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Intestinal-type primary vaginal adenocarcinoma. Review of the literature with report of a case: from diagnosis to management

M. Franchi[1], S. Garzon[1], A. Caliò[2], P. C. Zorzato[1], M. Bosco[1], J. Casarin[3], A. Festi[1], A. Cromi[3], F. Ghezzi[3], S. Uccella[1]

[1]Department of Obstetrics and Gynaecology, AOUI Verona, University of Verona, Verona, Italy
[2] Department of Diagnostic and Public Health, AOUI Verona, University of Verona, Verona, Italy
[3] Department of Obstetrics and Gynaecology, Filippo Del Ponte Hospital, University of Insubria, Varese, Italy

ABSTRACT

Background. Intestinal-type primary vaginal adenocarcinoma is an extremely rare neoplasm, and very few cases are reported in the literature. The differential diagnosis of an intestinal-type adenocarcinoma at vaginal level (an organ almost free from glandular tissue) is particularly challenging given the anatomical complexity and different embryologic derivations of organs in this district. The main diagnostic issue consists in determining whether the vaginal neoplasm is primary, or it is a metastatic disease that extends to the vagina. A fundamental role in guiding diagnostic and therapeutic pathways is played by the pathologist.
Objective. This study is a systematic review of the literature in order to summarize and analyze different diagnostic and therapeutic approaches chosen for every single case of intestinal-type primary vaginal adenocarcinoma described. Moreover, we report the case diagnosed and managed at our center.
Methods. PubMed, ClinicalTrials.gov, Scopus, and Web of Science databases were systematically searched for records from January 1st, 1989, to December 1st, 2019.
Results. Overall, 23 cases of intestinal-type primary vaginal adenocarcinoma are reported in the literature. This tumor often presents with atypical vaginal discharge (64.7% of cases) and it affects mainly the posterior wall (54.5%) and the lower third (83.3%) of the vagina. The average age at its presentation is 53.6 years. Diagnostic workup looks at ruling out possible primary distant sources of the disease and colonoscopy is often performed. The immunohistochemical profile of the lesion has a major role, and the key markers investigated are CEA, CK20, CK7, and CDX2. Most patients are diagnosed with early-stage disease (85% of patients FIGO I) and the lesion average size is 3 cm. Of 18 patients with available data, a surgical approach was adopted in 8 cases. Ten patients underwent radiotherapy.

SOMMARIO

Contesto. L'adenocarcinoma vaginale primario di tipo intestinale è una neoplasia estremamente rara con pochissimi casi riportati in letteratura. La diagnosi differenziale per l'adenocarcinoma di tipo intestinale a livello vaginale (organo pressoché privo di tessuto ghiandolare) è particolarmente impegnativa data la complessità anatomica e le diverse derivazioni embriologiche degli organi di questo distretto. Il principale problema diagnostico consiste nel determinare se la neoplasia vaginale è primaria o è una malattia metastatica che si estende alla vagina, e a questo scopo, un ruolo fondamentale, nella guida dei percorsi diagnostici e terapeutici, è svolto dal patologo.
Obiettivo. Questo studio è una revisione sistematica della letteratura al fine di riassumere e analizzare i diversi approcci diagnostici e terapeutici scelti per ogni singolo caso descritto di adenocarcinoma vaginale primario di tipo intestinale. Segnaliamo inoltre un caso diagnosticato e gestito presso il nostro centro.
Metodi. Una ricerca sistematica della letteratura è stata condotta nei database PubMed, ClinicalTrials.gov, Scopus, e Web of Science dall'1 gennaio 1989 all'1 dicembre 2019.
Risultati. In letteratura sono riportati 23 casi di adenocarcinoma vaginale primario di tipo intestinale. Questo tumore si presenta spesso con perdite vaginali atipiche (64.7% dei casi) e colpisce principalmente la parete posteriore (54.5%) e il terzo inferiore (83.3%) della vagina. L'età media alla sua presentazione è di 53.6 anni. L'iter diagnostico parte esaminando le possibili fonti primarie della malattia e viene spesso eseguita la colonscopia. Il profilo immunoistochimico della lesione ha un ruolo importante e gli indicatori chiave studiati sono CEA, CK20, CK7 e CDX2. Alla maggior parte dei pazienti viene diagnosticata una malattia allo stadio iniziale (85% dei pazienti FIGO I) e la dimensione media della lesione è di 3 cm. Dei 18 pazienti con dati

Patients managed surgically, compared with those who underwent radiotherapy, were younger and with a smaller mass at diagnosis, although differences were not statistically significant. Treatment options depended on clinical evaluation, patient's comorbidities, and patient's preferences.
Conclusions. Intestinal-type primary vaginal adenocarcinoma is a rare tumor, and no specific guidelines addressing this disease are available. Ruling out a metastatic disease at the vaginal level is fundamental, and the pathologist plays a major role in the differential diagnosis. A multidisciplinary approach to the disease is of fundamental importance and the treatment choice should be tailored considering the patient's comorbidities and the holistic evaluation of the case.

disponibili, in 8 casi è stato adottato un approccio chirurgico. Dieci pazienti sono stati sottoposti a radioterapia. I pazienti gestiti chirurgicamente, rispetto a quelli sottoposti a radioterapia, erano più giovani e con una massa inferiore alla diagnosi, sebbene le differenze non fossero statisticamente significative. Le opzioni di trattamento dipendevano dalla valutazione clinica, dalle comorbilità del paziente e dalle preferenze del paziente.
Conclusioni. L'adenocarcinoma vaginale primitivo di tipo intestinale è un tumore raro e non sono disponibili linee guida specifiche per affrontare questa malattia. È fondamentale escludere una malattia metastatica a livello vaginale e il patologo svolge un ruolo importante nella diagnosi differenziale. Un approccio multidisciplinare alla malattia è di fondamentale importanza e la scelta del trattamento deve essere adattata alle comorbilità del paziente e ad una valutazione olistica del caso.

Corresponding Author: Simone Garzon
E-mail: simone.garzon@yahoo.it

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Key words
Primary vaginal adenocarcinoma; immunohistochemistry; Skene glands; intestinal type; systematic review.

INTRODUCTION

Primary vaginal carcinoma is a rare disease and accounts for about 3% of all female genital tract neoplasms (1, 2). Of note, 80% of all vaginal malignancies are secondary (3, 4).
HPV-related squamous cell carcinoma is the most common type of vaginal cancer and accounts for 83.4% of all primary vaginal malignancies (5).
Vaginal adenocarcinomas are sporadic, 9.3% of all vaginal tumors. A positive history of in utero exposure to diethylstilbestrol (DES) is a known risk factor for vaginal adenocarcinoma (6). There is also a group of primary vaginal adenocarcinomas not associated with *in utero* DES exposure. Given the complexity of embryologic vaginal origin, many theories have been postulated on the origin of this type of tumor in a tissue lacking glands (7). Among non-DES-related adenocarcinomas, there is also an extremely rare variant called "intestinal-type" for its histological characteristics (8).
When a vaginal adenocarcinoma is diagnosed, it is initially mandatory to rule out metastatic disease, and this is particularly true for intestinal-type adenocarcinomas. Primary adenocarcinoma of the gastrointestinal tract is, indeed, the second most common tumor with secondary involvement of the vagina (9). Obviously, a correct diagnosis at the primary instance has dramatic importance on the therapeutic approach and, consequently, on prognosis. A primary vaginal tumor is mainly treated with radiochemotherapy, and the surgical approach is applied only in selected cases (10, 11). On the other hand, the management of a metastatic tumor follows the guidelines of the primary disease.
The diagnosis of an intestinal-type primary adenocarcinoma requires a multidisciplinary approach where the pathologist plays a key role (1). Despite the involvement of a dedicated pathologist, the diagnosis of this histological subtype is still challenging.
Herein we report a case of primary intestinal-type adenocarcinoma of the vagina diagnosed at our Gynaecology Oncology department. Given the complexity of the case, we also systematically reviewed the available literature.

Clinical case

A 62-year-old woman was referred to the Gynecologic Oncology Unit of the AOUI of Verona after an incidental finding of a 49 × 36 mm hyperechoic pelvic mass at abdominal ultrasound. The patient was affected by renal failure for stage V chronic

kidney disease, and she had a right pelvic kidney transplanted ten years earlier.

At the gynecological examination, the lesion involved the upper third of the anterior vaginal wall, with a strong suspicion of bladder trigone involvement. At the pelvic magnetic resonance, a clear cleavage plane between the vaginal mass and the bladder was not identified. Cervix and vulva were free of disease. The patient also underwent a positron emission tomography-computed tomography (PET-CT) scan, which excluded disease at sites other than the vagina.

During the cystoscopy, the urethra appeared regular, and the bladder showed bullous edema at the trigone. Biopsies of the bladder epithelium were negative for malignancy.

A vaginal biopsy was performed. In the specimen, small neoplastic emboli of carcinoma immunohistochemically positive for CDX2 and CK20 were found, ruling out a neoplasm of intestinal origin. The main clinical suspicion was of an intestinal-type primary vaginal tumor (**figure 1 a**).

Considering the patients' comorbidities and the risk linked to pelvic radio therapy due to the presence of the pelvic kidney, the patient was deemed eligible for surgical treatment.

She underwent anterior pelvic exenteration with type C2 radical hysterectomy (Querleu-Morrow classification), bilateral salpingo-oophorectomy, radical cystectomy, infralevatory vaginectomy, iliac and obturator lymphadenectomy, ileo-ureter-neocystostomy with the creation of a vaginal flap.

The gross examination showed a lesion with a maximum diameter of 6.5 cm fully infiltrating the vaginal and urethral wall, involving the external urethral meatus with free margins less than 1 mm. The lesion infiltrated the bladder wall reaching the muscular layer but not the epithelium. The left parametrium was infiltrated as well. Ureters were free from lesions. The tumor was pathologically staged as FIGO III. Histologically, the tumor was an undifferentiated adenocarcinoma with extensive necrosis (**figure 1 b**). The immunophenotypic profile confirmed the intestinal differentiation and excluded the urothelial or neuroendocrine carcinoma (**table I, figure 1 c, d**), and a possible origin from Skene glands was finally considered.

The woman underwent a PET-CT scan one month postoperatively, showing the progression of the disease. After collegial discussion, the multidisciplinary oncologic group decided on palliative care only. A month later, the patient died.

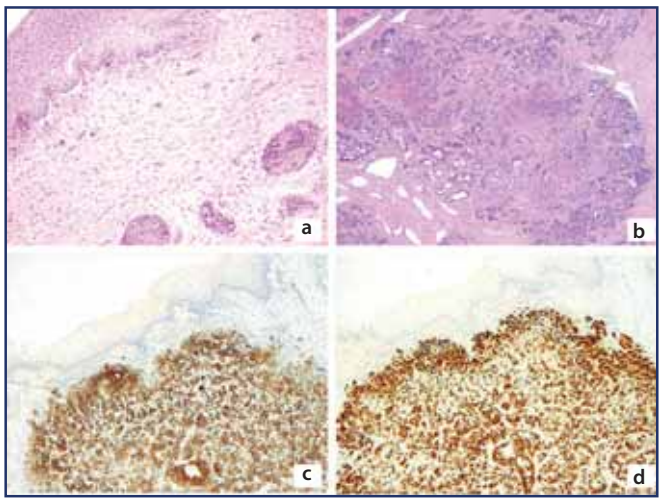

Figure 1. *The vaginal biopsy revealed small neoplastic emboli of carcinoma (a). After the resection, an undifferentiated adenocarcinoma with extensive necrosis was observed (b), immunohistochemically positive for cytokeratin 20 (c) and CDX2 (d).*

METHODS

This review was performed according to the PRISMA statement and was registered in the PROSPERO register. A reference librarian with expertise in electronic search strategies for systematic reviews conducted the literature search under a senior gynecologist (SU). PubMed, ClinicalTrials.gov, Scopus, and Web of Science databases were systematically searched for records from January 1st, 1989, to December 1st, 2019. The following MESH search terms were used: vaginal, primary, adenocarcinoma, intestinal, female, urethral, Skene, Skene gland, immunohistochemistry, immunohistochemical. The electronic search was followed up with a secondary hand search of the references of the identified articles. Every article identified was evaluated independently by two researchers (PCZ, MB). Disagreements were resolved by reexamining the article in question discussing it with the senior

Table I. *Patient immunohistochemical profile.*

	POS	NEG
Biopsy	**CK20; CDX2**	**CK7; PSA;** GATA3; p40 poli; PAX8 (BC12); ER; Synaptophysin clone 27g12.
Definitive	**CK20; CDX2; AMACR**	**CK7; PSA;** CK 5 (XM26); Chromogranin A (DAK-A3); DeltaN-p63 (p40); PSAP; GATA3; PAX8; AR; ER; S100P

CK: cytokeratin; ER: estrogen receptor; AR: androgen receptor; PSA: prostate specific antigen; PSAP: prostatic specific acid phosphatase.

authors (MF, SU). We included studies in English, French, and Spanish. The exclusion criteria were primary vaginal cancers other than intestinal-type phenotype, metastatic vaginal cancer, benign intestinal-type vaginal lesions, DES-related cases.
From each case, we evaluated the following aspects:

- clinical presentation;
- diagnostic work-up;
- histologic diagnosis/himmunophenotypic profile;
- stage of the disease;
- treatment;
- surgical margins;
- survival.

Main review outcomes:

- to summarize the available evidence on intestinal-type primary vaginal cancer;
- to identify a diagnostic tool to guide the diagnostic process;
- to evaluate the therapeutic approach adopted in each case given the lack of guidelines;
- to understand if this specific variant, regardless of the stage, has a worse or better prognosis than the classic variants.

Data are presented as absolute numbers (percentage). The Mann-Whitney nonparametric test was applied to compare the differences between the two groups. The significance level was set at $\alpha = 0.05$, and the test was 2-tailed. No institutional review board approval was required because the present study deals with already existing data. The legally entitled person to give the consent provided consent for the anonymized publication of the case data and images. All authors participated in the search strategy design and in that of the inclusion and exclusion criteria.

RESULTS

The search strategy provided a total of 342 citations. Of them, 266 were discarded because after reviewing the abstract, it appeared evident that these papers did not meet the criteria. The 76 remaining citations were screened for eligibility, and, the full text of 50 citations was examined in more detail (**figure 2**). After a full-text search, only 13 studies describing a total of 23 cases of intestinal-type primitive vaginal cancer were identified for inclusion in the review. Studies and patients' characteristics are summarized in **table II**.

Clinical presentation

The average age at symptoms onset was 53.6 years (range 32-86). Atypical vaginal discharge was the most common clinical presentation, observed in 64.7% (11/17) of cases. Nine patients presented with vaginal bleeding (52.9%), while the other 2 cases reported foul-smelling vaginal discharge. In 11.8% (2/17) of cases, the onset symptom was hematuria (12). Only one patient was diagnosed incidentally during a routine gynaecological examination. At diagnosis, the lesion mean size was 3 cm (range 0.8-7 cm). In 54.5% of patients (12/22), the lesion developed from the posterior vaginal wall, in 36.4% from the anterior wall (8/22), while in only 2 cases, the lesion was identified on the lateral wall. The lower third of the vagina was involved in 83.3% of cases (in 15 out of 18 patients), representing the most frequently involved site. No cases of tumor extending to the vulva at the time of diagnosis were reported.

Diagnostic workup

In 56.5% (13/23) of reports, the authors did not report complete information regarding preoperative investigations. All the patients underwent a transvaginal ultrasound scan and biopsy of the lesion. Given the intestinal phenotype, 80% of patients underwent colonoscopy (8 out of 10). Other diagnostic studies included: computed tomography (CT) scan in 5 patients, magnetic resonance imaging (MRI) in 4 cases, cystoscopy in 4 cases, chest radiography, PET, and transrectal ultrasound in 2 cases, barium enema, mammography, and abdominal ultrasound in 1 case each.

Immunophenotype

The most frequently evaluated immunohistochemical markers were CEA (in 9 patients), CK20, CK7 (each one assessed in 8 patients), and CDX2 (in 4 patients). **Table III** summarizes the immunohistochemical profile of the cases.

Staging

Primary vaginal carcinoma is staged according to the 2009 FIGO staging. An early-stage tumor (stage I and II) is confined to the pelvis, while advanced disease (stage III and IV) goes beyond the pelvic wall (10).
The majority of patients were diagnosed with an early-stage tumor (FIGO I stage in 17 of the patients). A

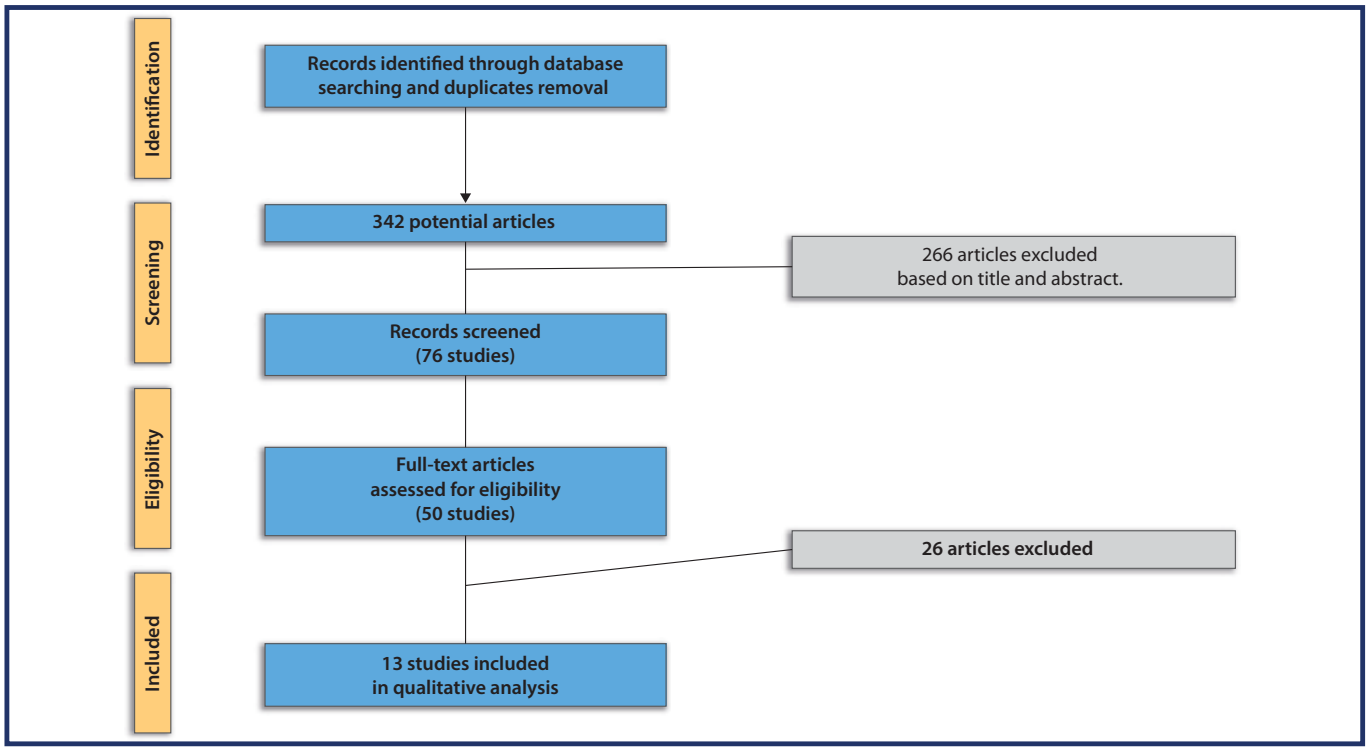

Figure 2. *Flow-chart of the Literature search.*

FIGO II tumor was encountered only in one patient, and only two patients staged FIGO III at diagnosis. No FIGO IV stage was found. Only two patients presented with metastatic disease, both of them at the nodal level. In one case, para-aortic nodes were involved, while in the other case, a bilateral inguinal node spread was found. Concerning surgical margins, data are available only for 5 of the 23 patients. Negative margins are described in 4 cases (7, 13-15) and positive margins in only 1 case (16). There has been no case of up-staging after surgery.

Management

Patients management was surgical in 8 cases, while 10 patients underwent radiotherapy.
Information regarding the type of management lacks in 5 reports. The average age of patients was 50.2 years among those managed surgically and 53.7 years among patients managed with radiotherapy ($p = 0.6$). Exclusive radiotherapy was the management of choice in 9 cases. One patient underwent concomitant radiochemotherapy (17).
Tumor size in patients managed surgically was smaller (2.4 cm on average) than in patients who underwent radiotherapy (4.1 cm on average). This difference is not statistically significant ($p = 0.12$).
A total vaginal removal along with hysterectomy + adnexectomy was reported in 2 patients after radiotherapy (15, 18). In one case, a residual mass was found, and the excision of the mass was chosen (17). Driss *et al.* (19) report a case managed with primary radiotherapy consisting of external beam radiation associated with interstitial radiotherapy. After three months, this patient was deemed eligible for anterior exenteration because of a peri-urethral recurrence, but she refused.
In 2 cases, the surgical approach consisted of a vaginectomy. In both cases, total vaginectomy and hysterectomy were performed, being impossible a total vaginectomy without concomitant hysterectomy; only in one case bilateral adnexectomy was additionally performed (18). In the other 2 cases, local excision of the lesion was chosen (associated with adnexectomy and omentectomy in one case (7, 18).
One case (stage FIGO II), underwent infra-levatorial total exenteration (11) while a second case, staged FIGO I, underwent anterior exenteration (14). Both these radical surgical approaches were decided only after a thorough discussion with the patient.
Two patients were managed with an anterior exenteration (in one of these, the disease was staged as FIGO I, in the other, staging data are lacking).
Only one case had an incidental diagnosis of vaginal mass encountered during a diagnostic work-up for postmenopausal vaginal bleeding. The approach, in this case, was a local wide resection followed by adjuvant radiotherapy and chemo-

Table II. *Characteristics of identified studies and patients.*

Author /year	Country	Age (y)	Symptoms	Site		Size (cm)	Diagnostic tools	Primary treatment		Staging		FU (m)
Fukushima (1986)	Japan	32		Lateral wall	lower	3		Radiationtx			Relapse	12
Fox (1988)	UK	35		Anterior wall		5		Surgery	Anterior Exenteration		NED	1,5
Yaghsezian (1992)	USA	52		Posterior wall	lower	1		Radiationtx		FIGO I	Relapse	3
Nagar (1999)	Dublin	36	VB	Anterior wall	upper		Colonoscopy; MRI	Surgery	Anterior Exenteration	FIGO I		
Heller (2000)	USA	55	VB	Anterior wall	lower	7	Colonoscopy; cystoscopy	Radiationtx + Chtx		FIGOI		
Heller (2000)	USA	52	VL	Anterior wall	lower	2.5	Colonoscopy; cystoscopy; CT	Radiationtx		FIGOI	NED	60
Mudhar (2001)	UK	56	VB	Posterior wall	lower	1.5	Colonoscopy	Surgery	Local excision; SOB; Omentectomy	FIGO I	NED	12
Saitoh (2005)	Japan	44	mass	Anterior wall	lower	4	CT; MRI	Radiationtx		FIGO I		12
Tjalma (2006)	Belgium	55	VB	Posterior wall	middle	4	Colonoscopy; US; MRI	Surgery	Total infralevatory exenteration	FIGO II	NED	20
Ditto (2007)	Italy	53	no	Posterior wall	lower	2	Colonoscopy; CT; PET	Surgery	Wedge resection	FIGO I	NED	32
Driss (2007)	Tunisia	70	hematuria	Anterior wall	lower	4	Colonoscopy; cystoscopy; US	Radiationtx			Relapse	3
Laalim (2013)	Marocco	46	VL	Posterior wall	lower	5	Colonoscopy; US; CT; MRI	Radiationtx		FIGO III	Relapse	24
Staats (2014)	Canada	36	VB	Posterior wall				Surgery	TA; Vaginectomy	FIGO I		
Staats (2014)	Canada	52	VB	Anterior wall						FIGO I		
Staats (2014)	Canada	51	mass	Lateral wall	middle	1				FIGO III	NED	24
Staats (2014)	Canada	78	mass	Posterior wall	lower	1.5				FIGO I		
Staats (2014)	Canada	86	hematuria	Posterior wall	lower			Radiationtx		FIGO I		
Staats (2014)	Canada	71		Posterior wall	lower	0.8				FIGO I		
Staats (2014)	Canada	51		Posterior wall	lower	0.9		Surgery	Local excision	FIGO I	NED	84
Staats (2014)	Canada	80	VB	Posterior wall	lower	1.5		Surgery	Vaginectomy	FIGO I		
Staats (2014)	Canada	60		Anterior wall				Radiationtx		FIGO I		
Staats (2014)	Canada	43	VB							FIGO I	DOD	12
Aloy (2019)	Nigeria	40	VB	Posterior wall	lower	7	CT	Radiationtx		FIGO I	NED	10
Franchi (current case)	Italy	62	mass	Anterior wall	upper	6.5	Cystoscopy; CT; PET	Surgery	Anterior Exenteration	FIGOIII	DOD	1

VB: vaginal bleeding; VL: vaginal loss; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; Tx: therapy; SOB: Salpingo-oophorectomy; TA: total abdominal hysterectomy; missed: not available; NED: no evidence of disease; DOD: death of disease; y: years; m: months.

Table III. *Immunohistochemical profile of the cases.*

	CK20	CK7	CDX2	CEA	ER	PR	PSA	PSAP	AMACR	CA125	CA153	p53	p16	villin	mucin	GATA3	PAX8
Heller (2000)				pos			neg	neg									
Heller (2000)				pos			neg	neg									
Mudhar (2001)	pos	neg		pos											pos		
Saitoh (2005)				neg								neg					
Tjalma (2006)	pos	pos		pos	neg	neg					pos	pos					
Ditto (2007)	pos	neg	pos														
Driss (2007)	pos	neg		pos													
Laalim (2013)	pos	neg															
Staats (2014)	30%	neg	pos	pos	neg					neg			5%	neg			
Staats (2014)	70%	30%	pos	pos	neg								5%				
Staats (2014)	pos	30%	pos	pos	neg					10%							
Franchi (Current Case)	pos	neg	pos	neg	neg	neg		neg	pos							neg	neg

PSAP: prostatic specific acid phosphatase; PSA: prostate specific antigen; AMACR: Alpha methyacyl CoA racemase.

therapy (16). This is the only case where the patient underwent adjuvant therapy because of positive surgical margins.
In a second case, adjuvant chemotherapy was added because of the evidence of bulky lymph nodes at diagnosis (15). This despite a tumor staged as pT-0N0M0 at definitive pathologic specimen analysis.

Follow-up

Data on follow-up are not reported in many cases (10 out of 23 cases), and when available, they are not standardized. The median follow-up was 12 months (range 1.5-84 months). In 5 out of 13 (38.4%) cases followed up, a recurrence was documented at different times (range 3-24 months). Eight patients were declared free from the disease on the occasion of the last follow-up visit. Since the incompleteness of the data, we did not perform an analysis of follow-up data.

DISCUSSION

Intestinal-type primary vaginal adenocarcinoma is an extremely rare neoplasm, and very few cases are reported in the literature. Symptoms are not specific. The most common clinical presentation is vaginal bleeding (52.9%), which is the most frequently encountered sign at the diagnosis of a gynecological neoplasm. This tumor may develop from both the anterior and posterior vaginal walls, but more regularly is identified in the lower third of the vagina (83.3%) without extending to the vulva and surrounding organs at the time of diagnosis.
In this review, most of the included cases were at an early stage (85% of patients had FIGO stage I tumors), and only two cases had lymph node metastasis at diagnosis (15, 18). Two cases presented with urinary symptoms (hematuria), while no presentation with gastrointestinal symptoms was reported. The mean age at diagnosis was 53.6 years, so it seems that this tumor presents at a younger age compared to vaginal squamous cell carcinoma, the most common histologic type of vaginal cancer, which usually peaks around 60 years, although the disease is seen occasionally in women in their 20 s and 30 s (20, 21).
The main diagnostic issue consists of determining whether the vaginal neoplasm is primary or a metastatic disease that extends to the vagina. Different diagnostic tools have been used by various authors, such as CT, MRI, PET, and colonoscopy.

The latter, used in 80% of cases, appeared to be the most conclusive.

Radiation therapy is the treatment of choice for most patients with vaginal cancer, even in early-stage tumors (4). Surgery may be an alternative approach for tumors of the posterior wall involving the upper third of the vagina, or in particular conditions such as patients with particular anatomical conditions, advanced stages, fistulas, or relapses.

Eight (44.4%) out of 18 patients with available data underwent surgery. Patients treated with a surgical approach tend to be younger (average age 52 versus 58 years in the radiotherapy group) and tumors surgically treated appear generally smaller (1.4 cm versus 3.2 cm). These differences are not statistically significant. In 6 out of the 8 surgically managed cases, the tumor was on the posterior vaginal wall with an average size of 1.9 cm.

Considering patients with advanced disease (3/20, 15%), a total infralevatory exenteration with vulvectomy was performed in a patient with stage II disease (13), and one of the two patients staged FIGO III (bilateral involvement of the inguinal lymph nodes) underwent radiochemotherapy followed by vulvectomy with vaginectomy and inguinal lymphadenectomy (15). No data are available about treatment for the second case, staged FIGO III.

Looking at patients managed with ultra-radical surgery (5/18, 27.7%), this approach was adopted in one case of extravaginal disease (FIGO II) (13) and in 3 cases of disease staged FIGOI (14, 18). An ultra-radical approach has allowed not to use of adjuvant therapy. Women treated with ultra-radical surgery had lesions with size > 2 cm (mean size 3.5 cm, range 1.5-5 cm).

We cannot draw conclusions about the prognosis because the follow-up data are incomplete and not systematically collected. However, during follow-up, no evidence of disease was reported in 5 (62.5%) out of the 8 patients surgically managed, while recurrence was detected in 4 (40%) out of the 10 patients treated with radiotherapy. Data are not available for 3 patients of the surgery group and 2 patients of the radiotherapy group. Data from the literature show that this type of primary vaginal tumor has a poor prognosis with an increased risk of local and distant metastases (10). A review of 26 women with non-DES-related vaginal cancer at the MD Anderson Cancer Center found an overall five-year survival of 34% (22).

Immunohistochemical analysis in this rare tumor plays an essential role since it helps to identify the origin of the tumoral cells. Cytokeratin 20 (CK20) is a low-molecular-weight cytokeratin expressed in several tumors, including colorectal carcinomas and urothelial carcinoma. CDX2 is a nuclear transcription factor expressed in intestinal-type adenocarcinoma that is more specific than CK20 (13).

Cytokeratin 7 (CK7) is a type II keratin of simple nonkeratinizing epithelia. It is expressed in the simple, pseudostratified, and ductal epithelium, mesothelium, and urothelium and generally is observed (with some variation) in the adenocarcinoma of lung, breast, thyroid, endometrium, cervix, ovary, salivary gland, upper GI tract, and urothelial carcinoma. At the same time, it is generally negative in colorectal carcinoma. A $CK7^+$ and $CK20^+$ profile is often found in urothelial-derived carcinoma (23). Instead, $CK7^+$ but $CK20^-$ usually favors a carcinoma from endometrium, lung, ovary, breast, thyroid, and salivary glands. The co-expression of both CK20 and CDX2, in the absence of CK7, instead indicates a carcinoma with intestinal differentiation, mainly colon cancer (24).

Markers such as progesterone receptor (PR), estrogen receptor (ER), and PAX8 are often used to evaluate the possibility of neoplasia of gynecological origin (25).

Prostate-specific antigen (PSA) search is performed to investigate cancers originating from the Skene glands. These glands are historically considered the female analog of the prostate in males (for similar structure and PSA production) (26). From more recent works, however, it emerged that positive PSA is not necessary to confirm that a tumor originates from Skene glands (27).

Along with PSA expression, an alpha-methyl acyl CoA racemase (AMACR) stain was performed. This cytoplasmic immunohistochemical staining is positive in prostatic adenocarcinoma, and it is sensitive (82-100%) and relatively specific (70-100%) in distinguishing prostate carcinoma from benign prostate (28). Based on the available literature, this marker is reported to be used to identify a Skene gland adenocarcinoma with intestinal differentiation (25).

In our case, the immunohistochemical investigations on the biopsy confirmed the "intestinal" profile ($CK20^+$, $CK7^-$, $CDX2^+$) and allowed us to exclude the urothelial nature ($CK7^-$, $GATA3^-$).

Pathological results from the final specimen revealed a neoplastic cell immunophenotype negative for CK7, PAX8, GATA3, ER and PR, S100, and PSA. The specimen stained positively for CDX2, CK20, and AMACR. Along with pathological re-

sults, only clinical aspects rose a diagnostic suspect of adenocarcinoma from the Skene glands.
In the specific clinical condition of an intestinal-type primary vaginal adenocarcinoma, the pathologists play a fundamental role in guiding diagnostic and therapeutic pathways.
This is particularly evident if considering that some aspects of tumor invasion in our case emerged only after the pathologic study of the final specimen and that imaging and clinical analysis were not able to rule out an invasion of the adjacent organs unequivocally.
Moreover, thanks to the immunohistochemical profile, the possibility of ruling out vaginal secondaries is of great importance for the gynecologic surgeon when deciding the best therapeutic approach.
An immunohistochemical finding of a tumor of urothelial origin along with urethra and bladder free from lesions (macroscopically and at biopsy) would make it mandatory to look for a primary disease arising from other urothelial sites (*i.e.*, the ureter or the kidney).
Similarly, an immunohistochemical finding of a vaginal lesion of gynecological origin usually indicates an endometrial or cervical disease with caudal spread. Also, primary colorectal cancers can spread to the vagina. Stage IV disease should be diagnosed, and the patient should not be eligible for surgery.
All these considerations should be taken into account when facing a malignant glandular lesion of the vagina.

CONCLUSIONS

We here described the clinical management of a fragile patient with a rare intestinal-type primary vaginal adenocarcinoma and a transplanted kidney for renal failure with no indication for surgery at initial evaluation. We also reviewed the literature to outline the clinical management for these patients, but we had to acknowledge the paucity of cases and incompleteness of data available. This is likely due to the very low prevalence of the disease (only 24 cases described in total).
Clinical aspects and preoperative evaluation must be actively integrated with a detailed pathological analysis. The presumptive diagnosis comes from clinical evaluation and imaging findings, and the pathologist confirms the diagnosis. The differential diagnosis of an intestinal-type adenocarcinoma at the vaginal level (an organ almost free from glandular tissue) is particularly challenging given the anatomical complexity and different embryologic derivations of organs in this district.
In our specific case, the initial clinical evaluation (a vaginal lesion presenting with vaginal bleeding, a urethra free from lesions and negative bladder biopsies) was associated with the immunohistochemical findings of an intestinal-type adenocarcinoma oriented the gynecologist toward a primary vaginal adenocarcinoma. After the pathologic analysis on the final surgical specimen, it was possible to appreciate a full-wall urethral invasion at its distal third. Given that Skene glands are at this urethral level and given the tumor positivity for potential specific markers (AMACR), the pathologist raised the possibility of a tumor from these glands.
A multidisciplinary approach to the disease is of fundamental importance where clinical, imaging, and laboratory evaluation meets pathologic analysis to obtain an adequate diagnosis. Due to the lack of specific guidelines addressing these rare diseases, the treatment of choice should be tailored considering the stage of the disease, the patient's comorbidities, and the multidisciplinary holistic evaluation of the case.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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