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AGGRESSIVE COURSE OF A RARE TYPE OF URETHRAL CANCER IN WOMEN

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The article provides a clinical case of urethral cancer in women. Primary urethral carcinomas are rare, less than 1% of all malignant tumors. According to the Rarecare Cancer Surveillance Agency for Europe (RARECARE), urethral cancer in women is 0.6 and 1.6 in men per 1 million people per year. A 56-year-old patient with histologically verified clear cell adenocarcinoma of the proximal urethra was monitored for 18 months. An aggressive course of the tumor process has been shown, which led to the need to perform anterior exenteration of the pelvic organs. The histogenesis of primary clear cell urethral adenocarcinoma has not been definitively determined. The atypical external localization in the described case suggests the periurethral origin of this cancerous tumor from the Skene's glands. The demonstration of a rare form of urethral cancer, clear cell adenocarcinoma, contributes to the accumulation of knowledge about its histopathology and clinical course, as well as increasing cancer alertness in the treatment of urethral diseases in doctors of any specialty.

Keywords: urethral cancer; urethral adenocarcinoma; treatment of urethral cancer.

АГРЕССИВНОЕ ТЕЧЕНИЕ РЕДКОГО ВИДА РАКА УРЕТРЫ У ЖЕНЩИНЫ

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В статье приведено клиническое наблюдение рака уретры у женщины. Первичные карциномы уретры редки, менее 1 % всех злокачественных опухолей. По данным организации, осуществляющей эпидемиологический надзор за редкими видами рака в Европе (RARECARE), частота рака уретры у женщин составляет 0,6, а у мужчин — 1,6 случаев на 1 млн человек в год. Под наблюдением в течение 18 мес. находится 56-летняя пациентка с гистологически верифицированной светлоклеточной аденокарциномой проксимального отдела уретры. Показано агрессивное течение опухолевого процесса, приведшее к необходимости выполнения передней экзентерации органов малого таза. Гистогенез первичной светлоклеточной аденокарциномы уретры окончательно не определен. Нетипичная наружная локализация в описываемом случае позволяет предположить периуретральное происхождение этой раковой опухоли из скиниевых желез. Демонстрация редкой формы рака уретры, светлоклеточной аденокарциномы, способствует накоплению знаний о ее гистопатологии и клиническом течении, а также повышению онкологической настороженности при лечении заболеваний уретры у врачей любой специальности.

Ключевые слова: рак уретры; аденокарцинома уретры; лечение рака уретры.

INTRODUCTION

Primary urethral carcinomas are rare and represent less than 1% of all malignant tumors. According to the organization that implements the epidemiological surveillance of rare cancers in Europe (RARECARE), the incidence of urethral cancer in women and men is 0.6 and 1.6 cases per 1 million persons per year, respectively [1, 2]. The tumor usually develops in the postmenopausal period and 75% of patients with urethral cancer are above 50 years old [3, 4]. The risk factors for its occurrence are chronic infectious and inflammatory diseases, proliferative processes, diverticula, and long-term trauma to the urethral mucosa.

Among the histological variants of urethral cancer in women, squamous cell carcinoma (60%)

prevails compared to the rare urothelial carcinoma (20%) and very rare adenocarcinoma (10%) [1, 2]; although according to A. Trabelsi et al., adenocarcinoma accounts for 29% of all urethral cancers in women and arises from the periurethral glands [4].

Compared with other malignant neoplasms of the urinary tract, the prognosis of urethral cancer is poor, which is largely due to the late detection of the tumor [3]. However, localized tumors of the distal segment of the urethra have a relatively favorable prognosis, while tumors of its proximal segment have an aggressive course with the involvement of adjacent organs (neck of urinary bladder, vagina, and vulva). The five-year survival rate for this localization accounts for 20% [5].

Due to the rarity of this pathology, clinical guidelines for urethral cancer were published by the European Association of Urology only in 2013 [6]. For this same reason, there were no clear indications for choosing the most appropriate treatment method until recently [7, 8].

DESCRIPTION OF THE CLINICAL CASE

Patient V., 56 years old, visited an urologist with complaints on frequent urination, discomfort, and recurrent bloody-purulent discharge from the urethra. She was consulted by a gynecologist and based on the results of the transvaginal ultrasound and bimanual examination, with a diagnosis of paraurethral cyst and suppuration on October 22, 2018, she was hospitalized at the urology department. According to the results of bladder ultrasound examination (10/26/18), a rounded hypoechoic formation with uneven blurred contours was revealed in the projection of the urinary bladder neck, with heterogeneous echostructures up to 30 × 26 mm in size. With color Doppler mapping, peripheral blood flow was located in the urinary bladder after micturition, and the volume of residual urine was 87.6 ml. Chest fluoroscopic image done on October 22, 2018 revealed no pathology. The concomitant pathology was a small uterine myoma. According to the ultrasound examination, the organs of the abdominal cavity and kidneys were normal. On October 29, 2018, in the operating room, when an attempt to isolate a paraurethral formation (cyst) from the tissues of the anterior vaginal wall through the external opening of the urethra was made, a hemorrhagic discharge with tissue detritus occurred. Cystourethroscopy was performed and it revealed the clean and pink mucous membrane of the bladder, and the slit-like orifices in a typical place. In the area of the urinary bladder neck, the mucous membrane was edematous and dull. When examining the urethra, pronounced venous congestion was noted, and in the middle third at the 7 o'clock position, an ulceration/defect of up to 3 mm was found, which was a source of scanty bleeding, and no tumor tissue was revealed. A biopsy of the flat zone of the mucous membrane was performed from the region of the bladder neck using a 24 Ch resectoscope. Tissue detritus from the urethra was sent for cytological and histological examination. On October 30, 2018, magnetic resonance imaging (MRI) of the pelvic organs was performed, which showed a 1.5–2 cm thick densely elastic tissue growing visually in the projection of the urethra (Fig. 1).

The histological and immunohistochemical examination results from September 11, 2018 showed that sample 1 (urinary bladder neck mucosa) was represented by a polypiform fragment of the bladder mucosa covered with focally hyperplastic urothelium, with multiple Brunn's nests in the submucosa;

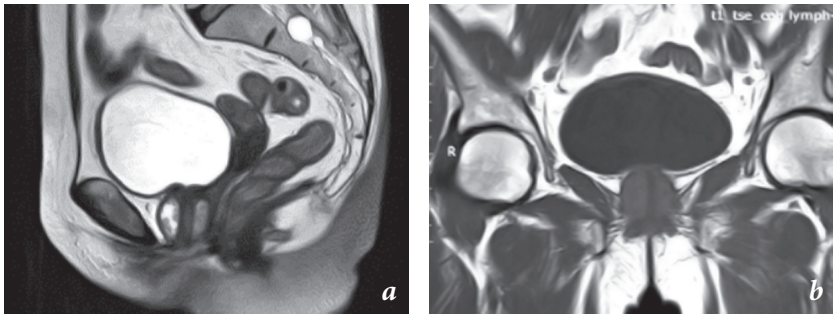

Fig. 1. MRI images of the pelvic organs of patient V., 56 y. o.: *a* — frontal projection, *b* — sagittal projection. A tumor with a clear outline is located around the urethra

Рис. 1. Магнитно-резонансная томография органов малого таза пациентки В., 56 лет: *a* — фронтальная проекция, *b* — сагиттальная проекция. Опухоль с четкими очертаниями расположена вокруг уретры

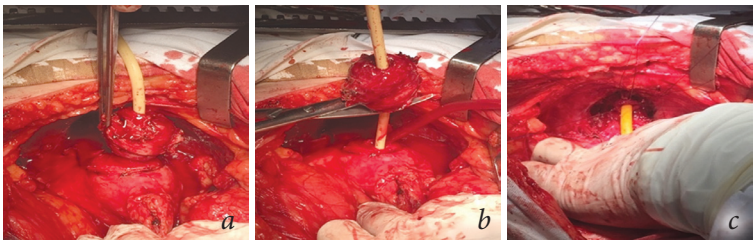

Fig. 2. The progress of the operation. Isolation of a tumor located around the urethra (*a*), excision of the tumor (*b*) with preservation of the neck the bladder and the distal part of the urethra (*c*)
Рис. 2. Ход операции. Выделение опухоли, расположенной вокруг уретры (*a*), иссечение опухоли (*b*) с сохранением шейки мочевого пузыря и дистальной части уретры (*c*)

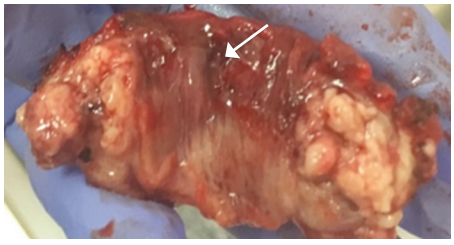

Fig. 3. Macropreparations. The urethra is dissected lengthwise, light tumor masses are visible around the urethral fragment and a lesion of ulceration of the mucous membrane (indicated by an arrow)
Рис. 3. Макропрепарат. Уретра рассечена вдоль, видны светлые опухолевые массы вокруг фрагмента уретры и очаг изъязвления слизистой оболочки (указан стрелкой)

sample 2 (tissue from the urethra) was represented by a papillary epithelial formation of cells with clear protoplasm, and with moderately pronounced cellular-nuclear polymorphism. Immunohistochemical study revealed a positive reaction with antibodies to cytokeratin 7 and p53, and weakly positive reaction with GATA 3. The reaction between antibodies and estrogen, progesterone, PSA, and cytokeratin 20 was negative. Therefore, a clear cell adenocarcinoma was concluded. The study of the gastrointestinal tract conducted on November 15, 2018 through fibrogastroduodenoscopy revealed gastritis without visible signs of atrophy; *Helicobacter pylori* test was negative; colonoscopy from November 16, 2018 showed no organic pathology. To remove the tumor, the patient was re-hospitalized with a clinical diagnosis of urethral cancer cT1 2N0M0. Laboratory tests (general urine analysis, 12/10/2018) showed specific gravity of 1025, protein 1.0 g/l, leukocytes 6–7–9 in the field of view, and erythrocytes 5–9 in the field of view; urine bacteriological examination (12/11/18) revealed no bacteriuria. Surgical treatment was performed on December 13, 2018.

Surgery course. A densely elastic tumor around the urethra was revealed intraoperatively (Fig. 2), which was easily isolated from the surrounding tissues. It was decided to excise the tumor with a fragment of the urethra, while preserving the urinary bladder neck and distal segment of the urethra with the imposition of a cystourethroanastomosis. The excised tumor was a round-shaped, tight-elastic formation located around the urethral fragment (Fig. 3). On the macro-preparation, there was no visually exophytic growth in the urethral lumen, and the mucous membrane was pellucid and focal hyperemic. When the surgical material was excised, a fragment of an elastic whitish tumor tissue of 4 × 3 × 2 cm in size with an adjacent lamellar segment of the urethra of 3 × 2.5 cm in size and 0.2 cm thick was described. The histological examination revealed papillary growths of an immature tumor of the tubular-papillary structure of cells with clear protoplasm and the presence of cellular-nuclear polymorphism, which has a clear cell carcinoma structure along the outer surface of the urethra with an ingrowth into the muscle layer of the urethra. The mucous membrane of the urethra has a plethora, without tumor growth (Fig. 4). Thus, the ana-

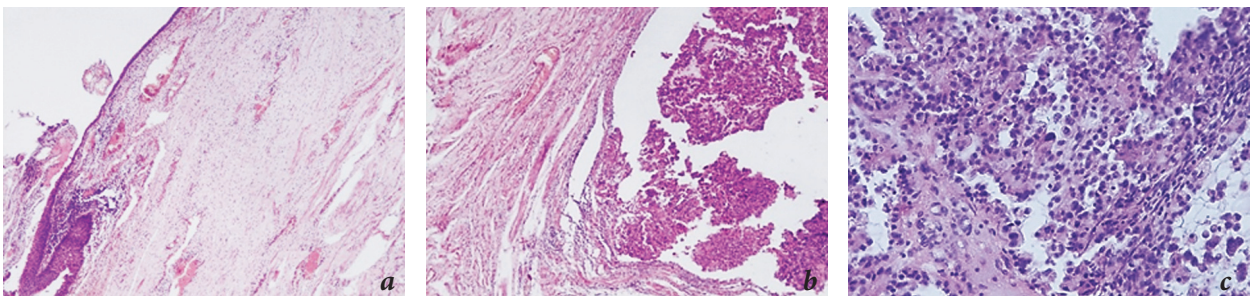

Fig. 4. Histological preparations of the urethra with a tumor: *a* – the mucous membrane of the urethra, there is no tumor growth (stain hematoxylin-eosin, ×40); *b* – clear cell carcinoma with invasive growth in the outer layers of the urethra (stain hematoxylin-eosin, ×100); *c* – clear cell carcinoma of the urethra (stain hematoxylin-eosin, ×200)
Рис. 4. Гистологические препараты уретры с опухолью: *a* — слизистая оболочка уретры, роста опухоли нет (окраска гематоксилином и эозином, увеличение ×40); *b* — светлоклеточная карцинома с инвазивным ростом в наружных слоях уретры (окраска гематоксилином и эозином, увеличение ×100); *c* — светлоклеточная карцинома уретры (окраска гематоксилином и эозином, увеличение ×200)

tomicopathological stage according to the T gradation was pT2. The patient was discharged from the hospital on day 12 after the surgery. At the time of discharge, she had no urine continence and was using diapers.

During the control examination in March 2019 the patient presented with complaints of urinary incontinence. According to contrast-enhanced MRI of the abdominal cavity and kidneys, no pathological formations were revealed. Contrast-enhanced MRI of the lesser pelvis revealed a myomatous nodule in the uterus measuring 1.4 × 1.7 cm and lymphadenopathy, and obturator lymph nodes on both sides up to 7 mm in size were regarded as reactive. The patient was hospitalized routinely for the elimination of urinary incontinence. On March 3, 2019, a urethral stricture was revealed during examination in the operating room. An internal optical urethrotomy with an excisional biopsy of the urethral mucosa was performed. The histological examination revealed fragments of connective tissue without surface epithelium and tumor growth. Due to family problems, the patient was discharged and came for examination only in August 2019, when MRI (08/22/19) revealed an extensive tumor process in the urinary bladder neck with involvement of the anterior vaginal wall. In September 3, anterior pelvic exenteration, lymph node dissection, and bilateral ureterocutaneostomy were performed.

Histological examination revealed the growth of a clear-cell adenocarcinoma of the glandular-papillary structure in the outer parts of the myometrium, serous membrane of the uterus, and in the isthmus, uterine cervix, micro foci of growth in the ovaries, and fallopian tubes, with the presence of tumor emboli in the lumens of many lymphatic vessels and individual blood vessels in each localization. In the urinary bladder, the growth of the carcinoma was detected at different locations throughout the entire thickness of the wall, including the mucous membrane. In all the four lymph nodes of the obturator fossa, metastases of the carcinoma were noted, that is, there was a continued growth of clear-cell adenocarcinoma with invasion into the urogenital organs and metastasis.

The patient was referred for monitoring by the oncologist and chemotherapy treatment started.

DISCUSSION

An atypical external localization in the reported case suggests a periurethral origin of this cancerous tumor from the periurethral glands. It is believed that according to the histological structure, primary adenocarcinoma of the urethra is usually represented by adenocarcinoma of the mucinous or endocervical type. Clear-cell adenocarcinoma is less common, and is similar in histological structure to clear cell endometrial carcinoma. Histomorphologically, these tumors have a tubulocystic, papillary and/or solid architecture and consist of cells with a clear cytoplasm, usually with significant nuclear polymorphism and numerous mitoses [9]. In the case presented, clear-cell adenocarcinoma had a glandular-papillary structure. However, the aspects of the histological structure of clear cell carcinoma do not affect the prognosis. Due to the aggressive behavior, it is unfavorable in any case [10]. Histogenesis of primary clear-cell adenocarcinoma of the urethra is not conclusively established. There are hypotheses that clear-cell adenocarcinoma may originate from the diverticulum [8], foci of glandular metaplasia of the urothelium [9], Müllerian residues [11, 12], and periurethral glands [4, 13]. Urethral cancer in women is usually manifested by urethral bleeding, symptoms in the lower urinary tract, and palpable mass or induration in the urethra. To establish the diagnosis of urethral cancer, verification with tumors of the vulva and vagina is necessary; as well as with inflammatory diseases and benign formations of the urethra, paraurethral cysts, and prolapse of the urethral mucous membrane in combination with prolapse of the vaginal walls. In the clinical case described, the initial diagnosis was paraurethral cyst, due to the similarity of the disease clinical presentation and the absence of oncological alertness of outpatient doctors, apparently due to the rare detection of urethral cancer.

Until recently, there were no uniform recommendations on the treatment approach of patients with urethral cancer. Russian clinical guidelines approved by the Ministry of Health of the Russian Federation were published only in 2019 [14]. The recommendations of the European Association of Urology stated that tumors of the distal urethra in advanced stages can be successfully treated by surgical methods in men or radiation therapy in women. In women with localized urethral cancer, the most effective approach is primary radical urethrectomy with removal of the entire periurethral tissue from the bulbocavernosus muscles on both sides, and distally to the pubic symphysis and urinary bladder neck with

all adjacent soft tissues [15, 16]. At the same time, the organ sparing approach in the surgical treatment is not rejected in the course of excision, electric excision, laser vaporization or coagulation of the tumor, and sleeve resection of the urethra in small localized tumors [14]. In the case presented, the organ sparing volume of the surgical intervention (taking into account the rounded shape of the formation, the elastic consistency, and the easy isolation of the tumor from the surrounding tissues during the surgery), as well as the desire to preserve the integrity and function of the lower urinary tract, was a mistake, as the rare morphological type of tumor with a relatively poor prognosis was not taken into account. The patient developed a rapid progression of the tumor process with the maximum spread of tumor emboli in the lymphatic system.

S.R. Rane et al. [17], in their analysis of a similar case of clear-cell adenocarcinoma of the urethra, drew attention to the importance of the awareness of histopathology in conjunction with the "behavior" of such a tumor, since it is prone to rapid recurrence and distant metastasis, and the prognosis in neglected cases is poor.

CONCLUSION

A case of an aggressive clinical course course of a rare urethral tumor, clear-cell adenocarcinoma, is presented. The aim of this case report is to increase oncological alertness among gynecologists, urologists, and surgeons.

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REFERENCES

1. Gatta G, van der Zwan JM, Casali PG, et al. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer*. 2011;47(17):2493-2511. https://doi.org/10.1016/j.ejca.2011.08.008.
2. Visser O, Adolfsson J, Rossi S, et al. Incidence and survival of rare urogenital cancers in Europe. *Eur J Cancer*. 2012;48(4):456-464. https://doi.org/10.1016/j.ejca.2011.10.031.
3. Swartz MA, Porter MP, Lin DW, Weiss NS. Incidence of primary urethral carcinoma in the United States. *Urology*. 2006;68(6):1164-1168. https://doi.org/10.1016/j.urology.2006.08.1057.
4. Trabelsi A, Abdelkrim SB, Rammeh S, et al. Clear cell adenocarcinoma of a female urethra: A case report and review of the literature. *N Am J Med Sci*. 2009;1(6):321-323. 3364636.
5. Champ CE, Hegarty SE, Shen X, et al. Prognostic factors and outcomes after definitive treatment of female urethral cancer: a population-based analysis. *Urology*. 2012;80(2):374-381. https://doi.org/10.1016/j.urology.2012.02.058.
6. Gakis G, Witjes JA, Comperat E, et al. EAU guidelines on primary urethral carcinoma. *Eur Urol*. 2013;64(5):823-830. https://doi.org/10.1016/j.eururo.2013.03.044.
7. Рич Д.П., Д'Амико Э.В. Онкоурология. – М.: Бином, 2011. – 896с. [Rich DP, D'Amiko EV. Onkourologiya. Moscow: Binom; 2011. 896 p. (In Russ.)]
8. Клинические рекомендации Европейской ассоциации урологов, 2017. – М.: Медфорум, 2017. – 1224 с. [Clinical recommendations of the European Association of Urology, 2017. Moscow: Medforum, 2017. 1224 p. (In Russ.)]
9. Ball RY. Pathology and genetics of tumours of the urinary system and male genital organs. *Histopathology*. 2005;46(5):586-586. https://doi.org/10.1111/j.1365-2559.2005.02096.x.
10. Mehra R, Vats P, Kalyana-Sundaram S, et al. Primary urethral clear-cell adenocarcinoma: comprehensive analysis by surgical pathology, cytopathology, and next-generation sequencing. *Am J Pathol*. 2014;184(3):584-591. https://doi.org/10.1016/j.ajpath.2013.11.023.
11. Weng WC, Wang CC, Ho CH, et al. Clear cell carcinoma of female urethral diverticulum – a case report. *J Formos Med Assoc*. 2013;112(8):489-491. https://doi.org/10.1016/j.jfma.2012.07.018.
12. Satyanarayan A, Redd L, Dyer A, et al. Adenocarcinoma of the urethra with mucinous features. *Rev Urol*. 2015;17(1):38-41. 4444775.
13. Scantling D, Ross C, Jaffe J. Primary clear cell adenocarcinoma of a urethral diverticulum treated with multidisciplinary robotic anterior pelvic exenteration. *Case Rep Med*. 2013;2013:387591. https://doi.org/10.1155/2013/387591.
14. legalacts.ru [интернет]. Министерство здравоохранения РФ. Клинические рекомендации «Рак уретры» (утв. Минздравом России). 2020 [доступ от 19.05.2020]. Доступ по ссылке: https://legalacts.ru/doc/klinicheskie-rekomendatsii-rak-uretry-utv-minzdravom-rossii/ [legalacts.ru [Internet]. Ministerstvo zdravookhraneniya RF. Klinicheskie rekomendatsii "Rak uretry" (utv. Minzdravom Rossii). 2020 [cited 19 May 2020]. Available from: https://legalacts.ru/doc/klinicheskie-rekomendatsii-rak-uretry-utv-minzdravom-rossii/ (In Russ.)]
15. Hohenberger P, Kasper B. Die International Rare Cancers Initiative. *Forum*. 2017;32(1):26-31. https://doi.org/10.1007/s12312-016-0210-x.

16. Karnes RJ, Breau RH, Lightner DJ. Surgery for urethral cancer. *Urol Clin North Am*. 2010;37(3):445-457. https://doi.org/10.1016/j.ucl.2010.04.011.

17. Rane SR, Ghodke AN, Vishwasrao S. Clear Cell Adenocarcinoma of Female Urethra. *J Clin Diagn Res*. 2017;11(7): ED01-ED02. https://doi.org/10.7860/JCDR/2017/25261.10127.

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