CASE REPORT

EXPERIMENTAL ONCOLOGY

https://doi.org/10.15407/exp-oncology.2024.04.402

V. SVINTSITSKIY, N. TSIP, S. NESPRYADKO, O. SAMOKHVALOVA, O. KHOPTIANA *, D. YERIUSHKIN, M. KROTEVYCH, S. TROKHYMYCH, L. SKORODA

State Non-Commercial Enterprise «National Cancer Institute», Kyiv, Ukraine

* Correspondence: Email: hoptyana.olha@ukr.net

OVARIAN EPITHELIOID HEMANGIOENDOTHELIOMA. CASE REPORT

Epithelioid hemangioendothelioma is a rare vascular sarcoma commonly occurring in the liver, soft tissues, and organs of the chest cavity. This study provides a detailed description of the clinical presentation, diagnosis, and treatment of epithelioid hemangioendothelioma of the ovary in a 71-year-old patient. According to the pathohistological examination, a mesenchymal tumor of the ovary with epithelioid cells was diagnosed. The immunohistochemical tests confirmed the diagnosis of epithelioid hemangioendothelioma. This clinical case is of interest for clinical practitioners due to the rare location of the tumor in female reproductive organs, which has not been previously documented in the medical literature.

Keywords: epithelioid hemangioendothelioma, ovary tumor, treatment.

Epithelioid hemangioendothelioma (EHE) is a rare vascular sarcoma characterized by its unpredictable clinical behavior and challenging management. This disease was firstly described in 1982 by Enzinger and Weiss, who observed 13 cases with the primary localization in the upper and lower extremities in their retrospective research [1].

EHE typically arises from vascular endothelial cells and can affect various organs including the liver, lungs, bones, and less commonly, the ovaries. Its ovarian manifestation presents unique challenges in terms of diagnosis, management, and prognostication due to its rarity and variable clinical course.

Having analyzed available literature, our team could not manage to find any cases with the primary localization of this disease within the organs of the female reproductive system. The clinical case that we present describes EHE originating from the vessels of the ovary.

Case report

A 71-year-old patient, V., was admitted to the Department of Oncogynecology of the National Cancer Institute in November 2023 with the complaints of frequent urgency to urination and pain in the lower abdomen. According to an ultrasound examination of the pelvis organs, a large tumor was detected, presumably originating from the right ovary.

Citation: Svintsitskiy V, Tsip N, Nespryadko S, Samokhvalova O, Khoptiana O, Yeriushkin D, Krotevych M, Trokhymych S, Scoroda L. Ovarian epithelioid hemangioendothelioma. Case report. *Exp Oncol.* 2024; 46(4): 402-407. https://doi.org/10.15407/exp-oncology.2024.04.402

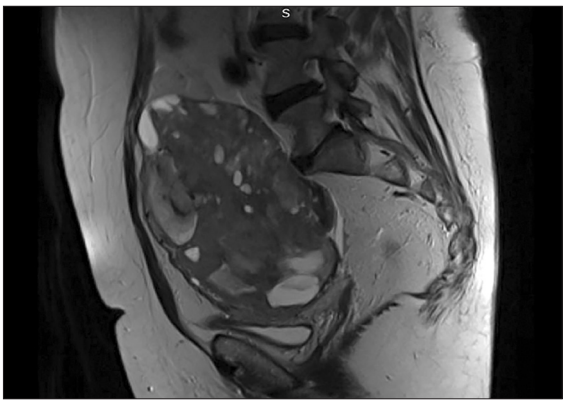


Fig. 1. MRI scan of the tumor (sagittal)

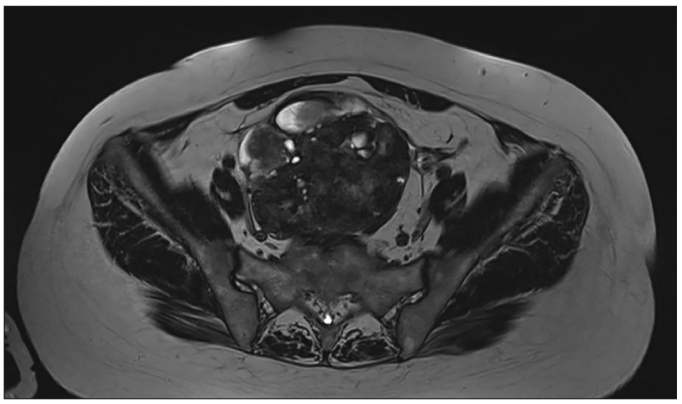


Fig. 2. MRI scan of the tumor (axial)

The CT study of the pelvic organs, abdominal cavity, and the lungs showed an irregularly shaped multiloculated cystic-solid formation along the posterior wall of the uterus being adjacent to the left ovary. Its size was 119 × 104 × 147 mm with a solid component showing a heterogeneous contrast accumulation. The anterior contour of the formation extended to the abdominal wall at the level of the L4 vertebra. The right ovarian vein was identified within the structure of the tumor. No other pathologies were detected.

A magnetic resonance imaging of the pelvic organs was performed, which revealed a cystic-solid formation of the same dimensions, with active contrast substance accumulation (Figs. 1, 2).

The cystic part of the formation was composed of multiple fluid-filled cystic inclusions. The left ovary was approximately 1.9 × 1.6 × 2.2 cm in size, with a single cystic inclusion present. The right ovary was not visualized due to the tumor mass. A differential diagnosis between cancer of the right ovary and a large malignant subserosal uterine nodule was not possible.

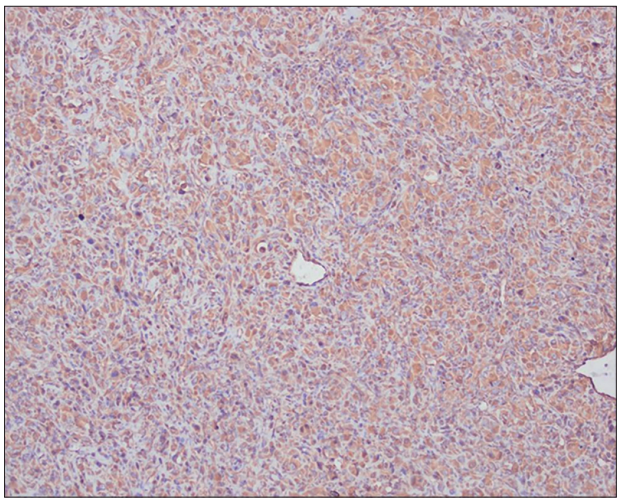
The CA-125 was 17.2 U/mL. Based on the findings of the histological examination of the material obtained from a curettage of the uterine cavity, the atypical endometrial hyperplasia was diagnosed.

The perioperative tumor highest measurement was up to 20 cm, originating from the posterior wall of the uterus. The right ovary and fallopian tube were not visualized. The left fallopian tube and ovaries appeared to be of normal sizes. The tumor was adhering to the recto-sigmoid part of the colon and omentum. An implant of a similar structure was removed from the sigmoid colon mesentery.

Surgery treatment included hysterectomy with bilateral salpingo-oophorectomy and paracolic resection of the large omentum. The postoperative period proceeded without complications, and on the 6th day, the patient was discharged in a satisfactory condition.

The final histopathological examination revealed a mesenchymal tumor consisting of the nests of epithelioid cells with marked polymorphism and multiple blood vessels (PEComa?). Immunohistochemical examination was recommended for the final verification. Similar tumor elements were found in the colonic mesentery. The other ovary showed fibrotic bodies and salpingitis. The endometrium demonstrated focal glandular hyperplasia. The tumor in the ovary included cells with clear vesicular nuclei, solid and solid-trabecular growth patterns, as well as numerous blood vessels of varying sizes. The tumor cells showed perivascular type of growth. The tumor exhibited areas of the cellular and nuclear polymorphism and the presence of atypical mitosis (12 in 10 areas of view), with less than 50% of the tumor area showing necrotic changes and focal lymphoid infiltration. According to the FNCLCC sarcoma grading system: epithelioid sarcoma 3p, mitotic index 3p, and a tumor necrosis 1p, resulting in a total score of 6 — G3.

Immunohistochemical studies were performed using the following monoclonal antibodies (mAb) manufactured by Leica Biosystem: mouse mAb against cytokeratin AE1/AE3 (BOND PA0909), mouse mAb against vimentin, clone V9 (BOND PA0640), mouse mAb against smooth muscle actin, clone alpha SM-1 (BOND PA0943); mouse mAb against desmin, clone DE-R-11 (BOND PA0032), mouse mAb against melanoma marker, clone



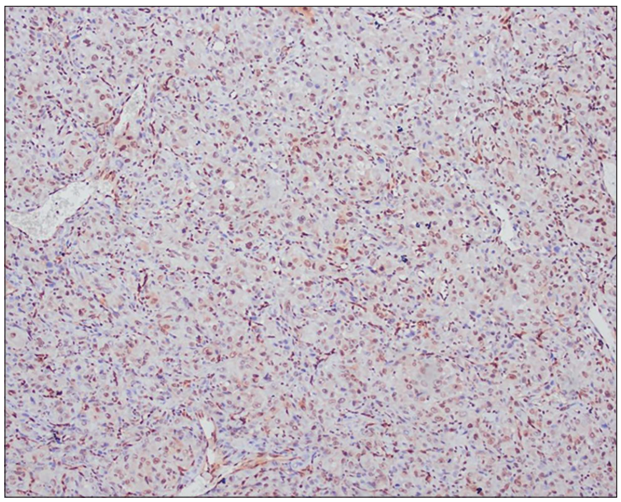
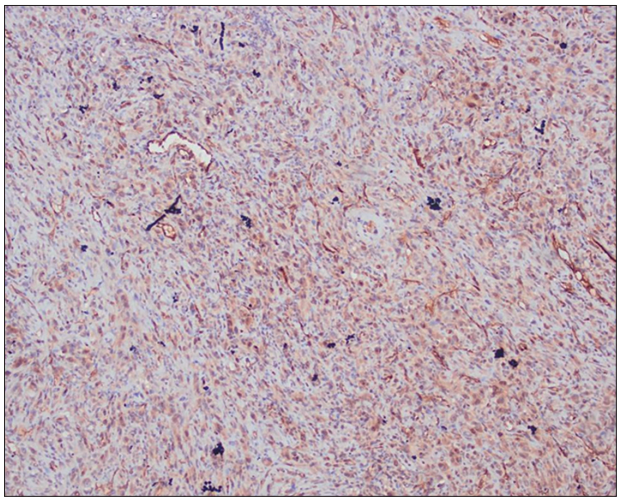


Fig. 3. Diffuse positive cytoplasmic staining for vimentin in tumor cells

Fig. 4. Diffuse positive nuclear staining for ERG in tumor cells



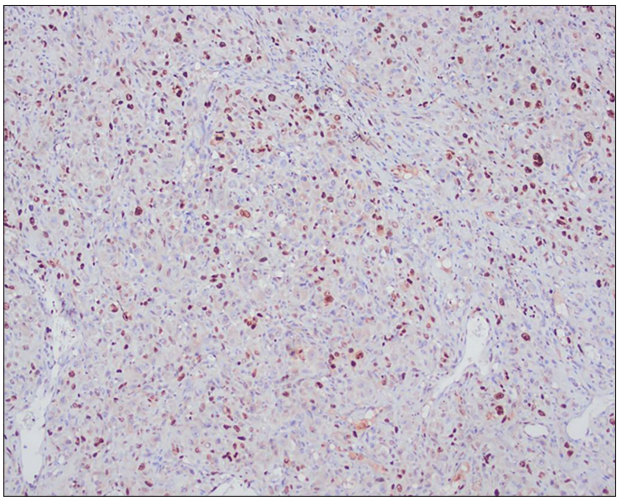
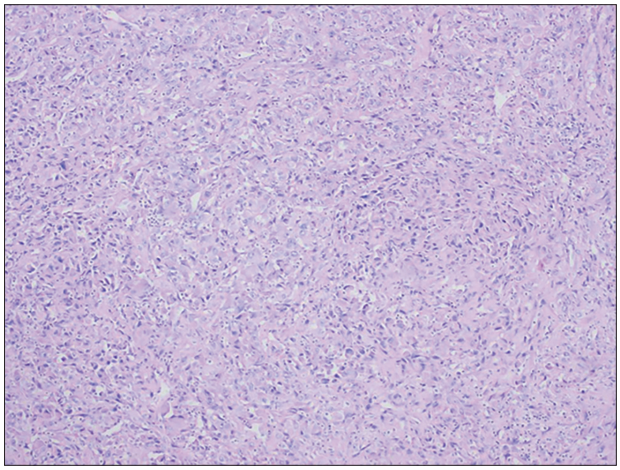


Fig. 5. Diffuse positive cytoplasmic staining for von Willebrand factor in tumor cells

Fig. 6. Positive nuclear staining with Ki-67 in 30% of tumor cells



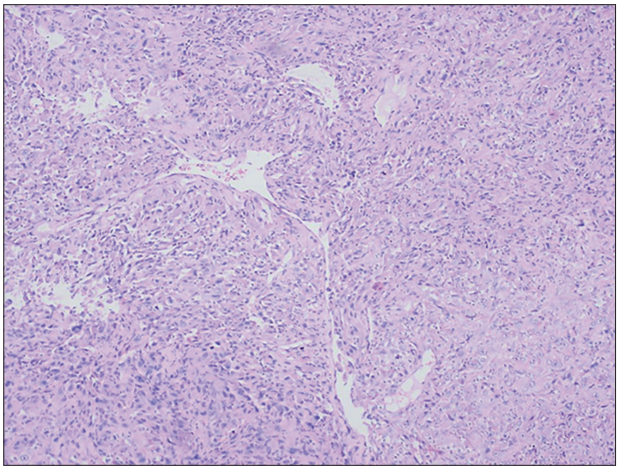


Fig. 7. Tumor composed of groups and cords of epithelioid cells of round and oval shape, with eosinophillic cytoplasm in fibrous stroma, forming vascular spaces (H&E, 10x)

HMB45 (BOND PA0027), mouse mAb against melan-A, clone A103 (BOND PA0233), mouse mAb against Ki-67, clone MM1 (BOND PA0118), mouse mAb against cyclin D1, clone EP12 (BOND PA0046), mouse mAb against Myf-4 (rhabdomyosarcoma marker), clone LO26 (BOND PA0226), mouse mAb against CD68, clone 514H12 (BOND PA0273), mouse mAb against inhibin alpha, clone R1 (BOND PA0488), mouse mAb against synaptophysin, clone 27G12 (BOND PA0299), mouse mAb against chromogranin A, clone 5H7 (BOND PA0515), mouse mAb against CD10, clone 56C6 (BOND PA0270), mouse mAb against CD99 (BOND CD99-187-L), mouse mAb against calretinin, clone CAL6 (BOND PA0346), mouse mAb against Wilms' tumor 1 (WT-1) protein, clone WT49 (BOND PA0562), mouse mAb against estrogen receptor (ER), clone 6F11 (BOND PA0151), mouse mAb against progesterone receptor, clone 16 (BOND PA0312), recombinant anti-ERG antibody, mouse mAb against Von Willebrand factor, clone 36B11 (BOND PA0055), mouse mAb against CD34, clone QBEnd/10 (BOND PA0212), mouse mAb against CD31, clone JC70A (BOND PA0414), and rabbit mAb against FLI-1 clone MRQ-1 (SKU:AMB24-5M).

The investigation was performed using the standard technique of visualization by Novolink Max Polymer Detection System (Leica). Antigen unmasking was performed in citrate buffer (pH 6.0) at 95 °C. Primary antibodies were incubated at room temperature for 40 min, secondary antibodies for 30 min. The sections were stained with hematoxylin. For the positive control, the tissue samples with determined positive reactivity were used; for the negative one, the procedure was carried out without the primary antibody application. The obtained samples were studied and photographed using an OLYMPUS BX46 microscope with a camera and CellSens software under the standardized conditions.

Differential diagnosis was carried out among the high-grade Sertolli — Leidig cell tumor, ovarian sarcoma, and the vascular tumors. Based on the such immunohistochemical findings as the positive expression of ERG, Von Willebrand factor, CD34, and CD31, the phenotype of the ovarian tumor was most inherent to epithelioid hemangioendothelioma (Figs. 3—7). The patient did not receive adjuvant chemotherapy.

Three months later, the patient admitted the appearance of pain in the abdomen. The CT study of the pelvis and abdomen showed recurrence of the disease in the abdomen: a tumor sizing 10 cm in the vaginal stump, another 6 cm tumor in the projection of the post-surgical scar, and a tumor sizing 3 cm in the pelvis. Carcinomatosis was noted. The patient underwent chemotherapy with vincristine, doxorubicin, and endoxan. After the 1st cycle, she complained about adverse events like nausea and vomiting. Hematological adverse events have been found. The patient refused to continue the treatment as advised.

Two months later, the CT study of the pelvis abdomen revealed ascites and a 12.5 cm tumor in the vaginal stump. Another 6.5 cm tumor was located at the post-surgical scar. Carcinomatosis was confirmed. A tumor of 4.6 cm was found in the pelvis.

The ascites was evacuated. The patient received palliative therapy. Patient's ECOG status was 3—4 according to the ECOG scale. The patient died three weeks later.

Discussion

Epithelioid hemangioendothelioma is a rare morphological form of malignant vascular tumors [2]. The incidence rate is 0.038/100,000 per year, with a prevalence of less than 1 per 1,000,000, occurring more frequently among women [3—5]. There used to exist a belief that clinically, EHE is a borderline tumor, exhibiting the features of both hemangioma and angiosarcoma. However, the experts from the World Health Organization describe this tumor as malignant, with a metastatic potential and variable course (slow and progressive) [6].

Due to the endothelial origin of such tumors, they express the FLI-1 protein, which is more specific for EHE, compared to the other endothelioid markers such as CD31 and CD34. However, in cases of primal localization in the uterine body, FLI-1 expression was not detected, likely due to differences in biochemical processes.

According to the literature, EHE can be found in the following locations: the liver, bones, soft tissues, and thoracic cavity. The authors described the cases of unifocal lesions, with locoregional spread or disease with multiple metastases. Given the low frequency of occurrence, there are scarce data on prognostic factors for EHE. However, the authors

identified that the mitotic activity and tumor size may influence prognosis.

The research by Tomassen et al. [7] included 57 cases of EHE with various tumor locations. The patients had a single lesion in 29 cases, multiple lesions in 5 cases, lymph node involvement in 8 cases, and distant metastases — in 15 cases. The one-year overall survival rate was 71.4%, and the five-year rate was 50.7%. There was no correlation between the age or sex and any histopathological features. 25 cases of unifocal tumors were treated surgically. In 6 cases, radiotherapy was supplementary to the main treatment. Patients with multifocal tumor location underwent hemihepatectomy (40%, n = 2), systemic therapy (40%, n = 2), and one patient was observed. In 7 cases, patients with affected lymph nodes underwent surgical treatment.

According to the consensus adopted by the expert group, the method of choice for the unifocal EHE is a surgical treatment (II, A). In case of achieving R1 in the adjuvant regimen, radiotherapy may be recommended. If achieving R0/R1 is not possible, a surgical treatment may be replaced with a definitive radiotherapy (V, A). The dynamic observation of patients with unifocal EHE is not recommended [8].

By the recommendations of the working group, there are no data on the feasibility of systemic therapy in the (neo) adjuvant regimen (V, D). However, chemotherapy may be considered in patients with metastatic disease or with the signs of progression. Retrospectively, the antitumor effects of interferon (V, C), thalidomide (V, C), tyrosine kinase inhibitors, and mTOR inhibitors have been evaluated [9—11]. Recurrence-free survival and overall survival were higher in the mTOR group [8].

Another study describes 28 cases of liver EHE treatment in children [12]. According to the data from the Children Cancer Hospital in Egypt, after conducting a retrospective study from 2008 to 2017, a total of 28 patients (18 females, 10 males) were diagnosed with on average three-month EHE. The lesions were multifocal (n = 12), focal (n = 10), and diffuse (n = 6). 11 patients did not receive any treatment, while 1 patient underwent surgery. 16 patients received medical treatment, with 9 responding well to the first-line propranolol/prednisolone, while 7 patients required the second-line therapy (1 million units/m^2/week interferon, 1.5 mg/m^2/week vincristine, 10 mg/kg/day cyclophosphamide). 25 patients survived, whereas 3 patients died.

In the study [13], evaluating the efficacy of bevacizumab, which is a recombinant human antibody against the vascular endothelial growth factor (VEGF), in combating metastatic or locally advanced forms of angiosarcoma and epithelioid hemangioendothelioma, 32 patients were enrolled and treated with bevacizumab in a dose of 15 mg/kg intravenously in a 21-day cycle [14]. The patients had diseases considered inoperable, ECOG status was ≤1, and the organ function was preserved. They did not receive any radiotherapy in the previous 28 days. It was found out that only 4 (2 angiosarcomas and 2 epithelioid hemangioendotheliomas) of 30 patients for whom the efficacy and toxic effect of bevacizumab were evaluated had a partial response. In 15 patients (11 angiosarcomas and 4 epithelioid hemangioendotheliomas), disease stabilization was observed with a median time to progression of 26 weeks. Bevacizumab was well tolerated with only one grade 4 adverse reaction. The expected drug toxicities were manageable.

In conclusion, EHE represents a rare and complex malignancy with unique molecular and clinical characteristics. While the tumor behavior and treatment responses vary across patients, the advancements in the genetic understanding, such as the role of transcriptional changes in the MAPK signaling pathway [14], have provided insight into the potential therapeutic targets. Although surgery remains the primary treatment for unifocal lesions, the cases with metastatic or multifocal disease underscore the potential need for systemic therapies, including the targeted drugs like bevacizumab and mTOR inhibitors. However, due to the rarity of EHE, further research and larger clinical trials are needed to establish more robust prognostic factors and refine treatment protocols, ultimately aiming to improve patient's survival and quality of life.

To date, no cases of primary tumor localization in the female reproductive organs have been published in the available literature. Therefore, this clinical case is of both scientific and clinical interest.

REFERENCES

1. Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma: a vascular tumor often mistaken for a carcinoma. *Cancer*. 1982;50(5):970-981. https://doi.org/10.1002/1097-0142(19820901)50:5<970::aid-cncr2820500527>3.0.co; 2-z
2. Wang ZB, Yuan J, Chen W, Wei LX. Transcription factor ERG is a specific and sensitive diagnostic marker for hepatic angiosarcoma. *World J Gastroenterol*. 2014;20(13):3672-3679. https://doi.org/10.3748/wjg.v20.i13.3672
3. Lau K, Massad M, Pollak C, et al. Clinical patterns and outcome in epithelioid hemangioendothelioma with or without pulmonary involvement: insights from an internet registry in the study of a rare cancer. *Chest*. 2011;140(5):1312-1318. https://doi.org/10.1378/chest.11-0039
4. Stacchiotti S, Frezza AM, Blay JY, et al. Ultra-rare sarcomas: a consensus paper from the Connective Tissue Oncology Society community of experts on the incidence threshold and the list of entities. *Cancer*. 2021;127(16):2934-2942. https://doi.org/10.1002/cncr.33618
5. de Pinieux G, Karanian M, Le Loarer F, et al. Nationwide incidence of sarcomas and connective tissue tumors of intermediate malignancy over four years using an expert pathology review network. *PLoS ONE*. 2021;16(2):e0246958. https://doi.org/10.1371/journal.pone.0246958
6. Nagtegaal ID, Odze RD, Klimstra D, et al. WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. 2020;76:182-188. https://doi.org/10.1111/his.13975
7. Tomassen T, Versleijen-Jonkers YMH, Hillebrandt-Roeffen MHS, et al. Prognostic factors in epithelioid hemangioendothelioma: Analysis of a nationwide molecularly/immunohistochemically confirmed cohort of 57 cases. *Cancers (Basel)*. 2023;15(13):3304. https://doi.org/10.3390/cancers15133304
8. Stacchiotti S, Miah AB, Frezza AM, et al. Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts. *ESMO Open*. 2021;6(3):100170. https://doi.org/10.1016/j.esmoop.2021.100170.
9. Radzikowska E, Szczepulska-Wójcik E, Chabowski M, et al. Pulmonary epithelioid haemangioendothelioma—Interferon 2-alpha treatment—case report. *Adv Respir Med*. 2008;76(4):281-285. https://doi.org/10.5603/ARM.27887
10. Thomas RM, Aloia TA, Truty MJ, et al. Treatment sequencing strategy for hepatic epithelioid haemangioendothelioma. *HPB (Oxford)*. 2014;16:677-685. https://doi.org/ 10.1111/hpb.12202
11. Esma S, Marie-Christine SP, Jean G et al. Metastatic hepatic epithelioid hemangio-endothelioma: long-term response to sunitinib malate. *Oncol Res Treat*. 2014;37(3):124-126. https://doi.org/10.1159/000360208
12. Mayur V, Mohammed S, Radwan D, et al. Hepatic hemangioendothelioma: An update. *World J Gastrointest Oncol.* 2020;12(3):248-266. https://doi.org/10.4251/wjgo.v12.i3.248
13. Agulnik M, Yarber JL, Okuno SH, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. *Ann Oncol*. 2013;24(1):257-263. https://doi.org/10.1093/annonc/mds237
14. Shuang M, Ryan K, Ajaybabu V P, et al. The TAZ-CAMTA1 fusion protein promotes tumorigenesis via connective tissue growth factor and Ras-MAPK signaling in epithelioid hemangioendothelioma. *Clin Cancer Res*. 2022;28(14):3116-3126. https://doi.org/10.1158/1078-0432.CCR-22-0421

Submitted: August 10, 2024

В. Свінціцький, Н. Ціп, С. Неспрядько, О. Самохвалова, О. Хоптяна,
Д. Єрюшкін, М. Кротевич, С. Трохимич, Л. Скорода

Державне некомерційне підприємство «Національний інститут раку», Київ, Україна

КЛІНІЧНИЙ ВИПАДОК: ЕПІТЕЛІОЇДНА
ГЕМАНГІОЕНДОТЕЛІОМА ЯЄЧНИКА

Епітеліоїдна гемангіоендотеліома (ЕГЕ) — це рідкісна судинна саркома, що зазвичай зустрічається в печінці, м'яких тканинах і органах грудної порожнини. В роботі детально описано клініку, діагностику та лікування епітеліоїдної гемангіоендотеліоми яєчника в 71-річної пацієнтки. За даними патогістологічного дослідження діагностовано мезенхімальну пухлину яєчника з епітеліоїдними клітинами, а імуногістохімічні тести підтвердили діагноз ЕГЕ. Описаний клінічний випадок цікавий для практикуючого лікаря через рідкісну локалізацію пухлини в жіночих репродуктивних органах, раніше не задокументовану в медичній літературі.

Ключові слова: епітеліоїдна гемангіоендотеліома, пухлина яєчника, лікування.