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Adenocarcinoma of the paraurethral glands: a case report

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Summary. Adenocarcinoma of the paraurethral glands represents a very rare neoplasm of the urinary tract. Due to the rarity of this disease, there is no standard therapeutic approach. We report a case of adenocarcinoma of the paraurethral glands in a 56-year-old woman, presenting with abnormal serous vaginal discharges. The radiologic examination revealed a 5-cm mass around the urethra, which underwent surgical resection. After surgical resection, the histology revealed a moderately differentiated adenocarcinoma, probably arising from the paraurethral glands. One month later, a pelvic recurrent mass was radiologically diagnosed; consequently, an anterior pelvic exenteration with lymph node dissection was performed. Histological examination revealed a moderately differentiated adenocarcinoma, with glandular and micropapillary architecture, with multiple lymph node metastases. The absence of modifications such as urethritis cystic glandularis on the urethral mucosa, as well as the lack of a lesion in situ, associated with the immunohistochemical expression of PAX8 and negativity for GATA3 and S100p, suggested that the adenocarcinoma originated from the paraurethral glands rather than from the urethral mucosa. Post-surgery CT scans revealed no evidence of metastatic disease.

The patient received 6 courses of adjuvant chemotherapy with carboplatin and paclitaxel. One year after the pelvic exenteration, because of inguinal lymph node progression, an inguinal lymphadenectomy was performed. Four months later, a TC-PET revealed a multidistrectual lymph node and a lung micronodule disease progression.

Invasive micropapillary carcinomas have been characterized as a rare distinctive variant of carcinomas in several anatomic sites and are distinguished by a marked tendency to lymphovascular invasion, justifying the association with high-stage disease and poor prognosis. In the present case, both the poor prognosis connected with micropapillary structure and the lymph node involvement, encouraged adjuvant cisplatinum-based chemotherapy.

Key words: Adenocarcinoma, Micropapillary, Paraurethral glands, Review

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Introduction

Primary urethral carcinomas are uncommon tumors of the genitourinary tract. Among these, adenocarcinoma represents one of the least frequent histotypes (Dalbagni et al., 1998; Gheiler et al., 1998; Sloboda et al., 1998; Kuroda et al., 2006; Swartz et al., 2006; Rabbani, 2011; Chen et al., 2011; Reis et al., 2011). Its histogenesis remains controversial. It was traditionally assumed that urethral adenocarcinoma arose from the Skene's glands, as supported by PSA immunohistochemical positivity (de Graaf, 1672; Skene, 1880; Pollen et al., 1984; Tepper et al., 1984). However, negative PSA staining does not

necessarily exclude this hypothesis (Reis et al., 2011). More recently, it seems that this neoplasia may originate from more than one tissue (Dodson et al., 1995; Murphy et al., 1999).

Different histological types of paraurethral carcinoma have been described (columnar/mucinous, cribriform, clear cell), with peculiar features and origins (Oliva and Young, 1996; Sloboda et al., 1998; Murphy et al., 1999; Hartmann et al., 2006; Kuroda et al., 2006; Chen et al., 2011; Liu et al., 2012).

Due to the rarity of these tumors, there is currently no consensus on the therapeutic management. A multimodal approach, including radiation therapy and/or chemotherapy in combination with surgery, should be preferred (Dalbagni et al., 1998; Gheiler et al., 1998).

We report a case of micropapillary urethral adenocarcinoma, occurring to a 56-year-old woman, focusing on the potential origins of this tumor, with regard to the various kind of pathological features and the different therapeutic options.

Materials and methods

Case history

A 56-year-old woman, gravida 2, para 2, with an unremarkable medical history, presented with abnormal serous vaginal discharges. A gynecological examination revealed a nodule in the anterior vaginal wall. Total-body computed tomography (CT) scans showed a 5-cm mass around the urethra, without evidence of macroscopic invasion of the adjacent structures (Fig. 1). The patient underwent surgical transvaginal resection of the nodule. Histology revealed a moderately differentiated adenocarcinoma, probably arising from the paraurethral glands.

A MRI revaluation of the pelvis identified a new 3-cm mamillated mass between the bladder and the vaginal canal, mainly on the left side of the urethra (Fig. 2). Pathological examination of the biopsy specimen demonstrated an adenocarcinoma with solid-glandular aggregation. An anterior pelvic exenteration, with complete resection of bladder, urethra and vagina, bilateral iliac-obturator lymph nodes dissection and ureteroileocutaneostomia, was performed. The diagnosis of adenocarcinoma with lymph node metastasis was made.

Post-surgery CT scans revealed no evidence of metastatic disease. The patient received carboplatin AUC5 and paclitaxel 175 mg/m^2 every 3 weeks as adjuvant chemotherapy. The tumor assessment performed after 3 courses showed no signs of recurrent disease, except for the appearance of some enlarged lymph nodes in the groin bilaterally, of not univocal interpretation. Pathologic examination of lymph node aspirate resulted aspecific. The patient underwent 3 additional cycles of the same regimen. The treatment was well tolerated, except for the presence of asymptomatic neutropenia (grade 3 according to Common Terminology Criteria for Adverse Events version 4.0). A further CT scan after treatment confirmed the presence in the left inguinal region of enlarged lymph nodes, one of which showed slight hypermetabolism to a subsequently performed PET-CT.

Thus, one year after pelvic extenteration, inguinal lymphadenectomy was performed, with histological diagnosis of metastatic adenocarcinoma in 1 of the 10 lymph nodes. Follow-up was then planned.

The PET-CT undertaken 4 months later (at the time this case report was written) was suggestive of lymph node recurrence of the tumor, showing an increased pathological uptake at interaortocaval, left para-aortic, bilateral common iliac, internal iliac bilaterally and inguinal right lymph nodes, with an additional lung micronodule in the middle lobe.

Due to the absence of any clinical symptoms related to disease progression, and the lack of standardised effective treatment options, the patient continued follow-up, with clinical evaluation and CT-PET scans programmed every 4 months.

Immunohistochemical studies

The resected tumor was fixed in formalin, sectioned at 5 μm, and stained with hematoxylin and eosin. Immunohistochemical staining was performed employing a Leica automated immunostainer. The following antibodies were used: cytokeratin (CK) 7 (Biogenex, Fremont, CA, USA; clone OV-TL 12/30; 1:400 dilution), CK20 (Novacastra, Burlingame, CA, USA; clone PW31; 1:100), PAX8 (Abcam, Cambridge, UK; 1:10), 34bE12 (Dako, Carpinteria, CA, USA; clone 34,E12; 1:40 dilution); alpha-methylacyl-CoA racemase (AMACR) (Dako, Carpinteria, CA, USA; clone 13H7; 1:50 dilution); CDX2 (Biogenex, Fremont, CA, USA; clone CDX2-88; 1:40), CK5 (Novacastra, Burlingame, CA, USA; clone XM26; 1:100 dilution), p63 (Santa Cruz biotechnology, Dallas, TX, USA; 4A4; 1:100), GATA3 (BD Pharmingen, San Diego, CA, USA; clone L50-823; 1:150), S100P (BD Pharmingen, San Diego, CA, USA; clone 16; 1:1000), estrogen receptor (ER) (Dako, Carpinteria, CA, USA; 1:20 dilution), progesterone receptor (PR) (Dako, Carpinteria, CA, USA;clone PgR 636; 1:20 dilution), prostate-specific antigen (PSA) (Dako, Carpinteria, CA, USA; clone ER-PR8; 1:50), prostatic acid phosphatase (PSAP) (Dako, Carpinteria, CA, USA; clone rabbit; 1:2000), TTF-1 (Dako, Carpinteria, CA, USA; clone 8G7G3/1; 1:50), Ki67 (Novacastra, Burlingame, CA, USA; MM1; 1:50).

CK7, CK20, CK5, PSA, PSAP, and S100P have been scored as percentage of neoplastic cells showing strong cytoplasmic/membranous immunoexpression. PAX8, CDX2, p63, GATA3, ER, PR, TTF-1, Ki67 have been evaluated as percentage of strong nuclear immunostaining.

CK34bE12 and AMACR were evaluated as percentage of neoplastic cells showing strong or weak cytoplasmic/membranous immunostaining.

We performed PAS reaction and Alcian Blue special staining on tissue sections.

Results

Histopathologic analysis of the anterior pelvic exenteration showed a moderately differentiated adenocarcinoma, with a glandular and micropapillary architecture (Fig. 3A-E) and with necrosis involving the whole vagina and urethra walls, ulcerating their mucous surface. Endovascular neoplastic embolization was identified both in the primary mass and in the bladder wall. There was no evidence of neoplastic involvement either in the vulva surgical margins, or in the uterus, ovaries, and ureteral stumps. Metastases were present in 4 out of the 12 right iliac-obturator nodes, and in 1 out of 8 left iliac-obturator lymph nodes.

Tumor cells immunostained for CK7 (Fig. 3F), CK20 and Pax8, but not for CDX2 protein, CK5, p63, GATA-3, S100p, ER and PR, PSA, PSAP and TTF-1. They were focally and weakly positive for cytokeratin 34bE12 and AMACR. The Ki67 labeling index was approximately 30%. The absence of modifications such as urethritis cystic glandularis on the urethral mucosa, as well as the lack of a lesion in situ, associated with the expression of the marker PAX8 and negativity for GATA3 and S100p, suggested a paraurethral glands origin rather than from the urethral mucosa. The special staining (PAS, carbohydrates and Alcian Blue stainings) evidenced scattered and patchy positivity along all tissue sections. Fig. 4 (A-H) summarized the immunophenotypical and histochemical profile of the current adenocarcinoma of the paraurethral glands.

Discussion

Urethral carcinoma is among the rarest of tumors involving the urinary tract, and the adenocarcinoma is one of the least frequent histotypes, accounting for less than 0.003% of all urogenital tract malignancies in women (Kuroda et al., 2006). In the US, the annual incidence rate of the urethral carcinoma for the period 1973-2002, as reported by the SEER database, was 4.3 per million among men and 1.5 among women, with downward trends over the last three decades, concerning in particular males and Afro-Americans (Swartz et al., 2006).

The most common histotype is the transitional cell carcinoma (55-77%), followed by squamous cell carcinoma (11.9-21.5%), adenocarcinoma (5-16.4%), and other histology including sarcoma and melanoma (5.5%) (Rabbani, 2011). Owing to the rarity of this disease, no consensus has been reached with regard to the optimal therapeutic strategy. To date, retrospective, single-case reports and small case series represent the best (although at a very lower level) evidence (Table 1).

The female urethra mucosa is lined in the proximal and the distal tract by transitional and squamous cells, respectively. For this reason, transitional cell carcinoma is more common in the proximal urethra while squamous cell carcinoma is located more often in the distal urethra. Conversely, adenocarcinoma does not have any preferential site of origin, and its histogenesis still remains controversial. It is traditionally assumed that urethral adenocarcinoma arises from the Skene's paraurethral glands, which are considered homologous to the prostate gland in men (De Graaf, 1672; Skene,

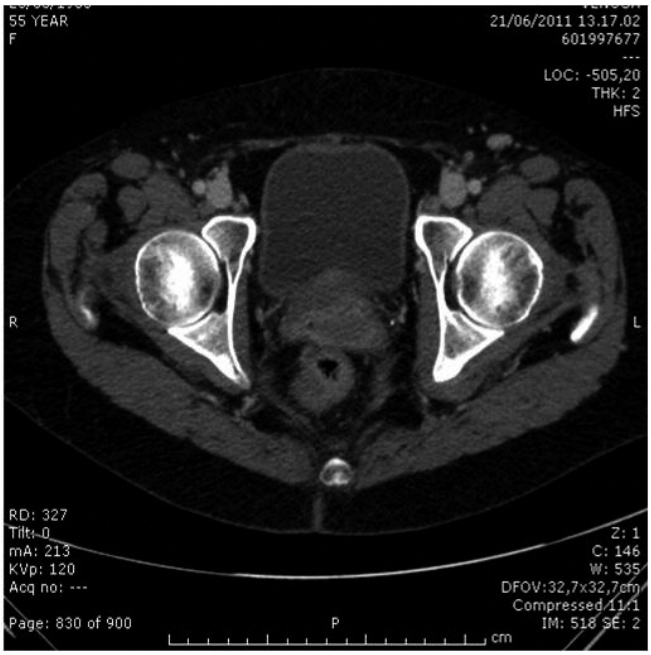

Fig. 1. Total-body computed tomography (CT) scans; a 5-cm mass around the urethra.

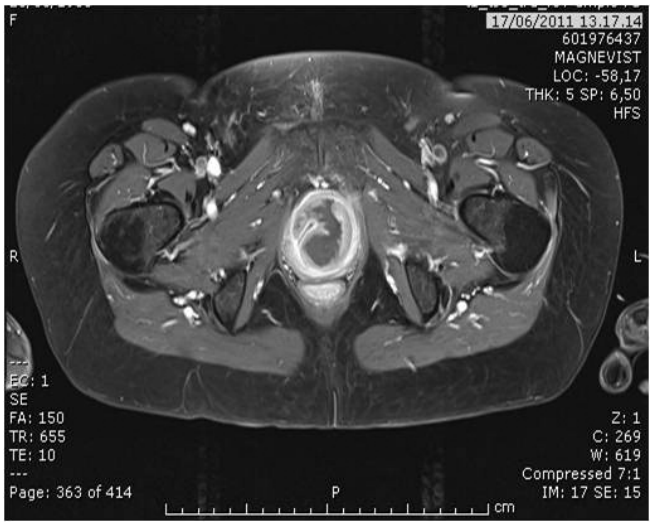

Fig. 2. MRI; 3-cm mamillated mass between the bladder and the vaginal canal.

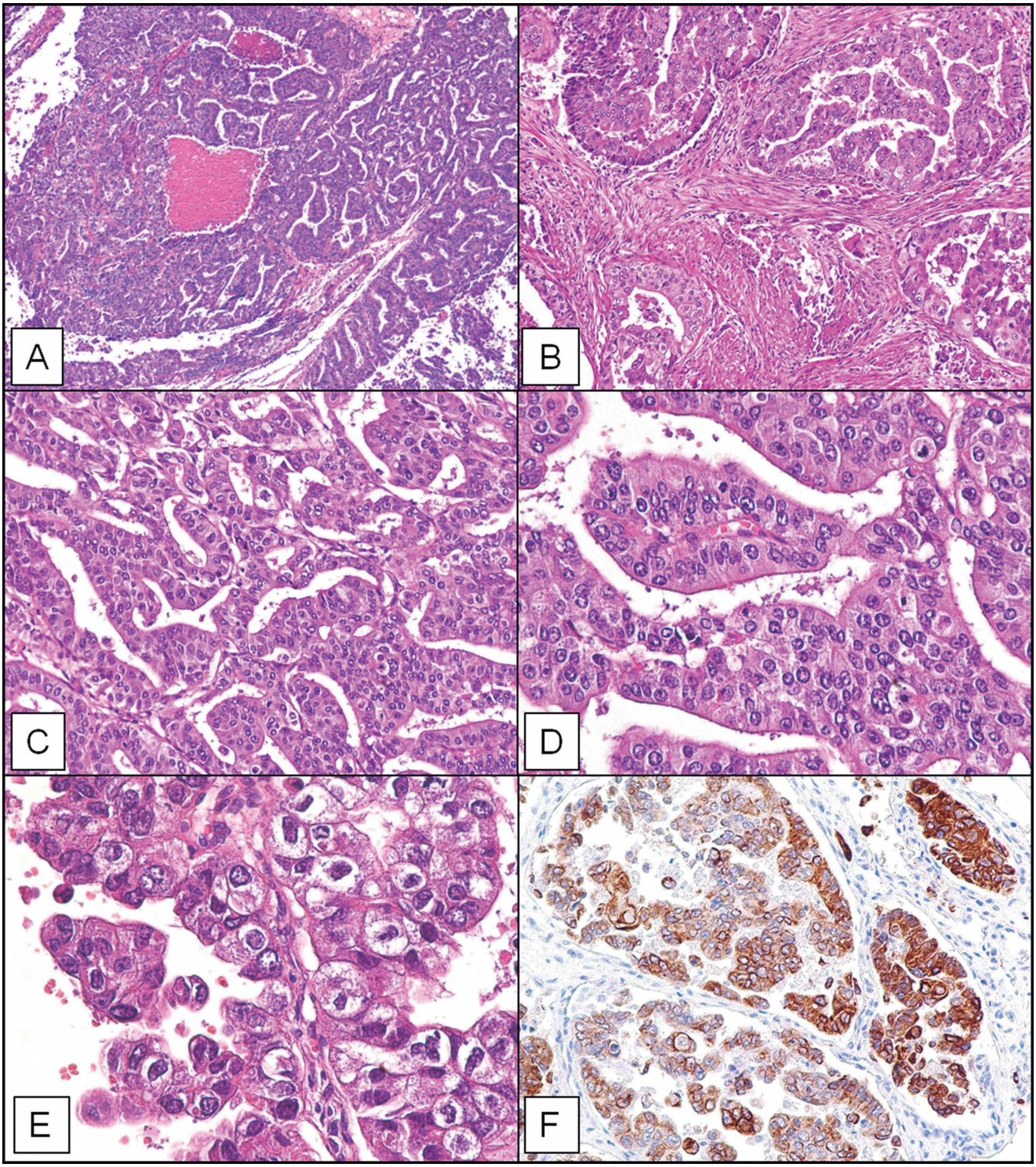

Fig. 3. Morphological and immunohistochemical features of adenocarcinoma of the paraurethral glands. **A, B.** Low-power magnification showing the glandular and micropapillary architecture of the neoplasm. H&E. **C, D.** The tumor cells are either cuboidal or columnar, with eosinophilic or clear cytoplasm. Cytoplasmatic clearing is often caused by glycogen deposition or, less commonly, intracytoplasmic mucin. H&E. **E.** High-power magnification showing the cellular atypia; the nuclei are large and hyperchromatic and prominent nucleoli can be present. In some cells the cytoplasmatic clearing is very conspicuous. H&E. **F.** The neoplastic cells demonstrate strong positivity for CK7. A, x 10; B-D, F, x 20; E, x 40

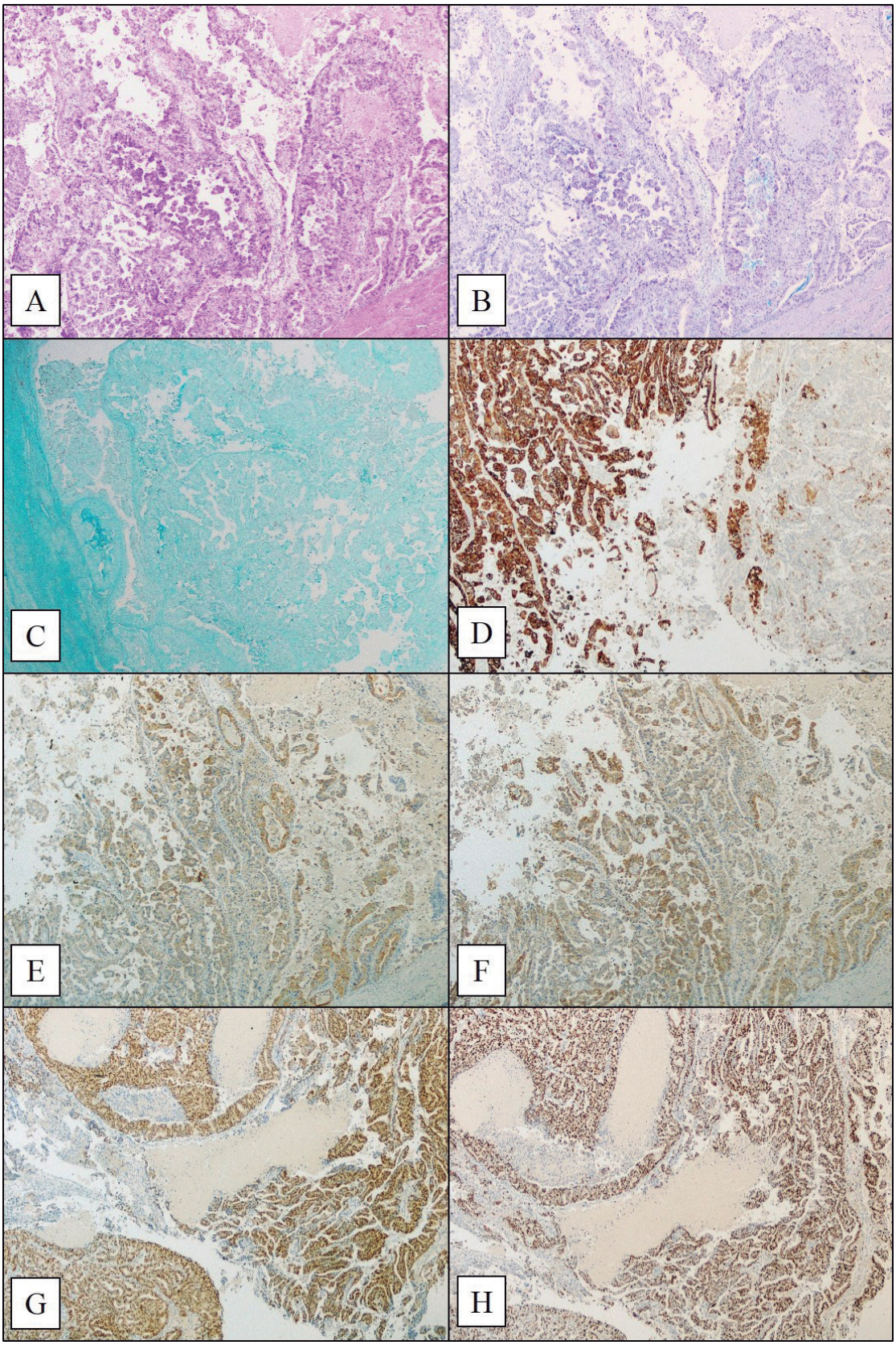

Fig. 4.
Immunophenotypical and histochemical profile of adenocarcinoma of the paraurethral glands. **A.** Carbohydrates staining showing focal expression along neoplastic cells. **B.** Patchy positivity for PAS histochemical expression along sheet of neoplastic cells. **C.** Neoplastic single cells staining for Alcian Blue. **D.** CK20 strong. **E.** PAX8 nuclear. **F.** CK34bE12 diffuse. AMACR wide **(G)** and robust Ki67% immunoexpression **(H)**. A-F, x 10; G, H, x 20

Table 1. Urethral adenocarcinoma: Treatment and outcome of some cases reported in the literature.

Reference	Year	Patients n	Histological subtype	Surgery	Radiotherapy (RT)	Chemotherapy	Outcome (months)
Zaviacic et al., 1993	1993	1	Cribriform/columnar	No	No	No	NR
Dodson et al., 1995	1995	11 2	Columnar/mucinous Clear cell adenocarcinoma	NR	NR	NR	NR
Oliva and Young, 1996	1996	19	Clear cell, tubulocystic, papillary adenocarcinoma	Yes	NR	NR	6 pts 10years DFS 4 pts DSS 5-42mo 3 pts 6.5year (recurrence)
Dalbagni et al., 1998	1998	25	NR	Anterior or total pelvic exenteration, TURBT, diverticulectomy, distal or total urethrectomy.	Neoadjuvant or definitive (external beam, brachitherapy, external+brachitherapy)	No	30 (median survival)
Gheiler et al., 1998	1998	5	NR	Distal or total urethrectomy, pelvic exenteration.	Neoadjuvant Radio-chemotherapy (3pts).	F radiosensitizing	38 (median DFS)
		3	NR	No	Definitive radio-chemotherapy.		19 (median DFS)
Grigsby, 1998	1998	13	NR	Local excision, urethrectomy, or total pelvic exenteration.	Neoadjuvant, adjuvant, or definitive RT	No	5-year cause-specific survival 0%
Kawano et al., 2001	2001	1	Clear cell adenocarcinoma	Total cystourethrectomy	No	No	12 (DFS)
Davis et al., 2003	2003	1	Clear cell adenocarcinoma of urethral divericulum	Anterior pelvic exenteration	Neoadjuvant radio-chemotherapy (Platinum-5-Fluorouracil)	Adjuvant: TC	10 (DFS)
von Pechmann et al., 2003	2003	1	Adenocarcinoma of the urethral diverticulum	Yes	No	No	3 (DFS)
Awakura et al., 2003	2003	1	Columnar/mucinous adenocarcinoma	Total urethrectomy	Neoadjuvant radio-chemotherapy: 40 Gy with Cisplatin,5-Fluorouracil.	FP radiosensitizing (intra-arterial and intravenous chemotherapy).	24 (DFS)
Dimarco et al., 2004	2004	14	NR	Pelvic exenteration, radical or partial urethrectomy, transurethral excision.	Neoadjuvant or adjuvant RT (external beam and/or brachitherapy).	Adjuvamt Cisplatin-based chemotherapty (alone or with RT).	5-year RFS 46%, 5-year DSS 66%
Thyavihally et al., 2005	2005	4	NR	Local excision or anterior exenteration	Adjuvant or definitive RT	I Line chemotherapy	51 (median OS)
Kato et al., 2005	2005	5 1	Mucinous adenocarcinoma Clear cell adenocarcinoma	Yes	NR	NR	NR
Kuroda et al., 2006	2006	1	Heterogeneous (columnar, clear cell, micropapillary)	Surgical resection of bladder, urethra, vagina and uterus	No	No	3 (DFS)
Miller and Karnes, 2008	2008	1	Clear cell adenocarcinoma	Anterior pelvic exenteration	No	No	24 (DFS)
Hong et al., 2009	2009	12	NR	No	No	I Line: GP, or FP or CMV II Line: T, or EP, or TC, or TP or CMV	8 (median TTP) 47 (median OS)
Trabelsi et al., 2009	2009	1	Clear cell adenocarcinoma	Total urethrocystectomy	No	No	3 (DFS)
Libby et al., 2010	2010	1	NR	Transurethral resection	Adjuvant radio-chemotherapy.	Adjuvant: PX (concomitant with RT)	16 (recurrence)
		1	NR	No	Definitive radio-chemotherapy.	Definitive: PX (concomitant with RT)	14 (DFS)

Ha et al., 2010	2010	1	Clear cell adenocarcinoma	Radiacal cystourethrectomy	No	No	6 (DFS)
Reis et al., 2011	2011	1	Cribriform adenocarcinoma	Urethrectomy	No	No	NR
		1	Clear cell adenocarcinoma	Urethrectomy	No	No	NR
Chen et al., 2011	2011	1	Poorly differentiated adenocarcinoma.	Radical cystectomy.	No	No	2 (recurrence)
		1	Columnar/mucinous adenocarcinoma.	Anterior pelvic exenteration	Adjuvant RT	IF	6 (recurrence)
Liu et al., 2012	2012	1	Clear cell adenocarcinoma	Transurethral resection R2	No	- I line: GP - II line: Nab-paclitaxel	29 (OS)
Dayyani et al., 2013	2012	13	NR	Yes	No	PGF (neoadjuvant, adjuvant or I line)	23.4 (median survival from start of chemotherapy)
Nakatsuka et al., 2012	2012	1	Clear cell adenocarcinoma of urethral divericulum	Cysturethrectomy	No	No	NR

NR: not reported; DFS: dease free survival; OS: overall survival; TTP: time to progression; RFS: recurrence free survival; DSS: disease specific survival; FP: 5-Fluorouracil/Cisplatin; F: 5-Fluorouracil; T: Paclitaxel; GP: Gemcitabine/Cisplatin; EP: Etoposide/Cisplatin; TC: Paclitaxel/Carboplatin; TP: Paclitaxel/Cisplatin; IF: irinotecan/5-Fluorouracil; PX: Cisplatin/Capecitabine; CMV: Cisplatin/Methotrexate/Vinblastine; PGF: Cisplatin/Gemcitabine/5-Fluorouracil.

Table 2. Histological subtypes of paraurethral carcinoma.

Morphological pattern	Positive immunostains	Origin	Chemotherapeutic options
Columnar/mucinous	CK7 CK20 mAbDas1	Glandular metaplasia (colonic or endometrial)	5-Fluorouracil and Irinotecan 5-Fluouracil and Cisplatin Capecitabine and Cisplatin
Cribriform	PSA PSAP	Skene's glands	Platinum-based chemotherapy
Clear cell	CA125	Mullerian duct/Nephrogenic metaplasia	Carboplatin and Paclitaxel Gemcitabine and Cisplatin

1880). Immunohistochemical positivity for prostate-specific antigen (PSA) further supported this hypothesis (Pollen and Dreilinger, 1984; Tepper et al., 1984; Zaviacic et al., 1993). However, primary female urethral adenocarcinomas do not consistently stain positively for PSA (Dodson et al., 1995). Indeed, as highlighted by Dodson and Murphy, the majority of them do not arise from the Skene's glands, but may have more than one tissue of origin (Dodson et al., 1995; Murphy et al., 1999). Nevertheless, it is important to point out how negative staining of PSA does not necessarily exclude the potential origin of this disease from the Skene's paraurethral glands: given that many of the cells in these glands do not produce PSA, it is possible that some PSA-negative adenocarcinomas (which present histologic, cytochemical and immunohistochemical similarities with normal Skene's glands) might still originate from them (Reis et al., 2011).

Adenocarcinomas occurring in the urethra may present various histological features (Table 2) (Kuroda et al., 2006; Chen et al., 2011). The major hystologic subtype is the columnar/mucinous adenocarcinoma. It presents microscopic appearance that traces colonic or endometrial adenocarcinoma and is significantly positive to CK7, CK20 and mAbDas1 immunostains, suggesting this histotype may arise from glandular metaplasia due to urethritis glandularis (Murphy et al., 1999). Cribriform carcinoma is another histological phenotype, which originates from the Skene's glands, and develops in the distal paraurethral duct. This phenotype presents a prostatic-cancer-like histology, characterized by distinctive immunohistochemical positivity of PSA and prostatic acid phosphatase (PSAP). It can be related to high rates of serum PSA that declines rapidly after operation (Sloboda et al., 1998). The third morphological pattern is clear cell adenocarcinoma, which often arises from the urethral diverticulum. It has an ovarian tumor-like histologic structure, and stains positive for carbohydrate antigen 125 (CA125). The origin of clear cell adenocarcinoma is currently debated: while some authors believe it originates from the Mullerian duct (origin of the ovary and fallopian tube),

others suggest it represents a progression from nephrogenic metaplasia (Oliva and Young, 1996; Hartmann et al, 2006; Liu et al., 2012). However, this classification should not be considered rigorously. With regard to the present case, the immunohistochemical positivity for CK7 and CK20 in addition to the negativity for CDX2 and CA19.9, does not suggest an intestinal phenotyping differentiation. Moreover, ER and PR expression are not pathognomonic/specific prostate markers.

The key histological feature of this case refers to the micropapillary structure. Invasive micropapillary carcinomas have been characterised as a rare distinctive variant of carcinomas in several anatomic sites, such as breast, urinary bladder, lung, colon and major salivary glands (Kuroda et al., 2006). These tumors are distinguished by a marked tendency to lymphovascular invasion, justifying the association with high-stage disease and poor prognosis compared to those of patients with conventional carcinomas arising in the same organs (Amin et al., 1994; Nassar, 2004). The clinical course correlates with the proportion of the micropapillary pattern: the higher the rate of this component, the worse the prognosis (Samaratunga and Khoo, 2004).

Micropapilllary urothelial carcinoma usually immunoreacts to CK7, CK20 and 34betaE12, highlighting a pattern of glandular differentiation within the context of transitional cell carcinoma. Immunohistochemical stains for CA125 (Johansson et al., 1999), Her2Neu (Sangoi et al., 2009), and MUC1 (Nassar et al., 2004) in invasive micropapillary malignancy have also been reported, contributing to differentiate it from typical urothelial carcinoma. The presence of the micropapillary component has been described in several sites among the urinary tract, including the bladder, the ureter and the renal pelvis. Some authors have reported micropapillary morphology within the female urethral adenocarcinoma, confirming the correlation with an aggressive clinical course (Kuroda et al., 2006).

Due to the rarity of this cancer, there is no standardised treatment. Although surgery represents the main therapeutic option in case of localised disease, several authors have pointed out the inadequacy of a single treatment modality in the management of advanced female urethral cancer, emphasizing the importance of an aggressive multimodal approach, which includes radiation therapy and/or chemotherapy in combination with surgery (Dalbagni et al., 1998; Gheiler et al., 1998).

The role of chemotherapy for urethral carcinoma is anecdotal. Despite the lack of data supporting its efficacy, adjuvant chemotherapy may theoretically be an option to reduce the high risk of recurrence, while systemic treatment can represent the only reasonable possibility for metastatic disease. Several agents have been used alone or in combination, and modern platinum-based regimens seem to be effective in advanced disease (Dayyani et al., 2013). Given the absence of a standard chemotherapy schedule, the selection of the treatment is often carried out according to the peculiar histotype, using cisplatin and gemcitabine (one of the standard options for transitional cell carcinoma (Hong et al., 2009; Liu et al., 2012) irinotecan and 5-fluorouracil in presence of an enteric subtype (Chen et al., 2011), carboplatin and paclitaxel in case of clear cell adenocarcinoma (Davis et al., 2003), or other schemes such as cisplatin, gemcitabine and 5-fluorouracil (Dayyani et al., 2013), cisplatin and capecitabine or cisplatin (Libby et al., 2010) and mitomycin C concomitant radiotherapy (Koontz and Lee, 2010).

In the present case, both the poor prognosis related to micropapillary structure and the lymph node involvement, encourage take adjuvant platinum-based chemotherapy.

In conclusion, we report a rare case of urethral micropapillary adenocarcinoma, treated by multimodal therapy, with a considerable tendency to lymph node metastasis, despite adjuvant chemotherapy, according to the peculiar histotype.

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Conflicts of Interests. None of the authors have potential conflicts of interest relevant to this work.

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