

# Diagnostic Challenges in Small Cell Carcinoma of The Ovary, Hypercalcemic Type: A Case Report With Histopathological and Molecular Correlation

Fatima Shamsuddin<sup>1</sup>, Lovy Agarwal<sup>2</sup>, Rohit kotipalli<sup>3</sup>

<sup>1</sup>Specialist, Department of Histopathology, Jaber Al-Ahmad Hospital, Kuwait. Email: fatimafrcpath@gmail.com

<sup>2</sup>Consultant, Department of Histopathology, Jaber Al-Ahmad Hospital, Kuwait. Email: lovyagarwal@hotmail.com

<sup>3</sup>Registrar, Department of Histopathology, Jaber Al-Ahmad Hospital, Kuwait. Email: pathdocrohit@gmail.com

Corresponding author Dr. Fatima Shamsuddin, Email: fatimafrcpath@gmail.com

## Abstract

**Background:** Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare and highly aggressive ovarian malignancy affecting predominantly young women. Owing to its overlapping histomorphological features with other ovarian small round cell tumors, diagnosis remains challenging and increasingly relies on integration of histopathology, immunohistochemistry, and molecular testing.

**Case Presentation:** We report the case of a 24-year-old woman presenting with abdominal pain, vomiting, weight loss, and paraneoplastic hypercalcemia. Imaging revealed a large right ovarian mass with metastatic para-aortic and supraclavicular lymphadenopathy. Histopathological examination demonstrated a highly cellular malignant neoplasm composed predominantly of small round to oval cells arranged in sheets, nests, and trabeculae with brisk mitotic activity, extensive necrosis, admixed rhabdoid cells, and characteristic follicle-like spaces. An extensive immunohistochemical panel excluded the principal differential diagnoses but was not entirely specific. Comprehensive next-generation sequencing identified two pathogenic truncating SMARCA4 frameshift mutations, confirming biallelic SMARCA4 inactivation and establishing the diagnosis of SCCOHT. The tumor was staged as FIGO IIIA2 (pT3aN1b). The patient underwent surgical resection followed by platinum-based chemotherapy with etoposide and cisplatin and remained disease-free at early follow-up.

**Conclusion:** This case highlights the diagnostic challenges posed by SCCOHT and emphasizes the importance of integrating morphology, immunophenotyping, and molecular analysis for accurate diagnosis. Identification of biallelic SMARCA4 inactivation provides definitive diagnostic confirmation and supports the evolving role of molecular pathology in distinguishing SCCOHT from its numerous histological mimics. Early recognition and multidisciplinary management are essential to optimize patient care.

**Keywords** Small cell carcinoma of the ovary, hypercalcemic type; SCCOHT; SMARCA4; BRG1; ovarian neoplasm; next-generation sequencing.

## Introduction

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is an exceptionally rare, highly aggressive ovarian malignancy that predominantly affects young women, with a median age of approximately 24 years. Nearly two-thirds of patients present with paraneoplastic hypercalcemia, although normocalcemic cases have also been described. Owing to its aggressive biological behavior, advanced stage at presentation, and limited response to conventional therapies, SCCOHT is associated with an unfavorable prognosis despite multimodal treatment, with long-term survival largely confined to patients diagnosed at an early stage.[1,3,5]

Histopathologically, SCCOHT is characterized by sheets, nests, and trabeculae of small round to oval cells with scant cytoplasm, brisk mitotic activity, and extensive necrosis, often admixed with larger rhabdoid-appearing cells and follicle-like spaces containing eosinophilic secretions. However, these features overlap with several ovarian neoplasms, including juvenile granulosa cell tumor, germ cell tumors, neuroendocrine carcinoma, lymphoma, desmoplastic small round cell tumor, and metastatic small cell carcinoma, making accurate diagnosis challenging.[1,4,5] Consequently, diagnosis relies on the integration of histomorphology with immunohistochemical and molecular findings. Recent advances in molecular pathology have established SCCOHT as a SMARCA4-deficient malignancy, characterized by biallelic inactivation of the SMARCA4 gene, resulting in loss of BRG1 protein function. This molecular alteration is now regarded as the defining genetic hallmark of SCCOHT and has fundamentally changed the diagnostic approach to this rare neoplasm.[6-10]

We report a young woman with advanced-stage SCCOHT presenting with hypercalcemia and a large ovarian mass. The diagnosis was established through careful correlation of the histopathological findings, an extensive immunohistochemical panel, and comprehensive next-generation sequencing, which demonstrated two pathogenic truncating SMARCA4 mutations consistent with biallelic inactivation. In addition, we review the contemporary literature to highlight the evolving clinicopathological and molecular understanding of this uncommon but highly aggressive ovarian malignancy.

### Case presentation

A 24 year old unmarried woman presented with a one-and-a-half-month history of persistent vomiting, lower abdominal pain, and an unintentional weight loss of approximately 7 kg over the preceding month. Clinical examination revealed a large, immobile pelvi-abdominal mass palpable above the level of the umbilicus. Imaging also demonstrated a right supraclavicular lymph node suspicious for metastatic disease.

Laboratory investigations showed elevated serum CA-125 (277 U/mL), while alpha-fetoprotein (AFP),  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG), and lactate dehydrogenase (LDH) levels were 1.67 ng/mL, <0.2 mIU/mL, and 351 U/L, respectively. The patient had previously been evaluated by the endocrinology service for hypercalcemia and was diagnosed with non-parathyroid-related hypercalcemia; however, the biochemical parameters were not available for review.

Magnetic resonance imaging of the pelvis (Figure 1) demonstrated a large right pelvi-abdominal neoplastic lesion, likely arising from the right adnexa, with differential considerations including mucinous cystadenocarcinoma. Para-aortic lymphadenopathy, mild abdominopelvic free fluid, and mild bilateral proximal hydroureteronephrosis secondary to mass effect were also identified.

The patient underwent resection of the right pelvi-abdominal solid-cystic mass with right salpingectomy, together with biopsies from a left ovarian nodule, bladder peritoneum, right and left pelvic peritoneum, cul-de-sac, and para-aortic lymph nodes. Intraoperatively, a large right adnexal mass was identified. Serosanguinous peritoneal fluid was present, and multiple peritoneal biopsies were obtained. Frozen section examination of the ovarian mass (Figure 3) demonstrated a high-grade malignant neoplasm, with differentials given as dysgerminoma, granulosa cell tumor and small cell carcinoma. The definitive tumor classification was deferred pending permanent sections and immunohistochemical evaluation.

Gross examination (Figure 2) revealed a right ovarian solid-cystic mass weighing 1,528 g and measuring 22 × 19.5 × 7 cm. The external surface was nodular, with a single capsular rupture measuring 4.5 × 1 cm, confirmed by the operating surgeon to be intraoperative in origin. On cut section, the tumor was variegated with solid and cystic, grey-white to hemorrhagic areas and extensive necrosis. The attached fallopian tube measured 7 cm in length and was stretched over the tumor surface.

Microscopically (Figures 4 and 5), the tumor was highly cellular and composed predominantly of sheets, nests, and trabeculae of small round to oval cells with scant cytoplasm, vesicular chromatin, and brisk mitotic activity. Foci of larger cells with abundant eosinophilic cytoplasm and prominent nucleoli were admixed with the small-cell component. Scattered follicle-like microcystic spaces containing eosinophilic secretions and extensive tumor necrosis were present (Figure 6). The ovarian surface was involved by tumor, and lymphovascular invasion was identified in the peritubal region of the right fallopian tube. Tumor deposits were present in the bladder peritoneum, omentum, and cul-de-sac. Cytological examination of the intraoperative peritoneal fluid was negative for malignant cells. Both para-aortic lymph nodes were involved by metastatic carcinoma, with the largest metastatic deposit measuring 29 mm.

Immunohistochemical studies (Figure 7) demonstrated diffuse vimentin and WT1 expression in both the small- and large-cell components. Pancytokeratin and CK8/18 highlighted the large-cell component, while p16 expression was diffuse in the large cells. Patchy staining for D2-40, calretinin, synaptophysin, inhibin, Melan-A, CD10, CD56, CD99, TTF-1, and focal EMA expression was observed. The tumor was negative for PLAP, OCT3/4, AFP, CD117, Ber-EP4, CD30, CK7, CK20, CDX2, LCA, HMB45, chromogranin, desmin, estrogen receptor, and progesterone receptor. p53 was wild-type. Ki67 proliferation index was high.

Comprehensive molecular profiling using the OncoPrint Comprehensive Assay identified two pathogenic SMARCA4 frameshift mutations, c.2947\_2950del (p.E983Sfs35) and c.3668\_3674del (p.N1223Tfs4), with variant allele frequencies of 43.28% and 55.49%, respectively. RNA fusion analysis revealed no gene rearrangements, and no additional pathogenic alterations were identified. The molecular findings confirmed biallelic SMARCA4 inactivation, the characteristic molecular hallmark of small cell carcinoma of the ovary, hypercalcemic type (SCCOHT). Based on the combined histopathological, immunophenotypic, and molecular findings, a final diagnosis of small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) was established. The tumor was staged as FIGO stage IIIA2 (2017 FIGO staging system) and pT3aN1b. The patient subsequently received platinum-based chemotherapy consisting of etoposide and cisplatin together with three-monthly goserelin (Zoladex) injections. At the most recent follow-up, approximately two months after surgery, there was no evidence of disease recurrence.

## Discussion

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), is a rare but highly aggressive ovarian malignancy that predominantly affects young women, with a median age of approximately 24 years. Although the precise histogenesis remains uncertain, SCCOHT is now recognized as a distinct clinicopathological entity characterized by inactivation of SMARCA4, a core component of the SWI/SNF chromatin-remodeling complex.[6-10] Owing to its rarity and overlapping morphological features with several ovarian neoplasms, diagnosis remains challenging and requires careful integration of clinical, histopathological, immunohistochemical, and molecular findings.

Clinically, patients most commonly present with abdominal pain, abdominal distension, nausea, vomiting, menstrual irregularities, or a rapidly enlarging pelvic mass. Approximately two-thirds develop paraneoplastic hypercalcemia, although normal serum calcium levels have also been reported.[1,3,13,14] Our patient closely mirrored the classical clinical profile, presenting at 24 years of age with persistent vomiting, lower abdominal pain, significant recent weight loss, and documented non-parathyroid-related hypercalcemia. Serum CA-125 was elevated, whereas AFP and  $\beta$ -hCG remained within normal limits, consistent with previously published reports. Unlike many reported cases diagnosed at an early stage, our patient demonstrated para-aortic and supraclavicular lymph node metastases at presentation, reflecting the aggressive biological behaviour of SCCOHT. The PET-CT findings of a large right adnexal mass with para-aortic lymphadenopathy and mild ascites correlated well with the advanced pathological stage observed at surgery.

Grossly, SCCOHT usually presents as a unilateral, large ovarian mass with mixed solid and cystic areas accompanied by extensive hemorrhage and necrosis.[1,2,14] Our tumour measured 22 × 19.5 × 7.0 cm, weighed 1528 g, and exhibited a nodular external surface with an intraoperative capsular rupture. The cut surface showed extensive solid grey-white areas interspersed with hemorrhage, cystic degeneration, and geographic necrosis, closely resembling the gross appearances described in previously reported cases. Frozen section examination correctly identified the lesion as a high-grade malignant neoplasm, allowing appropriate intraoperative surgical decision-making while definitive classification was deferred until permanent sections and ancillary investigations were completed.

Histologically, SCCOHT demonstrates a characteristic but heterogeneous appearance. Most tumours are composed predominantly of diffuse sheets, nests, cords, or trabeculae of closely packed small round to oval cells with scant cytoplasm, hyperchromatic to vesicular nuclei, conspicuous mitotic activity, and extensive necrosis. Approximately half of cases show a variable admixture of larger cells with abundant eosinophilic cytoplasm and prominent nucleoli, imparting a rhabdoid appearance. Another distinctive feature is the presence of follicle-like or microcystic spaces containing eosinophilic secretions, although this finding is not entirely specific and may also be encountered in other ovarian neoplasms.[1,4,5] Extensive hemorrhage, capsular involvement, lymphovascular invasion, and extraovarian spread are frequent in advanced-stage tumours and reflect their aggressive biological behaviour.

The present case demonstrated virtually the entire classical histomorphological spectrum of SCCOHT. The tumour was composed predominantly of sheets, nests, and trabeculae of small round to ovoid cells with scant cytoplasm, vesicular chromatin, brisk mitotic activity, and extensive necrosis. Intermixed foci of larger eosinophilic cells with conspicuous nucleoli were also identified. Characteristic follicle-like spaces containing eosinophilic secretions were readily apparent, providing an important morphological clue to the diagnosis. Furthermore, ovarian surface

involvement, lymphovascular invasion within the peritubal region of the right fallopian tube, metastatic deposits involving the bladder peritoneum, omentum, and cul-de-sac, together with para-aortic lymph node metastases, confirmed the highly invasive nature of the tumour. These findings are in keeping with the advanced FIGO stage IIIA2 disease documented in our patient.

The immunophenotype of SCCOHT is complex and frequently overlaps with other poorly differentiated ovarian neoplasms, necessitating the use of a broad antibody panel. Most tumours demonstrate diffuse vimentin expression together with variable positivity for epithelial markers, WT1, p16, calretinin, CD56, synaptophysin, and sex cord-stromal markers, whereas germ cell markers including OCT3/4, PLAP, AFP, and CD117 are typically negative. Loss of BRG1 expression by immunohistochemistry has emerged as the most diagnostically useful finding, although molecular confirmation is increasingly employed in diagnostically challenging cases.[9,10,14,15]

In the present case, an extensive immunohistochemical panel was performed to exclude the principal differential diagnoses. The tumour demonstrated diffuse vimentin and WT1 positivity with focal expression of PanCK, CK8/18, EMA, calretinin, inhibin, Melan-A, SALL4, CD56, CD99, CD10, and weak synaptophysin. Germ cell markers including OCT3/4, PLAP, AFP, and CD117 were negative, as were CK7, CK20, CDX2, chromogranin, LCA, desmin, HMB45, and ER/PR, effectively excluding germ cell, epithelial, lymphoid, melanocytic, and myogenic neoplasms. Although BRG1 immunohistochemistry was unavailable, the comprehensive immunophenotypic profile substantially narrowed the differential diagnosis and supported the subsequent molecular confirmation.

The discovery of recurrent SMARCA4 alterations has fundamentally changed the understanding of SCCOHT and established it as a member of the family of SMARCA4-deficient malignancies. SMARCA4 encodes BRG1, the catalytic ATPase subunit of the SWI/SNF chromatin-remodelling complex, which plays a crucial role in regulating gene transcription, cellular differentiation, DNA repair, and maintenance of genomic stability. Biallelic inactivation of SMARCA4 results in complete loss of BRG1 function and is now regarded as the defining molecular event in SCCOHT.[6-10,15] Approximately 40–45% of patients harbour germline SMARCA4 pathogenic variants, highlighting the importance of genetic counselling and consideration of family screening, particularly in young patients.[8,11]

Although loss of BRG1 expression by immunohistochemistry is widely used as a surrogate marker for SMARCA4 inactivation, comprehensive molecular testing is increasingly employed to confirm the diagnosis and identify patients who may benefit from genetic counselling or future targeted therapeutic strategies. In the present case, BRG1 immunohistochemistry was unavailable; however, comprehensive next-generation sequencing using the OncoPrint Comprehensive Assay identified two pathogenic truncating SMARCA4 frameshift mutations, c.2947\_2950del (p.E983Sfs35) and c.3668\_3674del (p.N1223Tfs4), consistent with compound heterozygous (biallelic) inactivation. No additional pathogenic variants or RNA fusions were detected. This molecular profile provided definitive confirmation of the diagnosis and represents one of the major strengths of the present report, illustrating the value of integrating histomorphology, immunophenotype, and molecular diagnostics in the evaluation of poorly differentiated ovarian neoplasms.

The differential diagnosis of SCCOHT is broad and includes juvenile granulosa cell tumour, dysgerminoma, small-cell neuroendocrine carcinoma, lymphoma, desmoplastic small round cell tumour, primitive neuroectodermal tumour, metastatic small-cell carcinoma, and other undifferentiated ovarian malignancies. Considerable overlap exists both morphologically and immunophenotypically, making reliance on a single histological or immunohistochemical feature hazardous.[1,3,9,10,14]

Juvenile granulosa cell tumour may demonstrate follicle-like spaces and focal inhibin or calretinin expression but generally exhibits characteristic nuclear morphology and lacks the diffuse high-grade cytological atypia and extensive necrosis typical of SCCOHT. Dysgerminoma usually demonstrates diffuse OCT3/4, SALL4, and CD117 expression with accompanying lymphocytic infiltrates, features absent in the present case. Similarly, lymphoma is excluded by negative leukocyte common antigen expression, whereas metastatic neuroendocrine carcinoma typically demonstrates diffuse chromogranin and synaptophysin positivity. The broad immunohistochemical panel employed in the present case effectively excluded these entities while supporting SCCOHT.

From a practical perspective, the present case also highlights an important diagnostic consideration during intraoperative frozen section consultation. Owing to the rarity of SCCOHT and its overlapping morphology with several ovarian small round cell tumours, definitive diagnosis on frozen section may not be feasible. In the present

case, the frozen section diagnosis appropriately favoured a high-grade malignant neoplasm, with dysgerminoma, juvenile granulosa cell tumour, and SCCOHT included in the differential diagnosis. Recognition of a highly cellular small round cell tumour showing follicle-like spaces, extensive necrosis, and brisk mitotic activity should prompt the pathologist to include SCCOHT in the differential diagnosis, even though it remains an uncommon ovarian tumour. Awareness of this possibility may facilitate appropriate tissue sampling and timely ancillary investigations on permanent sections.

Owing to its rarity, there is currently no universally accepted treatment protocol for SCCOHT. Most patients undergo aggressive cytoreductive surgery followed by platinum-based combination chemotherapy, while selected patients receive radiotherapy or high-dose chemotherapy with autologous stem-cell transplantation. Despite multimodal therapy, prognosis remains poor, particularly in advanced-stage disease, with stage at diagnosis consistently identified as the most important prognostic factor. Long-term survival is predominantly reported in patients with FIGO stage I disease, whereas advanced-stage tumours frequently recur within the first two years following diagnosis.[12-14]

Our patient underwent primary surgical resection followed by etoposide and cisplatin-based chemotherapy. At the most recent follow-up, there was no evidence of recurrence, although the duration of follow-up remains short. Given the advanced stage at presentation and the aggressive biological behaviour of SCCOHT, prolonged clinical surveillance is warranted. Emerging therapeutic strategies targeting the molecular alterations associated with SMARCA4 deficiency, including EZH2 inhibitors, immune checkpoint inhibitors, and other targeted approaches, remain under active investigation and may improve future outcomes in this otherwise highly lethal malignancy.

The present case illustrates several important clinicopathological and diagnostic aspects of SCCOHT. First, it demonstrates the classical clinical, gross, and microscopic features of this uncommon malignancy in a young woman presenting with hypercalcemia and advanced-stage disease. Second, an extensive immunohistochemical panel enabled systematic exclusion of the principal differential diagnoses before molecular confirmation. Third, comprehensive next-generation sequencing identified two pathogenic truncating SMARCA4 mutations consistent with biallelic inactivation, providing robust molecular confirmation of the diagnosis. Finally, the frozen section findings highlight an important practical lesson for surgical pathologists: although SCCOHT is exceptionally rare, it should remain within the differential diagnosis of highly cellular ovarian small round cell tumours demonstrating follicle-like spaces, extensive necrosis, and brisk mitotic activity. Early recognition and appropriate ancillary testing are essential for establishing an accurate diagnosis and facilitating optimal patient management.

## Conclusion

Small cell carcinoma of the ovary, hypercalcemic type, is a rare and highly aggressive ovarian malignancy that poses significant diagnostic challenges because of its overlapping morphological features with several ovarian neoplasms. Accurate diagnosis requires careful integration of clinical findings, histopathological examination, immunohistochemistry, and increasingly, molecular testing. The present case highlights the diagnostic value of comprehensive molecular profiling, which demonstrated biallelic pathogenic SMARCA4 inactivation and provided definitive confirmation of the diagnosis. Furthermore, this case emphasizes the importance of considering SCCOHT in the differential diagnosis of ovarian small round cell tumours, particularly during intraoperative frozen section evaluation when characteristic follicle-like spaces and high-grade cytological features are encountered. Early recognition and multidisciplinary management remain essential to optimize patient outcomes in this highly aggressive malignancy.

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## Figure legends

**Figure 1. Magnetic resonance imaging of the pelvis demonstrating a large heterogeneous pelvi-abdominal mass arising from the right adnexa/ovary.**

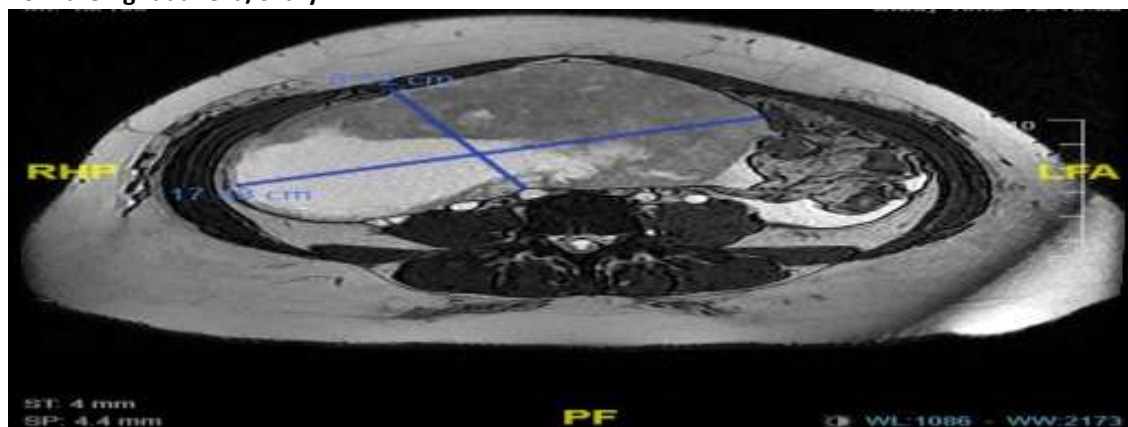


**Figure 2.** Gross examination of the ovarian tumor showing a large solid-cystic mass with a nodular external surface. The cut surface is variegated, with solid grey-white areas, cystic degeneration, hemorrhage, and extensive necrosis.

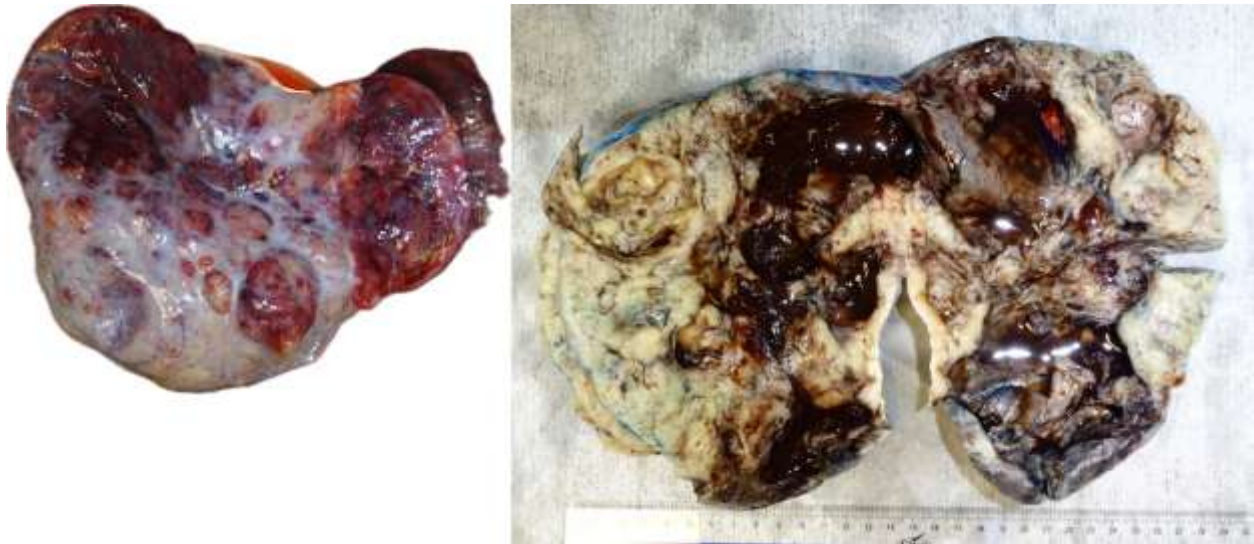


**Figure 3.** Intraoperative frozen section of the ovarian tumor. (A) Low-power view showing a highly cellular high-grade malignant neoplasm composed predominantly of small round to oval cells with areas of necrosis (hematoxylin and eosin [H&E],  $\times 10$ ). (B) High-power view demonstrating the small round to oval tumor cells with scant cytoplasm, brisk mitotic activity, and cytological atypia (H&E,  $\times 40$ ).

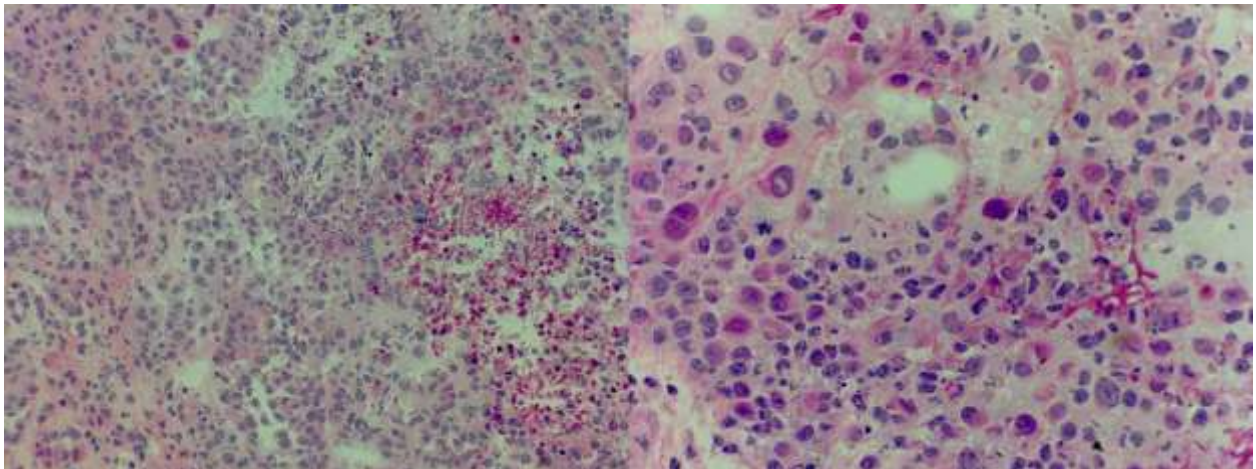


**Figure 4.** Histopathological features of small cell carcinoma of the ovary, hypercalcemic type. Low-power view demonstrating a highly cellular tumor composed of sheets, nests, and trabeculae, with two morphologically distinct areas: a predominantly small-cell component on the left and an area composed predominantly of larger tumor cells on the right (hematoxylin and eosin [H&E],  $\times 10$ ).

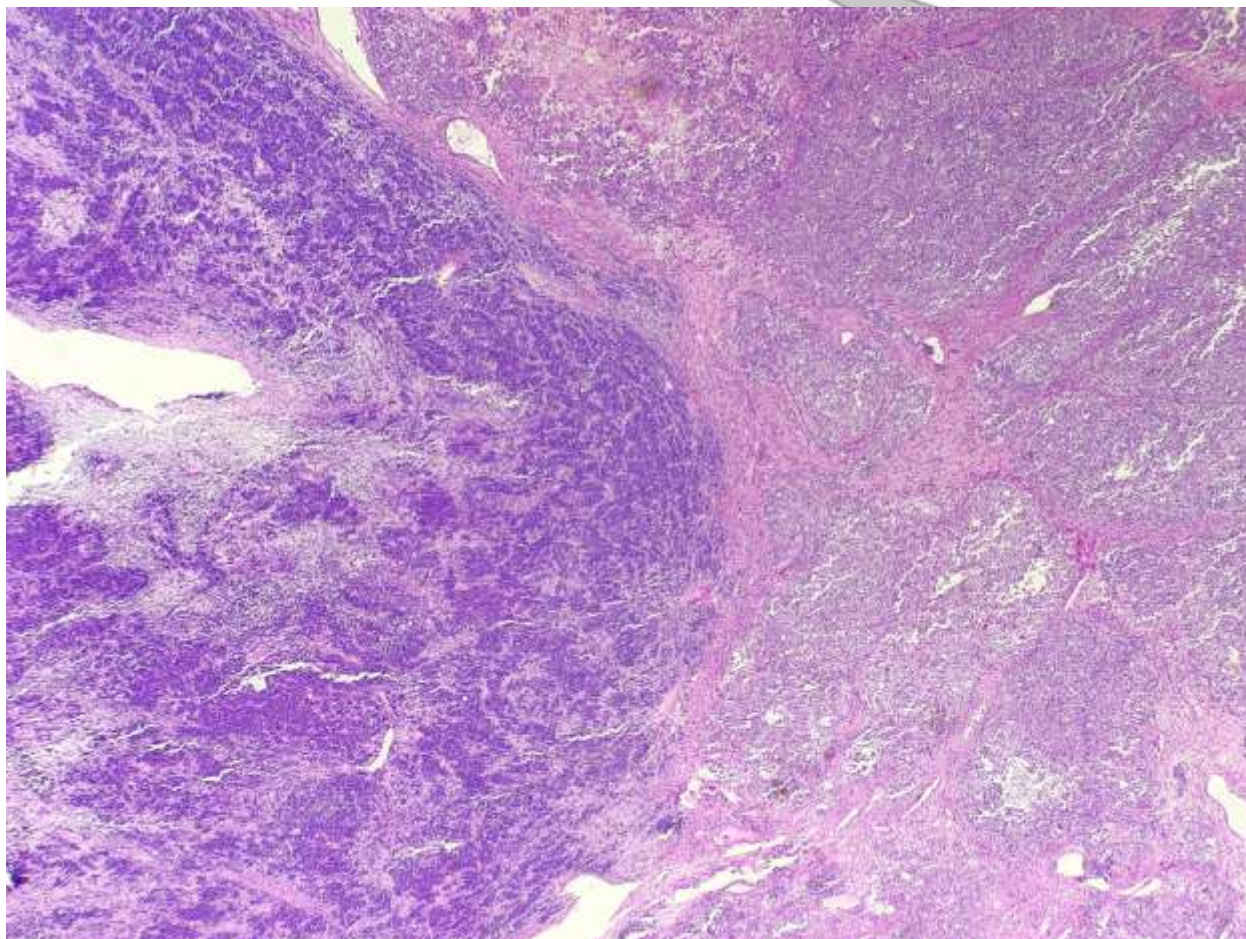


**Figure 5.** Histopathological features of the distinct cellular components of small cell carcinoma of the ovary, hypercalcemic type. (A) Larger-cell component showing tumor cells with abundant cytoplasm, open vesicular nuclei, and prominent nucleoli (H&E,  $\times 20$ ). (B) High-power view of the small-cell component showing small round cells with scant cytoplasm and small hyperchromatic nuclei (H&E,  $\times 40$ ).

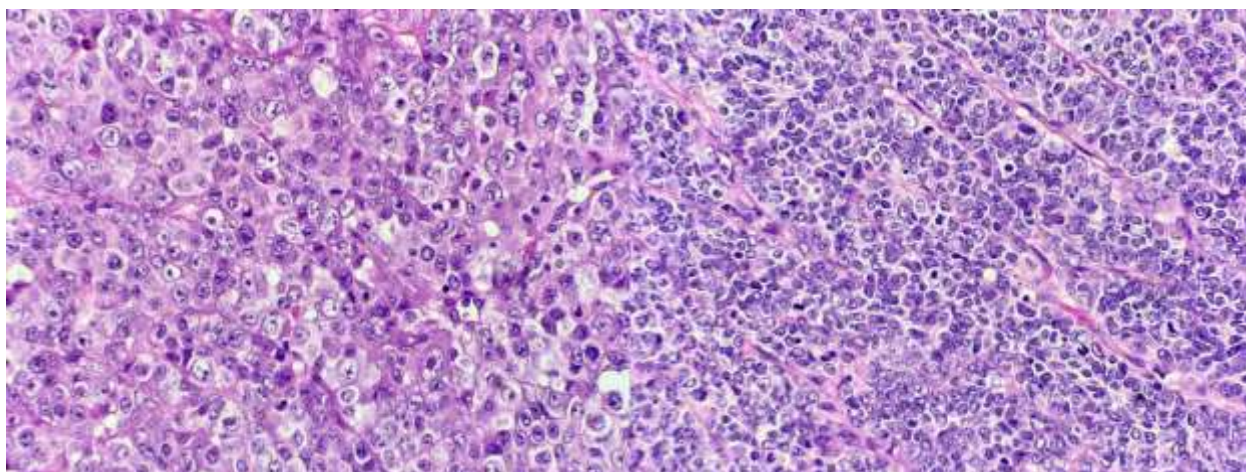


**Figure 6. Characteristic follicle-like spaces/microcysts in small cell carcinoma of the ovary, hypercalcemic type. (A) Low-power view demonstrating follicle-like and microcystic spaces within the tumor (H&E, ×20). (B) High-power view showing the follicle-like spaces containing eosinophilic secretions (H&E, ×40).**

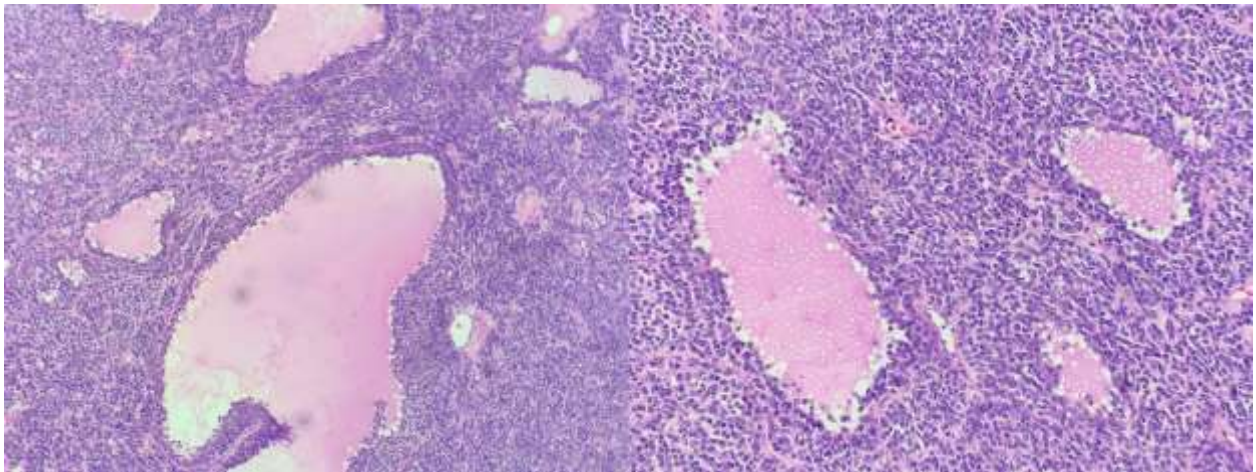


**Figure 7. Immunohistochemical findings in small cell carcinoma of the ovary, hypercalcemic type. (A) WT1 showing diffuse positivity in both the small- and larger-cell components. (B) Pancytokeratin (CK AE1/AE3) showing positivity predominantly in the larger-cell component. (C) CK8/18 showing positivity predominantly in the larger-cell component. (D) Vimentin showing diffuse positivity in both the small- and larger-cell components.**

