Retroperitoneal growth of high-grade serous ovarian carcinoma: A case report

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Abstract. High-grade serous ovarian carcinoma (HGSOC), an epithelial ovarian carcinoma, is primarily believed to originate from fallopian tube epithelial cells. This site of origin facilitates the dissemination of tumor cells to retroperitoneal organs or tissues, unrestricted by anatomical barriers, thereby promoting metastasis. The present report describes a rare case of HGSOC presenting with retroperitoneal involvement, and provides a comprehensive literature review on its pathogenesis, symptoms, diagnostic methods, treatment strategies and prognosis. The critical role of timely abdominal and pelvic imaging, along with tumor marker analysis, to evaluate patients with retroperitoneal tumors and nonspecific symptoms is emphasized. This approach aids in identifying the origin of retroperitoneal masses and facilitates the early diagnosis of metastatic HGSOC. Notably, an elevated serum CA125 level should raise suspicion of an ovarian malignancy.

Introduction

Epithelial ovarian cancer (EOC) is the most common type of ovarian malignancy. It accounts for 85-90% of all malignant ovarian tumors, with a higher incidence in middle-aged and elderly women worldwide (1). Based on histological differentiation, EOCs are classified into serous, mucinous and endometrioid carcinoma subtypes. The histological origins of these tumors are diverse, with high-grade serous ovarian carcinoma (HGSOC) believed to arise from serous tubal intraepithelial carcinoma before implantation on the ovarian surface. It represents the most prevalent histological subtype of EOC, constituting >70% of cases (1). HGSOC that develops on the ovaries or fallopian tubes lack anatomical barriers, allowing tumor cells to disseminate freely within the internal organs of the body (2). Once detached from the primary tumor, these cells may colonize the retroperitoneum or abdominal cavity, rapidly forming secondary tumor nodules (3,4). The present report describes a case of HGSOC presenting as a retroperitoneal tumor. This is a manifestation that, whilst not uncommon, presents notable diagnostic and therapeutic challenges due to its nonspecific symptoms and the anatomical complexity of the retroperitoneal space.

Case report

A 73-year-old woman presented to the Department of Urology of The First Affiliated Hospital of Guangxi Medical University (Nanning, China) in January 2024 with a 2-week history of right lower abdominal pain. The pain was described as paroxysmal colic, progressively worsening over time and the patient required painkillers for sleep. A physical examination revealed no notable renal tenderness or obvious abdominal mass. The medical history of the patient included uncontrolled hypertension and the obstetric history revealed three children, no miscarriages and menopause at 50 years old.

Abdominal CT revealed a 4.2x4.0x8.2 cm mass in the left posterior abdominal cavity, suspected to be a malignant tumor involving the left psoas major muscle and left ureter, with para-aortic lymph node metastasis (Fig. 1). The serum Cancer Antigen 125(CA125 level was mildly elevated at 39.7 U/ml (normal range, <35 U/ml), while other tumor markers remained within normal limits, such as cancer antigen 199 (CA199) and CA242. Preoperative renal function tests indicated renal insufficiency, with a serum creatinine level of 102 μmol/l (normal range, 50-98 μmol/l). Additionally, adrenal function abnormalities were noted, with norepinephrine levels elevated at 5,942.7 pmol/l (normal range, 615-3,240 pmol/l). Abdominal sonography detected a solid mass in the left retroabdominal cavity (data not shown), whilst renal emission CT (ECT) revealed a notably reduced left glomerular filtration rate (GFR) of 2.38 ml/min (normal range, 50-60 ml/min).

Following symptomatic management, including blood pressure control and analgesia, the patient was evaluated for surgical intervention. The selected surgical plan included a laparoscopic retroperitoneal mass resection, left ureteral stent placement, and if necessary, a left nephrectomy.

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Intraoperatively, the left upper ureter was revealed to be notably narrowed, precluding the successful placement of a 5-mm circumference double-J ureteral stent. Consequently, a left ureteroscopy was performed, and an external ureteral stent (5 mm in circumference) was inserted as a ureteral marker. Laparoscopic exploration revealed a retroperitoneal tumor located inferior to the left kidney, adherent to the lower pole of the kidney and the left renal vein, with the invasion of the left psoas major muscle and left upper ureter. Given the proximity of the tumor to the left kidney and ureter, and the likelihood of direct invasion, an open surgical approach was recommended. Following an intraoperative discussion with the family of the patient, an open left retroperitoneal tumor resection, left nephrectomy and partial left ureteral resection were performed to achieve radical tumor removal.

The surgery was successful, and the patient recovered well postoperatively. The pathology report revealed the following: i) The retroperitoneal mass was identified as a poorly differentiated adenocarcinoma with immunohistochemical markers suggestive of ovarian origin (Fig. 2A). Immunohistochemical analysis demonstrated positive CA125 (Fig. 2B) and paired box-8 (PAX-8) results (Fig. 2C); ii) the tumor had infiltrated the outer membrane, basal layer and lamina propria of the ureter; however, the urothelium remained unaffected; iii) no tumor infiltration was observed in the left renal parenchyma or perirenal fat (data not shown). For hematoxylin and eosin staining, tissues were fixed in 4% neutral buffered formalin at room temperature for ≥24 h, sectioned at 3-5 μm thickness and stained with hematoxylin (room temperature for 5-10 min) and eosin (room temperature for 1-3 min). Slides were observed under a light microscope. For immunohistochemistry, paraffin-embedded tissues (fixed as aforementioned) were embedded in paraffin and sectioned at 3-5 μm). Antigen retrieval was performed using citrate buffer (pH 6.0) at 120˚C for 2 min using an autoclave or 95˚C for 15 min using a microwave. Endogenous peroxidase activity was blocked using 3% H_2O_2. Sections were blocked with 5-10% Normal Goat Serum (Vector Laboratories) at room temperature for 30 min. Primary antibodies were added to the samples and incubated at 4˚C overnight or 37˚C for 1-2 h. HRP-conjugated secondary antibodies were added to samples and incubated at room temperature for 30 min, followed by DAB chromogen detection.

Given the suspected ovarian origin, further gynecological examinations were performed post-surgery. Gynecological sonography revealed a left adnexal hypoechoic mass, suspected to be metastatic, along with a right adnexal cyst (data not shown). Furthermore, a pelvic CT (Fig. 3) identified the following: i) A space-occupying lesion in the left adnexal region and peritoneum, raising suspicion of malignancy; and ii) A cystic mass in the right adnexal region, suggesting a benign cystic lesion. Additionally, PET/CT identified soft tissue metastasis in the left rectouterine pouch following the retroperitoneal malignant tumor resection (data not shown). A left adnexal mass of unknown nature prompted a needle biopsy, which confirmed poorly differentiated adenocarcinoma with immunohistochemical features consistent with HGSOC origin (Fig. 2D). The immunohistochemical markers, CA125 (Fig. 2E), PAX-8 (Fig. 2F) and Wilms tumor protein 1 (WT1; Fig. 2G), were positive.

Based on the aforementioned findings, the patient was diagnosed with left ovarian HGSOC and poorly differentiated adenocarcinoma in the retroperitoneal space. Following surgical resection of the retroperitoneal tumor, the patient recovered well and was transferred to the Department of Gynecology in March 2024 for further management of the left ovarian malignancy. During hospitalization, the patient underwent a laparoscopic radical procedure for ovarian cancer, which included a total hysterectomy, bilateral adnexa, greater omentum, resection of masses in the Douglas fossa and cecal surface, and pelvic lymph node dissection. Postoperative histopathology confirmed HGSOC of the left fallopian tube (Fig. 2H) with tumor invasion extending through the entire layer of the fallopian tube and into local mesangial fiber tissue. Metastatic fibrovascular tissue was identified in the rectouterine pouch mass. However, no metastatic involvement was detected in the appendages, pelvic lymph nodes, intestinal wall masses or right-sided omental tissue (data not shown).

The patient recovered well after surgery and was treated with postoperative chemotherapy consisting of intravenous paclitaxel (210 mg/m^2) and intravenous carboplatin (360 mg/m^2; TC regimen). To date, the patient has completed six cycles of TC chemotherapy and two cycles of bevacizumab maintenance therapy. The TC chemotherapy regimen followed a 3-week cycle. After chemotherapy, bevacizumab maintenance therapy was administered in 3-week cycles via intravenous injection at a dose of 15 mg/kg. After completion of the aforementioned treatments, the following surveillance protocol was recommended: Quarterly follow-up visits for the first 2 years post-surgery, semiannual evaluations from the years 3-5 and annual assessments thereafter. Surveillance components included gynecological examination, blood tests, pelvic ultrasound and either PET-CT or tumor-specific CT. Currently, the patient remains in good health and is self-sufficient without discomfort.

Discussion

Ovarian cancer is a significant public health concern. According to the World Health Organization, there are ~225,500 new cases and 140,200 deaths annually, making it the seventh most common cancer globally. HGSOC accounts for ~90% of these cases (5,6).

HGSOC is associated with a high mortality rate. According to the American Cancer Society, the overall 5-year survival rate for HGSOC across all stages is ~44%, which decreases to ~25% in advanced-stage cases. The majority of patients are diagnosed only after metastasis, with only ~13% diagnosed at an early stage (7). This presents a critical challenge in ensuring timely treatment and improving survival outcomes.

In most tumors, metastatic dissemination requires cells to typically undergo a series of cellular transformations by crossing the basement membrane, migrating and invading the vasculature, surviving in circulation and extravasating before forming a mass in a distant organ or tissue. However, HGSOC primarily originates from the fallopian tube epithelium, which lacks a physical anatomical barrier to prevent its spread. As a result, it disseminates mainly through direct peritoneal extension rather than through the blood or lymph. Consequently, its symptoms are often non-specific and predominantly

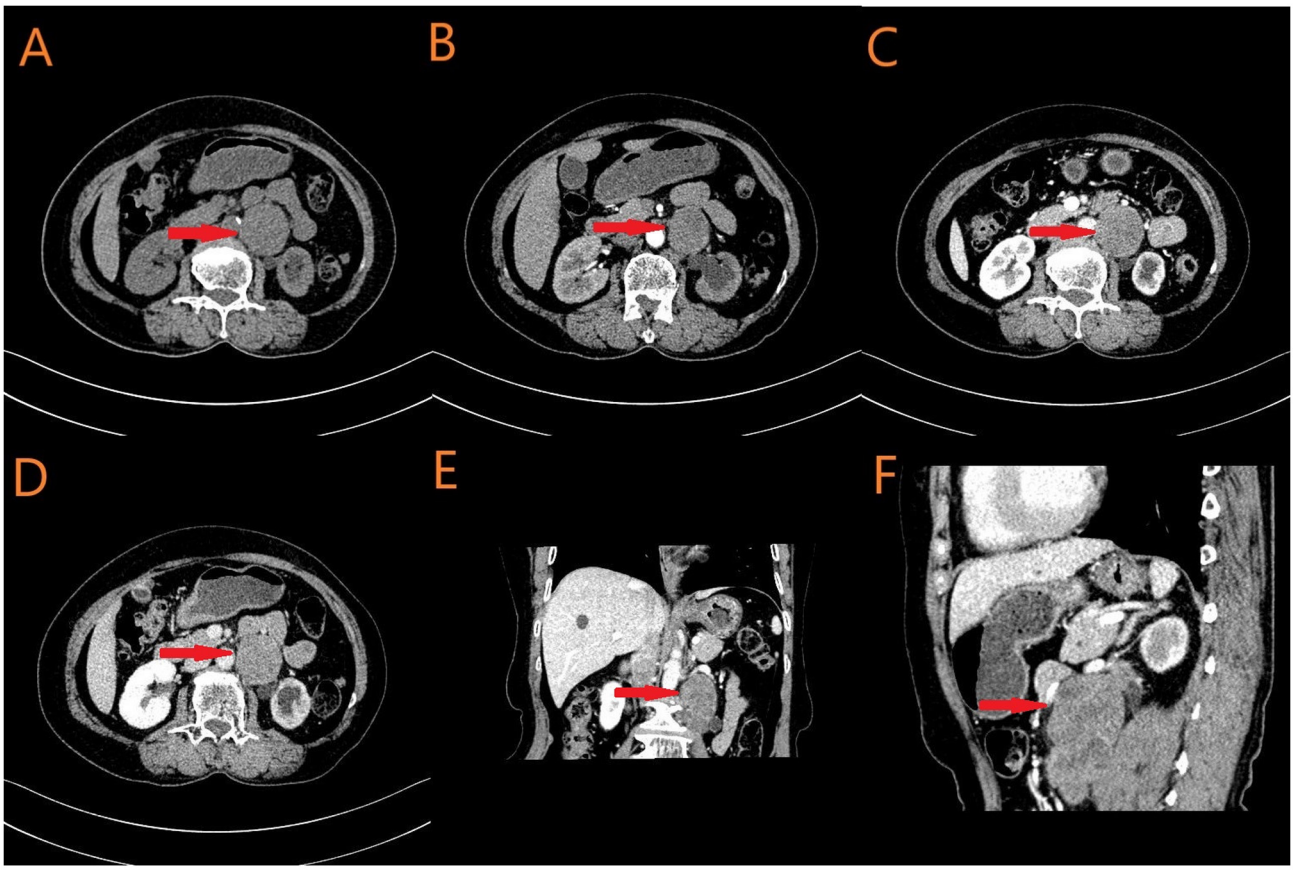

Figure 1. Abdominal CT images. (A) Plain phase, (B) arterial phase, (C) venous phase, (D) excretory phase, (E) venous phase coronal and (F) venous phase sagittal images.

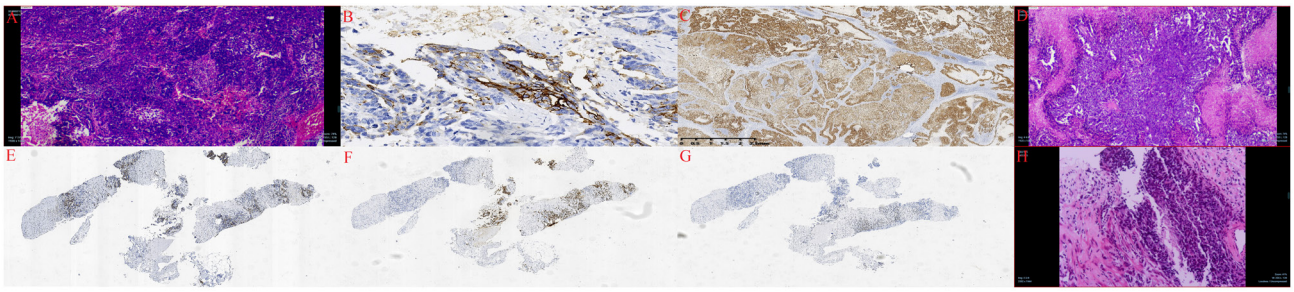

Figure 2. Histopathological features. (A) Retroperitoneal tumor (HE staining; magnification, x200) (B) Retroperitoneal tumor with CA125 immunohistochemical staining (magnification, x20) (C) Retroperitoneal tumor with PAX-8 immunohistochemical staining (magnification, x20) (D) Left adnexal puncture tissue (HE staining; magnification, x400) (E) Left adnexal puncture tissue with CA125 immunohistochemical staining (magnification, x20) (F) Left adnexal puncture tissue with PAX-8 immunohistochemical staining (magnification, x20) (G) Left adnexal puncture tissue with WT1 immunohistochemical staining (magnification, x20) (H) Post-radical surgery ovarian cancer tissue (HE staining; magnification, x200). HE, hematoxylin and eosin.

gastrointestinal due to tumor burden in the abdominal cavity or retroperitoneal space. Patients frequently present with abdominal pain, distension, nausea, constipation, anorexia, diarrhea and acid reflux, complicating early diagnosis and delaying treatment (1).

Currently, histopathological examination remains the gold standard for diagnosing HGSOC, whereas imaging serves primarily as a screening tool. Key imaging features of HGSOC include complex pelvic or peritoneal masses rich in blood vessels, though these findings are nonspecific (6). Identifying the precise origin of the tumor is often challenging, leading to frequent misdiagnoses and delayed treatment. In cases involving retroperitoneal tumors, comprehensive abdominal and pelvic imaging is essential to exclude tumors originating from other organs, facilitating earlier and more accurate diagnosis and treatment of HGSOC (8,9).

Clinical evidence from laboratory tests also serves a critical role in diagnosing HGSOC. CA125, a glycoprotein derived from embryonic coelomic epithelium, is absent in normal ovary tissue but frequently expressed in serous tumors. Elevated CA125 levels are observed in ~90% of patients with advanced HGSOC, often reaching 500-1,000 U/ml (10). However, in early-stage HGSOC, only ~50% of patients exhibit elevated CA125 levels, limiting its use as an early

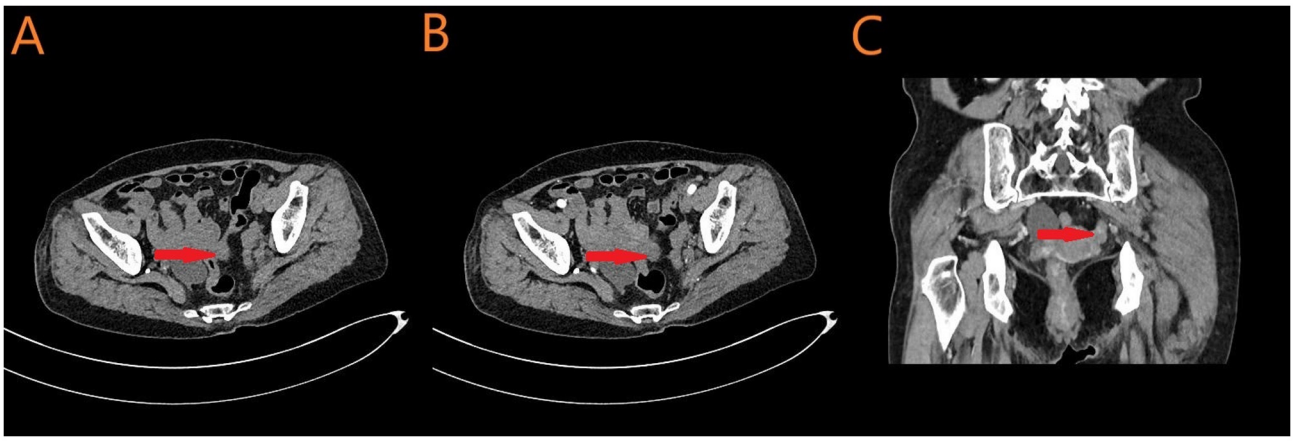

Figure 3. Pelvic CT images. (A) Plain phase, (B) arterial phase and (C) coronal images.

diagnostic marker. Furthermore, CA125 lacks specificity as elevated levels are also seen in menopausal women, and in conditions such as endometriosis, pregnancy and pelvic inflammatory disease. These limitations restrict its effectiveness as a screening tool for early-stage HGSOC (11). A total of two large-scale screening studies, the UKCTOCS trial in the UK (12) and the PLCO trial in the US (13), investigated the combined use of CA125 and gynecological ultrasound for early detection. Although these studies detected more cases of ovarian cancer, most patients were diagnosed at an advanced stage, and screening did not markedly improve overall survival (OS). Consequently, the American Congress of Obstetricians and Gynecologists recommends against using CA125 for routine early detection, citing the high risk of false positives, increased patient anxiety and stress, and unnecessary healthcare costs (13). Despite its limitations in early diagnosis, CA125 serves as a valuable biomarker for monitoring treatment response and disease recurrence in HGSOC. In patients with advanced ovarian cancer, a decrease in serum CA125 levels following treatment is associated with a favorable prognosis and treatment efficacy (14). Additionally, recurrent HGSOC is often asymptomatic, and CA125 monitoring is the primary method for detecting relapse. A CA125 level that exceeds twice the upper limit of normal is commonly used as a threshold for diagnosing recurrence (15). Therefore, whilst CA125 is not a reliable marker for early detection, it serves a crucial role in predicting chemotherapy response and assessing the likelihood of tumor recurrence in HGSOC (16).

In immunohistochemistry (IHC), CA125 exhibits specific expression patterns that make it useful for the auxiliary diagnosis, classification and differential diagnosis of HGSOC. Strong CA125 expression is observed in 80-90% of HGSOC cases, with diffuse staining of the cell membrane and cytoplasm. In the present case, the pathological examination of retroperitoneal tumors, ovarian biopsy tissues and ovarian cancer lesions demonstrated positive or strongly positive CA125 expression. CA125 can be used to distinguish primary ovarian cancer from metastatic cancers of gastrointestinal or breast origin, as these tumors typically lack CA125 expression in IHC. However, CA125 alone lacks sufficient specificity for a definitive diagnosis of HGSOC. When necessary, it should be used in combination with other immune markers, such as WT1 and PAX-8, along with morphological assessment, to improve the diagnostic accuracy of HGSOC (17).

Most patients with HGSOC are diagnosed at an advanced stage, limiting the effectiveness of radical surgery to a small subset of stage I patients, where the tumor remains confined to the ovary or fallopian tube. Due to the proximity of tumors to adjacent organs, even when surgical separation is technically feasible, concerns about tumor invasion into surrounding tissues pose significant challenges for surgeons. Therefore, cytoreductive surgery remains the primary surgical approach for HGSOC and is crucial for improving patient prognosis (6). Complete tumor resection is associated with improved long-term outcomes and certain patients may achieve clinical remission with chemotherapy. Standard cytoreductive surgery involves the removal of all visible tumors, reproductive organs and adjacent tissues such as the cecum, sigmoid colon and greater omentum. Lymph node resection is performed based on nodal involvement, with the primary aim of achieving optimal cytoreduction, defined as residual tumor <1 cm in diameter (5). In the present case, preoperative renal ECT revealed a left GFR of 2.38 ml/min, indicating severe functional impairment of the left kidney and ureter due to tumor infiltration affecting both renal function and urinary drainage. During the attempt to place a left ureteral internal stent intraoperatively, complete luminal obstruction was encountered at an undetermined level of the left ureter, which precluded passage of a 5-mm circumference stent. Consequently, ureteral dimensions were not estimated based on the stenotic segment and smaller-caliber internal stents were not used. Ultimately, an external ureteral stent (5-mm circumference) was placed at a non-stenotic portion of the left ureter for anatomical marking. Notably, external stent placement was not the initial approach due to its inherent risk of dislodgement. Upon initiating retroperitoneal tumor resection, surgical findings confirmed the preoperative assessment: The retroperitoneal tumor demonstrated complete encasement of the left kidney and proximal ureter, rendering safe dissection impossible whilst ensuring tumor-free margins. Therefore, an en bloc resection of the retroperitoneal mass was performed with the involved left kidney and proximal ureter. This complete cytoreductive procedure provided optimal oncological management, markedly improving the prognostic outlook of the patient.

Following successful cytoreductive surgery, most patients with HGSOC undergo adjuvant chemotherapy, except for a small number of stage I patients who may not require further treatment (5). The standard chemotherapy regimen, consisting of six consecutive cycles of paclitaxel plus carboplatin, has remained the standard treatment for ovarian cancer for the past two decades (18). For patients unable to undergo surgery or with extensive metastases, neoadjuvant chemotherapy (NACT) is a viable alternative. This approach typically consists of three cycles of chemotherapy before surgery, followed by cytoreductive surgery and an additional three cycles postoperatively. A total of two randomized trials have reported that NACT is a non-inferior option to surgery followed by chemotherapy in terms of both progression-free survival (PFS) and OS (19,20). Furthermore, advances in immunotherapy and targeted therapies have expanded treatment options for HGSOC. WT1 functions as a tumor suppressor protein and its inactivation has been implicated in the development of urogenital or renal embryonic tumors (21). SELLAS Life Sciences Group has performed clinical trials using a WT1-targeted vaccine for the treatment of ovarian cancer, malignant pleural mesothelioma and several hematologic and solid tumors (21). The WT1 vaccine is administered in combination with an adjuvant and an immune modulator, granulocyte-macrophage colony-stimulating factor, to enhance the immune response. Early-stage clinical trials in acute myelogenous leukemia and mesothelioma have reported promising improvements in both PFS and OS (22). P16, another tumor suppressor gene, is implicated in HGSOC pathogenesis. Anti-aging therapy or tumor immunization vaccines targeting P16 may serve a potential role in treating HGSOC, as aging and the abnormal retinoblastoma pathway contribute to P16 overexpression (23). Additionally, the formation of malignant tumors can result from accumulated genetic mutations in breast cancer (BRCA)1 or BRCA2. Patients with BRCA1- or BRCA2-positive HGSOC are more responsive to poly-ADP ribose polymerase inhibitors, which have shown efficacy in inhibiting tumor recurrence and progression (24).

A total of ~70% of patients with ovarian cancer initially respond well to platinum-based chemotherapy, with ≥50% showing no residual cancer on imaging and serum markers at 5 months post-treatment. However, recurrence rates are >80%, emphasizing the necessity for long-term follow-up and continuous monitoring (2). Based on clinical experience and the 2023 National Comprehensive Cancer Network guidelines (25), the authors of the present study recommend the following follow-up protocol: Imaging and tumor-marker assessments every 3 months for the first 2 years post-chemotherapy, every 6 months from years 3-5, and then an annual evaluation thereafter. High-risk patients with HGSOC, particularly those with retroperitoneal metastasis, should receive individualized treatment plans and close follow-up, with active symptom monitoring to promote early detection, diagnosis and timely treatment.

In conclusion, the present study assessed the mechanisms through which HGSOC metastasizes to the retroperitoneal space. It also discussed the symptoms, diagnosis and treatment strategies through a case initially diagnosed as a retroperitoneal tumor. The findings suggest that retroperitoneal metastasis of HGSOC may be more common in clinical practice than previously recognized. However, most patients with HGSOC are diagnosed at an advanced stage, often presenting with non-specific symptoms. Therefore, it is recommended that patients presenting with nonspecific symptoms of retroperitoneal tumor undergo timely abdominal and pelvic imaging and tumor marker tests to rule out metastases from other primary sites. Elevated serum CA125 levels may suggest an ovarian tumor. If other primary lesions are confirmed, a multidisciplinary approach including biopsy should be implemented to ensure accurate diagnosis and optimal treatment planning, ultimately improving patient outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

PH and WP conceived and designed the study. HM provided administrative support. PH and WP supplied study materials and patient data. PH and JY collected and assembled the data. PH and WP confirm the authenticity of all the raw data. HM and JY made substantial contributions to the conception, design of the work, and data acquisition and interpretation. JY and WP drafted and revised the work for important intellectual content. PH and HM approved the final version to be published and agreed to be accountable for all aspects of the work, ensuring proper resolution of integrity-related issues. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was performed in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the First Affiliated Hospital of Guangxi Medical University ethics board (approval no. 2024-E275-01).

Patient consent for publication

Written informed consent was obtained from the patient to publish the present report.

Competing interests

The authors declare that they have no competing interests.

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