphologically different from prostatic adenocarcinoma.[39, 40]

Epidemiology and clinical presentation

The disease is rare, occurs in females with age range of 46–88 years (mean of 71.5 years) and present clinically with hematuria, urinary retention, stress incontinence, urethritis or more commonly, as a mass arising from or around the urethral opening.[39]

Macroscopy

The reported tumors ranged in size from 0.5–3.5 cm with an average diameter of 2 cm. Gross features were variable.[39, 70]

Histopathology

Invasive urethral adenocarcinomas are divided into 2 morphologic subtypes; 1) mucinous/columnar cell type, and 2) clear cell type.[15, 39-43] In the mucinous/columnar cell type, the tumors are morphologically similar to endometroid or colonic adenocarcinomas with irregular tubular/glandular formation, solid, cribriform, papillary, mucinous and signet ring patterns. Most commonly, the tumor exhibits a combination of patterns. The nuclei are rounded to oval with mild to moderate nuclear atypia, prominent nucleoli and frequent mitotic and apoptotic figures. The cytoplasm is eosinophilic to amphophilic with infrequent extracellular mucin containing malignant cells.[15, 39, 42, 43, 70]

The morphology of the clear cell type is similar to the CCC at other sites of the female genital tract.[71] Briefly, the architectural patterns are irregular tubules (glands), cyst formation lined with one or few layers of neoplastic cells, papillary pattern of predominant small round papillae, and solid pattern. The cytoplasm is clear or eosinophilic, the nuclei are rounded or oval with prominent nucleoli, hobnail pattern with mild nuclear atypia and infrequent mitotic figures.[40, 41, 43, 70]

In a recent report, primary adenocarcinomas of the female urethra represent 34.5% of malignant tumors (10/29 cases) and all tumors

Table 3
Pathologic characteristics of cases reported as adenocarcinoma of Skene gland origin

Reference	Benign Skene gland	Architecture	Basal layer	Serum PSA	Immunophenotype
Tregnago and Epstein[9]	yes	Glands, papillae, pseudostratified columnar epithelium, intraluminal mucin, enlarged nuclei, coarse chromatin, loss of polarity, atypical mitotic figures, basal apoptosis	present (HMWCK and P63)	NA	CK7+, ER+, CDX2+ (focal), PSA-, NKX3.1-, P501S-, AMACR-, P63-, WT1-, PAX8-, SATB2-, CK20-, P16+, negative HPV ISH
		Large nests, cribriform, poorly formed glands, pale cytoplasm, similar to Gleason score 4 + 4 = 8 carcinoma of the prostate, monotonous nuclei, nucleoli	No (HMWCK-, P63) in 95% of the tumor	0.8	PSP+, P501S+, NKX3.1+, AMACR+
		Periphery: Well to poorly formed and fused glands, acini, cuboidal cells, eosinophilic cytoplasm, prominent nucleoli. Center: papillary fronds, cuboidal and columnar epithelium, abundant cytoplasm, prominent nucleoli, focal cribriform, (similar to Gleason score 4 + 4 = 8)	around papillary and cribriform (HMWCK+, P63+)	NA	
		Invasive poorly formed, fused, and small cribriform glands, pale eosinophilic cytoplasm, monotonous nuclei, nucleoli, (similar to Gleason score 4 + 4 = 8). Focal glands with prominent goblet cells	absent (P63-)	5	PSA+, P501S+, NKX3.1+, AMACR+, CK20 (focal). Goblet cell: CK20+, CDX2-, Prostate markers-, SATB2-
Dodson et al[38]	yes	Solid (70%) and glandular (30%), uniform cells, rounded nuclei, eosinophilic cytoplasm, occasional cytoplasmic vacuoles. Marinated chromatin, prominent nucleoli	NA	5.9	PSA+, PSAP+ (weak). ER-, PR-, BCL-2-
Kyriazis et al[44]	yes	Well-formed glands, papillary, micro-acinar and cribriform, poorly formed glands, solid areas similar to prostatic acinar carcinoma	No	1.7	PSA+, AMACR+, CK7-, CDX2-, CK20-
Zaviacic et al[45]	NA	well differentiated adenocarcinoma, cribriform, lined with columnar epithelium	NA	NA	PSA+, PSAP+
Muto et al[46]	Yes	Cribriform with signet ring features and focal intestinal metaplasia	present	NA	Cribriform: PSAP+, AMACR+, PSA-, NKX3.1-. Intestinal: CK20+, CK7-, CDX2+, MUC2
Svanholm et al[47]	NA	Proliferating glands, single-layer tall columnar epithelium with clear or slightly eosinophilic cytoplasm, mild nuclear atypia, focal cribriform and infiltrating single cells.	NA	NA	PSA+, PSAP+
Sloboda et al[48]	NA	cribriform, Individual glands, solid and clear cell features	NA	NA	PSA+, PSAP+
Murphy et al[49]	NA	cribriform pattern	NA	NA	PSA+, mAbDas1-
Pongtippan et al[50]	No	Small glands, cribriform and solid areas, uniform cells, low columnar, eosinophilic cytoplasm, cytoplasmic vacuoles, irregular nuclear membranes, single nucleolus.	NA	1.3	PSA+, cytokeratin+, CEA-
Korytko et al[51]	NA	Marked vacuolation of cytoplasm, monotonous cells, round nuclei, prominent nucleoli	NA	54.5	PSA+, PSAP+, AE1/AE3+, CAM5.2+, CK7, CK 20-, EMA-, HMB-45-, melan A-, synapto-, chromo-, S-100-

NA: Not available.

Table 4
Extent of spread and follow up data of cases reported as adenocarcinoma of Skene gland origin.

Reference	Lymph node metastases	Other malignancy	Follow up period (M)	Outcome
Tregnago and Epstein[9]	NO	None	132	alive/NED
	NO	None	19	alive/NED
	NO	cervical and urinary bladder of unknown histology	8	alive/NED
	NO	None	4	alive/NED
Dodson et al[38]	NO	None	NA	NA
Kyriazis et al[44]	NO	None	31	alive/NED
Zaviacic et al[45]	NO	renal cell carcinoma	NA	NA
Muto et al[46]	NA	NA	NA	NA
Svanholm et al[47]	NO	ovarian carcinoma	NA	NA
Sloboda et al[48]	Inguinal	None	NA	NA
Murphy et al[49]	NA	NA	NA	NA
Pongtippan et al[50]	NO	None	12	alive/NED
Korytko et al[51]	NO	None	32	alive/NED

NED, no evidence of disease; NA, not applicable (not reported).

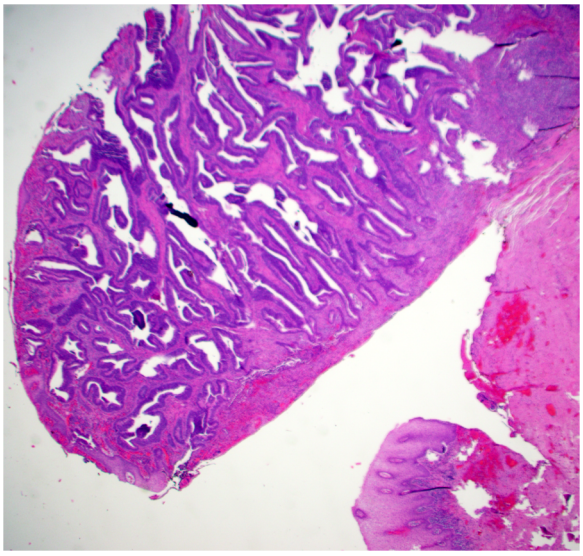

Fig. 4. Adenocarcinoma intestinal type. The tumor forms a polypoid mass on the surface with neoplastic glands similar to colonic type adenocarcinoma. Note the benign squamous epithelium of the vulva.

occurred in patients above the age of 40. The morphology of the cases was adenocarcinoma in situ ($n = 1$), CCC ($n = 5$) and adenocarcinoma NOS ($n = 4$) of which one case exhibited extensive mucinous features and located in a urethral diverticulum.[70]

Immunohistochemistry

Due to the rarity of urethral adenocarcinoma and the diversity of potential morphologic patterns, the results of the immunohistochemistry (IHC) are accordingly mixed. Mucin producing cell type adenocarcinomas are mostly positive for monoclonal CEA, CDX2, MUC2 and CK20, and are negative for CK7, PSA, prostate specific acid phosphatase (PSAP), and SATB2[9, 39, 42, 46]. One case has been reported to be positive for p16 although HPV was not detected by ISH.[9] Clear cell type tumors are negative for CEA, PSA, chromogranin and PSAP.[39, 42]

Prognosis and clinical outcome

Most patients with urethral adenocarcinoma present at an advanced stage with the tumor already extending to adjacent structures or to the regional lymph nodes. Tumors with clear cell morphology appears to behave slightly better than those of that are of the mucinous/columnar cell type.[15]

Key diagnostic points: adenocarcinoma of the terminal urethra

1 Mucinous/columnar type:

- Similar to endometroid or colonic adenocarcinomas
- Tubular/glandular, solid, cribriform, papillary, mucinous and signet ring features.
- Nuclei with mild to moderate atypia, prominent nucleoli and frequent mitotic and apoptotic figures.
- Eosinophilic cytoplasm with infrequent extracellular mucin

IHC

Positive: CEA, CDX2, MUC2 and CK20
Negative: PSA, PSAP, CK7, AMACR

1 Clear cell type

- Tubules (glands), cysts, small papillae and solid
- Clear to eosinophilic cytoplasm
- Nuclei with prominent nucleoli, hobnail, mild atypia and infrequent mitosis

Immunophenotype

Positive: no available data
Negative: PSA, PSAP, CEA

Extramammary Paget disease with invasive carcinoma

Definition

EMPD is an in-situ adenocarcinoma arising in the vulvar epidermis and which represents <3% of the malignant tumors of the vulva[19,.] An invasive component may be synchronously or metachronously identified in a subset of cases.[72-74] EMPD is comprehensively covered elsewhere in this issue, but this section will briefly address EMPD with an invasive component. Our survey of the literature suggests that invasive carcinoma arising from Paget disease is most likely the most commonly diagnosed primary glandular malignancy of the vulva.

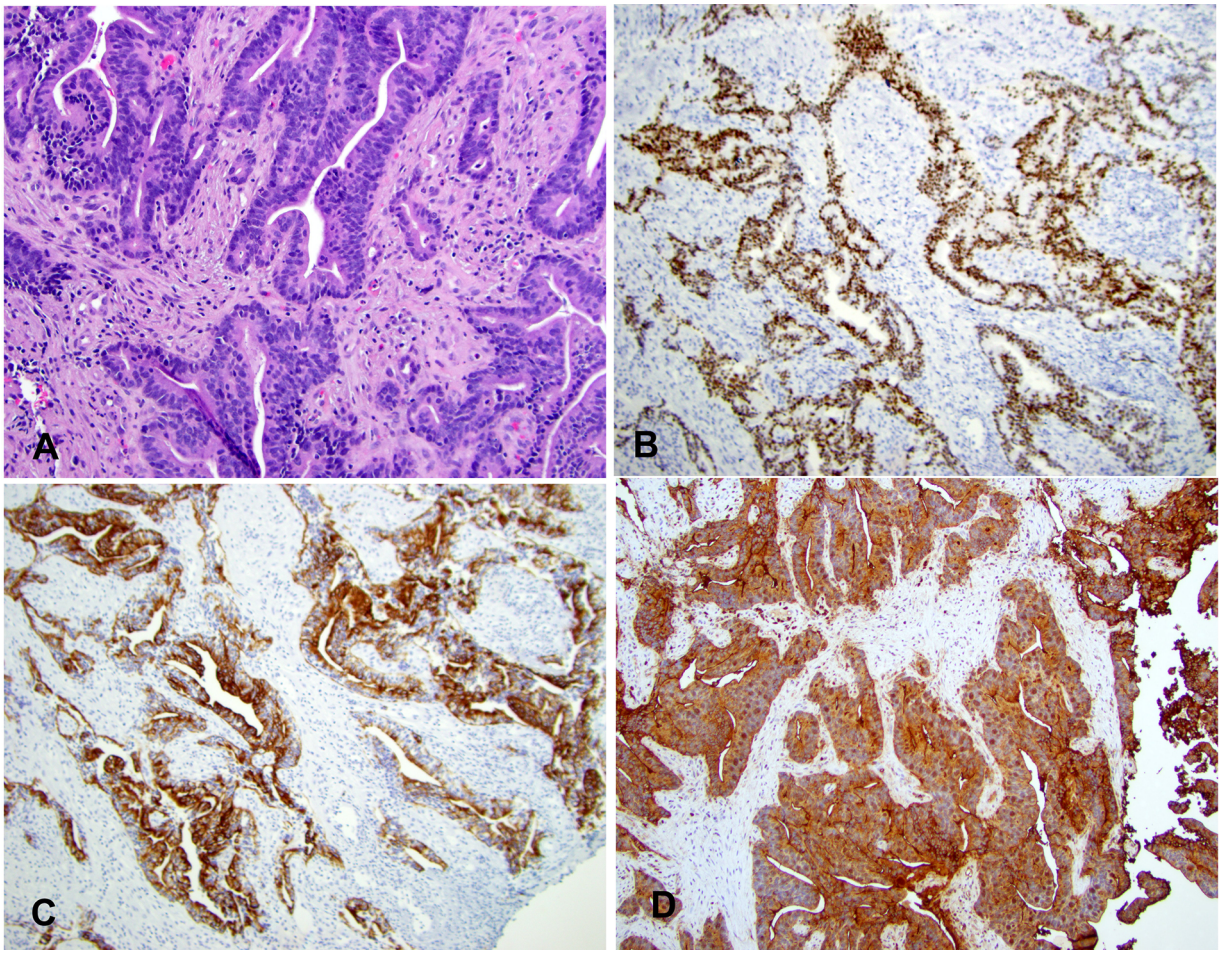

Fig. 5. A) Adenocarcinoma intestinal type. The tumor is composed of malignant glands morphologically similar to conventional colonic type adenocarcinoma (A). Tumor cells are positive for CDX2 (B), CK20 (C) and CEA-Polyclonal (D). B) Adenocarcinoma intestinal type positive for CDX2. C) Adenocarcinoma intestinal type positive for CK20. D) Adenocarcinoma intestinal type positive for CEA-Polyclonal.

Classification and clinical features

Primary vulvar EMPD occur predominantly in Caucasian females with a median age of 70–75 years, who present clinically with erythematous or white gray areas with scale formation mimicking eczema and/or itching.[19] EMPD is traditionally classified histogenetically into primary and secondary types, with the latter arising from regional sites such as the genitourinary or gastrointestinal tracts, and secondarily spreading to the vulvar. Primary EMPD are thought to arise *de novo* in the vulvar or related epithelium, although it is not uncommon for the patients to be diagnosed with separate, presumably unrelated cancers at extravulvar sites concurrent with, or following their diagnosis of EMPD.[1, 72] Primary vulvar EMPD is identical to its mammary homologue, but differs given that the former is not associated with an underlying invasive component in the majority of cases.[19, 75] Nonetheless, invasive carcinomas may be associated with EMPD in 7–12.7% of cases.[72-74] Approximately 2.9% of patients that are diagnosed and are managed for non-invasive EMPD will subsequently be found to have invasive disease.[1] Since most cases of invasive carcinoma associated with EMPD have a depth of stromal invasion that is ≤ 3 mm[72], the clinicopathologic presentations of these patients is largely similar to those of their counterparts without invasive disease. In one series, wherein most patients received post-excision adjuvant therapy, the mortality rate was 40% and the recurrence rate was 60%, with a mean time to first recurrence of 20 (range, 5–36) months.[73] However, most studies have shown that the risk of death when there is an invasive component in EMPD is strongly associated with the depth of invasion: 0–5% when the depth of invasion is ≤ 1 mm, and up to 29.1% when the depth is >1mm.[1]

Histopathology

The neoplastic cells of EMPD (Paget cells) spread individually as well as in groups and nests in the epidermis with skip lesions and occasional pseudo-glandular formation [Fig. 6]. The cytoplasm is abundant, pale, clear, basophilic or amphophilic. The nuclei are vesicular with prominent nucleoli, occasional hyperchromasia and multinucleation. Intracytoplasmic mucin with signet ring formation is not rare.[19, 76] Involvement of the skin adnexa (hair follicles, sebaceous glands, eccrine and apocrine sweat glands) is a common finding and should not be considered as an invasion.[10, 19] Foci of invasion are most commonly superficial. In one series of 5 cases where depth of invasion was known, they were listed as 2.5 mm, 2.5 mm, 1.3 mm, >1 mm and 4.5 mm[72]. The invasive carcinoma may display a variety of histologic patterns, including mammary-type adenocarcinomas, mucinous carcinomas, adenoid cystic carcinomas, or not infrequently, an unclassified, poorly differentiated carcinoma.[77, 78] Some adenocarcinomas that are identified in association with EMPD have no morphologically or immunophenotypically discernible relationship with the EMPD

TABLE 5
Clinicopathologic characteristics of representative reported cases of vulvar adenocarcinoma, intestinal type..

Reference	Age (y)	Symptoms	size (cm)	Site	Architecture	IHC	Lymph node met	follow up time (m)	outcome
Tiltman and Knutzen[57]	50	dyspareunia and discharge	2	periurethral	Moderately differentiated adenocarcinoma of colonic type	none	yes	12	Alive/NED
Kennedy and Majmudar[56]	54	painless mass	2	Left posterior	Well differentiated adenocarcinoma in continuity with the epidermis, large nuclei, prominent nucleoli, cytoplasmic mucin, underlying benign mucinous glands	CK+, CEA-	No	120	dead of unrelated cause
Kennedy and Majmudar[56]	63	painless mass	1.5	Posterior fourchette	well differentiated adenocarcinoma with minimal invasion of subcutaneous tissue, glands lined with large nuclei, prominent nucleoli, cytoplasmic vacuoles	na	No	48	Alive/NED
Ghamande et al[55]	67	spotting	1.7	vulva	Colonic type adenocarcinoma with mucinous features, associated villous adenoma	CEA+	no	17	Alive/NED
Willen at al[61]	57	polyp-like mass	1	Posterior vestibulum	Villous adenomatous type adenocarcinoma with goblet and endocrine cells	CK17+, Cam 5.2+, CEA-*P*+, CEA-M-,	no	26	Alive/NED
Zaidi and Conner[8]	43	vulvar discomfort, bleeding	1.4	right labium majus	Colonic type well to moderately differentiated adenocarcinoma	CEA+, p53+, CK+, ER-, PR-	no	18	Alive/NED
Rodriguez, et al[63]	69	nodule, pruritis, bleeding	1.5	right labium majus	Villoglandular growth pattern with thin fibrovascular cores lined by columnar cells with mild atypia and goblet cells	OC125+, CEA+, CK7+, OC19.9+, CK20+ (focal), ER-. PR-, chromogranin-	no	36	Alive/NED
Dube et al[64]	58	lump, discomfort	2	inferior labium majus	Well differentiated villoglandular adenocarcinoma of colonic type	CK7+, CK20+, ER-, PR-	no	16	Alive/NED
Dube et al[53]	64	vaginal discharge	0.7	posterior hymen	Villoglandular with no stromal invasion (in-situ lesion). The glands are lined with mildly atypical columnar cells with intracellular mucin, goblet cells	CK7+, CK20-, CEA+ (weak)	no	5	Alive/NED
Cormio et al[52]	59	mass, discomfort, burning	na	vulva	Well differentiated adenocarcinoma with mucin	CK7+, CK20 weak	yes after 36 m	54	DOD
	42	mass	1	vulva	mucinous carcinoma	CK7+, CK20 weak	no	39	Alive/NED
Karkouche et al[66]	31	painless mass resampling condyloma	na	fourchette	Tubule-villous adenomas in few nodules and complex glandular proliferation with focal cribriform pattern, moderate to severe atypia with high mitotic index similar to intramucosal adenocarcinoma of the colon.	CK20+, CK7-	no	15	Alive/NED
Sui et al[60]	43	pruritis, painless mass	1.5	perineal body	moderately differentiated mucinous adenocarcinoma	CK7+, CAM5.2+, p16-, ER-, PR-, GCDFP15-, CA125-, CK20-, Villin-, CA19–9-, TTF1-, NapsinA-	na	24	Alive/NED
Tepeoglu et al[58]	60	vulvar discomfort, bleeding	2	periurethral, left labium minus	Papillary adenocarcinoma of colonic type	CK20+, CEA-*P*+, CDX2+, CK7+ (focal), WT1-, GCDFP-15-	inguinal	38	Alive/NED
Lee et al[54]	64	mass, itching	3.5	right posterior labium majus	Well differentiated adenocarcinoma, focal papillary pattern, surface ulceration, intestinal type mucinous epithelium, hyperchromatic nuclei, goblet cells and intra and extra cellular mucin	CEA+, CK20+, CK7+, CDX2+, p53+, p16+	na	12	Alive/NED
He et al[68]	63	mass	2	Posterior fourchette	Well differentiated mucinous adenocarcinoma	CK20+, CDX2+, villin+, CEA+, CK7+ (focal), ER-, PR-, PAX8-, p16-, p53-	no	26	Alive/NED
Kurita et al[59]	63	papillary mass, bleeding	2	periurethral	Atypical glands, columnar epithelium, signet ring cells, mucinous background	CK20+, CDX2+, CK7-, GCDFP15-	no	12	Alive/NED
Kaltenecker et al[69]	53	mass, itching, discharge, pain	6	left labia majus	Villoglandular mucinous adenocarcinoma with necrosis	CD20+, CK7-, mCEA+, vimentin-, p53+	no	12	DOD

NED, no evidence of disease; DOD, dead of disease, DND, dead with no evidence of disease (unrelated cause).

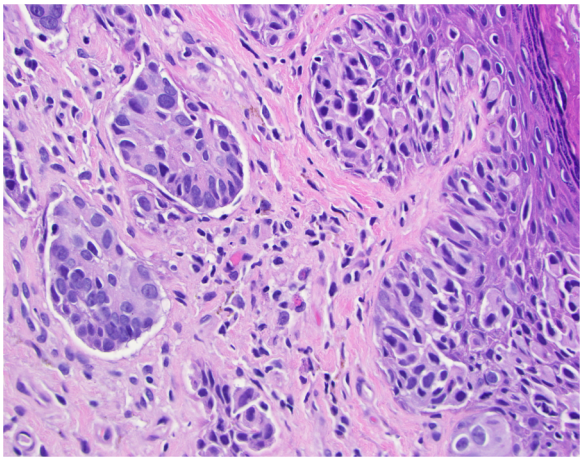

Fig. 6. Paget disease of the vulva with associated invasive component.

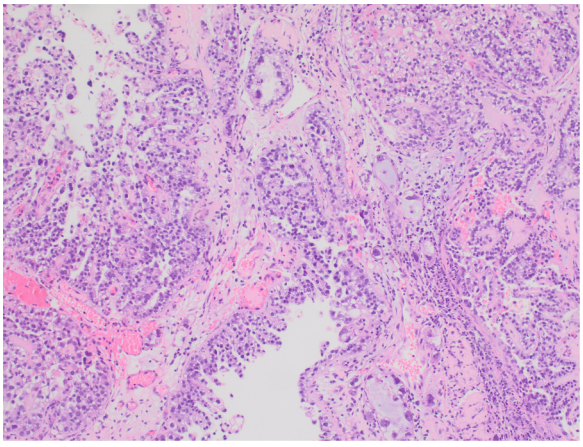

Fig. 7. Clear cell carcinoma showing characteristic cytoarchitectural patterns.

Clear cell carcinoma of the vulva

Definition

Primary CCC of the vulva with typical features of gyn tract CCC and with no clinicopathologic evidence of a similar tumor at extra vulvar sites, or other vulvar glands (e.g. Skene or Bartholin) .[7, 79-83]

Epidemiology and clinical presentation

Primary CCC of the vulva is extremely rare with approximately 8 reported patients that ranged in age from 36 to 70, with an average of 50 years. Most patients presented clinically with a painless mass or rarely with bleeding and pain.[6] Most of the cases reported are associated with vulvar endometriosis and/or an episiotomy scar.[7, 79-83] The entity is not separately included in the WHO classifications of vulvar glandular tumors.

Macroscopy

The tumors range in size from 1.8–10 cm with an average diameter of 5 cm. the tumors are dark to red, exophytic masses, with smooth outer surfaces, smooth borders. Cut surfaces are dark brown and solid.[6]

Histopathology

The tumors are morphologically identical to CCC arising in the ovary and endometrium with solid, tubulocystic and papillary

Table 6
Clinicopathologic characteristics of reported cases of primary vulvar clear cell carcinoma.

Reference	Age (y)	Symptoms	size (cm)	Site	Endometriosis	Pathological features	Lymph node met	distant met	treatment	follow up time (m)	outcome
Mesko et al[79]	57	NA	4	labia majora	yes	The carcinoma arose in the canal of Nuck in association with endometriosis in the superior aspect of the right labium majus	inguinal	skin, lung	excision and radiotherapy	24	AWD
Hitti et al[81]	43	NA	10	episiotomy scar	yes	CCC arose in association with endometriosis	inguinal	lung	chemoradiation	30	DOD
Bolis et al[80]	52	NA	3	labia majora	yes	CCC arose in association with endometriosis	unknown	unknown	excision	5	Alive/NED
Todd et al[82]	54	NA	3	episiotomy scar	yes	CCC in the perineum, many years after excision of a perineal endometrioma in an episiotomy scar	unknown	unknown	excision, radiotherapy	NA	NA
Kwon et al[83]	42	NA	2.5	episiotomy scar	na	CCC arose in association with endometriosis at the posterior commissure of the vagina at the site of an episiotomy	no	no	excision	10	Alive/NED
Han et al[84]	36	painless lump, pruritis	10	episiotomy scar	yes	Tubulo-cystic pattern with marked pleomorphism, clear cytoplasm, hobnail cells	no	no	excision, chemotherapy	6	Alive/NED
Buppasiri et al.[7]	46	lump and pain	7	labia majora	yes	Papillary growth, round cells, clear cytoplasm, pleomorphic nucleoli, NapsinA+	iliac and inguinal	no	chemotherapy	17	DOD
Kojima, et al.[6]	70	mass, bleeding	1.8	episiotomy scar	no	papillary and glandular, atypical cells, clear to eosinophilic cytoplasm, enlarged nuclei, prominent nucleoli *PAX8+, HNF-1β+, ER+, p16, CA125+, CD10-, GATA3-, PTEN-, PAX2-, ARID1A (retained), P53 (wild)	no	no		5	Alive/NED

NED, no evidence of disease; DOD, dead of disease, AWD, alive with disease; CCC, clear cell carcinoma, NA: Not available.

architectural patterns [Fig. 7]. The stroma shows hyalinization with variable mononuclear inflammatory cellular infiltration. The cytoplasm is clear or eosinophilic with atypical nuclei, hobnail like appearance and infrequent mitotic figures as we described in other gyn organs.[6, 7, 71, 79, 80] The tumors are usually associated with fibrosis due to previous episiotomy scars and endometriosis.[81-84]

Mutational analysis

Targeted mutational analysis of one case revealed no pathogenic mutations in commonly mutated genes e.g. *BRAF, EGFR, ERBB2, HRAS, KRAS, NRAS, PIK3CA, PTEN, CTNNB1*, and *TP53*[6].

Immunohistochemistry

Data is quite limited. However, in general, the reported cases were positive for Napsin-A,[7] PAX8, HNF-1β, CA125 and were negative for p16, ER, CD10, GATA3, PTEN, and PAX2. BAF-250a protein was retained and p53 showed wild type expression.[6]

Prognosis and clinical outcome

Too few cases have been reported to draw a definitive conclusion. Out of the seven cases with follow up data, four were alive with no evidence of disease, two were dead of disease after 17 and 30 months from the initial diagnosis and one was alive with disease.[6, 7, 79-81, 83, 84]

Table 6 summarizes the clinicopathologic features of published cases of vulvar CCC in the English literature.

Key diagnostic points: clear cell carcinoma

- Solid, Tubulo-cystic and papillary growth patterns.
- Clear or eosinophilic cytoplasm
- Atypical nuclei with hobnail like appearance
- Associated fibrosis due to episiotomy scars
- Endometriosis

Immunophenotype

Positive: Napsin-A, PAX8, HNF-1β, ER, CA125
Negative: p16, P53, CD10, GATA3, PTEN, PAX2

Adenocarcinoma, mammary gland type

Definition

Mammary gland type adenocarcinomas are group of malignant tumors that are morphologically similar to their counterparts that are primary in the breast.[78] "Mammary-like adenocarcinoma" is an acceptable diagnostic alternative term.

Epidemiology and clinical presentation

Adenocarcinoma, mammary gland type is a rare disease with less than 40 cases reported in the literature.[19] The tumors are almost restricted to the labia majora and appear as solitary masses ranging in size from 3 to 4 cm. The age range of the patients is wide (46–82 years) with an average age of 60 years. The disease may be associated with an EMPD.[85]

Histopathology

A variety of histotypes may be seen, including ductal, lobular, mucinous, secretory, tubulo-lobular,[19,81,82] However, most reported cases are of ductal phenotype. An associated ductal carcinoma in situ is occasionally present.[86] Diagnostic criteria that are applicable for comparable tumors in the breast should be applied,[87] as the tumors at these sites appear to show identical morphologic, IHC and molecular profiles depending on the specific histotype.[87-89]

Prognosis and clinical outcome

As a group, these carcinomas may behave more aggressively than their counterparts in the breast, with an estimated 60% metastatic rate to regional lymph nodes. Rare cases of distant metastasis have been reported. Radical or hemi-vulvectomy is the treatment of choice in most cases.[90]

Carcinoma of sweat gland origin

Carcinomas of sweat gland origin encompass a histologically variable group of malignancies of the cutaneous sweat gland type. These rare tumors include those that are reported as sweat gland adenocarcinoma, apocrine adenocarcinoma, eccrine adenocarcinoma; porocarcinoma NOS, adenoid cystic carcinoma as well as other cutaneous type adnexal tumors.[11, 14, 91-96] Patients with carcinoma of sweat gland origin are generally in the postmenopausal or late perimenopausal years, and present with a vulvar mass. They are diagnosed using the same histologic criteria as are applicable in their cutaneous counterparts for each histotype.[97] Given the variability of the constituent histotypes, prognostic factors are difficult to determine in this class of tumors. Nonetheless, in one series, 4 (36%) of 11 patients ultimately died of tumor progression.[93]

HPV-related vulvar adenocarcinomas

Most adenocarcinomas of the vulva have been insufficiently studied to determine whether they have a relationship with the HPV. Recently, a series of 2 cases of villoglandular adenocarcinoma of the vulva morphologically similar to mucin depleted (pseudo-endometrioid) cervical adenocarcinoma have been reported.[98] One case (in a 43-year-old) was associated with high grade squamous intraepithelial lesion of the vulva in which HPV 16 has been detected by in situ hybridization. The other case was diagnosed in a 38-year-old female and was not tested for HPV by in situ hybridization (ISH) or PCR techniques. Both cases strongly and diffusely expressed p16 by IHC.[98] The other case reported to be HPV related vulvar adenocarcinoma is a case report of vulvar in situ adenocarcinoma that ostensibly originated from the minor vestibular glands and in which HPV18 was detected by ISH.[37] One case of a Skene gland adenocarcinoma was strongly immunoreactive for p16, however, HPV was not detected by ISH.[9] A few cases of Bartholin gland adenocarcinoma tested for HPV either by p16 IHC stain or by HPV molecular testing reportedly tested negative.[30, 34-36] However, Bartholin gland squamous cell carcinoma are thought to be related to HPV,[30] therefore the issue requires additional study.

Adenocarcinoma, NOS

The close proximity of the various vulvar and related structures to each other may pose a challenge for the pathologist in determining the primary site of a given malignancy, especially for large, advanced stage tumors, and some tumors may ultimately be unclassifiable with respect to point of origin. Nonetheless, awareness of vulvar anatomy and histology, and paying close attention to preoperative imaging, gross, and microscopic findings may allow such a point of origin to be assigned. Most tumors, including CCC, adenocarcinoma of skene gland origin,

adenocarcinoma of the intestinal type, mammary-like adenocarcinoma and adenocarcinoma of sweat gland origin have such distinctive features that an informed opinion can be rendered on their likely point of origin. However, some tumors, even when their point of origin is clear, have non-specific morphologic and immunophenotypic features that do not fit into the aforementioned nosologic scheme. Most commonly, they are comprised of poorly differentiated glands without a clear-cut phenotype. Each of the entities that have been discussed in this review should be systematically excluded using the diagnostic modalities that are available in a given practice setting. Cases that cannot be further classified after this analysis may be designated "*adenocarcinoma, not otherwise specified*". In one population-based analysis, 22% of all primary vulvar glandular malignancies were classified as adenocarcinoma without further specification.[1] Whether these cases represent a clinicopathologically distinct group is unclear.

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