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CLINICAL CASE OF PRIMARY OVARIAN OSTEOSARCOMA

We describe an extremely rare clinical case of primary ovarian osteosarcoma (OS) in a 70-year-old woman, along with the diagnostic criteria for this condition. The patient underwent chemotherapy and has been under observation for 27 months. Currently, tumor progression with metastatic lesions of the peritoneum is observed. This case highlights the importance of further studies of primary ovarian OS. Ovarian OS is not included in the 2022 WHO classification of genital tumors, but such cases occur; their diagnosis is difficult, and there is no consensus on the treatment. Accumulating data on the structural features of these tumors and their response to treatment will help improve the understanding of their treatment.

Keywords: ovarian cancer, osteosarcoma of the ovary, osteosarcoma, teratoma.

Ovarian tumors are the eighth most common cancer among women worldwide, with the highest incidence rates observed in Central and Eastern Europe, North America, and Southeast Asia. Most of these tumors are high-grade carcinomas [1]. Stromal tumors are less common and arise primarily from the stromal tissue of the gonadal sex cords. Teratomas with a malignant component are even less common (about 2% of all tumors), and 80% of them contain a dermoid component or, less commonly, adenocarcinoma, melanoma, or another malignancy. Osteosarcoma (OS) may arise from teratoma, malignant mixed neuroectodermal tumor, primitive ovarian stromal cells, or metaplastic stromal cells [2]. In most cases, teratomas contain multiple components, which complicate correct diagnosis. Only 8% of malignant teratomas contain elements of sarcoma, and cases of the tumor consisting exclusively of a sarcomatous component are extremely rare. To confirm the diagnosis of primary ovarian OS, it is necessary to exclude soft tissue or bone tumors.

OS is more common in men in the second decade of life, especially during the pubertal bone growth spurt. The most common sites are the distal femoral metaphysis and the proximal tibial metaphysis, with 60% of cases occurring in individuals under 25 years of age [3]. OS is extremely rare in the elderly and occurs against the background of chronic osteomyelitis or Paget's disease. Pain is the main clinical symptom. Sometimes, OS can occur in soft tissues. Extraskeletal OS, according to the WHO classification, refers to soft tissue sarcomas.

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However, soft tissue morphology and bone osteogenesis have common features and contain varying amounts of neoplastic bone, cartilage, and/or fibroblastic components; based on the predominant matrix, they are divided into different types. Approximately 80%—90% of OS are represented by "classic" osteoblastic types, classified by WHO as OS without further specification (ICD-O code 9180/3) [4]. Less common types include chondroblastic OS (ICD-O code 9181/3) and fibroblastic OS (ICD-O code 9182/3). Telangiectatic OS (ICD-O code 9183/3) and small cell OS (ICD-O code 9185/3) share similar biological features. Superficial osteogenic paraosseous OS is low-grade, and periosteal OS is moderately differentiated. However, the classic OS is always high-grade [5]. Since our case describes a classic osteoblastic ovarian OS, we will focus on this type of malignancy.

As follows from the previously mentioned classification, OS histology is polymorphic, but it is always possible to identify signs of tumor bone formation, which is predominant in the osteoblastic type. Neoplastic bone can be represented by small amorphous fragments or a fine network of osteoid, sometimes resembling bone trabeculae. Areas of malformed pleomorphic cells resembling pleomorphic sarcoma may be present, as well as atypical cartilage and fibrous tissue. The mitotic activity is usually high, often with an abundance of atypical mitotic figures, which is useful in the differential diagnosis with benign tumors. Despite the diverse morphology, neoplastic bone formations are important for diagnosis. There is no required threshold value for the minimum number of neoplastic bone formations; any number is sufficient for diagnosis. Bone matrix, including tumor matrix, appears eosinophilic in hematoxylin-eosin-stained sections if not mineralized and basophilic if mineralized. The differentiation between non-mineralized matrix (osteoid) and other eosinophilic extracellular substances, such as collagen or fibrin, can be challenging. Immunohistochemistry (IHC) using SATB2 antibodies to indicate osteoblastic differentiation can facilitate the diagnosis. SATB2 belongs to the matrix attachment region-binding transcription factor family. This marker has a positive nuclear expression in all OS, both skeletal and extraskeletal. However, it is not specific as it is often expressed in osteoblastoma, osteoid osteoma, fibrous dysplasia, giant cell tumor, and colorectal adenocarcinoma. Therefore, a histological diagnosis is made based on a combination of various data, namely the morphological structure in different tumor areas and IHC results using a panel of antibodies, including markers characteristic not only of OS but also helping to exclude carcinoma elements. Typically, in OS, in addition to SATB2, osteocalcin (BGLAP), osteonectin (SPARC), osteoprotegerin (TNFRSF11B), RUNX2, S100, actins, and CD99 are expressed [4, 6].

Diagnosis of primary ovarian OS before surgery is unlikely, as calcifications on radiographs are not specific to it. Calcifications were noted in two-thirds of the teratomas in the series described by Siegel et al. [7]. Of the 80 gonadal blastomas reported in two series, 7 cases had calcifications that could be visualized on abdominal radiographs. Finally, in a Mayo Clinic series, extensive calcification was observed in 4% of 263 ovarian fibroids [8].

All cases of primary OS described in the literature were diagnosed based on surgical or pathological examination data.

In our 40-year-long practice (annually, Kyiv City Oncological Center performs an average of 180 surgeries for ovarian tumors, 90 of which are malignant), the first case of primary ovarian OS has been diagnosed.

Case presentation

The patient was a 70-year-old woman with a history of one birth and no abortions; by the time of treatment (in Kyiv City Oncological Center from May 2023), she had been in menopause for 25 years. The patient presented with complaints of abdominal bloating and lower abdominal pain for the past 6 months and had not visited a gynecologist for the past 7 years. There was no family history of cancer. The patient underwent a comprehensive examination, including CT of three zones with contrast, esophagogastroduodenoscopy, and tumor marker analysis.

CT revealed a complex cystic mass with contrast enhancement in the left ovary projection, sized 14 × 10 cm, with lobular, clearly defined contours, compressing the uterine body, without intestine and large vessels invasion (Fig. 1).

No signs of secondary involvement were seen: the lymph nodes were not enlarged, and no bone lesions were found, which indicates primary ovarian malignancy.

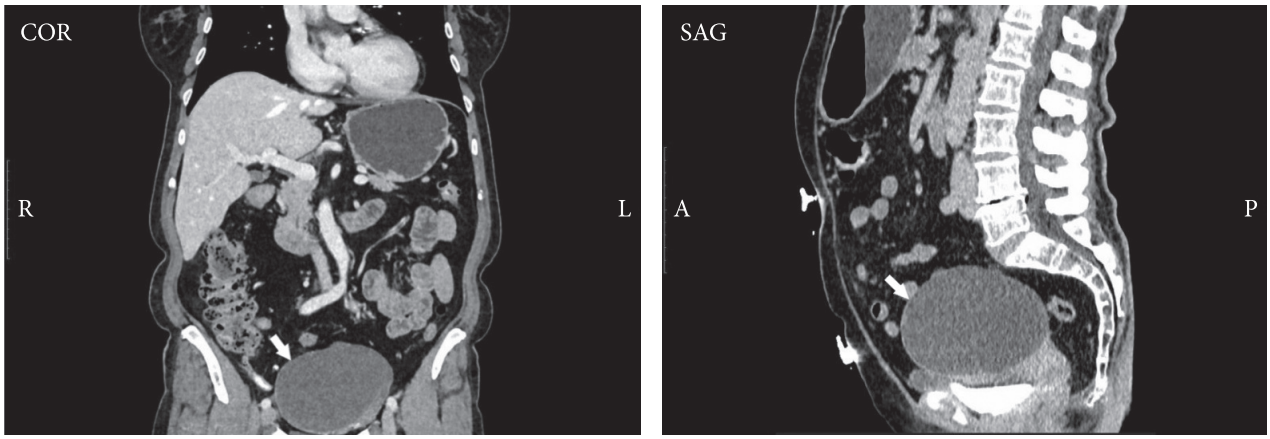

Fig. 1. Chest, abdominal, and pelvic CT images show a complex cystic mass in the pelvic projection

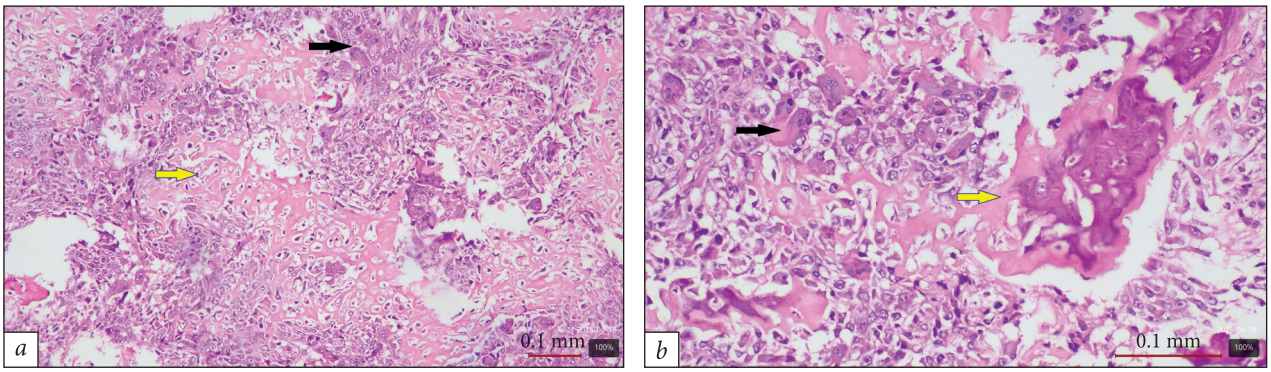

Fig. 2. OS histopathology: *a* — a homogeneous osteoid mass is seen in the tumor, with osteoclasts of different sizes (yellow arrow) and polymorphic nuclei on the periphery (black arrow), along with a loose fibrous matrix. H&E, ×100; *b* — typical osteoid (yellow arrow) against the background of osteoblast proliferation, with isolated osteoclasts (black arrow). H&E, ×200

Tumor markers: CA-125 — 6.76 U/mL (normal range <35), HE4 — 138.13 pmol/mL (normal range <70), ROMA index — 17.3%.

Preliminary diagnosis: Neoplasm of the left ovary, suspected of being malignant. Surgical treatment was performed: visceral separation, abdominal hysterectomy with bilateral tubo-oophorectomy (type II), and omentectomy. During the revision, damage to the tumor capsule of the left ovary was found. The right ovary was enlarged to 4.5 cm; the surface was smooth. The uterine body was of normal size; adjacent organs were not changed. No signs of dissemination were detected. The omentum and liver showed no abnormalities. No residual tumor was found.

Gross pathology: The body of the uterus was not enlarged, the endometrium was atrophic, and the cervix and cervical canal were normal. The left ovary presented a complex cystic mass, measuring 14 × ×10 cm; on section, the solid component occupied 2/3 of the area and had a dense, bony structure. The cystic component was represented by dark hemorrhagic contents, the outer capsule was smooth, and multiple papillary structures were visible on the inner surface. The Fallopian tubes were normal. The right ovary was enlarged to 4.5 cm, the surface was smooth, and on the section, it appeared intact.

Histopathological description: A tumor in the left ovary was characterized by proliferation of atypical polygonal and spindle-shaped cells and the formation of neoplastic osteoid and numerous osteoclast-like giant cells (Fig. 2, *a, b*). The tumor cells showed high-grade nuclear atypia and significant mitotic activity. The microscopic fragments of the cyst epithelial lining, represented by monomorphic single-layer epithelium, were found in the capsule of the tumor node. The right ovary, Fallopian tubes, endometrium, cervix, and omentum showed no sign of tumor.

IHC analysis: Cytokeratin pan (AE1 and AE3) — negative reaction in tumor cells (Fig. 3, *a*), positive reaction in a small number of cells of single-layered

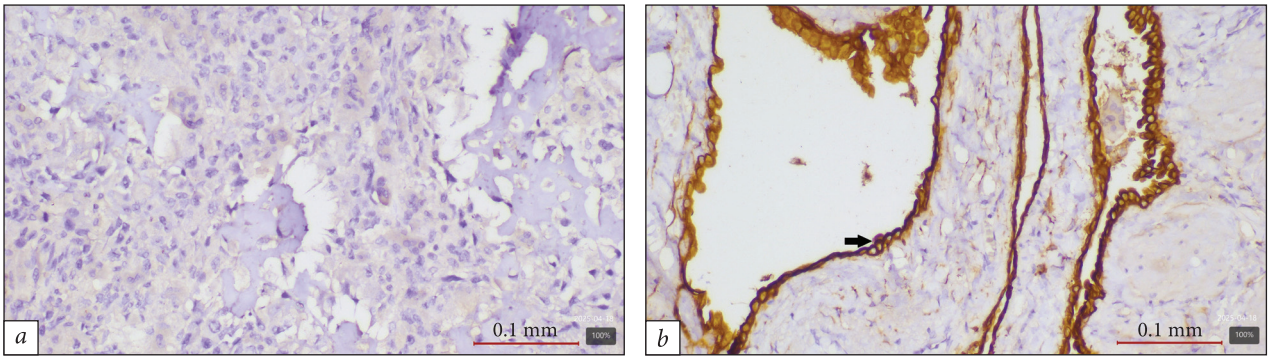

Fig. 3. Immunostaining for CK-Pan A: *a* — negative reaction in atypical tumor cells, which argues against the presence of carcinoma, ×200; *b* — CK-Pan, positive reaction in the cyst epithelial lining, detected within the tumor capsule, ×200

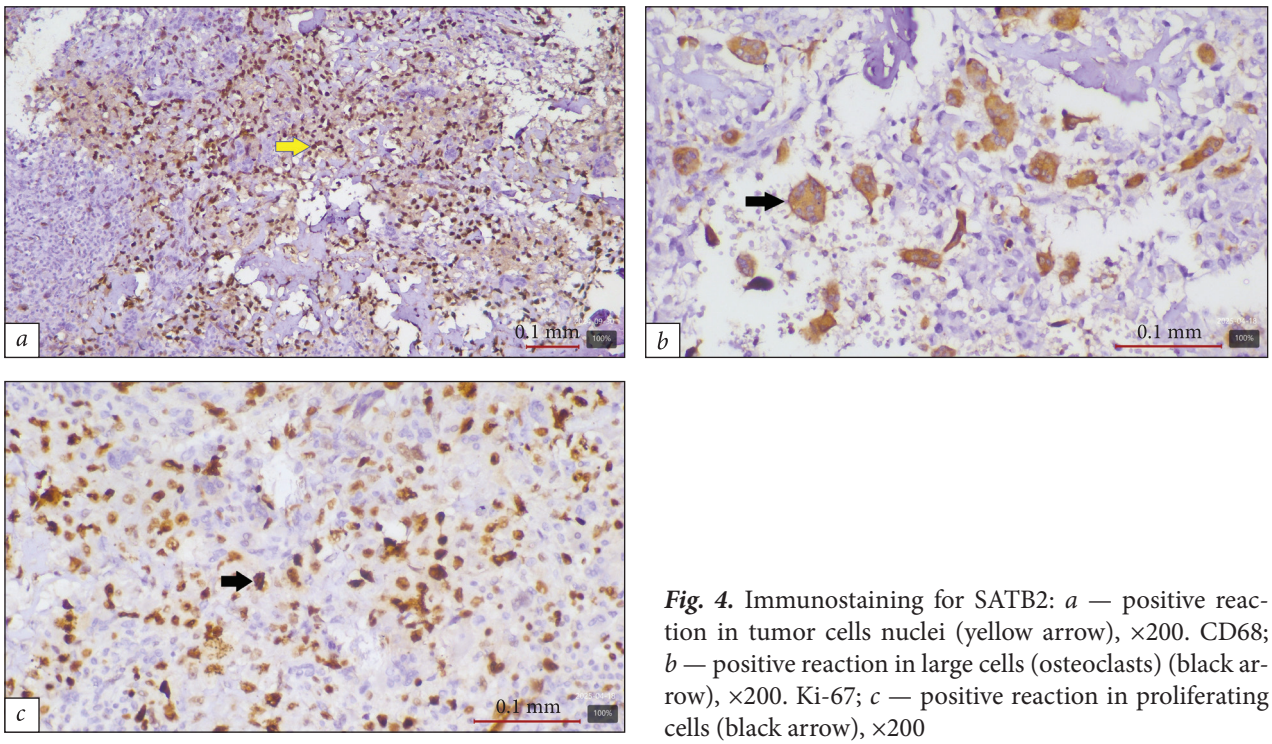

Fig. 4. Immunostaining for SATB2: *a* — positive reaction in tumor cells nuclei (yellow arrow), ×200. CD68; *b* — positive reaction in large cells (osteoclasts) (black arrow), ×200. Ki-67; *c* — positive reaction in proliferating cells (black arrow), ×200

cyst epithelium, found in the tumor capsule (Fig. 3, *b*); CD 68 (KP1) — positive reaction in osteoclast-like giant cells (less than 5%); Ki-67 (MIB-1) — 45% in tumor cells; vimentin (Vim3B4) — positive reaction in tumor cells; SATB2 (EP281) — positive reaction in tumor cells (Fig. 4); cytokeratin 7 (OV-TL 12/30) — positive reaction in less than 5% of single-layered epithelium area.

Based on histopathological and IHC examination data, the OS of the left ovary was diagnosed.

The postoperative period was uneventful, and the patient was discharged in satisfactory condition on the eighth day after the surgery.

One month after the surgery, chemotherapy was started, four courses were administered according to the IP scheme (ifosfamide 1.5 g/m² — 12 g per course, cisplatin 20 mg/m² — 160 mg per course). According to the NCCN recommendations, cisplatin/ifosfamide are used to treat ovarian carcinosarcomas, including OS. At the clinical tumor council, we decided, based on the available research, to conduct treatment according to the IP regimen [9—13].

After completion of the specialized treatment, the patient felt well. A CT scan of three zones and an MRI of the pelvis with contrast revealed no sign of disease progression.

A year later, the disease relapsed. CT with contrast revealed multiple nodular formations in the parietal peritoneum and pelvic cavity, in contact with the walls of the sigmoid colon and bladder, and the ascites. In addition, the levels of tumor markers increased: CA-125 — 30.6 U/mL, HE4 —

534.9 pmol/L, and the ROMA index — 72.06%. Considering the results and the 12-month relapse-free period, we believe that the treatment was appropriate for the patient and deserved attention.

Discussion

OS of the ovary is very rare, with only a few cases documented in the literature. This highlights the importance of each case for understanding the origin and clinical behavior of this tumor. These rare cases provide a critical perspective and may help identify risk factors, optimize diagnostics, and develop effective treatment strategies. Further documentation and study of such cases are necessary to improve knowledge in this area and optimize patient care.

Our patient was alive for 27 months after the surgery, although she had multiple metastases in the abdominal cavity.

In 2006, Fadare et al. [6] described their observation of ovarian OS and reviewed all previously reported cases. A total of 13 patients: 6 primary cases of OS (mean age of patients 52.6 years), 5 OS in teratoma (mean age 52 years), and 2 cases of OS metastases to the humerus and maxilla (mean age 37.5 years) were described. Most patients had FIGO stage 3 or 4, with survival rates of 4.8 and 3.5 months, respectively.

Hines et al. [5] described a case of primary ovarian OS in a 53-year-old woman who had 5 successful deliveries and survived 5 months after surgery. In a younger patient (aged 43), the primary ovarian OS was large and spread to the uterus, small intestine, and bladder. The patient survived 18 days after surgery and died of intestinal obstruction.

Yesmin et al. [9] reported a case of primary ovarian OS based on autopsy findings in a 50-year-old woman. No evidence of occult teratoma was observed, leaving the pathogenesis of this case unclear.

A brief review of the literature on ovarian OS is presented in Table (see the list of corresponding references in [6]).

In all reported cases, the patients were 24—80 years old, the tumors ranged in size from 8 to 22 cm, and survival time ranged from 1 to 16 months, with two patients remaining asymptomatic for 16 months and 3 years.

Summary of the clinicopathological features, treatment, and outcomes of primary ovarian OS cases presented in the literature

Original study	Patient age, years	Tumor size, cm	FIGO stage	Treatment	Follow-up
Azoury and Woodruff, 1971	41	21	III	Surgery	DOD 5 months
Shakfeh and Woodruff, 1987	24	NS	IV	Surgery	DOD 5 months
Hirakawa et al., 1988	47	17	III	Surgery/Chemotherapy	DOD 8 months
Hines et al., 1990	53	2	I	Surgery/Chemotherapy	NED
Sakata et al., 1991	75	10	IV	Surgery	DOD 4 months
Stowe and Watt, 1952	67	15	III	Surgery	DOD 5 months
Burgess and Shutter, 1954	47	19	I	Surgery	NS
Ngwalle et al., 1990	52	3,1	I	Surgery/Chemotherapy	RFT 16 months
Ajithkumar et al., 1999	80	10	III	Surgery/Chemotherapy	DOD 2 months
Aygun et al., 2003	14	22	III	Surgery/Chemotherapy	RFT 7 months
Yeasmin et al., 2009	50	8	IV	Chemotherapy	DOD 1 months
Present case	70	14	I	Surgery/Chemotherapy	RFT 12 months

Notes: DOD — death after diagnosis; NED — no evidence of disease; RFT — relapse-free time; NS — not stated.

Our patient was alive for 27 months, despite the development of peritoneal metastases 12 months after the surgery. As in all the other cases, the diagnosis of OS was made postoperatively, although calcifications were visualized on CT; however, this sign is not specific for this tumor. The intraoperative express histological examination was impossible due to the high tissue density and extensive foci of bone tissue requiring decalcification. Microscopic examination of sections stained with hematoxylin and eosin revealed pure ovarian OS. Considering the discrepancies with cases described in the literature, it was decided to verify the diagnosis using IHC, which would confirm the absence of other stromal and epithelial components (CK^-) in the tumor, and the presence of osteogenic differentiation ($SATB2^+$). OS usually does not cause difficulties in morphological diagnosis due to its typical localization in bones and soft tissues. In our case, during the examination of the tumor capsule, a microscopic fragment of the cyst epithelial lining was detected, which is an extremely valuable finding for the ovarian OS histogenesis understanding, confirming its teratoma origin.

Considering that primary ovarian OS is an extremely rare disease, there is no unified treatment protocol. Researchers agree that survival rates improve after radical surgical treatment, but at a late stage, this may not be possible. There is no consensus regarding chemotherapy, as it does not always provide encouraging results.

Before 1972, many studies of adjuvant chemotherapy using high doses of methotrexate in combination with leucovorin, doxorubicin, cisplatin, cyclophosphamide, dactinomycin, and vincristine had been conducted, but the results were disappointing. Among all drugs, doxorubicin showed the best response [14, 15]. Doxorubicin, high-dose methotrexate, and cisplatin are the most effective agents for OS treatment [15, 16]. Many combinations are currently being studied, including doxorubicin–cisplatin, vincristine–methotrexate, and doxorubicin–methotrexate. Thus, Hines et al. [5] have described a course of adjuvant chemotherapy in a patient, consisting of doxorubicin (60 mg/m^2) and cisplatin (75 mg/m^2) for eight cycles, followed by a remission for more than 5 months. Vyas et al. [8] have examined data from 11 cases of ovarian OS, treated by adjuvant radiotherapy, multimodal chemotherapy, and surgical intervention. 8 of 11 patients died of progressive disease within 2—8 months, and one patient had a local recurrence after 7 months. Only two patients were long-term survivors, and both received combination chemotherapy with doxorubicin and cisplatin after complete resection. The best survival rates were observed in cases where complete resection of the primary tumor was performed, whereas patients with incomplete resection experienced early recurrence and died within a few months.

Based on the evaluation of the data presented in the literature and our observation, we can conclude that OS is an extremely rare, highly malignant ovarian tumor, probably originating from a teratoma. Exclusion of bone or soft tissue tumors is important in primary OS diagnosis. Preoperative diagnosis is extremely confusing. Although CT scanning visualizes a heterogeneous mass with areas of suspected ossification or calcification, this is not sufficient to suspect OS, since these features may also be present in other tumors. Most OS cases are represented by the osteoblastic type; therefore, malignant osteogenesis is common; chondroblastic and fibroblastic components are much less common. The absence of carcinoma and other types of sarcomas allows us to exclude multicomponent malignant teratoma. OS clinical course is very aggressive, with extensive metastases. In our case, the patient showed signs of relapse 12 months after the surgery. The observation has been ongoing for 23 months; the patient was diagnosed with multiple metastases in the abdominal cavity. Therefore, radical surgical treatment with adjuvant chemotherapy improves survival rates.

Ethical approval and consent to participate

We publish this case considering the patient's signed informed voluntary consent according to the Declaration of Helsinki. The Ethics Committee of the Kyiv City Clinical Oncology Center reviewed our application and the patient's informed consent, and no permission was required. Approval number 061/17-1267 from 12/06/2024.

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Conflict of interest

The authors declare no conflict of interest.

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КЛІНІЧНИЙ ВИПАДОК ПЕРВИННОЇ
ОСТЕОСАРКОМИ ЯЄЧНИКІВ

Ми описуємо надзвичайно рідкісний клінічний випадок первинної остеосаркоми (ОС) яєчників у 70-річної жінки, а також діагностичні критерії цього стану. Унікальність цього захворювання та його агресивність, діагностичні помилки в періопераційному періоді роблять цей випадок гідним до представлення. ОС яєчників не включено до класифікації пухлин статевих органів ВООЗ 2022 року, але такі випадки трапляються, їх діагностика складна, і єдина думка щодо лікування відсутня. Накопичення даних про структурні особливості цих пухлин та їхню реакцію на лікування допоможе покращити результати лікування. Пацієнтка пройшла хіміотерапію та перебуває під спостереженням впродовж 27 місяців. Наразі спостерігається прогресування пухлини з метастатичним ураженням очеревини. Цей випадок підкреслює важливість первинного дослідження ОС яєчників, яке потребує подальшого вивчення.

Ключові слова: рак яєчників, остеосаркома яєчника, остеосаркома, тератома.