

## Research Article

# Metastatic High-Grade Serous Adenocarcinoma of Probable Female Genital Tract Origin Presenting as Sealed off Gall Bladder Perforation: A Case Report with Comprehensive Review of Literature.

DR. VIRAJ SHINDE<sup>1</sup>, Dr. Aditi Goyal<sup>2</sup>, Dr. Amey D.Kulkarni<sup>3</sup>

<sup>1</sup> (professor general surgery , dr. dy patil medical college, pune)

<sup>2</sup> (Jr-1, general surgery resident, dr dy patil medical college, pune)

<sup>3</sup>(jr-1, general surgery resident , dr dy patil medical college, pune)

### \*Corresponding Author

Dr. Aditi Goyal

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**Abstract: Introduction:** High-grade serous adenocarcinoma (HGSC) is the most aggressive and common subtype of epithelial malignancies arising from the female genital tract, typically originating from the ovary, fallopian tube, or primary peritoneum, and is characterized by rapid progression, early trans coelomic dissemination, and advanced-stage presentation. We report a rare and diagnostically challenging case of a 73-year-old postmenopausal female who presented with abdominal pain, bloating, and dyspeptic symptoms of short duration, initially suggestive of hepatobiliary pathology. Radiological evaluation revealed features of cholelithiasis with sealed-off gall bladder perforation along with peritoneal thickening and adnexal lesions. Cytological examination of gall bladder collection fluid was negative for malignant cells, further complicating the diagnostic process. However, subsequent whole-body positron emission tomography-computed tomography (PET-CT) demonstrated extensive fluorodeoxyglucose (FDG)-avid bilateral adnexal lesions, peritoneal carcinomatosis, omental deposits, and nodal metastases, strongly indicating disseminated malignancy of probable female genital tract origin. High-grade serous carcinoma is known for its propensity for widespread peritoneal dissemination at the time of diagnosis, with studies showing that a majority of patients present with advanced disease and diffuse intra-abdominal metastasis. This case highlights the diagnostic dilemma posed by overlapping inflammatory and malignant conditions, particularly when cytology is negative, and underscores the critical role of advanced imaging modalities such as PET-CT in detecting occult primary malignancy and assessing metastatic burden. Early clinical suspicion, integration of multimodal imaging, and histopathological confirmation remain essential for timely diagnosis and optimal management of this highly aggressive malignancy.

**Keywords:** High-grade serous carcinoma, ovarian cancer, peritoneal carcinomatosis, PET-CT, adnexal mass, metastasis.

## INTRODUCTION

Epithelial malignancies of the female genital tract represent a major contributor to cancer-related morbidity and mortality in women, among which high-grade serous carcinoma (HGSC) is the most prevalent and lethal histological subtype. It accounts for the majority of deaths associated with ovarian cancer due to its aggressive biological behavior and late clinical presentation. HGSC is characterized by rapid tumor growth, marked genomic instability, and a high propensity for early dissemination within the peritoneal cavity, which significantly contributes to its poor prognosis. Despite advancements in diagnostic and therapeutic strategies, the survival outcomes remain unfavorable, largely because most cases are diagnosed at advanced stages of disease.

Recent advances in molecular pathology have redefined the origin of HGSC. Traditionally thought to arise from the ovarian surface epithelium, emerging evidence strongly supports that a significant proportion of these tumors originate from the distal fallopian tube

epithelium, particularly from serous tubal intraepithelial carcinoma (STIC) lesions, which subsequently disseminate to involve the ovary and peritoneum. These tumors are characterized by nearly universal TP53 mutations, extensive chromosomal instability, and aggressive proliferative capacity, which together facilitate rapid disease progression and metastatic spread. The unique anatomical and physiological environment of the peritoneal cavity allows exfoliated tumor cells to disseminate widely, leading to extensive intra-abdominal involvement.

The predominant mode of spread in HGSC is transcoelomic dissemination, wherein malignant cells detach from the primary tumor and spread via peritoneal fluid dynamics to implant on various peritoneal and serosal surfaces. This results in characteristic features such as peritoneal carcinomatosis, omental caking, mesenteric involvement, ascites formation, and deposits along visceral organs. Unlike many other malignancies, HGSC does not rely primarily on hematogenous spread but instead disseminates directly within the peritoneal cavity, allowing rapid and widespread disease

involvement. Studies have shown that a significant proportion of patients—often up to 80–100%—present with peritoneal dissemination at the time of diagnosis, highlighting the aggressive nature of this disease.

Clinically, HGSC presents a major diagnostic challenge due to its non-specific and vague symptomatology, which often includes abdominal discomfort, bloating, early satiety, dyspepsia, and altered bowel habits. These symptoms frequently mimic benign gastrointestinal or hepatobiliary conditions, leading to delayed diagnosis and advanced-stage presentation (FIGO Stage III or IV). In certain cases, as illustrated in the present report, the disease may mimic or coexist with inflammatory conditions such as cholecystitis or gall bladder perforation, further complicating the clinical picture and delaying appropriate diagnosis.

The present case was evaluated at a tertiary care center, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune, and is based on detailed clinical records, radiological imaging, cytological analysis, and metabolic imaging findings. The patient, a 73-year-old postmenopausal female, initially presented with symptoms suggestive of gall bladder pathology and

was found to have cholelithiasis with a sealed-off gall bladder perforation. However, further evaluation through contrast-enhanced CT and whole-body PET-CT revealed bilateral adnexal lesions along with extensive peritoneal, omental, and nodal metastases, indicating an underlying disseminated malignancy of probable female genital tract origin. Notably, cytological examination of gall bladder collection fluid did not reveal malignant cells, underscoring the limitations of cytology in detecting malignancy in advanced peritoneal disease.

This case highlights a rare and diagnostically challenging presentation of metastatic high-grade serous adenocarcinoma masquerading as a hepatobiliary emergency, emphasizing the importance of maintaining a high index of suspicion in elderly postmenopausal women presenting with atypical abdominal symptoms. It further underscores the pivotal role of advanced imaging modalities, particularly PET-CT, in identifying occult primary tumors and accurately staging metastatic disease. Early recognition and a multidisciplinary diagnostic approach are crucial for timely management and improved clinical outcomes in such aggressive malignancies.

## MATERIALS AND METHODS

A 73-year-old postmenopausal female presented to the tertiary care center with complaints of abdominal pain of 15 days duration, associated with abdominal bloating, regurgitation, heartburn, and constipation. The patient had attained menopause in 2007 and had been otherwise stable prior to the onset of current symptoms. The abdominal pain was insidious in onset and gradually progressive in intensity. It was described as a dragging type of pain, predominantly localized to the epigastric region and right hypochondrium, with radiation to the back. The pain was noted to be aggravated following meals and partially relieved by rest, suggesting an initial clinical suspicion of hepatobiliary pathology. Associated symptoms included a persistent sensation of abdominal fullness and bloating, intermittent episodes of heartburn, regurgitation of gastric contents, and passage of hard stools. There was no history of fever, vomiting, jaundice, or any significant alteration in bowel or bladder habits, thereby making an acute infective or obstructive etiology less likely at initial presentation.

The patient's past medical history was significant for long-standing hypertension of 14 years duration, which was reportedly well controlled on medication. She had undergone cataract surgery in 2021 and had a past history of typhoid fever three years prior to presentation. Her surgical history included tubectomy performed approximately 40 years ago. There was no documented history of malignancy or similar complaints in the past. The absence of prior gynecological symptoms further contributed to the diagnostic ambiguity in this case.

On general physical examination, the patient was conscious, alert, and oriented to time, place, and person.

She was afebrile at the time of examination, with stable vital parameters including a pulse rate of 88 beats per minute and blood pressure of 130/80 mmHg. There were no signs of pallor, icterus, cyanosis, clubbing, or lymphadenopathy. Systemic examination at presentation did not reveal any acute abdominal guarding or rigidity; however, mild abdominal distension and discomfort were noted, correlating with her presenting complaints.

Given the clinical presentation suggestive of upper abdominal pathology, initial evaluation was directed towards hepatobiliary causes, and subsequent imaging studies revealed features consistent with cholelithiasis with a sealed-off gall bladder perforation, which explained the localized pain in the right hypochondrium. However, the persistence of symptoms along with associated abdominal distension prompted further radiological evaluation. Advanced imaging subsequently revealed bilateral adnexal lesions along with extensive peritoneal, omental, and nodal involvement, raising strong suspicion of an underlying disseminated malignancy.

Thus, what initially appeared to be a localized hepatobiliary condition was ultimately identified as a manifestation of metastatic high-grade serous adenocarcinoma of probable female genital tract origin, highlighting the atypical and deceptive clinical presentation of this aggressive malignancy. This case underscores the importance of thorough evaluation and maintaining a high index of suspicion, particularly in elderly postmenopausal women presenting with non-

specific abdominal symptoms mimicking benign or inflammatory conditions.

### INVESTIGATIONS

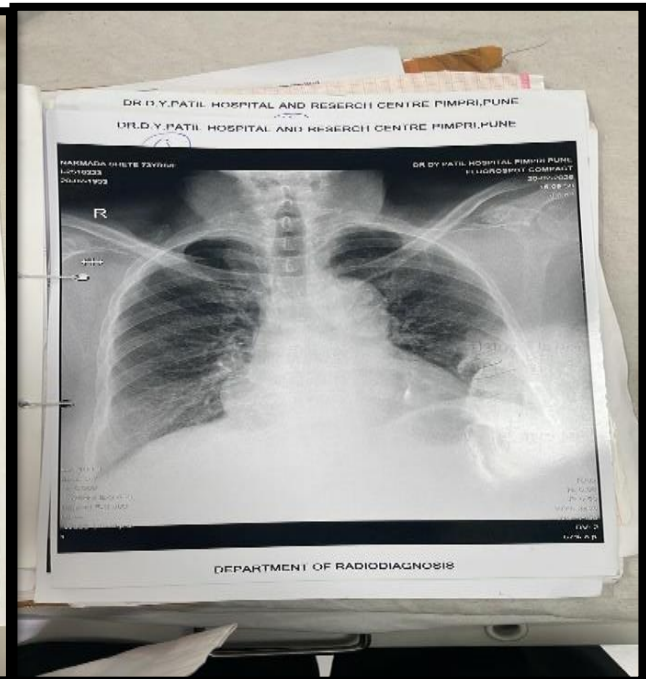
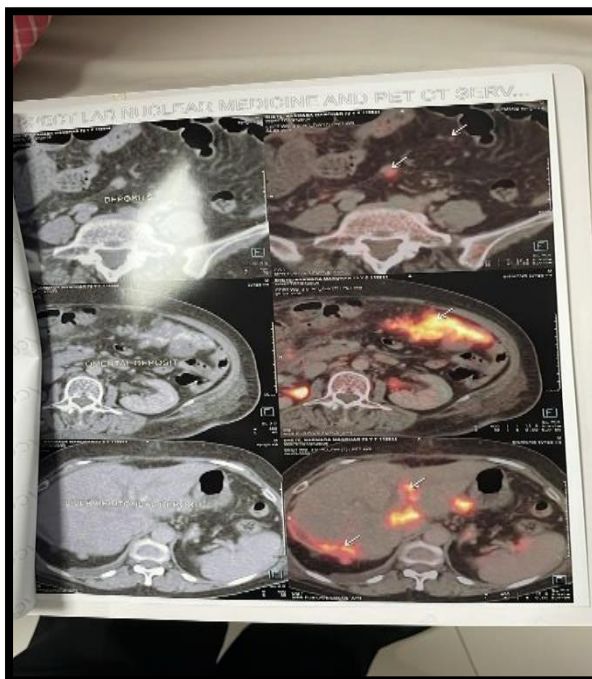
Initial radiological evaluation with contrast-enhanced computed tomography (CECT) of the abdomen and pelvis was performed in view of the patient's persistent upper abdominal pain and clinical suspicion of hepatobiliary pathology. The imaging revealed right-sided peritoneal thickening, which is a non-specific but important finding that may represent either inflammatory changes or early peritoneal metastatic involvement. The uterus appeared small and atrophic, consistent with postmenopausal status, with focal calcifications noted, likely representing degenerative changes. A significant finding was the presence of a right adnexal elongated cystic lesion measuring approximately  $38 \times 15$  mm, demonstrating peripheral enhancement. This raised the differential diagnosis of hydrosalpinx versus a neoplastic etiology, particularly in the context of the patient's age. Additionally, a left ovarian cyst measuring  $27 \times 20$  mm was identified. Although these adnexal findings were subtle, in the clinical context of a postmenopausal female, they warranted further evaluation, raising an early suspicion of underlying adnexal pathology rather than a purely benign process.

Given the imaging findings suggestive of gall bladder involvement, cytological analysis of fluid obtained from the gall bladder collection (associated with suspected sealed-off perforation) was performed. Microscopic examination revealed a mixed inflammatory infiltrate with the presence of degenerated cells, but importantly, no malignant cells were identified. However, this finding must be interpreted with caution, as negative cytology does not reliably exclude malignancy, particularly in cases of peritoneal carcinomatosis. This limitation may be attributed to sampling error, inadequate cellular yield, or tumor heterogeneity, especially in cases where

malignant cells are not shed uniformly into the sampled fluid. Therefore, in the presence of strong clinical and radiological suspicion, further diagnostic evaluation is essential despite negative cytological findings.

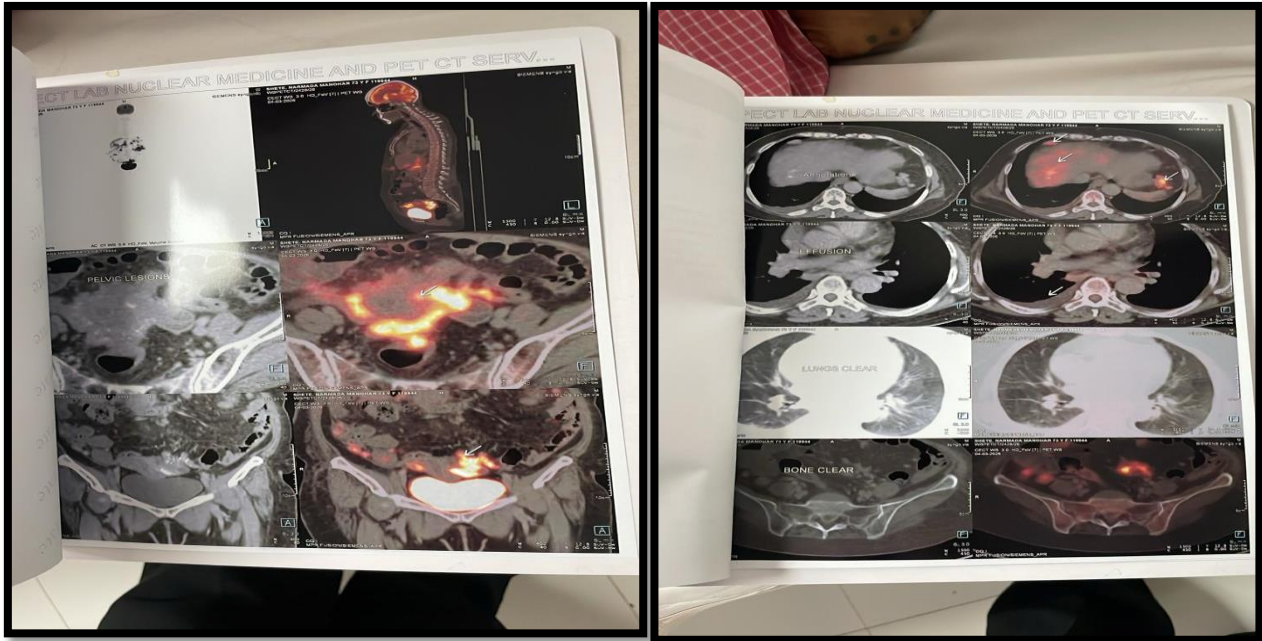
To further characterize the extent of disease and identify a possible primary source, a whole-body positron emission tomography-computed tomography (PET-CT) scan was performed, which proved to be a critical diagnostic modality in this case. The PET-CT demonstrated intensely FDG-avid bilateral adnexal lesions, strongly suggestive of metabolically active neoplastic pathology. Additionally, there was a prominent FDG-avid deposit in the pouch of Douglas with a standardized uptake value (SUV) of approximately 15.26, indicative of high metabolic activity consistent with malignancy. Extensive diffuse peritoneal deposits were noted, along with omental thickening forming the classical "omental cake" appearance, which is highly characteristic of advanced peritoneal carcinomatosis.

Further findings included multiple mesenteric and paracolic nodules, along with perihepatic and perisplenic deposits, suggesting widespread dissemination of disease across peritoneal surfaces. Notably, metabolically active deposits were also identified along the gall bladder and gastrohepatic ligament, which likely contributed to the clinical presentation mimicking gall bladder pathology, including sealed-off perforation. In addition to peritoneal involvement, there was evidence of metastatic lymphadenopathy involving aortocaval, retrocaval, and epiphrenic lymph nodes, indicating advanced-stage disease with both peritoneal and nodal spread. Mild bilateral pleural effusion was also observed, likely reactive in nature, although early pleural involvement could not be entirely excluded.



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Overall, the PET-CT findings were highly suggestive of extensive metastatic disease with a probable primary origin in the female genital tract, most consistent with high-grade serous adenocarcinoma. The imaging played a decisive role in establishing the diagnosis, especially in the context of non-specific clinical presentation and negative cytology, and provided comprehensive mapping of disease burden essential for staging and management planning.



## INTRAOPERATIVE FINDINGS

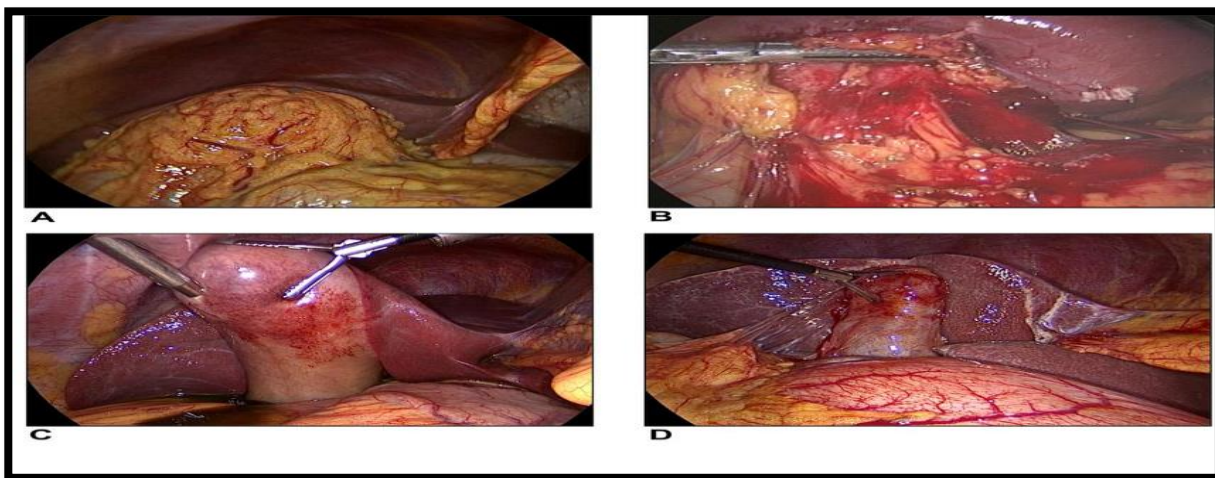
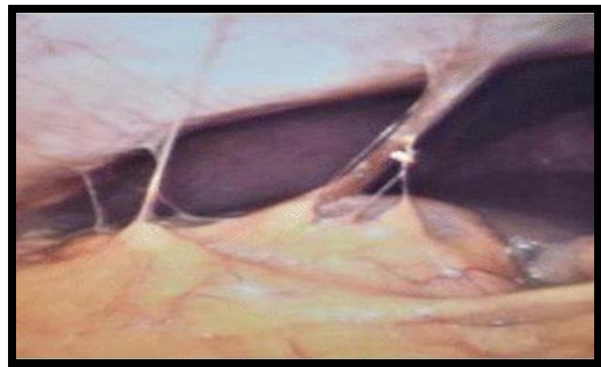
Exploratory laparotomy was undertaken in view of imaging findings suggestive of disseminated intra-abdominal pathology. On entering the peritoneal cavity, approximately \_\_\_ ml of serous/hemorrhagic ascitic fluid was encountered and aspirated for further analysis. The presence of free fluid, along with visible peritoneal abnormalities, immediately raised suspicion of advanced intra-abdominal disease.

The peritoneal surfaces were extensively involved with multiple whitish nodular deposits of varying sizes scattered diffusely over both parietal and visceral peritoneum, consistent with peritoneal carcinomatosis. The greater omentum was markedly thickened, indurated, and transformed into a dense mass, producing the characteristic “omental cake” appearance, which is highly suggestive of advanced metastatic disease.

Both adnexal structures were found to be abnormal. The ovaries were enlarged, irregular, and firm in consistency, with nodular surface deposits and adhesions to adjacent structures. The fallopian tubes appeared thickened and distorted, indicating possible primary involvement. The pouch of Douglas was completely obliterated due to dense adhesions and tumor infiltration, further supporting the diagnosis of extensive pelvic disease.

Multiple metastatic deposits were observed over the mesentery and along the serosal surfaces of the small and large bowel. Additionally, nodular deposits were present over the liver capsule and diaphragmatic peritoneum, indicating widespread transcoelomic dissemination of the tumor within the peritoneal cavity.

The gall bladder appeared thickened, contracted, and densely adherent to surrounding tissues. A sealed-off perforation was identified, surrounded by localized inflammatory adhesions and collection. No obvious intraluminal mass was noted, suggesting that the gall bladder findings were secondary to adjacent metastatic involvement rather than a primary pathology. Enlarged retroperitoneal lymph nodes, particularly in the aortocaval and para-aortic regions, were palpated intraoperatively, consistent with nodal metastasis. The overall disease burden was extensive, and optimal cytoreduction was deemed not feasible due to diffuse involvement of critical peritoneal and visceral surfaces. Biopsy specimens were obtained from the omentum, ovarian masses, and peritoneal nodules for histopathological examination. The intraoperative findings were strongly indicative of advanced-stage metastatic malignancy of probable female genital tract



### FINAL CLINICAL DIAGNOSIS

Based on the comprehensive evaluation of clinical presentation, radiological imaging, and metabolic findings, the final clinical diagnosis was established as metastatic high-grade serous adenocarcinoma of probable female genital tract origin, presenting with extensive peritoneal carcinomatosis and associated with sealed-off gall bladder perforation, consistent with advanced-stage (probable Stage IV) disease. The diagnosis was primarily supported by the presence of metabolically active bilateral adnexal lesions, diffuse FDG-avid peritoneal and omental deposits, mesenteric and nodal metastases, and involvement of the pouch of Douglas as demonstrated on PET-CT imaging. The

concomitant findings of deposits along the gall bladder and gastrohepatic ligament likely contributed to localized inflammatory changes and the clinical presentation mimicking hepatobiliary pathology, including sealed-off perforation. Although cytological analysis of gall bladder collection fluid did not reveal malignant cells, this was considered a false-negative finding in the context of advanced peritoneal malignancy. Taken together, the constellation of imaging features and clinical findings strongly indicated a diagnosis of disseminated high-grade serous carcinoma arising from the female genital tract, most likely ovarian or fallopian tube in origin, with widespread intra-abdominal and nodal metastasis.

### DISCUSSION

High-grade serous adenocarcinoma (HGSC) is a biologically aggressive malignancy characterized by rapid progression, early dissemination, and poor prognosis. Current evidence strongly supports that the majority of HGSCs originate from serous tubal intraepithelial carcinoma (STIC) lesions located in the fimbrial end of the fallopian tube. These precursor lesions undergo malignant transformation driven

predominantly by TP53 mutations, followed by genomic instability and uncontrolled cellular proliferation. Tumor cells exfoliate from the tubal epithelium into the peritoneal cavity, where they disseminate and implant across peritoneal surfaces. This mechanism explains the early and widespread intra-abdominal involvement seen in most patients at the time of diagnosis, as also observed in the present case.

The pattern of spread in HGSC is distinct and primarily occurs through transcoelomic dissemination, rather than hematogenous routes in the early stages. In this case, imaging findings demonstrated classical features of such dissemination, including involvement of the peritoneum, omentum, mesentery, pouch of Douglas, and liver capsule. The presence of omental thickening forming an “omental cake,” along with multiple peritoneal and mesenteric nodules, is highly characteristic of advanced peritoneal carcinomatosis. Additionally, deposits along the gall bladder and gastrohepatic ligament contributed to the unusual clinical presentation mimicking hepatobiliary pathology, including sealed-off gall bladder perforation, thereby masking the underlying malignancy.

One of the major challenges in diagnosing HGSC is its non-specific clinical presentation, which often includes vague abdominal pain, bloating, dyspepsia, and altered bowel habits. These symptoms frequently overlap with benign gastrointestinal or inflammatory conditions, leading to delayed diagnosis. In the present case, the clinical picture was further complicated by imaging findings suggestive of gall bladder pathology and cytological analysis of gall bladder collection fluid that was negative for malignant cells. Such false-negative cytology is not uncommon in peritoneal carcinomatosis and may result from inadequate sampling, low tumor cell yield, or uneven shedding of malignant cells. This highlights the limitation of relying solely on cytology and underscores the importance of correlating clinical, radiological, and metabolic findings.

In this context, positron emission tomography-computed tomography (PET-CT) played a pivotal role in establishing the diagnosis. PET-CT is highly sensitive in detecting metabolically active lesions and is particularly useful in identifying occult primary tumors, assessing the extent of metastatic disease, and accurate staging. In the present case, PET-CT revealed FDG-avid bilateral adnexal lesions along with extensive peritoneal, omental, mesenteric, and nodal metastases, thereby providing crucial evidence in favor of metastatic malignancy of probable female genital tract origin. The ability of PET-CT to detect disease not apparent on conventional imaging makes it an invaluable tool in complex diagnostic scenarios such as this.

The differential diagnosis in such cases includes conditions that can mimic peritoneal carcinomatosis both clinically and radiologically. These include peritoneal tuberculosis, which is relatively common in endemic regions and can present with ascites, peritoneal thickening, and nodularity; primary peritoneal carcinoma, which shares histopathological and clinical features with ovarian serous carcinoma; and metastatic gastrointestinal malignancies, particularly from the stomach or colon. Careful evaluation using imaging, tumor markers, histopathology, and

immunohistochemistry is essential to differentiate between these entities.

Although tumor marker levels were not available in this case, CA-125 is typically elevated in patients with HGSC and serves as an important adjunct in diagnosis, monitoring treatment response, and detecting recurrence. Other markers such as HE4 (Human Epididymis Protein 4) may also be elevated and can improve diagnostic accuracy when used in combination with CA-125. However, tumor markers alone are not diagnostic and must be interpreted in conjunction with imaging and histopathological findings.

The standard management of advanced HGSC involves a multimodal approach. Primary treatment includes cytoreductive (debulking) surgery, aiming to remove as much tumor burden as possible, followed by platinum-based chemotherapy, most commonly a combination of carboplatin and paclitaxel. In selected patients, neoadjuvant chemotherapy may be administered prior to surgery. Recent advances have introduced targeted therapies, including anti-angiogenic agents such as bevacizumab and poly (ADP-ribose) polymerase (PARP) inhibitors like olaparib, particularly in patients with BRCA mutations or homologous recombination deficiency. These therapies have shown promising results in improving progression-free survival.

Despite advances in treatment, the prognosis of HGSC remains poor, especially in advanced stages. The majority of patients present with Stage III or IV disease, as in the present case, where extensive peritoneal and nodal involvement was evident. The 5-year survival rate is significantly reduced, and outcomes largely depend on factors such as the extent of disease at diagnosis, completeness of cytoreduction, and response to chemotherapy. Early diagnosis remains the most critical factor in improving survival, underscoring the importance of clinical vigilance and timely use of advanced diagnostic modalities.

## CONCLUSION

This case highlights the highly aggressive nature of high-grade serous adenocarcinoma of the female genital tract, which is characterized by rapid progression and a marked tendency for early and extensive transcoelomic dissemination within the peritoneal cavity. The present case is particularly significant due to its atypical clinical presentation, mimicking a localized hepatobiliary condition in the form of a sealed-off gall bladder perforation, thereby posing a substantial diagnostic challenge. Despite negative cytological findings from gall bladder collection fluid, the presence of metabolically active bilateral adnexal lesions along with diffuse peritoneal, omental, and nodal involvement on advanced imaging strongly indicated an underlying disseminated malignancy. This underscores the limitation of cytology in excluding malignancy in cases

The case further reinforces the pivotal role of advanced imaging modalities, particularly PET-CT, in identifying occult primary tumors, accurately delineating the extent of metastatic disease, and guiding clinical decision-making in complex presentations. Early clinical suspicion, especially in elderly postmenopausal women presenting with vague and non-specific abdominal symptoms, is essential to avoid diagnostic delays. A multidisciplinary approach integrating clinical evaluation, radiological imaging, and histopathological confirmation remains crucial for timely diagnosis and optimal management. Ultimately, early detection and prompt initiation of appropriate therapy are key factors in improving prognosis and survival outcomes in patients with this highly aggressive malignancy.

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