Virchows Arch (2000) 436:622–627

CASE REPORT

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Primary vaginal adenocarcinoma arising from the metanephric duct remnant

Abstract Primary vaginal adenocarcinoma unrelated to *in utero* exposure to diethylstilbestrol (DES) is very uncommon. We report a case of 65-year-old Japanese woman who presented with primary adenocarcinoma in the anterior wall of the vagina, where the left ureter-like metanephric duct remnant abnormally terminated. Histological examination in serial sections revealed the direct connection between the carcinoma and the metanephric duct remnant. Moreover, the remnant epithelium showed varying degrees of dysplastic changes, including carcinoma *in situ* in close proximity to the carcinoma. This patient also had a bicornate uterus and left renal aplasia. To our knowledge, this is the first reported case of a primary vaginal adenocarcinoma arising from the metanephric duct remnant. Although the precise mechanism involved in carcinogenesis in this clinicopathological setting remains unknown, adenocarcinoma should be included in the differential diagnosis of vaginal tumors in patients with renal aplasia and/or an ectopic termination of the ureter or metanephric duct remnant, especially when the tumor is in the anterior wall.

Key words Vaginal adenocarcinoma · Metanephric duct remnant · Renal aplasia · Ureteral ectopia

Introduction

Primary adenocarcinoma of the vagina unassociated with *in utero* exposure to diethylstilbestrol (DES) is rare [11, 17]. It often poses diagnostic problems and must be differentiated from metastatic adenocarcinomas, most frequently from the endometrium, cervix and the gastrointestinal tract and occasionally from the breast [17]. Moreover, unlike clear cell adenocarcinoma in women exposed to DES [3, 7], its accurate histogenesis remains obscure. Some adenocarcinomas have been reported to originate possibly from adenosis [12, 17], endometriosis [1], or cloacal remnants [2]. Rare paravaginal wolffian duct (mesonephros) adenocarcinoma also has been described [4].

We report the first case of primary vaginal adenocarcinoma arising from the metanephric duct remnant in a patient without *in utero* exposure to DES. The ureter-like metanephric duct remnant had an ectopic termination in the vaginal wall at its distal end, where papillotubular adenocarcinoma arose from. This patient also showed left renal aplasia and a bicornate uterus.

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Clinical history

A 65-year-old nulliparous woman was referred to Miyazaki Medical College Hospital because of continuous vaginal bleeding which had lasted for three months before admission. She had menopause at the age of 50 and had been previously diagnosed at a nearby hospital as having the congenital aplasia of the left kidney and a bicornate uterus. There was no history of intrauterine exposure to hormones by maternal intake of DES or treatment with agents known to be estrogen modulators such as tamoxifen or danazol.

On examination with the colposcope, a dome-shaped protruding tumor 2 cm in diameter was found on the anterior wall of the vagina. Ectocervical cytologic evaluation led to classification as class V (Papanicolaou system), and the tissue biopsy specimen revealed adenocarcinoma. Vaginal endosonography and CT scanning revealed a bicornate uterus and normal-sized ovaries, the tumor being restricted to the vagina without evidence of intrauterine or abdominal spread. The right kidney and ureter were seen to be of normal size and shape on intravenous pyelogram. Gastroscopy and colonoscopy showed no evidence of malignant lesions.

The patient was treated by radical hysterectomy, bilateral oophorectomy, vaginectomy and bilateral pelvic lymph node dissection. During the operation, the left ureter-like cord-shaped structure was found between the urinary bladder and the left common il-

iac artery. At its cephalic end the cord-like structure was interrupted and merged into the retroperitoneal connective tissue around the left common iliac artery. At its caudal end, the cord-like structure did not go into the urinary bladder wall, but instead into the mid-anterior wall (12° position) of the vagina. No other left ureter-like structure was found on gross examination during the operation.

Materials and methods

The resected tissue were fixed in 10% formalin, routinely processed, and embedded in paraffin. Sections were stained with hematoxylin and eosin (HE) for light microscopic examination. Immunohistochemistry was perfomed on paraffin sections using an ordinary biotin–streptavidin method. Monoclonal antibodies used include those against cytokeratin 7, 8, 19 and 20 (Dako, Carpinteria, Calif.), vimentin (Dako) epithelial membrane antigen (EMA, Dako) and Leu-7 (Becton Dickinson, San Jose, Calif.).

Pathological findings

Grossly, there was a dark-red, dome-shaped, protruding tumor with a maximum diameter of 2 cm in the anterior wall of the vagina in the surgical specimen (Fig. 1a). The tumor had a small crater-like hole in its center. The uterus was bicornate. The left ureter-like structure reached to the anterior wall of the vagina, where the tumor was located (Fig. 1b). An examination with a sound revealed that it opened to the vaginal lumen through the central hole of the vaginal tumor.

Microscopically, the tumor had a predominantly papillotubular growth pattern (Fig. 2a). It consisted largely of columnar cells with round to oval, hyperchromatic nuclei and macronucleoli (Fig. 2b). Nuclear stratification and mitotic figures were occasionally seen. Portions of the carcinoma cell-lined papillae and tubules showed a back-to-back arrangement in part. The tumor infiltrated deeply into the smooth muscle layer of the vagina, and neither vascular nor lymphatic invasion was observed. In addition, deep in the vaginal wall, ahead of the invasion

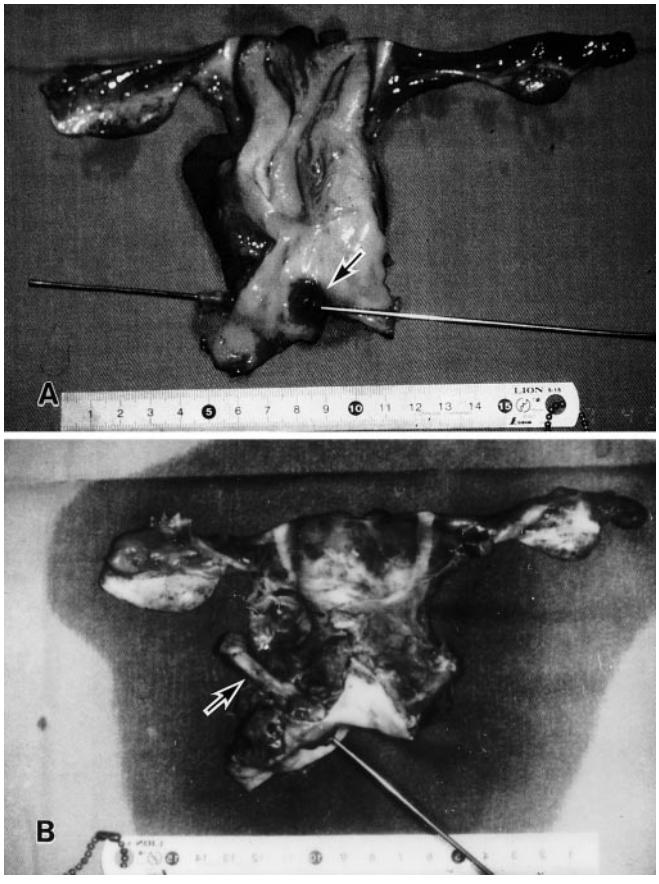

Fig. 1. a Surgical specimen from hysterectomy and partial vaginectomy, showing a protruded tumor mass (*arrow*) in the vagina. The specimen was cut at the midposterior line (6° position). The uterus shows bicornate features. **b** The anterior view of the hysterectomy specimen. The ureter-like, cord-shaped structure (*arrow*) reaches to the anterior wall (12° position) of the vagina, just outside of the vaginal tumor. A sound in **a** and **b** shows the continuity of the lumen of the ureter-like structure with the hole in the middle of the vaginal wall

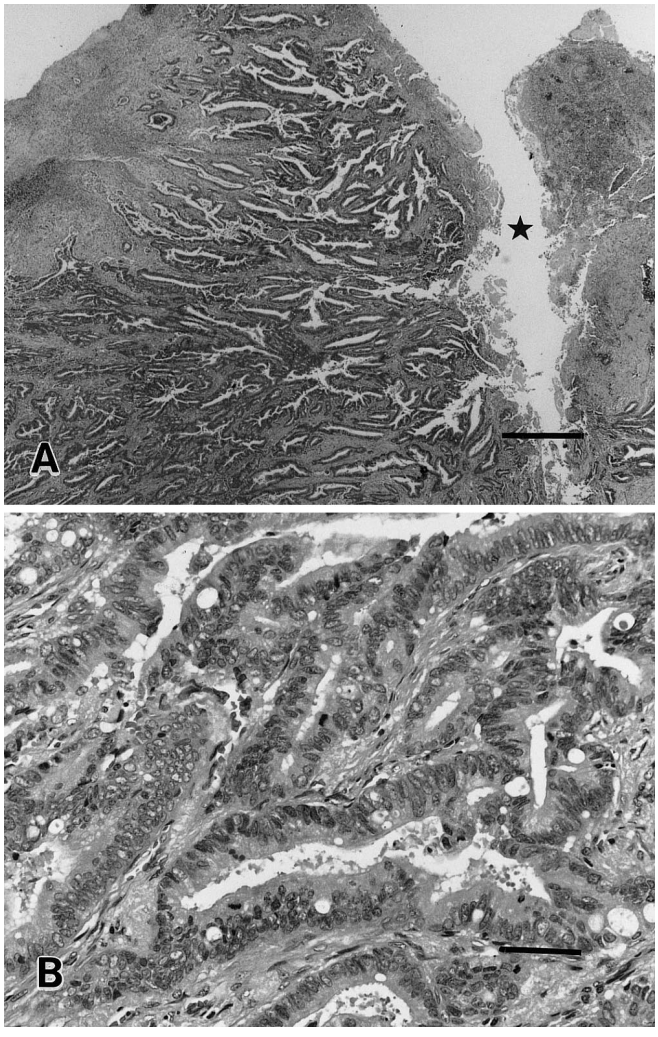

Fig. 2. a The tumor tissue shows a papillotubular growth pattern. An *asterisk* shows a central hole, which is continuous with the lumen of the left ureter-like tube structure. *Bar* 500 µm **b** Columnar cells with large oval or elongated hyperchromatic nuclei proliferate forming irregular papillae or tubules, which show a back-to-back arrangement in part. *Bar* 50 µm

Table 1 Immunophenotypic results

Cell types	EMA	CK 7	CK 8	CK 19	CK 20	Vimentin	Leu 7 (CD57)
Carcinoma cells	+	+	+	–	–	–	–
Epithelium of an intramural tube	+	+	+	+	–	+[b]	+[c]
Epithelium of a ureter-like tube	+	+[b]	+[b]	+[b]	–	+[b]	+[c]
Normal urothelium	+[a]	+	+	+	+[a]	–	–

[a] Only umbrella cells of the transitional epithelium are positive
[b] Only basal cells of the two–cell thick epithelium are positive
[c] A small number of scattered positive cells are seen

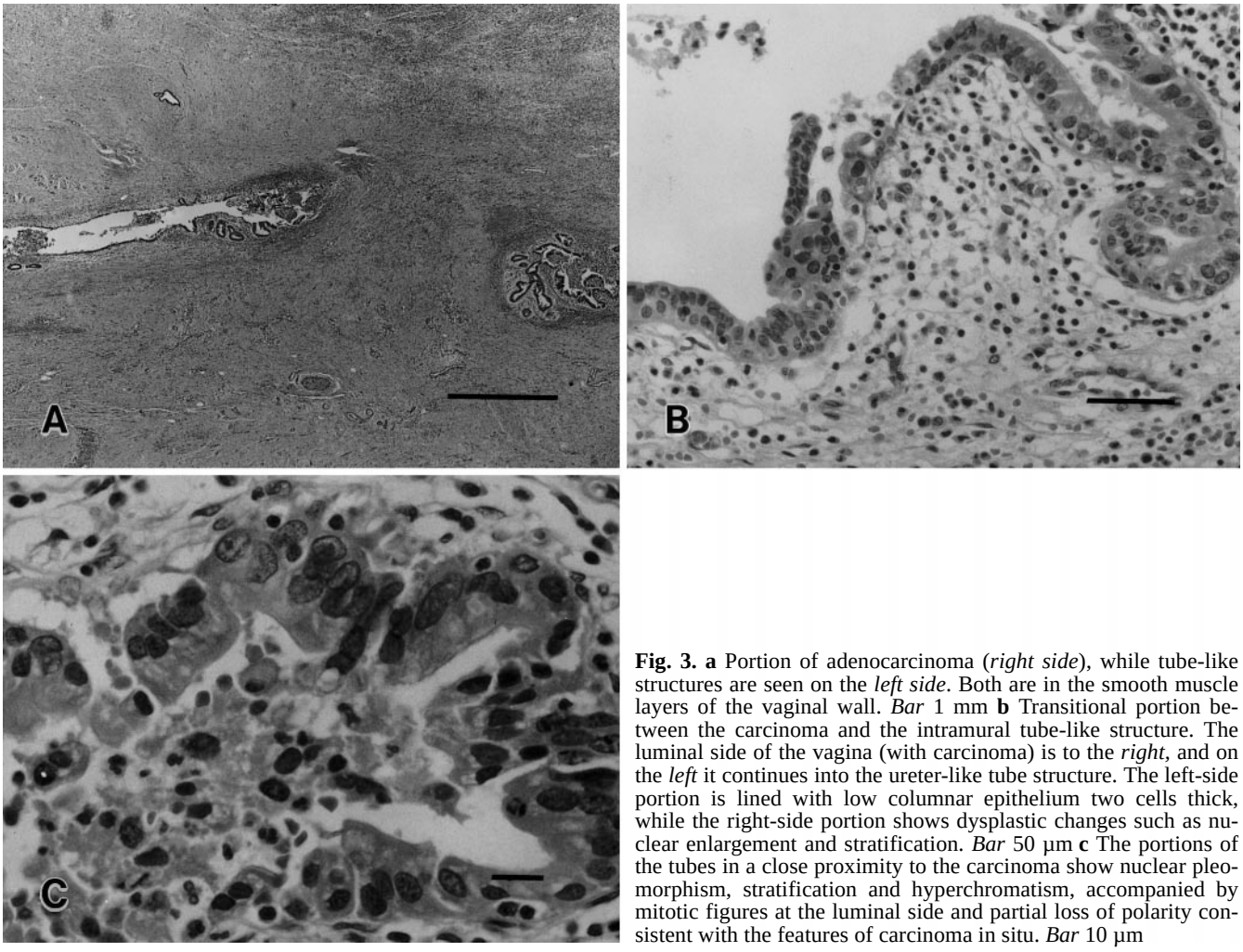

Fig. 3. a Portion of adenocarcinoma (*right side*), while tube-like structures are seen on the *left side*. Both are in the smooth muscle layers of the vaginal wall. *Bar* 1 mm **b** Transitional portion between the carcinoma and the intramural tube-like structure. The luminal side of the vagina (with carcinoma) is to the *right*, and on the *left* it continues into the ureter-like tube structure. The left-side portion is lined with low columnar epithelium two cells thick, while the right-side portion shows dysplastic changes such as nuclear enlargement and stratification. *Bar* 50 µm **c** The portions of the tubes in a close proximity to the carcinoma show nuclear pleomorphism, stratification and hyperchromatism, accompanied by mitotic figures at the luminal side and partial loss of polarity consistent with the features of carcinoma in situ. *Bar* 10 µm

front of the carcinoma, there were tube or duct-like structures lined with cuboidal or low columnar epithelium two cells thick (Fig. 3a, b). Serial sections revealed that these structures were portions of a tube that connected the carcinoma and the left ureter-like structure, which attached to the anterior wall of the vagina. The tube epithelium in close proximity to the carcinoma showed nuclear enlargement and pleomorphism with a partial loss of polarity (Fig. 3c), features consistent with carcinoma in situ (intraepithelial carcinoma). In the vaginal wall we examined there were groups of glands around the above tube, but they showed connection to the tube in serial sections. No separate Gartner's duct residue-like tubules were seen. Neither adenosis nor endometriosis was found.

The ureter-like cord outside the vaginal wall had a lumen lined with cuboidal or low columnar epithelium two cells thick in the same way as the tube within the vaginal wall. In addition, it had lamina propria and the subjacent thick smooth muscle layers (Fig. 4a, b). Small foci of dysplastic lesion were also found in this cord epithelium outside the vaginal wall (Fig. 4c). The resected lymph nodes revealed no metastatic lesion, and the uterus and ovaries showed no neoplastic lesions.

The results of immunohistochemical studies are summarized in Table 1. Although the epithelium of the ure-

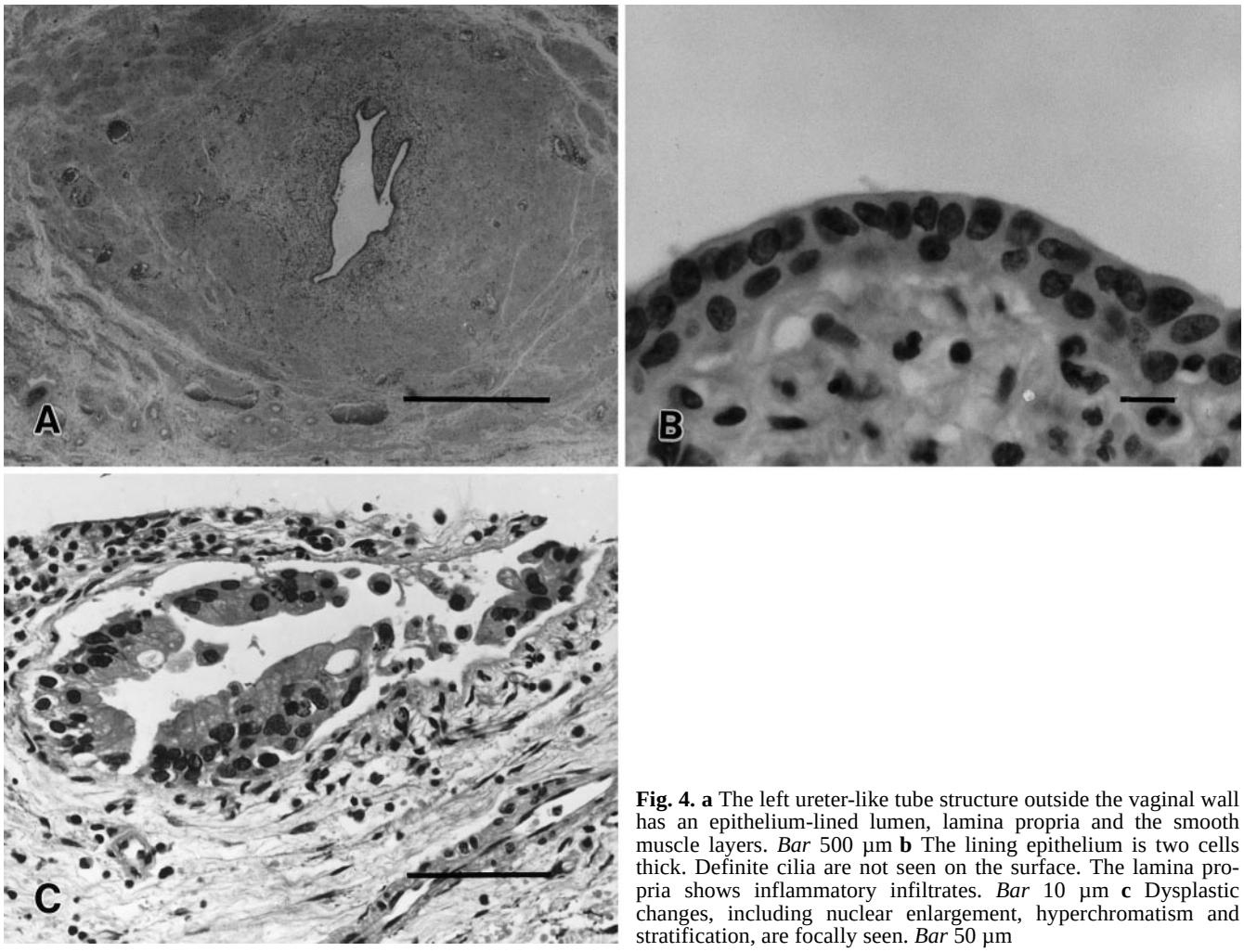

Fig. 4. a The left ureter-like tube structure outside the vaginal wall has an epithelium-lined lumen, lamina propria and the smooth muscle layers. *Bar* 500 µm **b** The lining epithelium is two cells thick. Definite cilia are not seen on the surface. The lamina propria shows inflammatory infiltrates. *Bar* 10 µm **c** Dysplastic changes, including nuclear enlargement, hyperchromatism and stratification, are focally seen. *Bar* 50 µm

ter-like tubes in and outside the vaginal wall showed positive staining for EMA and cytokeratin 7, 8 and 19, the umbrella cell-specific positive staining for cytokeratin 20 which is seen in the mature urothelium was not demonstrated in the tube epithelium, indicating the loss of differentiation toward a mature urothelial phenotype. Instead, vimentin was positive in the outer cells of the two-cell-thick epithelium of the tubes, and a small number of Leu 7-positive cells were seen scattered within the epithelium, indicating similarity to a fetal metanephric phenotype [5]. Adenocarcinoma cells were positive for EMA and cytokeratin 7 and 8, but negative for all of cytokeratin 20, vimentin and Leu 7.

Discussion

Adenocarcinoma of the vagina is rare, because the organ is normally devoid of glands and lined with squamous epithelium [10]. In women with *in utero* exposure to DES, clear cell adenocarcinoma has been most frequently reported and in that setting frequently associated with vaginal adenosis [3, 7, 9]. Non-clear-cell adenocarcinoma without *in utero* exposure to DES includes papillary, endometrioid, mucinous, intestinal-type and mesonephric carcinomas [10, 11, 17]. It tends to occur in women in the late reproductive and postmenopausal years [17], which is a marked contrast to clear cell adenocarcinoma in DES-exposed women: 91% of the clear cell carcinoma were diagnosed when the patient was between the ages of 15 and 27 (the mean age, 19 years) [7]. The carcinomas unassociated with DES exposure are reported to originate possibly from adenosis [12, 17], from implants of endometriosis [1], from cloacal remnants [2], or from mesonephric duct rests [4]. Our case has clearly added the metanephric duct remnant as another probable origin for the vaginal adenocarcinoma unassociated with DES exposure.

In our case, in addition to adenocarcinoma in the anterior wall of the vagina, there was a left ureter-like tube, which had a blind proximal end and showed a direct connection with the adenocarcinoma at its distal end in the vaginal wall. Furthermore, the epithelium of this tube showed varying degrees of dysplasia, including carcinoma *in situ* portions in the close proximity of the carcinoma. Other than the glands connected directly to the tube

lumen, neither adenosis nor Gartner's duct rests (mesonephric duct rests) were found in the nearby tissue of the carcinoma. These lines of evidence led us to believe that the adenocarcinoma had arisen from the tube epithelium. As for the origin of this tube, two ducts are the possible candidates in this location: the metanephric duct and the wolffian (mesonephric) duct. According to the findings below, this ureter-like tube is probably the remnant of the incompletely developed metanephric duct. The findings include (1) the tube wall has the lamina propria and proper smooth muscle layers like the metanephric duct does as it matures into the ureter, (2) the tube epithelium is two cells thick with eosinophilic cytoplasm in a large part, while the wolffian duct epithelium is lined by the single layer of cells with clear or scant cytoplasm [13], and (3) the tube epithelium shows the immunophenotypic profile which is compatible with that observed in fetal metanephric tubules or metanephric adenoma of the kidney [5]. Moreover, tumors of presumed wolffian origin have been reported to occur in the broad ligament [6, 15] or in the paravaginal tissue [4] where wolffian remnants are regularly found and no intravaginal tumor has been reported as far as we know. Microscopically, the tumors consist predominantly of uniformly and closely packed, winding, branching, and anastomosing tubules, intermingled with occasional solid islands and diffuse areas [4, 6, 15], all of which resembles arrhenoblastoma (androblastoma, Sertoli-Leydig cell tumor). This characteristic histology differs from that in our case, in which papillotubular structures are widely or irregularly spaced, being separated by fibrovascular stroma.

The concomitant presence of an anomalous termination of the metanephric duct in the vagina, renal aplasia and a bicornate uterus indicates a congenital failure in the development of the urogenital system. There is a report of vaginal adenocarcinoma with the clinical features very similar to our case [10]. Its histology is clear cell adenocarcinoma, but it occurred in a 17-year-old German girl, who had a history of hypoplasia of the left kidney with an ectopic termination of the ureter in the upper vagina. The left ureter with an ectopic ostium in the left lateral fornix of the vagina had been surgically removed 2 years before adenocarcinoma was found. Since the carcinoma was present in the right anterior wall of the upper vagina, its direct connection with the removed ureter seems unlikely. The authors suggested that the ectopic termination of the ureter might have interfered with the homogeneous replacement of müllerian epithelium by the up-growing squamous epithelium of the vagina and that the müllerian epithelium that consequently persisted might have provided a histological basis for carcinogenesis, as adenosis may do in clear cell adenocarcinoma in women exposed to DES *in utero*. In our case, this possibility cannot be denied completely, but carcinoma's originating from the metanephric duct remnant epithelium is more likely as discussed above. Whatever the origin of the carcinoma is, these two cases suggest that we should include adenocarcinoma in the differential diagnosis of the vaginal tumor, especially when it is in the anterior wall, in patients with abnormal ureter terminations or renal aplasia/hypoplasia. Also, in the management of patients with these anomalies, the possibility of vaginal adenocarcinoma should be considered.

During fetal development, both the urogenital sinus and the müllerian tubercle take part in the formation of the vagina. On the posterior side of the urogenital sinus, the metanephric duct starts to grow as a ureteric bud from the wolffian duct near its entry into the sinus [8]. During this phase, an abnormal juxtaposition of metanephric ducts to the müllerian tubercle, possibly because of their incomplete development and failure to separate from mesonephric duct orifices, may lead to an ectopic termination of the metanephric duct in the vagina. The genetic background underlying this abnormal urogenital development is not completely elucidated, but it is known that glial cell line-derived neurotrophic factor (GDNF) is synthesized by the embryonic kidney mesenchyme and its receptor, Ret, by the tips of the growing ureteric buds (metanephric duct) that eventually form the ureters [14]. Thus, abnormal expressions of GDNF and Ret might have been involved in the interrupted and incomplete metanephric duct development in our case. Whether there are any specific genetic mechanisms which link carcinogenesis and the abnormal urogenital development is currently unknown. Since, in renal multicystic dysplasia, the persistent expression of embryonic genes, such as Pax2 and Bcl-2, is thought to lead to continuous cell proliferation and enhanced cell survival [16], aberrant overexpression of these genes might participate in part in carcinogenesis.

Acknowledgments The authors are grateful to Mr. T. Miyamoto for his skillful assistance in preparation of the manuscript.

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