Prostatic ductal adenocarcinoma

V.A. Biryukov[1], N.A. Gorban[2], O.B. Karyakin[1], D.V. Neledov[1], A.D. Kaprin[1]

[1]A.F. Tsyb Medical Radiology Research Center, Branch, National Medical Radiology Research Center, Ministry of Health of Russia; 10, Zhukov St., Obninsk, Kaluga region, 249036, Russia;

[2] FSCI "The Main Military Clinical Hospital named after N.N. Burdenko" of the Ministry of Defence of Russia; 3, Gospitalnaya Sq, Moscow, 105229, Russia

***Contacts:** Vitali Aleksandrovich Biryukov vitbirukov@mail.ru*

Prostate cancer (PC) is the most common form of cancer among men. Ductal carcinoma is the second common histological type of prostatic adenocarcinoma. Various types of ductal carcinoma have been described in the literature, each of which has its own distinct histological picture. Ductal carcinoma is a relatively rare histological subtype of PC, which is traditionally known as a more aggressive form of PC, with a high Gleason score (9, 10) and lack of standardized treatment. In this work we report 3 cases of ductal PC which were diagnosed in our clinic.

***Keywords:** prostate cancer, prostatic ductal adenocarcinoma, docetaxel*

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Prostate cancer (PC) is the most common form of cancer among men in Europe, as well as in Russia. The incidence rate for PC in Russia has already exaggerated 30 cases per 100.000 males [1, 2]. The vast majority of prostatic tumors developing in adult males are typical acinar adenocarcinoma. Another type of PC is ductal adenocarcinoma [3]. In pure form, ductal adenocarcinoma accounts for approximately 0,2 % to 0,8 % of PC [4] and it is usually located centrally around the prostatic urethra [3, 5]. More frequently (approximately 5 %) it is located peripherally admixed with typical acinar adenocarcinoma [6].

According to the 2004 WHO classification prostatic ductal adenocarcinoma is defined as a subtype of adenocarcinoma, which is composed of larger glands lined by tall pseudostratified columnar cells [3].

Initially, this type of cancer was described by M.M. Melikow and M.R. Pachter, who used the term «endometrial» carcinoma as it often histologically resembles endometrial adenocarcinoma of the female uterus. Therefore, Melikow and Pachter suggested that the morphologic appearance and common location of this tumor near the prostatic verumontanum indicated from origin the mullerian (female) remnant of the utriculus masculinus, implying that these tumors are estrogen-dependent [7]. However, this hypothesis of true uterine («endometrial») is now abandoned because the tumor turned out to be very sensitive to hormonal therapy. Moreover, the data of further immunohistochemical (IHC), ultrastructural and histochemical studies have shown that endometrioid carcinoma is merely a histopathologic variant of prostatic adenocarcinoma. Thus, the term «endometrial» is not recommended to use.

This type of cancer occurs exclusively in older men [8]. The clinical symptoms of pure ductal carcinoma and mixed ductal-acinar carcinoma overlap with those with typical acinar carcinoma [6]. Hematuria and urethra obstruction are common clinical manifestations if the tumor is located around the urethra. In some cases, adenocarcinoma is detected by digital rectal examination. Elevated levels of prostate specific antigen (PSA) is found in more than half of the cases and is usually associated with peripherally located acinar adenocarcinoma [8]. Cystoscopically, ductal carcinoma may appear as multiple friable polypoid or wormlike white masses protruding from ducts at or near the mouth of the prostatic urticle of the verumontanym. More often, however, no distinguishing cystoscopic findings are identified [9].

Histologically, pure ductal carcinoma consists of masses of complex papillae or anastomosing glands, cribriform or solid patterns lined by a pseudostratified columnar epithelium. The papillary and cribriform patterns of ductal carcinoma coexist in approximately half of cases, and both usually display nuclear anaplasia, nucleomegaly, and frequent mitotic figures. The neoplastic cells have abundant cytoplasm that is lightly amphophilic, eosinophilic or clear cytoplasm. Unlike high-grade prostatic intraepithelial neoplasia (PIN), cribriform masses of ductal carcinoma may have lack of basal cell layer.

In some cases comedo necrosis is present, which is characterized by the appearance of the abundant necrotic debris in duct lumina surrounded by malignant cells of high mitotic activity. It makes the picture quite similar to comedocarcinoma of the breast [3, 5, 6, 8].

Immunohistochemically, ductal adenocarcinoma is strongly positive for PSA, PSAP and racemasa. Discontinuous level of basal cells is detected in 30 % of cases. Ductal carcinoma is focally positive for CEA, CK7, CK20 and has high values of Ki67 expression. CDX2 marker is rarely positive [3, 5, 6, 8].

Materials and methods

Further we report 3 cases of ductal PC which were diagnosed in our clinic (table)

***Patient M.**, 1957 y. b., was referred to a local urologist due to the complaints of hematospermia which have been periodically since 2009. Further examination revealed benign prostatic hyperplasia (BPH). 14.11.2014 due to intermittent hematuria, transurethral resection (TUR) of the BHP was performed. 24.02.2014 persisting hematuria led to one more TUR of the posterior urethra. Final pathological report: prostate tissue with poorly differentiated complexes of «traditional» cell carcinoma. The patient underwent the first cycle of polychemotherapy (PCT) with gemcitabine/cisplatin, given in the 1, 2 and 8 days of the cycle. Then patient was referred to the MRRC, Obninsk.*

Complex examination in the MRRC revealed the following: total PSA level (25.03.2014) 0,6 ng/ml; free/total PSA ratio 11,6 %; low hemoglobin level (119,0 g/l) in the complete blood count test (25.03.2014); iron level 5,5 μmol/l in the biochemical analysis. Other parameters were in their reference ranges.

Magnetic resonance imaging (MRI) of the pelvis did not detect bladder cancer. MRI revealed the signs of PC, T3b: prostate has heterogenous multinodular structure; external part (primarily of the left side) is deformed with extraprostatic extension through Denonvilliers» fascia with rectal wall deformation without compromising its integrity. Seminal vesicle infiltration. Prostate volume – 158 cm^3. Solitary 19 mm-sized lymph nodes (LN) along the both sides of the common and external iliac vessels. Bone abnormalities in the imaging area were not found (fig. 1 and 2).

01.04.2014 the patient underwent multiple prostate biopsies before the diagnosis of PC was done. Histological report: growth of solid prostatic ductal adenocarcinoma with focal areas of necrosis, Gleason score 10 (5+5).

Final diagnosis was PC cT3bN1M1a and was based on the results of the findings. Since April, 2014 the patient underwent hormonal therapy with luteinizing hormone-releasing hormone (LHRH) analogues. Since April, 2015 he has noticed the appearance of the nagging pain in the perineum and urinary retention. Examinations revealed the local progression of PC with persistent low PSA level (0,26 ng/ml) and castrate level of testosterone.

The patient was recommended 6 cycles of docetaxel chemotherapy (75 mg/m^2) with further MRI scan. After that the decision about the course of external radiation therapy of the prostate, seminal vesicles and pelvic lymph nodes would be taken

***Patient Ye.**, 1955 y. b., medical history № 5878/14, was referred to the MRRC, Obninsk on 30.06.2014. Among the main complaints were intermittent hematuria and frequent urination. There was a history of prostate biopsy, which was done in 2011, but there were no any signs of the tumor cell growth according to the medical history. 17.01.2014 due to persistent hematuria, TUR of the bladder neck tumor was performed. Histological report revealed poorly differentiated transitional cell carcinoma. Final diagnosis was bladder cancer T3NxM0 and was based on the results of histological findings and cystoscopy findings. Then the patient underwent 3 cycles of PCT with gemcitabine/cysplatinum. 03.06.2014 initial persisting hematuria led to one more TUR of the seminal vesicle tumor (cystoscopy findings: villous mass with bullous edema without clear boundaries). Histological report (based on the TUR findings): prostate tissue with complexes of poorly differentiated transitional cell carcinoma.*

Revision of the TUR findings, which was done in the MRRC, found prostatic ductal adenocarcinoma, Gleason score 9 (4+5). MRI of the pelvis: postoperative MRI scan of the bladder neck and the posterior urethra. Ultrasound imaging (USI) revealed PC T3b. Prostate volume 40 cm^3. MR scan of PC T3b (seminal vesicle invasion). Lymphadenopathy

Examination results of patients with prostatic ductal adenocarcinoma

Patient	Clinical symptoms	PSA	USI, MRI	Bone scintigraphy	Histology
M. 1957 y.b. TUR, cT3bN1M1a	Hematospermia, hematuria	0,6 ng/ml; free/total – 11,6 %	Locally advanced cancer, T3b, metastases in LN (N1)	Pathology is not revealed	Ductal carcinoma, Gleason score 10 (5+5)
Ye. 1955 y.b. TUR, cT3bN0M0	Hematuria	8,26 ng/ml; free/total – 44,3 %	Locally advanced cancer, T3b	Pathology is not revealed	Ductal carcinoma, Gleason score 9 (4+5)
X. 1964 y.b. Resection of retroperitoneal mass, cT3bN1M1b	Nagging pain in the iliac region,hydronephrosis on the left side	2,66 ng/ml; free/total – 23,4 %	Locally advanced cancer, T3b, metastases in LN (N1), bones (M1)	Pelvic bone metastases, Soloway 1	Ductal carcinoma, Gleason score 9 (4+5) and acinar carcinoma, Gleason score 9 (4+5)

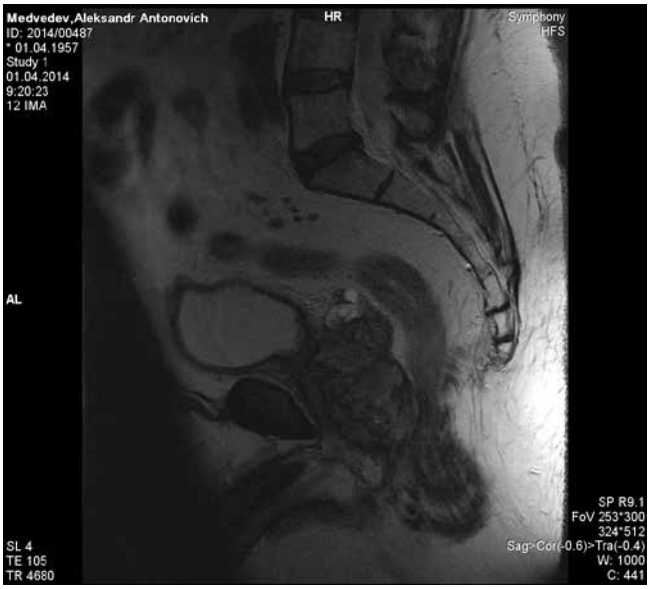

Fig. 1. *Patient M. MR scan of locally advanced ductal PC*

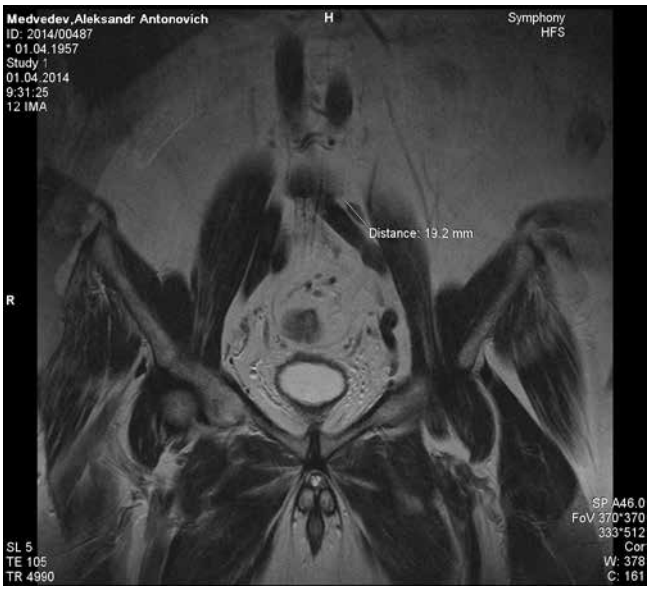

Fig. 2. *Patient M. MR scan of iliac lymphadenopathy*

as well as bone abnormalities in the imaging zones were not found (fig. 3).

Bone scintigraphy does not reveal any abnormal accumulation of the agent. Total PSA level (08.07.2014) was 8,26 ng/ml; free/total PSA ratio 44,3 %. Chest x-ray did not find any abnormalities. Complete blood count test (17.07.2014) revealed grade 1 anemia (hemoglobin level 105,0 g/l) and biochemical analysis revealed low iron level (6,5 μmol/l). All other parameters were in their reference ranges. The patient underwent transrectal US-guided prostate and seminal vesicles biopsies, which conformed the diagnosis of prostatic ductal adenocarcinoma.

Final diagnosis was PC cT3bN0M0 and was based on the results of the USI, MRI, revision of the TUR findings and results of the prostate biopsy. Comorbidity: coronary heart disease (2003); aortic and coronary artery atherosclerosis, grade II exertional angina; ischemic cardiomiopathy; grade I heart failure; grade II stage IV arterial hypertension; type 2 diabetes.

The patient underwent the following combination of the radiation and hormonal therapy: since 17.07.2014 bikalutamide 50 мг/daily during 1 month; since 25.07.2014 injections of gosorelin acetate 3,6 mg for up to 2 years. Since 21.07.2014 the patient underwent the course of conformal radiation therapy of the prostate and seminal vesicles, single radiation dose 2 Gy, up to the cumulative dose of 74 Gy. No serious adverse events were noticed during his treatment. Hematuria stopped since the second week of the combined therapy. Compete blood count test (04.08.2014) revealed the increase of hemoglobin level up to 117,0 g/l with further increase till normal levels.

Control USI which was done in September, 2015 revealed remission of the disease with normal kidney and bladder structures. PSA level was 0,23 ng/ml. Today the patient continues his course of adjuvant hormonal therapy with LHRH analogues.

***Patient X.**, 1964 y. b., was referred to a local urologist due to the nagging pain in the left iliac and lumbar regions which have been for about 4 months. In spring 2014 the patient was examined, after which he underwent surgery (partial removal of the retroperitoneal tumor with reimplantation of the left ureter).*

Histological analysis of the resected tumor which was done in the MRRC revealed fibro-adipose tissue with the invasive growth of the prostatic ductal carcinoma, Gleason score 9 (4+5). Total PSA level (21.07.2014) was 2,66 ng/ml; free/total PSA ratio 23,4 %; carcinoembryonic antigen – 3,15 ng/ml; chorionic gonadotropin – 0,1 IU/l; all parameters of complete blood count test (24.07.14) were in their reference ranges. Biochemistry revealed elevated levels of urea (11,2 mmol/l), creatinine (135 μmol/l), as well as elevated values of aminotransferase enzymes: alanine aminotransferase – 105 IU/l and aspartate aminotransferase – 80 IU/l. Test for antibodies to the hepatitis C virus was positive.

MRI (21.07.2014) revealed the signs of PC with extraprostatic extension and seminal vesicle infiltration. Lymphadenopathy of the left pelvic LN. Pelvic bone metastases (fig. 4 and 5).

Bone scintigraphy (21.07.2014) revealed abnormal accumulation of the agent in the pelvic bones: bones that form left acetabulum (up to 152 %) and right ilium (up to 125 %). Spiral thoracic CT (17.06.2014) did not find any abnormalities.

Due to the histological findings, MR scan and results of the digital rectal examination, the patient was suggested to undergo multiple prostate and seminal vesicles biopsies. Histological report: adenocarcinoma with small acinar prolifera-

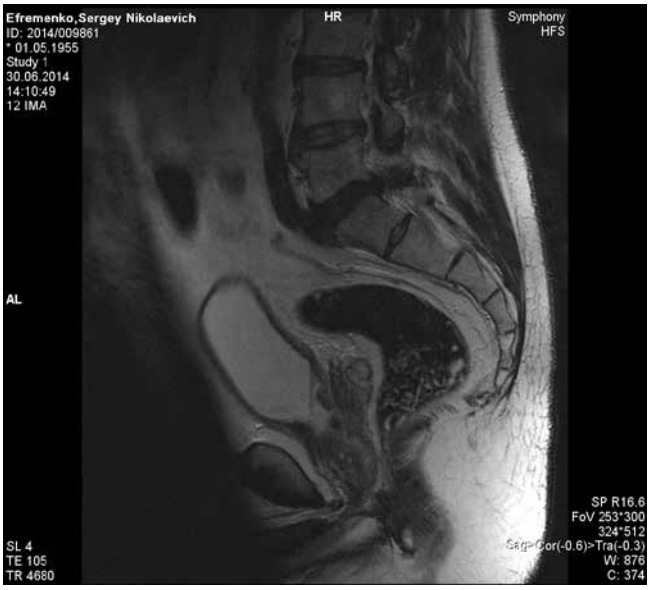

Fig. 3. *Patient Ye. MR scan of locally advanced ductal adenocarcinoma, after TUR of the bladder neck and posterior urethra*

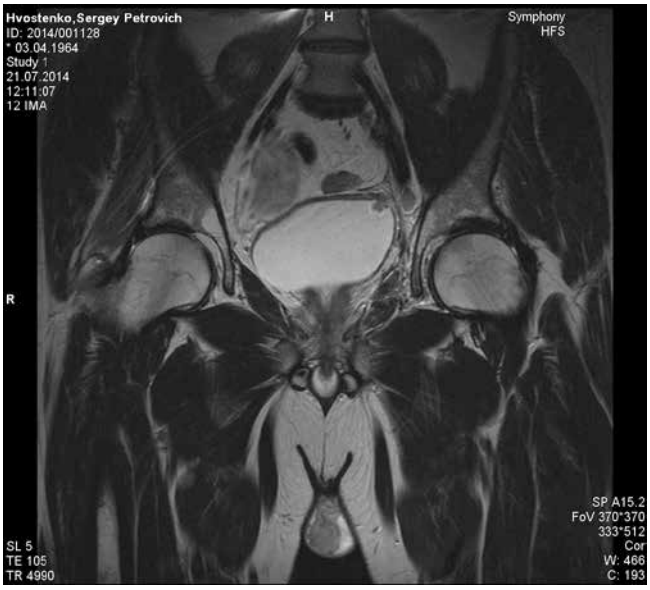

Fig. 4. *Patient X. MR scan of locally advanced PC, pelvic lymphadenopathy*

tion, Gleason score 9 (4+5), perineural growth and seminal vesicle invasion. Final diagnosis was PC cT3bN1M1b and was based on the results of the findings. Comorbidity: arterial hypertension, compensated type 2 diabetes, hepatitis C.

Due to the spread of the disease, histological findings of the primary tumor and LN metastases, the patient underwent the following combined treatment: 24.07.2014 – firmagon 240 mg injection, taxane based chemotherapy;25.07.14–160 mg docetaxel every 21 days № 6. After that the patient underwent the course of conformal radiation therapy of the prostate, seminal vesicles and metastases (up to the cumulative dose of 74 Gy).

Control examination which was done in October, 2015 revealed remission of the disease with complete regression of the detected pelvic LN, stable bone metastases. Today the patient continues his hormonal therapy with LHRH analogues.

Discussion

Morphological diagnosis of ductal carcinoma is a complicated procedure. On the one hand, this is due to the relative rarity of this disease and a lack of alertness from pathologists. On the other hand, it is associated with the objective difficulties due to the certain peculiarities of its histology. The differential diagnosis should be done between ductal carcinoma and PIN, acinar cribriform hyperplasia and urothelial cancer.

Thus, in the first 2 reported cases the initial morphological diagnosis was papillary urothelial carcinoma. The tumor of the first patient is predominantly solid. The tumor of the second patient consists mainly of papillary structures, which are quite similar to urothelial cancer, from the first sight. However, the typical clinical picture of ductal carcinoma is complemented by the distinct pattern of immunophenotypic features distinguished by IHC. Among them are positive staining for PSA, PSAP and negative staining for CK7, CK20 and p63 (fig. 6, 7).

The existing variants of ductal carcinoma make diagnostics even more complicated. Thus, ductal carcinoma may be comedocarcinoma with high mitotic activity, which makes the picture quite similar to comedocarcinoma of the breast. In this case it is very difficult to distinguish it with acinar adenocarcinoma with Gleason score 5.

The recent work [5] describes the urothelial type of ductal adenocarcinoma which can contain both intraductal and invasive components. The intraductal component usually merges with regions of papillary or cribriform pattern. The urothelial type of adenocarcinoma is diffusely positive for CK7 and focally positive for 34 E12, thrombomodulin, and CK20, weakly or even negative staining for PSA и PAP.

Cystic growth is a less common pattern that usually occurs in the peripheral zone, often with exophytic papillary and cribriform growth within large accommodating spaces in a manner similar to that of endometrial tumors expanding within the uterine cavity or ovarian tumors growing within cystic spaces [5].

Among the rare patterns of ductal carcinoma are PIN-like (ductal) adenocarcinoma, mucinous prostatic ductal adenocarcinoma and prostatic ductal adenocarcinomas with associated foamy gland, micropapillary and Paneth cell-like neuroendocrine features.

The differential diagnosis includes the following types of cancer:

1) secondary colorectal carcinoma invading the prostate;

2) urothelial carcinoma;

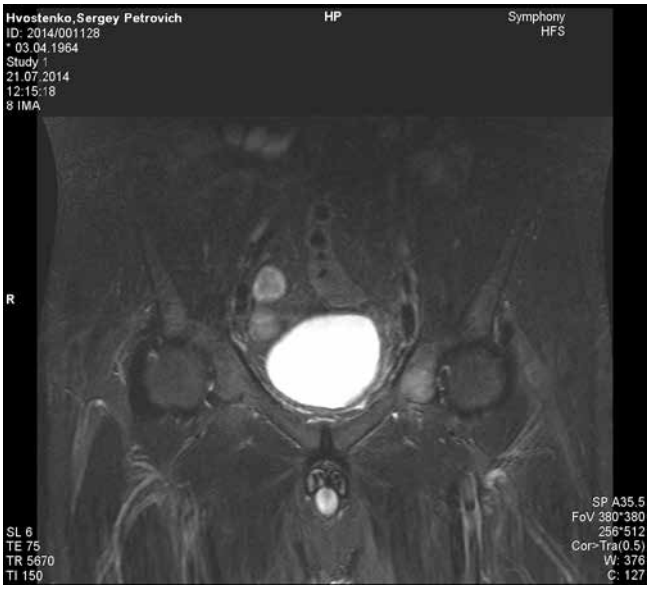

Fig. 5. *Patient X. MR scan of pelvic bone metastases*

3) acinar adenocarcinoma;

4) cribriform PIN.

Secondary adenocarcinoma of colonic origin is diffusely CDX2 and CK20 positive and negative for PSA, PSMA. Urothelial carcinoma has coexpression of CK7 and CK20, p63 and it is negative for PSA, PSMA.

Ductal carcinoma is primarily admixed with typical acinar carcinoma and is often detected as acinar carcinoma (Gleason pattern 4 or 5). In this case the clinical symptoms of the disease are of acinar adenocarcinoma with elevated PSA level. Moreover, symptoms of obstruction and hematuria are not typical for this case as both ductal and acinar components are located in the peripheral zone. The ductal component discovered during the trepanobiopsy of the prostate is submitted to a minimum. Thus, in patient X prostate histology, the tumor consists mainly of the acinar component, whereas the ductal component is found in the metastasis. Apparently the last one was not taken during biopsy, but as a more aggressive component it prevailed in the metastatic tumor. Due to the fast spread of ductal element in ductal-acinar carcinoma, ductal component or both elements are primarily found in the metastatic tissue [8].

Prostatic ductal adenocarcinoma is the only non-acinar adenocarcinoma, to which Gleason score is applied. Whereas the recommended Gleason grading for it is 4, comedocarcinoma and solid tumors have a Gleason score of 5 [3].

Ductal adenocarcinoma is a more aggressive tumor in comparison to acinar adenocarcinoma. Some reported that 25–40 % of patients with ductal carcinoma have metastases at the time of diagnosis and 5-year overall survival rate is 15–43 % [3, 8]. Localized ductal element in the biopsy is one of the main reasons of the combined treatment approach to this disease.

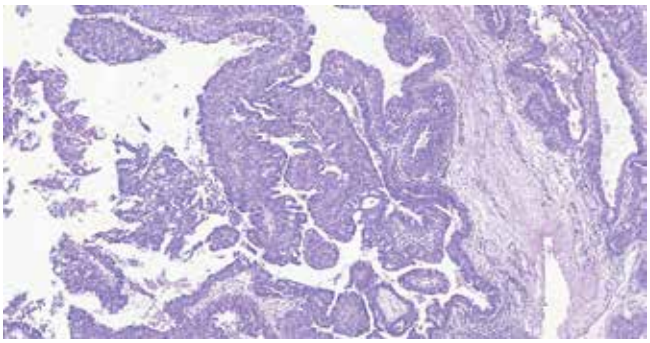

Fig. 6. *Ductal carcinoma with papillary patterns (patient's Ye. histology)*

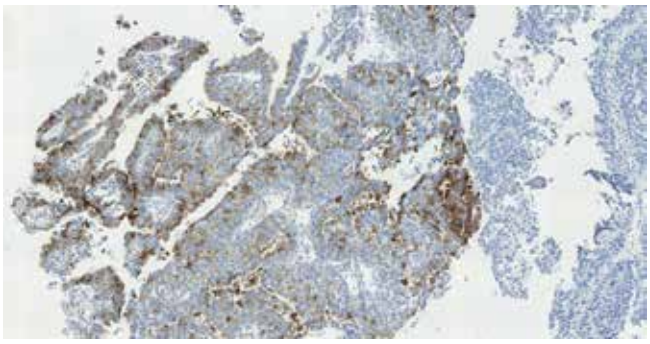

Fig. 7. *Ductal carcinoma with papillary patterns, PSA is expressed by tumor cells (patient's Ye. histology.)*

Among the established methods of treatment of prostatic ductal adenocarcinoma are prostatectomy for a localized PC, radiation therapy and hormonal therapy for locally advanced PC, hormonal therapy for metastatic disease. Several authors think that the advantages of a combined radiation and hormonal therapy outweigh any potential benefits of a surgical approach [4, 6, 10]. Thus, in the study conducted by S. Iğdem et al [10] combined radiation and hormonal therapy resulted in 3-years PSA PFS rate of 79 %, whereas in the group of patients with performed prostatectomy it was 65 %. Docetaxel has been found to be of limited clinical use in the treatment of prostatic ductal adenocarcinoma with no more than 3 cases described in the literature [11–13]. However, in all these cases docetaxel was given to patients with castration-resistant PC, whereas in our work 2 out of 3 patients received it together with the hormonal therapy at the beginning of treatment.

It should be noted that the standard of treatment of prostatic ductal carcinoma hasn»t been established yet due to the limited number of patients with this disease.

Conclusion

Ductal carcinoma is a relatively rare histological subtype of PC, which is traditionally known as a more aggressive form of the disease, with a high Gleason score (9, 10), primary metastatic tumors and lack of standardized treatment.

In comparison to acinar adenocarcinoma, which does not have symptoms of the disease for a long time, ductal

carcinoma is primarily located around the urethra. Therefore, among its common clinical manifestations are obstruction, dysuria and hematuria. Due to the persistent hematuria and obstruction, TUR is often performed which reveals bleeding exophytic mass of the prostatic urethra with the involvement of the bladder neck. Digital rectal examination enables to reveal dense prostate of the deformed shape. Inspite of the spread of the disease, this subtype of PC is barely known for its elevated PSA level. Combined PC (ductal-acinar carcinoma) has the clinical symptoms of typical acinar adenocarcinoma which makes it difficult to detect. Therefore, its verification could be primarily done by histology.

Proper diagnosis is also based on the data of histological studies, IHC analysis of the TUR-material, prostate and seminal vesicles» biopsy. Modern imaging techniques (USI and MRI) play a significant role as well as collaborative work between clinicians, laboratories and diagnostic structures. The last approach enables to evaluate properly the results of the examination and develop the optimal treatment strategy.

Surgery is highly recommended to treat localized forms of the disease. Combination of the radiation therapy and hormonal therapy is recommended for locally advanced PC. Interestingly, that for a long time this combined approach has been considered as less effective that was denied by the results of the latest studies. Multimodal approach has the greatest benefit to the treatment of this subtype of PC. It enables to achieve high results by combining surgery, radiation therapy and chemohormonal therapy together.

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