CASE REPORT

EXPERIMENTAL ONCOLOGY

https://doi.org/10.15407/exp-oncology.2025.04.506

P. Yakovlev [1, *], L. Rosha [2], V. Yunger [2]

[1] SI "O.O. Shalimov National Scientific Center of Surgery and Transplantation of the NAMS of Ukraine", Kyiv, Ukraine
[2] Clinical Hospital "Feofaniya", Kyiv, Ukraine

* Correspondence: Email: dr.yakovlev.urology@gmail.com

CLINICAL CASE OF COMPLEX RADICAL TREATMENT OF METASTATIC PROGRESSION TO RARE SITE OF PRIMARY ORGAN CONFINED CHROMOPHOBE RENAL CELL CARCINOMA TREATED WITH LAPAROSCOPIC PARTIAL NEPHRECTOMY

We present a case of stage I chromophobe renal cell carcinoma, which initially was treated with laparoscopic partial nephrectomy, and four years later progressed to multifocal metastatic nodules in the perirenal adipose capsule without local recurrence in the kidney itself. The curative approach included the surgical complete removal of perirenal adipose tissue with adjuvant pembrolizumab. We discuss the molecular and genetic peculiarities of chromophobe renal cell carcinoma as applied to the diagnosis and a rationale for adjuvant pembrolizumab.

Keywords: kidney cancer, chromophobe cancer, partial nephrectomy, immunohistochemical study, molecular profile, pembrolizumab.

Chromophobe renal cell carcinoma (RCC) is a rare histological subtype, accounting for approximately 5—10% of all RCC [1, 2]. In contrast to the more common clear cell carcinoma, chromophobe RCC is usually characterized by the less aggressive course, lower metastasis rate, and better survival prognosis [3, 4]. In this regard, organ-sparing treatment in patients with localized forms of chromophobe RCC is appropriate and effective [1, 5]. However, in rare cases, chromophobe RCC is capable of an aggressive clinical course with the development of distant metastases that poses significant challenges for clinicians in choosing the optimal treatment tactics [6]. Among all cases of chromophobe RCC, metachronous metastases are detected in 5—6% of patients [7], and chronologically they can manifest themselves even 18 years after the initial radical treatment [8]. In such situations, radical surgery of metastatic foci may be considered as a potentially radical curative approach, especially in the absence of systemic progression.

Our paper aims to present a clinical case of multifocal metastatic progression in the perirenal adipose tissue of chromophobe RCC after primary laparoscopic partial nephrectomy, with successful

Citation: Yakovlev P, Rosha L, Yunger V. Clinical case of complex radical treatment of metastatic progression to rare site of primary organ confined chromophobe renal cell carcinoma treated with laparoscopic partial nephrectomy. *Exp Oncol.* 2025; 47(4): 506-512. https://doi.org/10.15407/exp-oncology.2025.04.506

© PH "Akademperiodyka" of the NAS of Ukraine, 2025. This is an open access article under the CC BY-NC-ND license (https://creativecommons.org/licenses/by-nc-nd/4.0/)

subsequent use of radical surgical treatment with adjuvant immunotherapy, to provide a generalized description of the molecular genetic features of chromophobe RCC and approaches to adjuvant treatment.

The report describes the clinical case of a patient treated in the Center for Urology and Urological Oncology of the Feofania Clinical Hospital. Written informed consent for publication of this clinical case and accompanying images was obtained from the patient.

The patient X., 70 years old, in satisfactory somatic condition, ECOG = 0, without any complaints about the urinary system, during a regular check-up study, was diagnosed with a kidney tumor. The CT of the thorax, abdomen, and pelvis with intravenous contrast enhancement (10/26/2020) yielded a clearly demarcated hypervascular mass of the left kidney, 3 cm in diameter along the lateral contour of the upper pole, 50% extrarenal location, nephrometric index RENAL Score = 6p, and radiological staging cT1N0M0.

On 11/04/2020, a radical operation was performed — a laparoscopic partial nephrectomy.

Pathology report: Morphological picture in favor of chromophobe RCC (Fig. 1), resection margins in the kidney tissue without signs of tumor growth: pR0.

After the surgery, the patient underwent regular MRI of the abdomen, and CT of the chest and abdomen examination every 6 months; no signs of local recurrence or progression of cancer were detected. The last CT screening with intravenous contrast enhancement on 08/11/2024 (4 years after laparoscopic left partial nephrectomy) revealed the appearance of enlarged paranephric lymph nodes on the left — a probable sign of progression of the oncological disease. No signs of tumor recurrence were detected in the left kidney itself (Fig. 2).

Tumor markers (total PSA, AFP, CA-19-9, CEA, CA 72-4) were within the reference values.

On 11/23/2024, according to the decision of the cancer treatment board, the patient underwent surgery: laparotomy, intraoperative biopsy of the perirenal adipose tissue metastasis, and the removal of all perirenal tissue. The express intraoperative pathology study revealed two fragments of fatty tissue with 6 foci of chromophobe carcinoma growth.

In the postoperative period, according to the decision of the cancer treatment board, the patient received intravenous injections of pembrolizumab 200 mg every three weeks.

A control intravenous contrast-enhanced CT study of the chest, abdomen, and pelvis conducted on 05/01/2025 and 10/10/2025 showed neither recurrence nor metastatic progression of cancer. The cancer treatment board recommended that the patient continue pembrolizumab in a monotherapy regimen over one postoperative year, with CT control every 3 months during the postoperative year.

Being so far one year on the postoperative follow-up with postoperative immunotherapy, the patient has no signs of either local recurrence or metastatic progression. The general health condition is assessed as satisfactory, and his diagnosis is as follows: Chromophobe RCC of the left kidney pT-1N0M0. Status after surgical treatment: Laparoscopic partial nephrectomy on the left, pR0 (04.11.2020). Prolongatio morbi: Multiple metastases in the perirenal adipose tissue. Status after surgical treatment: Laparotomy. Biopsy of the perirenal adipose tissue metastasis. Removal of all perirenal adipose tissue (23.11.2024). Status after 12 courses of Pemrolizumab in monotherapy regimen. Stabilization of the process according to CT data from 10.10.25. ECOG 0.

The results of the microscopic examination of the tumor of the left kidney removed in 2020, are presented in Fig. 1.

Immunohistochemical (IHC) study was performed, which demonstrated the following results (Figs. 3—7): Ki-67(SP6) — focal expression up to 3%; Keratin 7 Ab-2(Clone OV-TL 12/30) — positive expression; Keratin 20 Ab-1(Ks20.8) — nega-

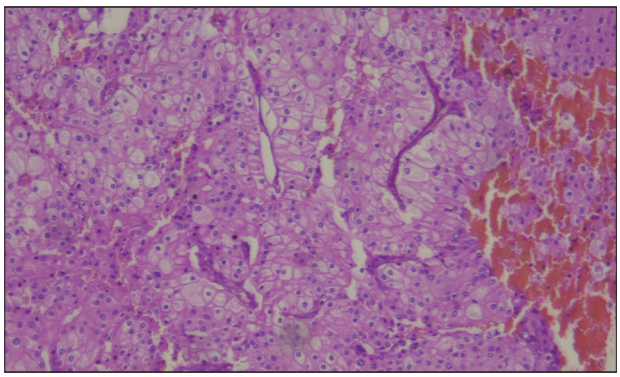

Fig. 1. Microscopy of removed chromophobe RCC, hematoxylin-eosin staining, ×100

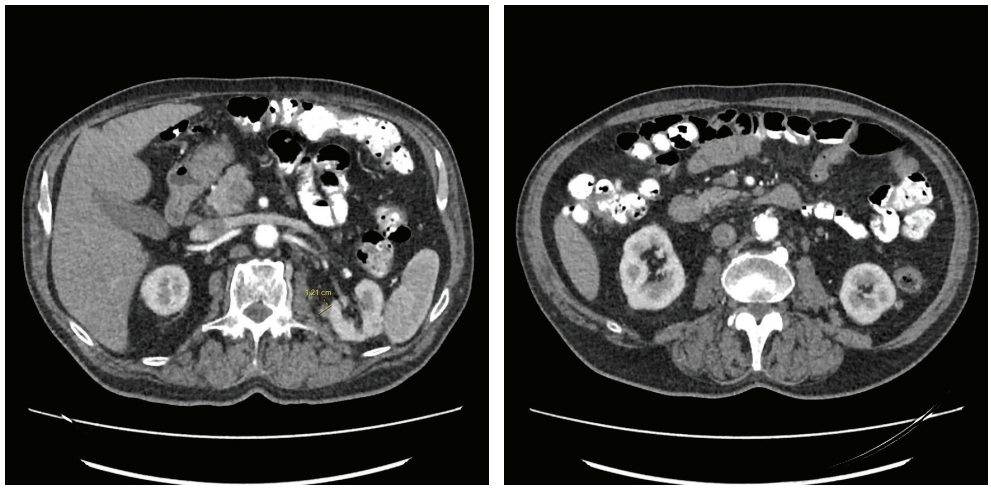

Fig. 2. CT scan of the abdominal cavity of patient X., 08/11/2024, which reveals a multifocal tumor lesion of the perirenal adipose tissue on the left, without signs of recurrence in the left kidney itself

tive expression; CD10 (CD10/CALLA (Neutral Endopeptidase) Ab-2) (56C6) — negative expression; CD117/c-Kit / SCF-Receptor — positive expression; P 504S/AMACR(Clone 13H4) — negative expression; CD15 Ab-3 (MMA) — negative expression; Cadherin E/ E-Cadherin (Ep700Y) — positive expression; and Dog-1 (1.1) — focal positive expression.

Based on the immunohistochemical study, the diagnosis was made: ChromophobeRCC.

After the second surgery in 2024, the pathological examination of the removed perirenal adipose tissue revealed fat with 10 foci of chromophobe RCC growth, sizing from 0.2 cm to 1.3 cm, R0.

An IHC study was performed on 11/28/2024, which showed the following results: anti-vimentin DAKO, clone V9: negative reaction in tumor cells; CD117, c-kit DAKO, clone CD117: c-kit-positive reaction in tumor cells; alpha-methylacyl-CoA racemase (AMACR, p504s) DAKO, clone 13H4: positive reaction in part of tumor cells; cytokeratin 7 DAKO, clone OV-TL 12/30: positive reaction in tumor cells. IHC conclusion: morphological picture and immunophenotype correspond to the growth of chromophobe carcinoma (CK7+, CD117+, vimentin –).

Pathological histological conclusion: Secondary growth of chromophobe carcinoma (ICD-O coding 8317/6 Chromophobe cell renal carcinoma).

The mainstay of treatment for chromophobe RCC diagnosed at stages I—III is surgery [1]. Although adjuvant therapy is not clinically beneficial in these patients [9], systemic therapies such as tyrosine kinase inhibitors, antiangiogenic inhibitors, and immune checkpoint inhibitors have been shown to be of palliative benefit in cases of advanced or recurrent chromophobe RCC [10]. Although chromophobe RCC is usually less aggressive than clear cell RCC, a subset of patients may develop metastatic disease, which is currently reported in 5—6% of patients with this type of RCC [7]. The most common sites of metastasis are the lungs, bones, and regional or distant lymph nodes [11—13]. Liver metastases in chromophobe RCC are less common, mainly in later stages or with multifocal lesions [12], but isolated liver metastases have been reported up to 18 years after primary radical treatment [8].

A few clinical cases also describe metastases to the brain, skin, skeletal muscle, and endocrine organs (adrenal glands, thyroid), suggesting the possibility of atypical disease spread [1, 14].

In our clinical observation, metastases were found in the perirenal adipose tissue without involvement of other organs, which is consistent with the rare pattern of metastasis for this subtype of RCC.

The diagnosis of both chromophobe RCC and its metastases is based on morphological features and is confirmed by IHC markers that allow it to be differentiated from the other subtypes of RCC (especially, clear cell and oncocytic) [7, 13, 15].

The main IHC markers used to confirm or exclude the diagnosis of chromophobe RCC are listed in Table 1.

When performing differential diagnosis, the following aspects should be considered: Oncocytoma may also be positive for CD117, but negative for

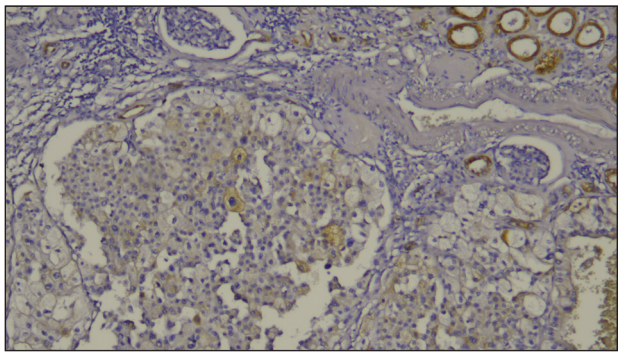

Fig. 3. Microscopy of removed chromophobe RCC; AMACR staining, ×100

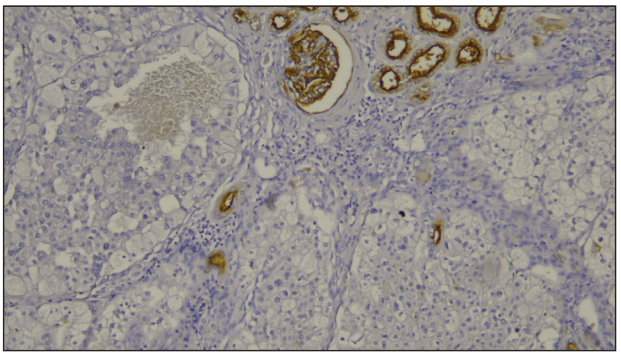

Fig. 4. Microscopy of removed chromophobe RCC; CD10 staining, ×100

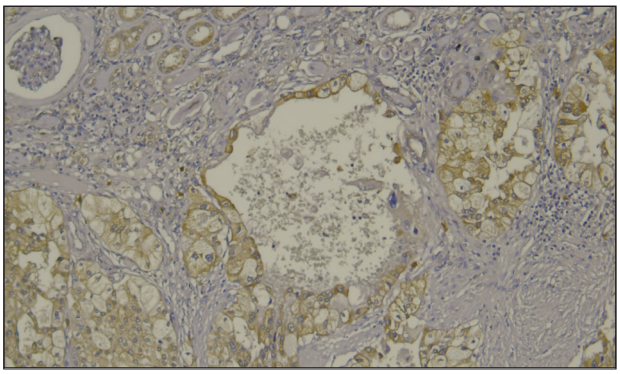

Fig. 5. Microscopy of removed chromophobe RCC; CD117 staining, ×100

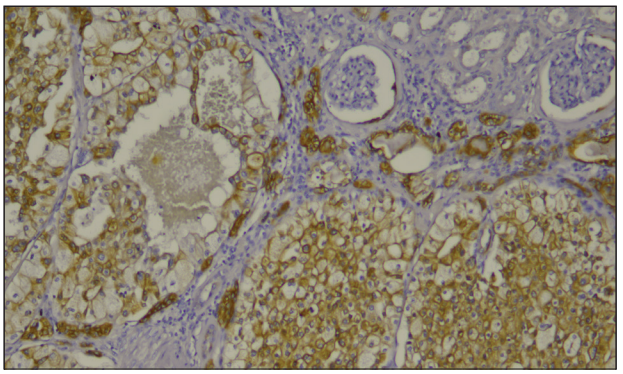

Fig. 6. Microscopy of removed chromophobe RCC; CK7 staining, ×100

CK7, or positive only focally; clear cell RCC is CK7 negative, CAIX positive, and CD10 positive.

From a molecular genetic perspective, chromophobe RCC has a unique genomic profile, which distinguishes it from the other subtypes of RCC. The most characteristic feature of chromophobe RCC is a multiple chromosomal loss of whole or parts of chromosomes. The losses of chromosomes 1, 2, 6, 10, 13, 17, and 21 are most commonly detected. Unlike the clear cell type, mutations in the VHL gene are rarely observed in chromophobe RCC, but abnormalities in other tumor suppressor genes, including *TP53* and *PTEN*, are possible. In some cases, mutations in the *TSC1*, *MTOR*, and *FLCN* genes, which are involved in regulation of cell growth and metabolism, are also detected, which may have clinical significance when prescribing targeted therapy [16].

In addition, chromophobe RCC is associated with a specific immune microenvironment with low T-cell infiltration, which partly explains its poor immunogenicity and limited sensitivity to immunotherapy. Therefore, the study of the molecular profile of chromophobe RCC is of key importance

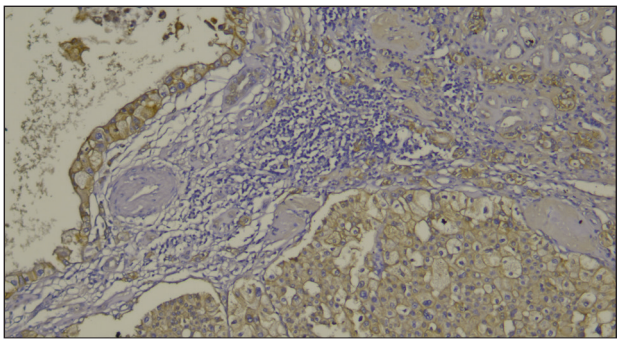

Fig. 7. Microscopy of removed chromophobe RCC; E-cadherin staining, ×100

for personalized therapy selection and disease prognosis. Table 2 presents the main genetic features of chromophobe RCC [3, 4, 7].

Since the rate of progression of chromophobe RCC is usually slow, in the presence of isolated metastases, a radical approach to treatment may be justified, in particular, the surgical removal of metastatic foci [8]. The accumulation of data on such clinical cases will contribute to a deeper understanding of tumor biology and improve clinical decisions. In contrast to the considerable amount of knowledge regarding the treatment of metastatic

clear cell RCC, the treatment of metastatic chromophobe RCC lacks studies that would include large groups of patients. Therefore, we can currently observe examples of successful treatment within isolated cases. To date, Zhang et al. [10] have reported on a successful control of the metastatic progression of chromophobe RCC for 5 years in a 54-year-old woman with stage pT1bN0M0 RCC after laparoscopic radical nephrectomy, in whom lung metastases were diagnosed 4 years after surgery, which regressed on sunitinib as monotherapy. After 3 years, progression was detected in the lungs and

Table 1. **Positive and negative IHC markers for confirming or excluding the diagnosis of chromophobe RCC**

Positive markers (typical for chromophobe RCC)		
Marker	Status	Comments
CK7	Positive (diffuse)	One of the most sensitive markers for chromophobe RCC, usually diffusely positive
CD117 (c-Kit)	Positive	Clear membranous expression; also positive in oncocytoma
E-cadherin	Positive	Useful for differentiating from clear cell RCC
Parvalbumin	Positive	Characteristic of chromophobe RCC, not expressed in clear cell RCC
Negative markers (unlike clear cell RCC)		
CD10	Negative or focally positive	Usually negative in chromophobe RCC; positive in clear cell RCC
CAIX (Carbonic Anhydrase IX)	Negative or mosaic	Differential marker, in clear cell RCC — diffusely positive
Vimentin	Negative	Usually positive in clear cell RCC
RCC marker	Negative	Specific for clear cell RCC

Table 2. **Main genetic features of chromophobe renal cell carcinoma**

Gene/Chromosome	Type of change	Comment
Chromosome 1	Chromosome loss	Loss of an entire chromosome is often observed
Chromosome 2	Chromosome loss	Loss is associated with dysregulation of cell growth
Chromosome 6	Chromosome loss	Typical for chromophobe RCC, possible diagnostic value
Chromosome 10	Chromosome loss	Often lost in this form of carcinoma
Chromosome 13	Chromosome loss	Disruption of suppressor genes
Chromosome 17	Chromosome loss	Loss leads to changes in cell cycle checkpoints
Chromosome 21	Chromosome loss	Less common, occurs in some cases
TP53	Mutation/inactivation	One of the most common genetic defects with an aggressive course
PTEN	Mutation/inactivation	Loss promotes tumor cell proliferation
TSC1	Mutation	Regulates the mTOR pathway, a potential target for targeted therapy
MTOR	Mutation	Mutations activate cell growth
FLCN	Mutation	Mutations may indicate the presence of Birt-Hogg-Dubé syndrome
VHL	Rare or absent mutation	Typical mutation for the clear cell form, not characteristic of chromophobe RCC

bones, which are currently successfully in remission while receiving the immunotherapeutic drug sintilimab with the targeted drug axitinib.

In our clinical observations, we have proved that the surgical tactic is capable of achieving a radical solution to chromophobic RCC that has metastasized in the perirenal adipose tissue.

The question of the appropriateness of prescribing pembrolizumab (a humanized monoclonal antibody to the PD-1 receptor) after removal of chromophobe RCC metastases, like in our clinical case, is very important and requires a careful individual approach taking into account the following factors:

1. Chromophobe RCC has low immune infiltration, low PD-L1 expression, and low mutational burden. All of these suggest limited sensitivity to immunotherapy, particularly pembrolizumab.

2. The pivotal trials (KEYNOTE-427, CheckMate 9ER) focused primarily on the clear cell subtype or included only a limited number of patients with chromophobe RCC; therefore, evidence of efficacy in this population is limited [17].

3. Pembrolizumab as adjuvant therapy after metastasectomy in clear cell RCC is considered in patients with a high risk of recurrence. This is not a standard practice for chromophobe RCC and is used primarily in clinical trials or off-label [18].

Pembrolizumab may be considered when i) there are signs of an aggressive course (short relapse-free interval after primary surgery, multiple metastases, abnormalities in the *TP53*, *MTOR*, *PTEN* genes); ii) PD-L1 expression >1% is detected (by immunohistochemistry); iii) other treatment options are not available or ineffective, and iv) the patient is participating in a clinical trial.

So, we can conclude that chromophobe RCC is usually characterized by an indolent course and a low metastatic potential. However, in rare cases, aggressive clinical behavior with the development of distant metastases is possible. The described clinical case demonstrates that even in the presence of metastatic progression, carefully planned radical surgery can provide long-term relapse-free remission and improve the patient's prognosis. Given the peculiarities of the genetic profile of chromophobe RCC, a personalized approach to the treatment, taking into account both morphological and molecular genetic characteristics of the tumor, is of great importance for the clinical outcome. Pembrolizumab is not a standard of care for chromophobe RCC after metastasectomy, but may be considered individually in cases of a high risk of relapse, in the presence of immunophenotypic indications, or as part of experimental therapy.

REFERENCES

1. Motzer RJ, Jonasch E, Agarwal N, et al. Kidney cancer, version 3.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2022;20(1):71-90. https://doi.org/10.6004/jnccn.2022.0001
2. Znaor A, Lortet-Tieulent J, Laversanne M, et al. International variations and trends in renal cell carcinoma incidence and mortality. *Eur Urol*. 2015;67(3):519-530. https://doi.org/10.1016/j.eururo.2014.10.002
3. Henske EP, Cheng L, Hakimi AA, et al. Chromophobe renal cell carcinoma. *Cancer Cell*. 2023;41(8):1383-1388. https://doi.org/10.1016/j.ccell.2023.07.006
4. Alaghehbandan R, Przybycin CG, Verkarre V, et al. Chromophobe renal cell carcinoma: Novel molecular insights and clinicopathologic updates. *Asian J Urol*. 2022; 9(1):1-11. https://doi.org/10.1016/j.ajur.2021.11.010
5. Bigot P, Bernhard JC, Flamand V, et al. Localized chromophobe carcinomas treated by nephron-sparing surgery have excellent oncologic outcomes. *Urol Oncol*. 2016;35(1):35.e15-35.e19. https://doi.org/10.1016/j.urolonc.2016.08.012
6. Singla A, Sharma A, Makkar A, et al. Rare metastatic sites of renal cell carcinoma: a case series. *Pan Afr Med J*. 2022;42:26. https://doi.org/10.11604/pamj.2022.42.26.33578
7. Moch H, Ohashi R. Chromophobe renal cell carcinoma: current and controversial issues. *Pathology*. 2021;53(1):101-108. https://doi.org/10.1016/j.pathol.2020.09.015
8. Ökrösi A, Ponhold L, Turba S et al. Liver metastasis from a chromophobe renal cell carcinoma 18 years after initial diagnosis: a case report. *J Med Case Reports*. 2025;19:116. https://doi.org/10.1186/s13256-025-05154-w
9. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet*. 2016;387(10032):2008-2016. https://doi.org/10.1016/S0140-6736(16)00559-6
10. Zhang H, Cong X, Chen C, Liu Z. Sintilimab combined with axitinib in the treatment of advanced chromophobe renal cell carcinoma: a case report. *Front Oncol*. 2024;2(14):1325999. https://doi.org/10.3389/fonc.2024.1325999
11. Linehan WM, Ricketts CJ. The metabolic basis of kidney cancer: biology and implications for therapy. *Cancer Discov*. 2013;3(3):203-211. https://doi.org/10.1158/2159-8290.CD-18-1354
12. Davis CF, Ricketts CJ, Wang M, et al. The somatic genomic landscape of chromophobe renal cell carcinoma. *Cancer Cell*. 2014;26(3):319-330. https://doi.org/10.1016/j.ccr.2014.07.014

13. Ohashi R, Schraml P, Angori S, et al. The molecular features and evolution of the chromophobe renal cell carcinoma. *J Pathol*. 2019;247(3):303-313. https://doi.org/10.1016/j.ajur.2021.11.010
14. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of papillary renal-cell carcinoma. *N Engl J Med*. 2016;374(2):135-145. https://doi.org/10.1056/NEJMoa1505917
15. El-Shorbagy SH, Alshenawy HA. Diagnostic utility of vimentin, CD117, cytokeratin-7 and caveolin-1 in differentiation between clear cell renal cell carcinoma, chromophobe renal cell carcinoma and oncocytoma. *J Microsc Ultrastruct*. 2017;5(2):90-96. https://doi.org/10.1016/j.jmau.2016.07.005
16. Garje R, Elhag D, Yasin HA, et al. Comprehensive review of chromophobe renal cell carcinoma. *Crit Rev Oncol Hematol*. 2021;160:103287. https://doi.org/10.1016/j.critrevonc.2021.103287
17. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus Cabozantinib versus Sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2021;384 (9):829-841. https://doi.org/10.1056/NEJMoa2026982
18. McDermott DF, Lee JL, Ziobro M, et al. Open-label, single-arm, phase II study of pembrolizumab monotherapy as first-line therapy in patients with advanced non-clear cell renal cell carcinoma. *J Clin Oncol*. 2021;39(9):1029-1039. https://doi.org/10.1200/JCO.20.02365

Submitted: June 08, 2015

П. Яковлев [1], Л. Роша [2], В. Юнгер [2]

[1] ДУ "Національний науковий центр хірургії та трансплантології імені О. Шалімова НАМН України", Київ, Україна
[2] КЛ "Феофанія", Київ, Україна

ПРИКЛАД КОМПЛЕКСНОГО РАДИКАЛЬНОГО ЛІКУВАННЯ МЕТАСТАТИЧНОЇ ПРОГРЕСІЇ РІДКІСНОЇ ЛОКАЛІЗАЦІЇ ПЕРВИННО ОРГАНО-ЛОКАЛІЗОВАНОГО ХРОМОФОБНОГО НИРКОВО-КЛІТИННОГО РАКУ НИРКИ ПІСЛЯ ЛАПАРОСКОПІЧНОЇ РЕЗЕКЦІЇ НИРКИ

Ми представляємо клінічний випадок мультифокальної метастатичної прогресії в паранефральній клітковині хромофобної нирково-клітинної карциноми (НКК) після первинної лапароскопічної резекції нирки, з успішним подальшим застосуванням комплексної тактики радикального лікування, та подаємо узагальнений опис молекулярно-генетичних особливостей хромофобної НКК та підходів до ад'ювантного лікування.

Ключові слова: рак нирки, хромофобний рак, часткова нефректомія, молекулярний профіль, пембролізумаб.