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# METASTATIC TUMORS OF THE ADRENAL GLAND: THE EXPERIENCE OF OUR CLINIC.

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**Abstract:**

Differential diagnosis between benign, primary and secondary malignant tumors is a critical issue in the clinical management of adrenal tumors, especially in patients with isolated adrenal lesions. In most cases, the correct diagnosis can be established microscopically with standard hematoxylin and eosin staining. However, in some cases, it is almost impossible to differentiate metastasis from primary adrenal cancer, so immunohistochemistry is required to establish the diagnosis .

This article presents five unique cases of secondary adrenal tumors that we diagnosed in the current surgical material: metastasis of clear cell renal cell carcinoma, follicular variant of papillary thyroid cancer, metastasis of keratinizing squamous cell carcinoma of the cervix, lymphoepithelioma-like carcinoma of the bladder, and malignant mesothelioma . Given the extreme rarity of the presented cases, we present an analysis of the literature data.

**Keywords:** metastases; adrenal glands; immunohistochemical study

## RELEVANCE

Adrenal tumors measuring 1 cm or more in diameter are found in approximately 1% of the population. Most adrenal incidentalomas are benign, functionally inactive adenomas, but malignant neoplasms can also be detected [1].

A significant increase in the incidence and difficulties in differential diagnosis of adrenal tumors have caused increased interest in this pathology. The adrenal glands are a common site of metastasis for some malignant neoplasms due to their rich sinusoidal blood supply [2]. According to data from autopsy series, secondary adrenal damage in the presence of a history of cancer is found in 32–73% of cases [3].

Due to significant differences in treatment tactics, diagnosis and differentiation of the metastatic process from primary adrenal tumors are of fundamental importance.

The purpose of this study is to conduct a clinical and morphological analysis of unique cases of metastatic lesions of the adrenal glands, which were diagnosed at the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology ( RSSPMCOiR ) of the Ministry of Health of the Republic of Uzbekistan . over a 7-year observation period from 2015 to 2022.

## CASE STUDY #1

Patient I., 63 years old. History of left-sided nephrectomy for clear cell renal cell carcinoma, pT3aN0Mx, performed in the fall of 2020. At the same time, a formation in the projection of the right adrenal gland measuring 42×26×41 mm, with high native density, was first detected .

According to multispiral computed tomography (MSCT) in March 2022, negative dynamics were revealed in the form of an increase in the size of the tumor of the right adrenal gland to 62 × 69 × 49 mm, with a high native density of +30 ... + 40 HU, density in scanning phases of 100–105–60 HU, the relative washout coefficient is 42.8%, absolute - 69%. According to the results of laboratory examination, data in favor of hormonal activity were not obtained: 1) in daily urine collected with a preservative, metanephrine - 218.4 μg / day (25–312), normetanephrine - 443.4 μg / day (35–445); 2) aldosterone - 102.51 pmol / l (70.9–980), renin — 10.12 IU/L (2.8–39.9), potassium — 4.77 mmol /L; 3) basal ACTH — 1.11 pmol /L (1.6–13.9),

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cortisol during the overnight suppression test with 1 mg dexamethasone — 12.0 nmol /L (less than 50). Whole-body positron emission tomography with computed tomography (PET/CT) with 18F-fluorodeoxyglucose (18F-FDG) revealed background metabolic activity of the right adrenal mass, no secondary lesions of other organs or systems were detected. Conclusion: Right adrenal mass (malignant CT phenotype; adrenocortical cancer? metastasis? pheochromocytoma ?).

Given the high malignant potential of the formation in the projection of the right adrenal gland, surgical treatment was performed in the volume of right-sided adrenalectomy with the tumor. During revision, the right adrenal gland is represented by a tumor-like formation up to 6 cm in diameter, grayish in color, abundantly vascularized .

According to the results of the pathological examination, the adrenal gland with a tumor and fatty tissue measures 90 × 45 × 50 mm. On the section adjacent to the adrenal gland is a tumor of a flabby consistency of a variegated appearance with yellowish-gray, whitish and brown areas. In the center is a translucent yellowish area, along the periphery there is a cystic cavity, the tumor measures 5.5 cm in the largest dimension, with clear even contours, surrounded by a thin capsule (Fig. 1a). Histological examination: in the adrenal gland of uneven thickness with relatively preserved layers of the cortex and medulla, tumor growth is observed from large polymorphic light cells of an alveolar structure with foci of cystic degeneration, fresh and old hemorrhages (Fig. 1b). Results of immunohistochemical (IHC) study: tumor cells do not express SF-1, Melan A, Inhibin A and Chromogranin A. There is a pronounced positive reaction to PAX2, cytokeratins (CK 8/18), RCC, CD10 and vimentin . Taking into account the clinical and anamnestic data, tumor growth can be interpreted as a metastasis of clear cell renal cell carcinoma (RCC) to the adrenal gland.

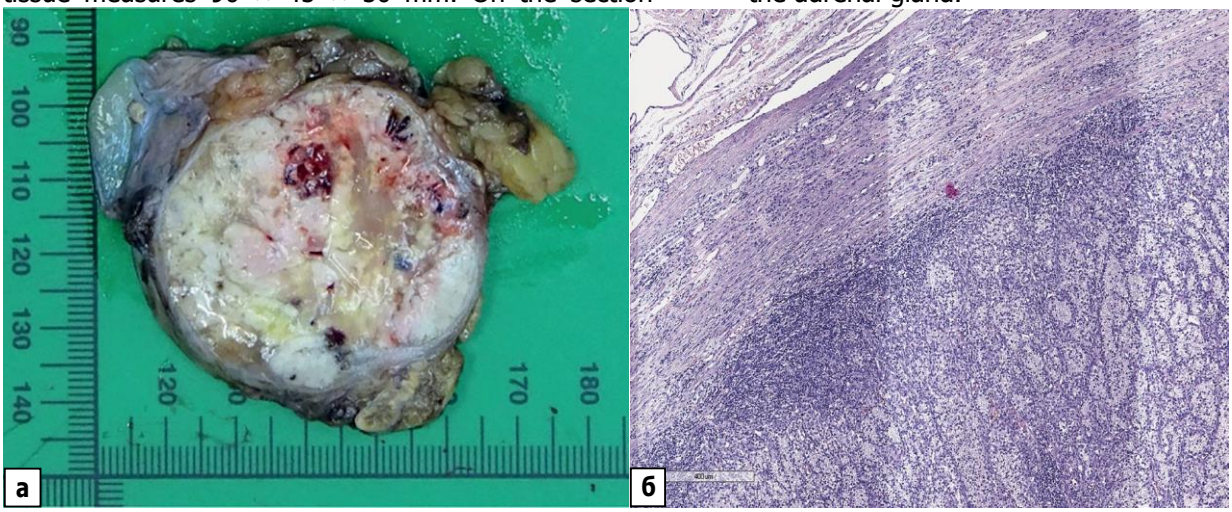


Figure 1a. Macroscopic specimen of the adrenal gland with a clear cell renal cell carcinoma metastasis, 5.5 cm in diameter.

Figure 1b. Metastasis of clear cell renal cell carcinoma to the adrenal gland. The tumor is represented by large polymorphic clear cells of alveolar structure with foci of cystic degeneration. Magnification ×100. Stained with hematoxylin and eosin.

## CASE STUDY #2

Patient P., 66 years old. It is known from the anamnesis that more than 20 years ago she underwent surgery for highly differentiated papillary thyroid cancer (PTC) in the amount of thyroidectomy .

In 2015, during a chest MSCT scan for pneumonia, a focal lesion of the lower lobe of the left lung was detected; an atypical resection of the lower lobe of the left lung was performed due to suspected metastatic lesions. Based on the results of a pathological examination of the surgical material, a metastasis of highly differentiated thyroid cancer in the lung tissue was verified.

Received 4 courses of radioiodine therapy (the last one in August 2019, 6 GBq ). At the post-therapeutic Technetium-99m-pertechnetate scintigraphy with SPECT-CT - upper mediastinal lymph node with a maximum size of up to 1 cm, requiring differentiation. No other signs of structural progression were detected.

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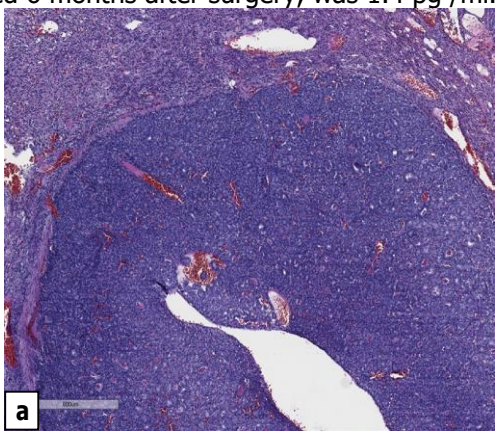
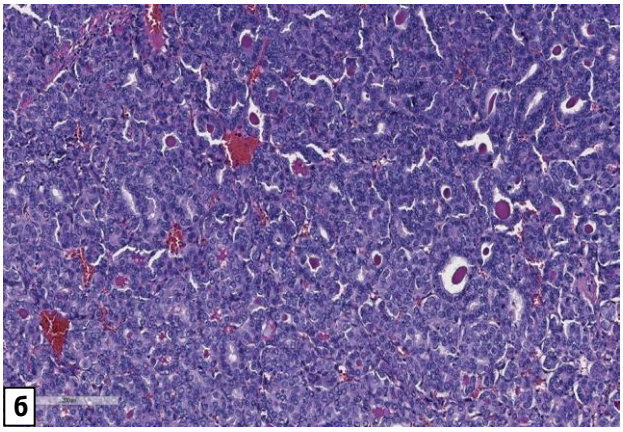
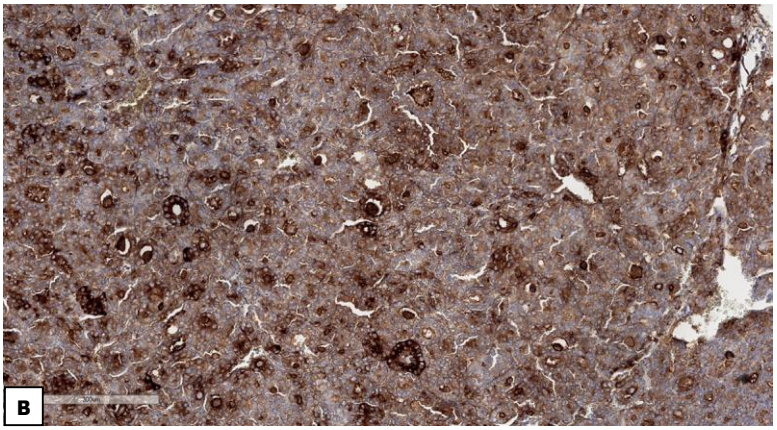
According to 18F-FDG whole-body PET/CT data, the appearance of a hypervascular formation with hyperfixation was determined for the first time in 2020 radiopharmaceutical with approximate dimensions of 31×21 mm, the level of maximum standardized accumulation of the radiopharmaceutical ( SUVmax ) is 5.73, in the projection of the right adrenal gland. No data in favor of other hypermetabolic formations were received. Taking into account the high levels of blood thyroglobulin - 405.9 pg / ml and the absence of other foci suspicious for secondary damage, solitary metastasis of PTC to the right adrenal gland is suspected. Based on the examination results, no data were received in favor of hormonal activity: 1) in daily urine collected with a preservative, metanephrine - 130.8 mcg / day (25-312), normetanephrine - 342 mcg / day (35-445); 2) aldosterone - 112.51 pmol /l (70.9–980), renin - 12.3 IU/l (2.8–39.9), potassium - 4.77 mmol /l; 3) basal ACTH - 7.4 pmol /l (1.6–13.9), cortisol during the overnight suppression test with 1 mg dexamethasone - 42.0 nmol /l (less than 50).

The patient was given the main diagnosis: hormonally inactive formation of the right adrenal gland with high malignant potential. In this regard, laparoscopic right-sided adrenalectomy with the tumor was performed. Intraoperatively , it was revealed that the adrenal gland contains a dark cherry-colored tumor with a diameter of 3.5 cm.

According to the results of pathological examination, metastasis of the follicular variant of PTC was detected in the postoperative material (Fig. 2a, 2b). In the IHC study, the tumor cells express thyroglobulin (Fig. 2c) and TTF1 (Fig. 2d) are not expressed napsin A. The Ki67 proliferation index is about 7%. The postoperative TG level, determined 6 months after surgery, was 1.4 pg /ml.



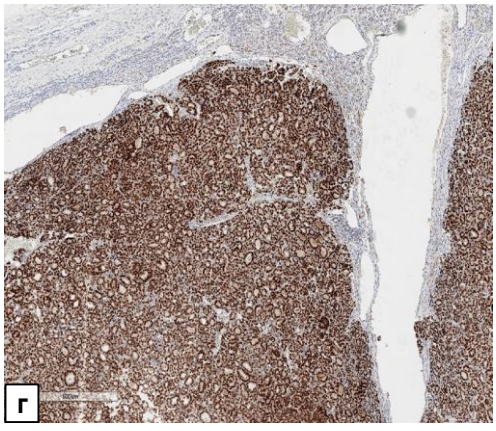




Figure 2a. Metastasis of the follicular variant of papillary thyroid cancer to the adrenal gland. Magnification ×100. Hematoxylin and eosin staining.

Figure 2b. Metastasis of the follicular variant of papillary thyroid cancer to the adrenal gland. The tumor is represented by follicles of different sizes, lined with cells with large, irregular, closely spaced nuclei. Magnification ×200. Stained with hematoxylin and eosin.

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Figure 2c. Metastasis of the follicular variant of papillary thyroid cancer to the adrenal gland. Expression of thyroglobulin by tumor cells. Magnification ×200. IHC reaction with an antibody to thyroglobulin .
Figure 2d. Metastasis of the follicular variant of papillary thyroid cancer to the adrenal gland. Positive staining of tumor cells in the reaction with the antibody to TTF1. Magnification ×100. IHC reaction with the antibody to TTF1.

## CASE STUDY #3

Patient G., 65 years old, diagnosed with cervical cancer, pT2bNxM0. Received combination therapy: 2015 - combined radiation therapy against the background of chemotherapy Ftorafur , 2019 - thoracoscopic resection of the upper and lower lobes of the right lung for mts , 2020 - stereotactic external beam radiation therapy for recurrent disease in the area of the root of the right lung. During the next dynamic examination according to PET / CT of the whole body with 18F-FDG dated 07.12.2021, a picture of a space-occupying lesion in the projection of the right adrenal gland measuring 38 × 22 mm was revealed, with high uptake of the radiopharmaceutical , no other foci of hypermetabolism were detected. According to the results of MSCT from 10.01.2022, a volumetric formation measuring 45×24 mm, with a high native density of +20…+45 HU, is determined in the projection of the right adrenal gland. Uneven accumulation of the contrast agent is noted, mainly in the peripheral parts. Over a length of 17 mm, the outer contour of the formation is intimately adjacent to the right lobe of the liver, with no clear boundary between them. According to the results of laboratory examination from 12.2021 to 01.2022, aldosterone is 283 pg / ml (25.2-392), renin is 16.1 μIU / ml (4.4-46.1), cortisol (morning) is 399 nmol / l (101-535), in daily urine collected with a preservative, total metanephrine is 71.68 μg / day (18-277), total normetanephrine is 198.8 μg / day (42-423). The patient denies arterial hypertension. Thus, a solitary formation in the projection of the right adrenal gland with a high malignant potential was detected in a patient with an aggravated oncological history .

intraoperative revision, the right adrenal gland at the upper pole of the kidney is yellowish in color, and a tumor-like formation up to 4.5 cm in diameter is determined in the lateral pedicle of the adrenal gland. Performed Laparoscopic right adrenalectomy with tumor.
Results of pathological examination: a neoplasm is determined in the adrenal gland tissue, represented by keratinizing squamous epithelium with a large number of mitoses, including pathological ones, extensive foci of necrosis and the presence of comedo necrosis , spreading beyond the adrenal gland into the adjacent adipose tissue (Fig. 3). IHC examination shows the absence of expression of SF-1, Melan A, Inhibin A and Chromogranin A. Positive reaction to CK5/6, p63. Taking into account the clinical and anamnestic data and the morphological picture, the tumor is a metastasis of keratinizing squamous cell carcinoma of the cervix to the adrenal gland.

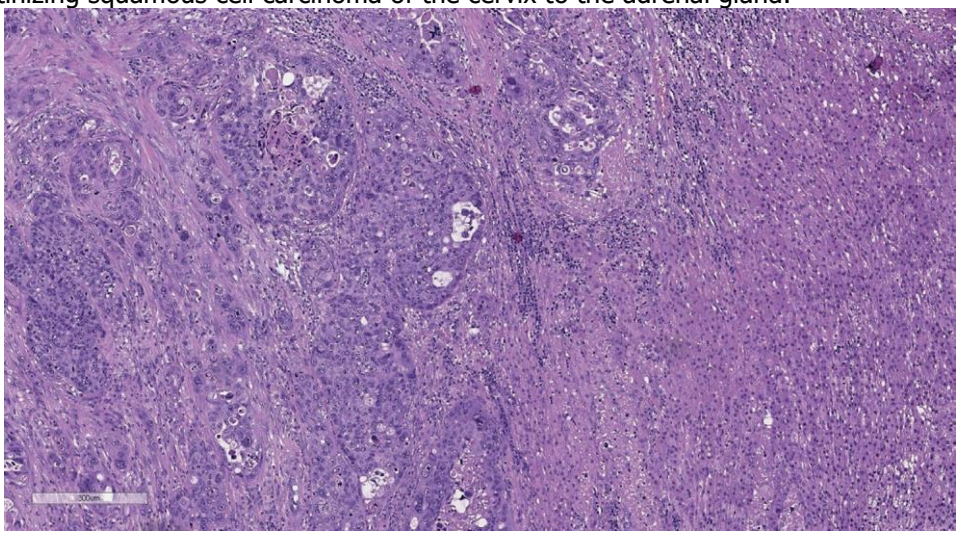

Figure 3. Metastasis of keratinizing squamous cell carcinoma of the cervix to the adrenal gland. The tumor is represented by keratinizing squamous epithelium with a large number of pathological mitoses and extensive foci of necrosis. Magnification ×100. Stained with hematoxylin and eosin.

## CASE STUDY #4

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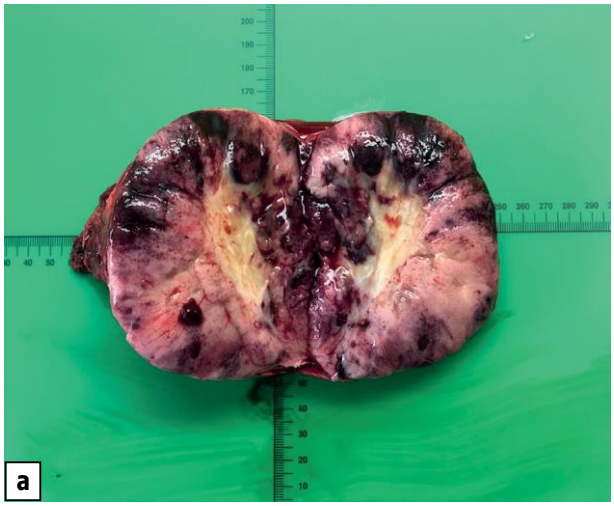
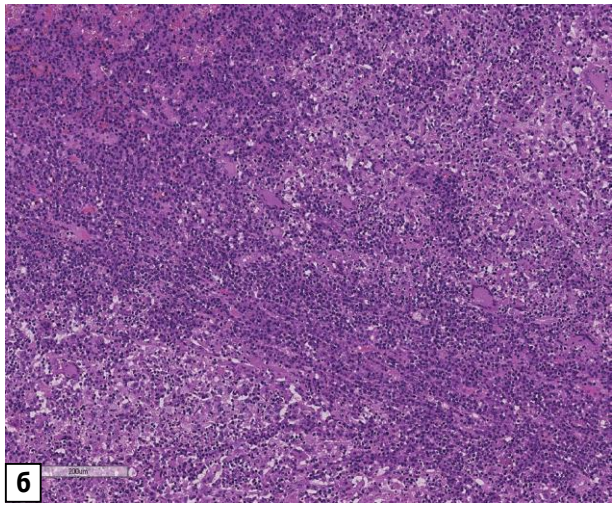
Patient T., 65 years old. It is known from the anamnesis that in 2011 he underwent transurethral resection surgery for a bladder tumor; based on the results of pathological examination of the surgical material, low-grade papillary transitional cell carcinoma without invasion into the submucosal layer, pT1aN0M0, was verified. Taking into account the presence of oncological disease in the anamnesis, he has been under dispensary registration since 2011.
During the next examination in 2015, according to the MSCT data, a space-occupying lesion was detected in the projection of the right adrenal gland with clear, smooth contours, dimensions of 17 × 25 × 27 mm, mosaic native density of +17…+31 HU. During the dynamic observation, according to the control MSCT data in 2017, an increase in the size of the space-occupying lesion in the projection of the right adrenal gland to 40.7 × 35 × 44.3 mm was noted, with clear, somewhat uneven contours, density of up to 37 HU, heterogeneous structure due to calcifications and a hypodense area with a density of up to 17 HU. The formation unevenly accumulates the contrast agent up to 70 HU in the arterial phase, 71 HU in the venous phase, and 68 HU (9%) in the delayed phase. No data were obtained in favor of the presence of other space-occupying formations with high malignant potential in the chest, abdominal cavity, and pelvis. Based on the results of the laboratory examination, no data were obtained in favor of hormonal activity: 1) in the daily portion of urine collected with a preservative, metanephrine - 87.88 μg / day (25-312), normetanephrine - 175.5 μg / day (35-445); 2) aldosterone - 82.7 pmol / l (70.9-980), renin - 9.541 IU / l (2.8-39.9), potassium - 4.2 mmol / l; 3) Basal ACTH - 13.09 pg /ml (7–66), free cortisol in the daily urine portion - 262.756 nmol / day (60–413).
Considering the high malignant potential of the formation in the projection of the right adrenal gland, surgical treatment was performed on the right side
adrenalectomy with a tumor. In the tissue of the atrophic right adrenal gland, a dark-colored tumor with a diameter of 4.0 cm with zones of necrosis was found (Fig. 4a).
According to the results of the pathological examination, a tumor of a solid structure, consisting of large epithelial cells with pale cytoplasm (Fig. 4b), expressing, is adjacent to the adrenal gland of normal histological structure. multi - cytokeratin (MCK) (Fig. 4c) and p53, the tumor stroma consists of soft fibrous connective tissue infiltrated by lymphoid elements expressing CD45 (Fig. 4d). Tumor cells do not express markers of the adrenal cortex ( Melan A, Inhibin A), as well as the medulla ( Chromogranin A). Extensive areas of necrosis are noted in the tumor tissue. The described histological features and the immunophenotype of the tumor most likely correspond to a metastasis of lymphoepithelioma- like carcinoma of the bladder ( lymphoepithelioma-like carcinoma of the bladder). carcinoma , LELC) in the adrenal gland.



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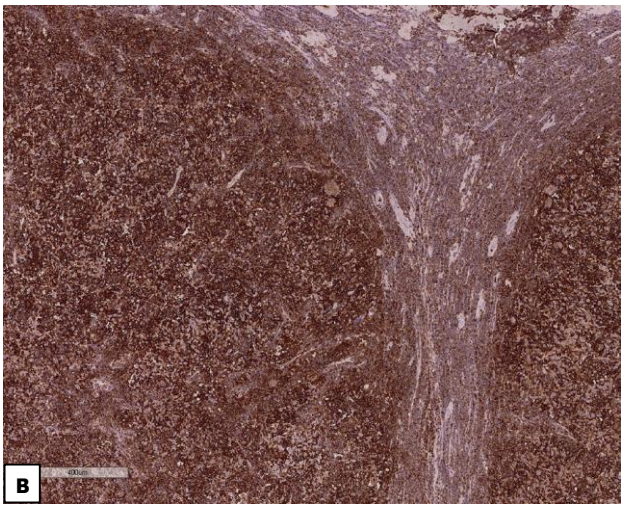


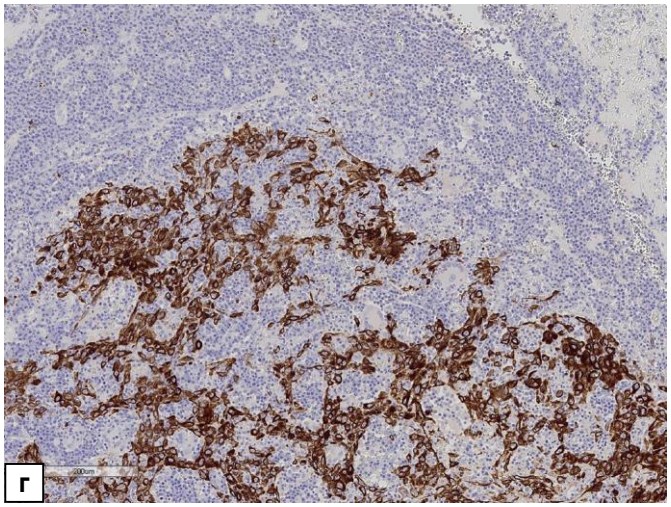


Figure 4a. Macroscopic specimen of the adrenal gland with a metastasis of lymphoepithelioma-like carcinoma of the urinary bladder, 4.0 cm in diameter.
Figure 4b. Metastasis of lymphoepithelioma-like carcinoma to the adrenal gland. The tumor is represented by large epithelial cells with pale cytoplasm, stroma of soft fibrous connective tissue infiltrated by lymphoid elements. Magnification ×100. Stained with hematoxylin and eosin.
Figure 4c. Metastasis of lymphoepithelioma-like carcinoma to the adrenal gland. Positive staining of tumor cells in the reaction with MSK ( total cytokeratin ). Magnification ×100. IHC reaction with MCK antibody.
Figure 4d. Metastasis of lymphoepithelioma-like carcinoma to the adrenal gland. Positive staining of tumor-infiltrating immune cells in reaction with CD45 (common leukocyte antigen). Magnification ×100. IHC reaction with CD45 antibody.

## CASE STUDY #5

Patient V., 76 years old. For three years, he complained of weight loss of 20 kg, pain in the lumbar region, chills in the evening, subfebrile temperature over the past 5 months , intermittent claudication in the left leg. According to the ultrasound examination of the abdominal cavity, a space-occupying lesion of the left adrenal gland was detected. MSCT of the abdominal organs was performed , the results of which revealed a solid formation of the left adrenal gland with smooth, clear contours (presumably neurofibroma ), native density of +23…+32 HU, dimensions of 60×56×53 mm, heterogeneous structure due to single small calcifications . During dynamic observation after 6 months. Negative dynamics were noted in the form of an increase in the size of the formation to 86×82×82 mm with a native density of +33…+45 HU, accumulating contrast in the phases of arterial - venous-delayed scanning : 48–58–62 HU. Quantitative lymphadenopathy
paraaortic lymph nodes. According to laboratory tests, hormonal activity of the adrenal gland formation was excluded: 1) in daily urine collected with a preservative, metanephrine - 186 mcg / day (25-312), normetanephrine - 453 mcg / day (35-445); 2) basal ACTH - 32 pg / ml (7-66), cortisol against the background of a night suppression test with 1 mg dexamethasone - 32 pg / ml (less than 50). Exclusion of primary hyperaldosteronism was not required due to the absence of arterial hypertension. Upon admission and during hospitalization, the patient had a fever of up to 38.3°C. During the examination, infectious and inflammatory causes of fever were excluded. According to the general clinical blood test, leukocytosis up to 15.5×109 cells /l, an increase in ESR up to 91 pg /ml were noted.
During surgery, a tumor-like formation of dense consistency measuring 10 cm in diameter was detected in the abdominal cavity at the upper pole of the kidney. Due to the high malignant potential of the tumor, laparoscopic left-sided adrenalectomy was performed .
Results of pathological examination: in the examined postoperative material of adrenal tissue, tumor growth is determined, predominantly of solid structure, in places with the formation of glandular structures. Tumor cells are large, predominantly with eosinophilic cytoplasm and large polymorphic nuclei with large lumpy chromatin and one or more well-defined

noticeable nucleoli. The stroma is represented by thin, in places hyalinized fibrovascular septa, the pronounced lymphocytic infiltration of the stroma is noteworthy (Fig. 5a).

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Results of the IHC study : the tumor shows a pronounced diffuse reaction of CK 7 (Fig. 5b), CAM 5.2, mesothelin (Fig. 5c), focal expression of calretinin and vimentin (Fig. 5d), and a focal positive reaction with inhibin is also noteworthy . PDL1 expression was detected in 1% of tumor cells. The Ki67 proliferation index was up to 30%. A negative IHC reaction with antibodies against Melan A allows us to exclude adrenocortical cancer (ACC), a negative reaction with RCC, CD10, PAX8 excludes the presence of a kidney tumor, a negative reaction with TTF1 and napsin excludes lung cancer metastases. The described picture and tumor immunophenotype correspond to localized malignant mesothelioma .

From the 2nd day after the surgery, a stable normalization of body temperature was observed.

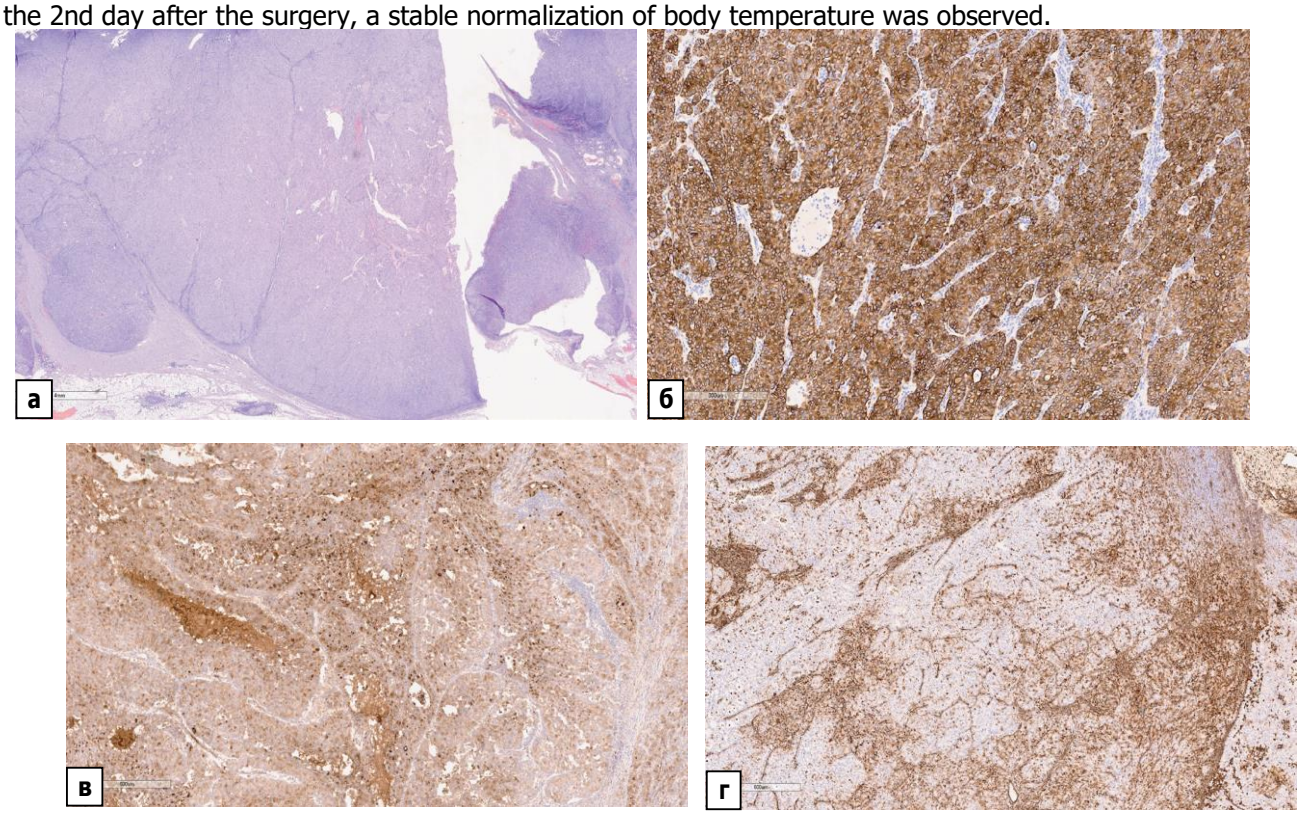


Figure 5a. Metastasis of malignant mesothelioma in the adrenal gland. The tumor is represented by large cells. Fibrovascular stroma with pronounced lymphocytic infiltration. Magnification ×60. Hematoxylin and eosin staining.

Figure 5b. Metastasis of malignant mesothelioma in the adrenal gland. Positive staining of tumor cells in reaction with cytokeratin 7 (CK7).

Magnification ×200. IHC reaction with CK7 antibody.

Figure 5c. Metastasis of malignant mesothelioma in the adrenal gland. Positive staining of tumor cells in reaction with mesothelin . Magnification ×100.

IHC reaction with antibody to mesothelin .

Figure 5d. Metastasis of malignant mesothelioma in the adrenal gland. Focal expression of vimentin by tumor cells. Magnification ×100. IHC reaction with antibody to vimentin .

## DISCUSSION

According to the guidelines, among neoplasms of the adrenal glands the following are distinguished: 1) adrenocortical formations: cancer or adenoma; 2) tumors of the adrenal medulla: pheochromocytoma ; 3) metastatic lesions of the adrenal glands; 4) other formations: cysts, lipomas, teratomas, etc.; 5) " pseudoadrenal " formations: tumors of the kidneys , pancreas, spleen, stomach, right lobe of the liver, retroperitoneal lymph nodes or blood vessels [4].

One of the key factors in choosing treatment tactics is establishing the presence of hormonal activity and determining the malignant potential of the tumor, therefore all patients with adrenal tumors are recommended to undergo laboratory and imaging studies.

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According to the literature, metastases to the adrenal glands are usually asymptomatic, but there are cases that manifest as pain in the lumbar region, retroperitoneal bleeding or adrenal insufficiency [5]. In the cases presented by us, only one patient with localized malignant mesothelioma had clinical symptoms in the form of weight loss, pain in the lumbar region, chills and fever, in the other cases, metastatic adrenal lesions did not have any clinical symptoms.

The time between detection of the primary tumor and the occurrence of metastases to the adrenal glands depends on the localization of the primary lesion and can vary considerably, averaging about 2.5 years [2]. Often, isolated metastases to the adrenal glands occur before the detection of the primary malignancy, as in the cases of metastases from clear cell RCC and pleural mesothelioma presented in this study.

In the study by J. Mao et al . (2020), 579 cases of metastasis to the adrenal glands were analyzed. Most often, metastases from lung tumors (226, 39.0%), the genitourinary system (160,
27.6%), gastrointestinal tract (79, 13.6%) and others (114, 19.7%) organ systems. Interestingly, 210 (36.3%) were detected by chance, and only in 29 (5.0%) cases was the examination performed based on clinical symptoms [5]. In our study, we focused on cases of tumor diagnosis that, according to the literature, metastasize to the adrenal glands extremely rarely, which is why the diagnosis of such tumors has many difficulties.

In most cases, adrenal biopsy is uninformative and is strictly contraindicated in ACC. During biopsy, the node capsule ruptures, which in the case of a malignant neoplasm leads to dissemination of the process and a worsening prognosis of the disease, therefore, puncture biopsy can only be used for an inoperable tumor if the result of a pathomorphological study can affect the treatment tactics of patients [4, 6]. Nevertheless, in a meta-analysis of 32 studies, I. Bancos et al . (2016) provide data on examinations of 2174 patients with adrenal incidentalomas . A total of 2190 biopsies were analyzed, the average tumor diameter was 3.9 cm. In 74% (n=1621) of the studies, adrenal pathology was detected: 689 (42.5%) cases of metastases , 464 (28.6%) - adenomas, 68 (4.2%) - ACC, 64 (3.9%) -
other malignant tumors, 226 (14%) other benign tumors, 36 (2.2%) pheochromocytomas and 74 (4.6%) other tumors [7].

Today, adrenalectomy is the main treatment method for suspected ACC or metastatic adrenal lesions. Laparoscopic approach is considered the preferred method for adrenalectomy [8]. According to literature, surgical intervention for metastatic adrenal lesions has a positive effect on the prognosis of patients (median survival after adrenalectomy is 31.0 months , without surgical intervention - 8.5 months ) [9, 10].

Often, the diagnosis of metastatic lesions to the adrenal glands can be established only after pathological examination of the postoperative material. However, basic staining with hematoxylin and eosin is not enough to perform differential diagnostics, especially when studying adrenal tumors without an established primary focus. The most difficult task in the case of detection of an adrenal tumor is differential diagnostics with ACC due to the high degree of morphological heterogeneity both in cases of different tumors and within a single neoplasm [11].

ACC is a rare malignant endocrine tumor of the adrenal cortex with a prevalence of 1-2 cases per year per 1 million population . According to the WHO classification, several morphological variants of ACC are distinguished . Moreover, even within the classical g and In the stologic variant, various morphological features have been identified: the predominance of large polymorphic cells, monomorphic cells of small or medium size (" carcinoid -like "), or rhabdoid cells that form alveolar structures [12].

SF-1 is a nuclear transcription factor that regulates the production of steroid hormones in the renal cortex and is the most sensitive (98%) and specific (100%) marker of ACR. If ACR is suspected, a series of immunohistochemical studies must be performed. The main panel of markers that allow one to exclude or confirm the diagnosis of ACR also currently includes Melan A and Inhibin A, but their use is not as specific [13].

The absence of SF-1 expression allows us to exclude cortical histogenesis of adrenal tumors. IHC reaction with SF-1 is usually negative in RCC, hepatocellular carcinoma, melanoma and pheochromocytoma . For differential diagnosis with pheochromocytoma, it is advisable to use Chromogranin A, which expressed exclusively by cells of the adrenal medulla [14].

In an autopsy study of over 400 patients undergoing nephrectomy for RCC, the contralateral adrenal gland was the sole site of metastasis in only 2.5%. Among patients with widespread RCC metastases identified at autopsy, the contralateral adrenal gland was involved in 12.7% of patients [15].

If RCC metastases are suspected, it is rational to include markers such as PAX2, PAX8, RCC, panCK , vimentin , and CK7 in the IHC panel . PAX2 has a wide range of expression and is detected in most renal cell

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carcinomas, with the exception of the chromophobe variant. CD10 is positive in most clear cell and papillary renal cell carcinomas [16]. PTC metastases most often occur in regional lymph nodes. Distant metastases are rare and usually involve the lungs or bones. Thyroid tissue and thyroid carcinomas are characterized by expression of TTF-1 and thyroglobulin . Follicular, papillary and medullary thyroid cancers are usually strongly positive for TTF-1, whereas undifferentiated ( anaplastic ) thyroid cancers are most often negative [17]. Napsin A expressed in most lung adenocarcinomas and is used as a specific marker.

Descriptions of cases of metastatic lesions of the adrenal glands due to gynecological neoplasms found in the literature are few: a cohort study involving 34 patients was published, which describes 2 cases (6%) of metastasis of cervical carcinoma to the adrenal glands [18]. To confirm the assumption of metastasis of keratinizing squamous cell carcinoma of the cervix, we used p63 and CK5/6, which are traditional markers indicating squamous cell differentiation [19].

Lymphoepithelioma-like carcinoma of the bladder is a rare histological type of malignancy, accounting for 0.4–1.3% of all bladder cancer cases [20]. Histological features of this tumor include inflammatory infiltrate and dense lymphocytic infiltrate, in addition, syncytial arrangement of large neoplastic epithelial cells with prominent nuclei and nucleoli can be observed during histological examination of this tumor. Despite the infiltrative predisposition, the metastatic potential of this tumor seems to be low [21]. IHC detection is necessary to establish a definitive diagnosis cytokeratins , which prove the epithelial origin of the tumor. In the presented case, the markers MCK (total cytokeratin ) and CD45 (total leukocyte antigen) were used to identify metastasis of lymphoepithelioma-like carcinoma of the bladder to the adrenal gland [22].

A series of pathological studies of 318 patients showed that pleural mesothelioma metastases are most often detected in the liver (32%), spleen (11%), thyroid gland (7%) and brain (3%) [23]. At the same time, only a few cases of mesothelioma spreading to the adrenal glands have been registered in the literature, which is characterized by the presence of a number of markers: calretinin , WT-1 antigen, vimentin , mesothelin [24].

## CONCLUSION

Differential diagnosis between benign, primary and secondary malignant tumors is a critical issue for both clinical physicians and pathologists, especially in patients with isolated adrenal lesions.

In all the cases we presented, during the diagnostic search at the preoperative stage, the results of laboratory and instrumental examinations in one way or another indicated a possible diagnosis of ACC. However , it was possible to establish a final diagnosis only on the basis of IHC studies .

As is known, therapy has a decisive influence on survival. The presence of metastases influences the treatment tactics of the primary malignant neoplasm, and further examination is often required, especially in patients with cancer that does not have other metastasis localizations except the adrenal glands. Thus, an incorrect diagnosis can lead to incorrect treatment of tumors on the d- renal glands: overtreatment or ignorance.

Because of morphological heterogeneity of ACC, there are cases when it is almost impossible to distinguish metastases from primary adrenal cancer using standard hematoxylin and eosin staining. That is why when examining adrenal tumors, it is necessary to be vigilant and to use the entire spectrum of modern methods, in particular IHC studies , in order to avoid erroneous diagnoses.

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