Adult granulosa cell tumour camouflaged as mucinous neoplasm

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SUMMARY

This case report delves into the diagnostic intricacies and clinical management of adult granulosa cell tumour (AGCT) in a woman in her 50s, presenting with pain abdomen. Initial imaging investigations like ultrasound suggested diagnosis of benign cystadenoma. Further MRI revealed a large well-defined multiloculated lesion so a diagnosis of neoplastic aetiology/likely mucinous cystadenocarcinoma was offered. However, the definitive diagnosis was established through meticulous histopathological examination, revealing characteristic features of AGCT, a rare ovarian neoplasm. The case underscores the diagnostic challenges posed by AGCT, the importance of integrating clinical, radiological and histopathological data, and the necessity for a multidisciplinary approach for accurate diagnosis and optimal patient management.

BACKGROUND

Adult granulosa cell tumour (AGCT) of the ovary is a rare neoplasm, constituting about 2–3% of all ovarian malignancies, predominantly affecting women in their 50s.[1 2] Originating from the pure sex-cord cells of the ovary,[3] AGCT exhibits a tendency to recur years after initial diagnosis.[4] This tumour can lead to a range of symptoms and signs resulting from estradiol secretion, such as vaginal bleeding and precocious puberty, as well as abdominal pain and haemoperitoneum due to tumour rupture.[4]

Clinically, AGCTs often present as a pelvic mass which is detectable on examination.[4] Despite their malignant potential, they tend to have a long natural history, and their prognosis is generally favourable, especially when compared with other epithelial ovarian tumours.[1 2] Surgical intervention that can be performed ranges from conservative unilateral salpingo-oophorectomy to total abdominal hysterectomy with bilateral salpingo-oophorectomy, which plays an important role in histological diagnosis, appropriate staging and tumour debulking.[4]

The stage of the disease at diagnosis is necessary for prognosis, with advanced stages associated with a higher risk of relapse.[4] The role of postoperative chemotherapy or radiotherapy in AGCT is a subject of ongoing debate, with no definitive management reached so far. The uncertainty primarily revolves around the indolent nature of the tumour and the lack of large, randomised clinical trials. For patients

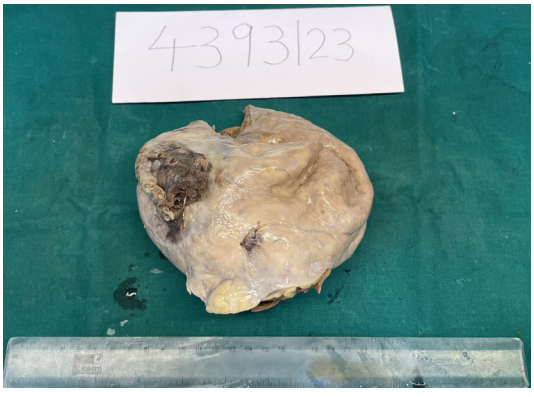

Figure 1 Gross image of the right ovary measuring 20×12×8 cm. External surface was congested with intact capsular surface.

Figure 2 Right ovary cut section shows predominantly solid areas with the presence of papillary excrescences and focal areas of necrosis.

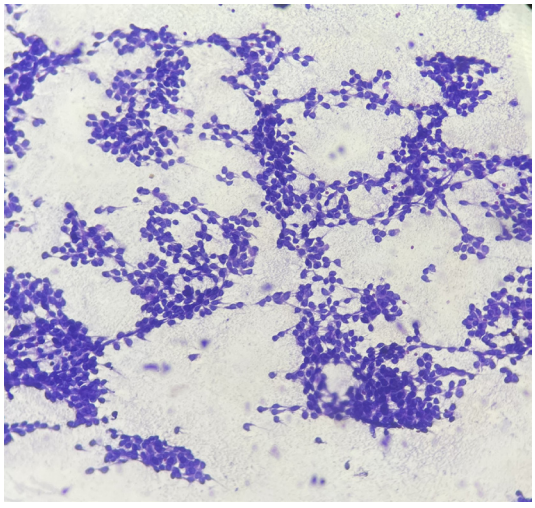

Figure 3 Frozen section imprint smear shows papillary pattern (Giemsa, ×400).

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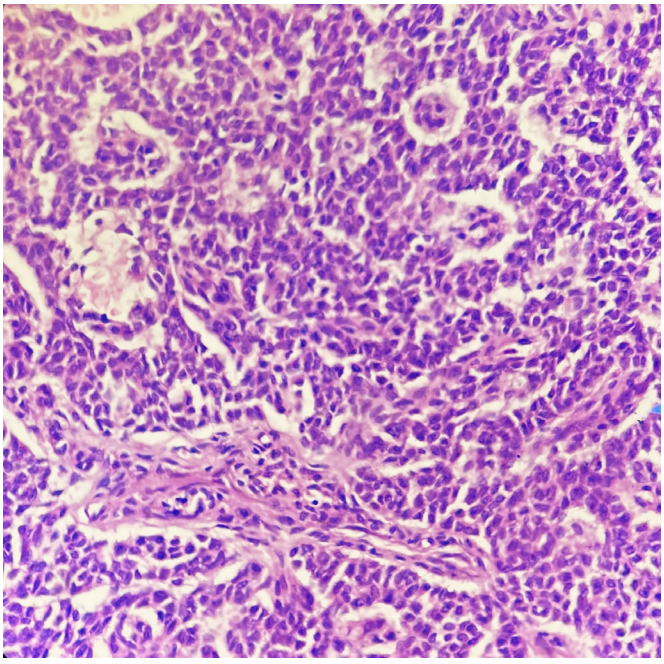

Figure 4 Microscopic image of the right ovary shows microfollicular pattern (H&E, ×100).

with stage I disease and those with completely resected tumours, the benefits of adjuvant therapy remains unclear. Some clinicians advocate for a more personalised approach, considering the patient's age, the tumour stage and histological features, and the potential side effects of chemotherapy.[5]

CASE PRESENTATION

A woman in her 50s presented to the outpatient gynaecology clinic complaining of pain over the abdomen for the past 2 months. The pain was radiating to the back. She denied any significant weight loss, changes in appetite or other systemic symptoms. There was history of abdominal hysterectomy and bilateral tubectomy 20 years ago.

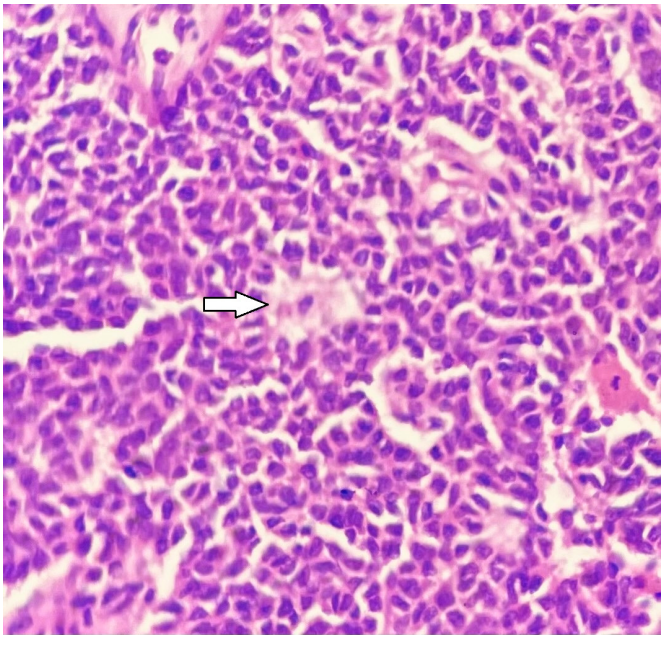

Figure 5 Microscopic image of the right ovary with Call Exner bodies (H&E, ×400).

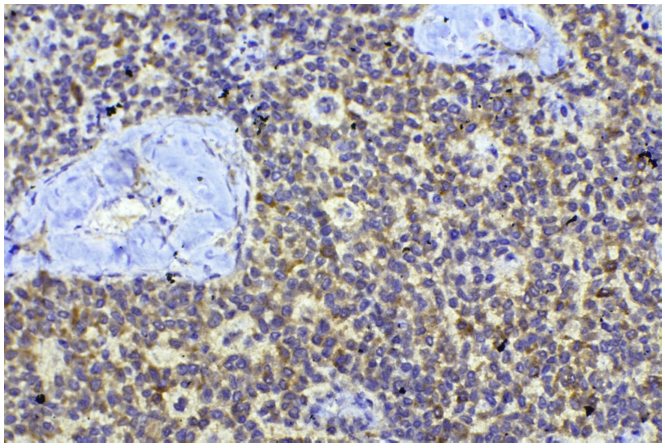

Figure 6 Photomicrograph of immunohistochemistry showing diffuse cytoplasmic positivity of tumour cells for inhibin (×400).

On physical examination, a palpable mass extending from the pelvis to the umbilicus was noted. The mass was non-tender, smooth and firm to palpation. Pelvic examination revealed a mobile, non-tender pelvic mass corresponding to the size of an 18 weeks of gestation. There was no evidence of ascites grossly or lymphadenopathy.

Routine laboratory tests including complete blood count, liver function tests and renal function tests were within normal limits. Tumour marker such as CA-125 was within the normal range (21.9 U/mL).

The abdominal ultrasound examination revealed a prominently large, well-circumscribed, multiloculated solid-cystic lesion situated in the right adnexal region. On colour Doppler imaging, the lesion demonstrated minimal peripheral vascularity. So preliminary diagnosis of benign cystadenoma was proposed on ultrasonography. Subsequent MRI provided further insights into the lesion's characteristics. The lesion, which was centralised in the right ovary, appeared as a large, well-defined, multiloculated mass. It demonstrated hypointense signal characteristics on T1-weighted images and hyperintense signal on T2-weighted images. The lesion also exhibited multiple septations and a few solid components. Given these imaging findings,

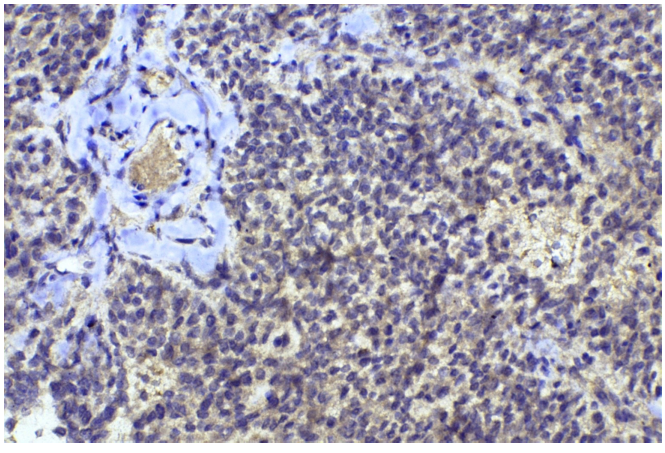

Figure 7 Photomicrograph of immunohistochemistry showing diffuse cytoplasmic positivity of tumour cells for calretinin (×400).

the radiological impression leaned towards a likely diagnosis of mucinous cystadenocarcinoma.

The contrast between the ultrasound and MRI findings required a careful consideration of the differential diagnoses. Given the size of the tumour, the patient was counselled and opted for surgical intervention with frozen section. During the surgery, an intraoperative frozen section was performed.

On frozen section, a right cystic ovarian mass measured 20×12×8 cm with attached fallopian tube measuring 6 cm. External surface was congested and well encapsulated (figure 1). On cut section, around 1.5 L of blood mixed serous fluid was drained. Predominantly solid areas with papillary excrescence were noted (figure 2). Imprint smears showed tumour cells arranged in papillary pattern (figure 3). Rapid H&E-stained frozen section slides showed tumour cells arranged in papillary pattern and solid sheets with focal areas of necrosis. Diagnosis of papillary serous cystadenocarcinoma was given intraoperatively.

Bilateral salpingo-oophorectomy and bilateral pelvic lymph node excision along with omentectomy by laparotomy were performed and sent for histopathological examination.

On gross examination, along with right cystic ovarian mass, left cystic ovary was also recieved which measured 5×3×2.5 cm. On cut open, there was a multiloculated cyst which drained 5 mL of clear fluid. Twelve lymph nodes were retrieved from bilateral pelvic lymph node specimen. Omentum was measured 33×15×1 cm. Sections were given from right ovarian mass, left cystic ovary, lymph nodes and omentum.

On microscopic examination of the right ovary, tumour tissue arranged in microfollicular, insular pattern, nesting pattern and pseudopapillary pattern, with the presence of Call Exner bodies were noted. Tumour cells were monotonous with round to oval nuclei, irregular nuclear membrane and scanty cytoplasm. Few cells showed nuclear grooves and large areas of necrosis (figures 4 and 5). Diagnosis of AGCT was suspected and immunohistochemistry was suggested. On immunohistochemistry, tumour cells were positive for inhibin (figure 6) and calretinin (figure 7) and negative for PAX-8 and p53 confirming the diagnosis.

The sections studied from the left ovary showed features of benign mucinous cystadenoma. All 12 lymph nodes and omentum were free of tumour tissue.

This definitive diagnosis was in variance with the initial frozen section interpretation, highlighting a rare but challenging aspect of ovarian tumour pathology. Such discrepancies can occur, particularly in tumours which exhibit a heterogeneous morphology.

OUTCOME AND FOLLOW-UP

A follow-up examination was conducted to assess the patient's condition after 3 months. The patient presents with no new complaints and demonstrates positive inhibin levels.

There are no signs of metastasis and the patient remains in good health.

DISCUSSION

AGCTs represent a distinct and challenging subgroup of ovarian neoplasms, originating from pure sex cord cells of the ovary.[6] Their pathogenesis is linked to mutations in the FOXL2 gene, influencing ovarian development and function.[7] AGCTs exhibit a wide range of clinical presentations, from abnormal uterine bleeding and signs of hyperestrogenism to acute abdominal situations due to tumour rupture.

Diagnosing AGCT can be challenging due to their varied radiological appearances. While initial imaging methods such as ultrasound and MRI provide valuable insights, they lack the specificity required for a definitive diagnosis. This was evident in the present case, where initial imaging raised suspicions of a benign or different malignant entity, only to be clarified later through extensive histopathological examination.

The intraoperative frozen section analysis added another layer to the diagnostic process. The initial interpretation suggested a high-grade serous carcinoma, based on the observed papillary patterns and areas of necrosis. However, the limitations of frozen section analysis, particularly its reliance on a limited tissue sample and potential challenges in identifying specific histological patterns, necessitated a cautious approach to interpreting these findings.

Histopathological analysis remains the cornerstone for diagnosing AGCT, requiring the identification of characteristic microscopic structures and immunohistochemistry markers.

Surgical management stands as the primary mode of treatment for AGCT, aiming for complete tumour resection. However, the role of adjuvant chemotherapy or radiotherapy remains ambiguous, especially in early-stage disease, necessitating a tailored and personalised treatment approach.[5]

Here, the choice to carry out major surgical procedures, such as omentectomy and lymphadenectomy, without obvious metastasis was due to the original concern of a more severe form of epithelial ovarian cancer.

Intraoperative frozen section analysis, while not definitive for guiding immediate surgical decisions, presents notable limitations, particularly in the context of complex ovarian tumours like AGCT. The primary limitation stems from the nature of the procedure itself, which involves rapid tissue processing and examination of only a small portion of the tumour. This approach can lead to sampling errors, where the section analysed may not represent the overall pathology of the entire tumour, especially in heterogeneous neoplasms such as AGCT. Here, in this case, the imprint smears showed presence of papillary excrescence and rapid H&E staining on frozen slides demonstrated the presence of papillary pattern along with haemorrhagic and necrotic areas, which led to the diagnosis of papillary serous cystadenocarcinoma.

The rapid processing required for frozen sections can also compromise the histological quality of the samples. Important diagnostic features, such as Call-Exner bodies or the subtle nuclear grooves characteristic of AGCT, may not be noticeable in frozen sections compared with permanent sections prepared with more refined histological techniques. Lack of these important diagnostic histopatholigical features can lead to misinterpretation which are crucial for a definitive diagnosis.

The findings from a frozen section must always be corroborated by detailed postoperative histopathological review with full immunohistochemical profiling. This is particularly crucial in tumours with complex and variable presentations like AGCT.

A notable aspect of AGCTs is their tendency for late recurrence, which significantly impacts long-term patient management and necessitates vigilant follow-up.[8] This propensity underscores the need for prolonged surveillance, even in cases where the tumour is diagnosed at an early stage and completely resected. Clinicians must maintain a high index of suspicion for recurrence, with regular follow-up appointments and timely investigation of any suspicious findings. This approach ensures early detection and intervention, ultimately influencing patient outcomes.

Young *et al* described four cases, with patients presenting with postmenopausal bleeding, dysfunctional uterine bleeding and amenorrhea. The tumours were all stage Ia, solid, lobulated and yellow, with abundant eosinophilic cytoplasm.[9] Ahmed *et*

al reported four cases with hepatic cell differentiation,[10] while Raivoherivony *et al* discussed a case in a 26-year-old woman with abdominal pain and distension.[11] Castro *et al* presented a unique case of androgenic manifestation in a 13-year-old prepubertal girl.[12] These case reports highlight the diverse clinical and histological features of AGCTs in the ovary.

Learning points

- This case exemplifies the complexity in diagnosing ovarian masses, highlighting adult granulosa cell tumour (AGCT) as a crucial differential diagnosis in postmenopausal women presenting with large ovarian masses.
- Initially reported as a benign cystadenoma and later suspected as a high-grade tumour through MRI and frozen section analysis, this case ultimately revealed a pure sex cord tumour—specifically, AGCT. This misdiagnosis highlights the critical differences in management strategies, as AGCT typically does not require chemotherapy or radiotherapy postoperatively.
- Due to the potential for late recurrence in AGCT, clinicians must emphasise the importance of prolonged and vigilant follow-up with simple tests like serum beta inhibin.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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