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Clear cell Carcinoma of Ovary - With A Look Into The Past And An Attempt at 'Forecasting'

[1]Dr. Sony Mandal, [2]Dr. Manju Raghava, [3]Dr. Anjana Mittal, [4]Dr. Chetna Mehrol
[1]Assistant Professor, [4]Associate Professor, [2,3]Professor
Department Of Pathology
Mahatma Gandhi Medical College and Hospital, Jaipur, India

***Corresponding Author:**
Dr. Chetna Mehrol
Associate Professor, Department Of Pathology,
Mahatma Gandhi Medical College and Hospital, Jaipur, India

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Abstract

Introduction:

Ovarian clear cell carcinoma (OCCC) is a rare subtype of ovarian malignancy that often affects younger women and is associated with nulliparity and endometriosis. Accurate diagnosis is crucial as OCCCs have a low response rate to platinum-based chemotherapy and poorer prognosis compared to other epithelial ovarian carcinomas (EOCs). This study aims to analyze the clinical and histopathological characteristics of OCCC cases.

Materials and Methods:

A retrospective analysis was conducted on patients diagnosed with OCCC over a 24-month period. The study included patients with histologically confirmed OCCC, excluding those with mixed OCCC or metastatic ovarian carcinoma. Ethical approval was obtained, and all procedures followed institutional and national research committee guidelines.

Results:

The study included five cases of OCCC from a tertiary care hospital in Western India. The median age at diagnosis was 46.5 years. The majority of patients were nulliparous. Endometriosis was present in two cases, supporting its association with OCCC. Surgical procedures included total hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, and omentectomy. Most patients were diagnosed at early stages (FIGO IA, IC1, IC3). All patients received platinum plus paclitaxel-based chemotherapy and remained disease-free during follow-up.

Conclusion:

OCCC is a distinct subtype of ovarian carcinoma associated with younger age, nulliparity, and endometriosis. Understanding the clinical and histopathological features of OCCC is crucial for accurate diagnosis and optimal treatment strategies. Further research is needed to explore targeted therapies and novel diagnostic biomarkers for OCCC.

Keywords: Carcinoma, Chemotherapy, Clear cell, Endometriosis, Epithelial, Ovarian

Introduction

Ovarian clear cell carcinoma (OCCC) account for <5% of all ovarian malignancies and 3.7–12.1% of all epithelial ovarian carcinomas (EOC) [1]. OCCCs often present in younger age groups in comparison with other EOC's [2-4]. They are often associated with nulliparity and endometriosis. The differential

diagnosis of these tumors includes EOCs with a clear cell component, yolk sac tumor, dysgerminoma, metastatic renal cell carcinoma and Krukenberg tumor. A clinico-radiological correlation and thorough histopathological examination is necessary to diagnose OCCCs accurately as these tumors have a low response rate to platinum-based chemotherapy and hence poorer prognosis when compared to other EOCs. At present, the treatment strategy resembles the treatment of high-grade serous carcinoma which includes maximal cytoreduction followed by a combination of platinum plus paclitaxel-based chemotherapy.

Materials And Methods:

We conducted a retrospective analysis of patients diagnosed with ovarian carcinomas, specifically focusing on OCCC, over a period of 24 months. Our study included patients with histologically confirmed OCCC with only pure clear cell histology who underwent complete surgical staging or cytoreductive surgery with adjuvant chemotherapy as the primary treatment. Patients who received neo-adjuvant chemotherapy, had insufficient data, had mixed OCCC or metastatic ovarian carcinoma, or were lost to follow-up within 1 month of surgery were excluded from our study.

To gather patient information for analysis, we collected data from medical records, including demographic details, pathological characteristics, pre-operative biomarkers, surgical procedures, and chemotherapy. To ensure patient confidentiality, all records and information were anonymized before analysis, obviating the need for individual consent. Approval for this retrospective study was obtained from the Ethics Committee (MGMC&H/IEC/JPR/2023/1542, dated 19/05/2023) and all procedures adhered to the ethical standards outlined by the institutional and national research committee, following the principles of the Helsinki Declaration.

All tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system, while the histological cell types were determined based on the criteria established by the World Health Organization (WHO). Concomitant endometriosis was confirmed through thorough examination of the surrounding ovarian tissue.

Results:

We report five cases of OCCCs received in a tertiary care hospital in Western India over a span of 24 months. The median age at diagnosis was 46.5 years (range 42–55 years). Three of them presented with large abdominal masses and two presented with abdominal pain as the predominant symptom. Interestingly, four of these women were nulliparous and one of them also had a history of endometriosis 10 years prior to this surgery, for which she had undergone medical treatment. CA125 assay was performed in 4 patients, with a median CA125 level of 63.3 IU/mL (range 10.16-619 IU/mL). The primary surgical procedure that was performed was total hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, and omentectomy, with or without peritoneal biopsies from multiple random/suspicious areas.

We received all five cases for interpretation in the frozen room. The typical gross appearances of these cases were of large solid cystic tumors with one or more white to yellow solid areas of tumor. Variable amounts of hemorrhage and necrosis were present. Squash cytology as well as frozen sections were done. Squash cytology showed clusters and papillae of large cells with granular eosinophilic cytoplasm and pleomorphic nuclei. The characteristic clear cell appearance was deceptively absent.[Figure 1,2] The frozen sections of ovarian tumors showed glandular and papillary architectural patterns with the glands and papillae lined by large eosinophilic pleomorphic cells resembling mucinous adenocarcinoma. A thorough sampling of the ovarian tumor was done for routine histopathological examination. On paraffin sections, the tumors showed characteristic patterns comprising of solid, papillary, cystic or glandular architecture in varying proportions. [Figure 3a,b,c,d] A variety of cell types were identified, including clear cells, cells with granular eosinophilic cytoplasm and hobnail cells. The clear cells were cuboidal, low columnar, or polygonal with abundant clear cytoplasm, central vesicular nuclei and conspicuous nucleoli. Cells with eosinophilic cytoplasm were similar to the clear cells except their granular eosinophilic cytoplasm. Hobnail cells were large columnar cells with clear or eosinophilic cytoplasm which had hyperchromatic bulbous apical nuclei protruding into the lumen.[Figure 4] Mitotic activity was low in all cases. The diagnosis of clear cell

Volume 6, Issue 6; November-December 2023; Page No 81-93

carcinoma of ovary was restricted to those cases which showed a combination of characteristic cytologic features and architectural patterns rather than just the mere presence of clear cells. The final histopathological diagnosis was of OCCC with the majority of patients (3/5, 60%) diagnosed at early-stage (FIGO IA, IC1 and IC3), whereas one case had tumor implants on the pelvic peritoneum (FIGO IIB) and another case had tumor implants in the omentum along with metastasis in retroperitoneal lymph nodes (FIGO IIIC). Concomitant ovarian endometriosis was found on the contralateral ovary in one case.

Post-operative chemotherapy comprising of a combination of platinum plus paclitaxel-based drugs (6 cycles) were administered to all patients. These patients are on regular follow-up, and are disease free till date.

Discussion:

OCCC was originally described as "mesonephroma" by Schiller in 1939 [5]. They were first formally defined in 1973 by the WHO as a malignant ovarian tumor composed of glycogen containing clear cells and hobnail cells and occasionally other cell types.[6]

The median age at diagnosis of OCCCs in our study was 46.5 years. This is in keeping with the observation that OCCCs tend to be diagnosed at a younger age in comparison with the general age distribution of other epithelial ovarian carcinomas (56 years vs 70 years) [2-4]. The most common presenting symptom is of large pelvic or abdominal masses. Symptoms such as abdominal pain can be attributed to mass effect or invasion of adjacent structures.

Risk factors such as early menarche, late menopause, limited use of oral contraceptives, and low pregnancy rate are linked to OCCC. One possible explanation for this phenomenon is that women who have experienced a higher number of ovulations may undergo increased cellular divisions to repair the epithelium after each ovulation. Consequently, this heightened cellular activity could lead to a greater likelihood of spontaneous mutations and malignant transformations occurring [7-9]. Interestingly, four out of the five women in our study were nulliparous.

In our study, one patient with OCCC had a history of endometriosis and one patient had concurrent endometriosis in the contralateral ovary. Two meta-analyses of clinical studies have demonstrated an increased risk of ovarian cancer in patients diagnosed with endometriosis, with the greatest association observed specifically in the clear cell subtype [10,11]. OCCC is frequently associated with endometriosis [12,13]. While the precise molecular mechanisms responsible for the malignant transformation have yet to be fully elucidated, there is widespread acceptance that endometriosis, particularly in the ovaries, serves as a direct precursor to the development of endometrioid and clear cell carcinomas of the ovary [14,15]. This is supported by evidence indicating that women with histologically confirmed endometriosis exhibit a significantly elevated age-adjusted incidence rate ratio of 2.29 (95% CI 1.24 to 4.20) for OCCC [16]. Furthermore, the presence of endometriosis is identified in the final pathology reports of approximately 51% of cases involving clear cell carcinoma [17]. The presence of endometriosis in two of our cases further supports the notion of a potential link between these two conditions and emphasizes the importance of evaluating women with endometriosis for the development of ovarian malignancies.

Tumor markers, such as CA125, play a significant role in the diagnosis, monitoring, and follow-up of ovarian cancer patients. In our study, CA125 assay was performed in four patients with OCCCs, and the median CA125 level was 63.3 IU/mL. A mere 57.6% of cases involving ovarian clear cell carcinoma (OCCC) display elevated levels of CA 125, suggesting that CA 125 is an unreliable marker due to its mildly increased baseline value and the frequent occurrence of false-negative outcomes [18-20]. Nevertheless, CA-125 levels can serve as a useful tool in predicting advanced stage disease, suboptimal debulking, and platinum-resistance by utilizing specific threshold values: ≥ 46.5 U/mL, ≥ 11.45 U/mL, and ≥ 66.4 U/mL [21]. The identification of potential biomarkers for the detection of OCCC is crucial, and two promising candidates are hepatocyte nuclear factor 1β (HNF1β) and left-right determination factor (LEFTY). Tsuchiya et al. demonstrated for the first time that HNF1β was positively detected in the cells of 95% of patients with OCCC [22]. HNF1β is now used as a diagnostic marker to predict ovarian histological subtypes [23]. Left-right determination factor (LEFTY), a novel member of the transforming growth factor-β

Volume 6, Issue 6; November-December 2023; Page No 81-93

superfamily, demonstrates great potential as a molecular marker specifically for OCCC as it exhibits significantly higher expression levels in OCCC when compared to other subtypes of EOC [24].

According to the NCCN guidelines (version 1.2020), the primary therapeutic approach is standard staging surgery or optimal cytoreduction in combination with systemic chemotherapy. In our study, all patients underwent a primary standard staging surgery consisting of total hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, omentectomy, and peritoneal biopsies from multiple random or suspicious areas followed by a combination of platinum plus paclitaxel-based chemotherapy. This comprehensive surgical approach aims to achieve optimal staging and debulking of the tumor. The preferred postoperative systemic therapy regimens include paclitaxel, carboplatin and bevacizumab. However, the use of bevacizumab as first-line chemotherapy for OCCC is still a matter of controversy and requires further validation through global clinical trials to achieve personalized medicine for rare tumors [2].

The management of OCCCs poses several challenges due to its unique characteristics. OCCCs are generally considered less responsive to conventional platinum-based chemotherapy regimens compared to other histological subtypes. The identification of novel therapeutic targets in OCCC, including the ARID1A gene, downstream pathways of receptor tyrosine kinases, angiogenesis, and HNF1β, opens up new avenues for personalized treatment approaches [2]. Further research and clinical trials are needed to evaluate the efficacy of these targeted therapies and their combinations in OCCC patients.

Several sequencing analyses have been conducted in OCCC, providing insights into gene alterations. The most frequently observed gene alterations involve the AT-rich interaction domain 1A (ARID1A) and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (PIK3CA) genes, occurring in approximately 50% of cases. ARID1A is a key component of the SWI/SNF chromatin remodeling complex, which regulates gene expression related to multiple tumorigenesis pathways. Additionally, mutations in ARID1B and SMARCA4 genes affect the SWI/SNF chromatin remodeling complex. PIK3CA encodes the catalytic subunit p110α of phosphatidylinositol 3-kinase (PI3K), and its somatic mutation leads to increased PI3K activity and activation of the downstream AKT pathway. Other genetic changes affecting the PI3K/AKT pathway include mutations in PIK3R1, PTEN, and amplification of AKT2. Interestingly, an association has been observed between loss of ARID1A expression and activation of the PI3K/AKT pathway in clear cell carcinoma [25].

Alterations in the mitogen-activated protein kinases (MAPK) pathway have also been reported, such as mutations in PPP2R1A and KRAS, and amplification of ERBB2 and MET. OCCCs usually express wild-type p53 protein and have a lower frequency of BRCA1 and BRCA2 mutations. Telomerase reverse transcriptase (TERT) promoter mutation is more common in OCCC when compared to other histological types of epithelial ovarian cancer [25].

OCCCs can be classified into subgroups based on mutational signatures, including C-APOBEC and C-AGE. The APOBEC mutational process has been proposed as a therapeutic target. Copy-number alterations in OCCC are distinct from low-grade serous carcinoma and high-grade serous carcinoma. The most significant copy-number gain is observed at chr20q13.2, which includes the potential oncogene ZNF217. Transcriptomic analyses have identified unique expression profiles for OCCC, including upregulation of HNF1β and oxidative stress-related genes. These analyses have also revealed different gene transcriptomic subtypes associated with differential outcomes [25].

Histopathologically, the tumors show a mixture of patterns comprising of solid, papillary, cystic or glandular architecture of clear cells. Mitotic activity is low when compared to other EOCs and this might be the reason why these tumors are not responsive to the conventional chemotherapeutic drugs [26]. These tumors have to be differentiated from other EOCs with clear cell component, yolk sac tumors, dysgerminoma, Krukenberg tumor and metastatic clear cell renal cell carcinoma. A thorough clinical information of these cases will differentiate these tumors from dysgerminoma, Krukenberg tumor and metastatic renal cell carcinoma. Yolk sac tumors usually have a raised serum alpha fetoprotein (AFP). Histologically, these tumors also display distinctive

Volume 6, Issue 6; November-December 2023; Page No 81-93

features including prominent reticular patterns and Schiller-Duval bodies. Negative staining for AFP is useful for excluding yolk sac tumors. The closest differential of OCCCs is EOCs with a clear cell component. OCCC is characterized by the presence of napsin A and hepatocyte nuclear factor 1-beta (HNF1β), while it lacks Wilms tumor 1 (WT1) and estrogen receptor (ER). On the other hand, high-grade serous carcinoma displays the opposite immunoprofile, and endometrioid carcinoma is negative for napsin A and WT1 but positive for ER [27-29].

OCCCs tends to present at earlier stages partly due to the fact that they present with large abdominal masses, with 59–71% of all patients presenting with FIGO stage I and II diseases [30-32]. Endometriosis-associated OCCC tends to occur more frequently in younger women who are often nulliparous. It is typically diagnosed at an early stage, and these patients exhibit greater sensitivity to platinum-based chemotherapy regimens and longer overall survival and progression-free survival. It is noteworthy that the difference in survival outcomes, although not substantial overall, is significantly better in stage I cases. The endometriosis group also exhibits a higher percentage of stage I disease (70.9% vs. 32.1%). This observation leads to a hypothesis that the improved survival outcome in endometriosis-associated OCCC can be primarily attributed to the higher proportion of patients being diagnosed at an early stage. This may be due to the fact that patients with endometriosis commonly experience symptoms such as dysmenorrhea, dyspareunia, and/or pelvic mass, prompting them to seek medical attention and resulting in early detection of endometriosis-associated OCCC [4].

Our study has several limitations. Firstly, it is based on a small sample size from a single tertiary care center, which may limit the generalizability of the findings. Larger multicenter studies with longer study periods are required to validate our results and provide a more comprehensive understanding of OCCCs. Secondly, the retrospective nature of the study due the rarity of this tumor introduces inherent biases and limitations in data collection. Prospective studies with standardized protocols would provide more robust and reliable data. Additionally, the lack of long-term follow-up data in our study limits our ability to comment on patient outcomes and survival rates.

Conclusion:

OCCC continues to be enigmatic with its unique biological and clinical behavior with numerous issues to be resolved. The need of the hour is to understand the developmental origins, pathogenic mechanisms and molecular alterations of this tumor based on which novel diagnostic biomarkers and an optimum chemotherapeutic regimen can be developed to improve the survival of these patients.

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Volume 6, Issue 6; November-December 2023; Page No 81-93

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Volume 6, Issue 6; November-December 2023; Page No 81-93

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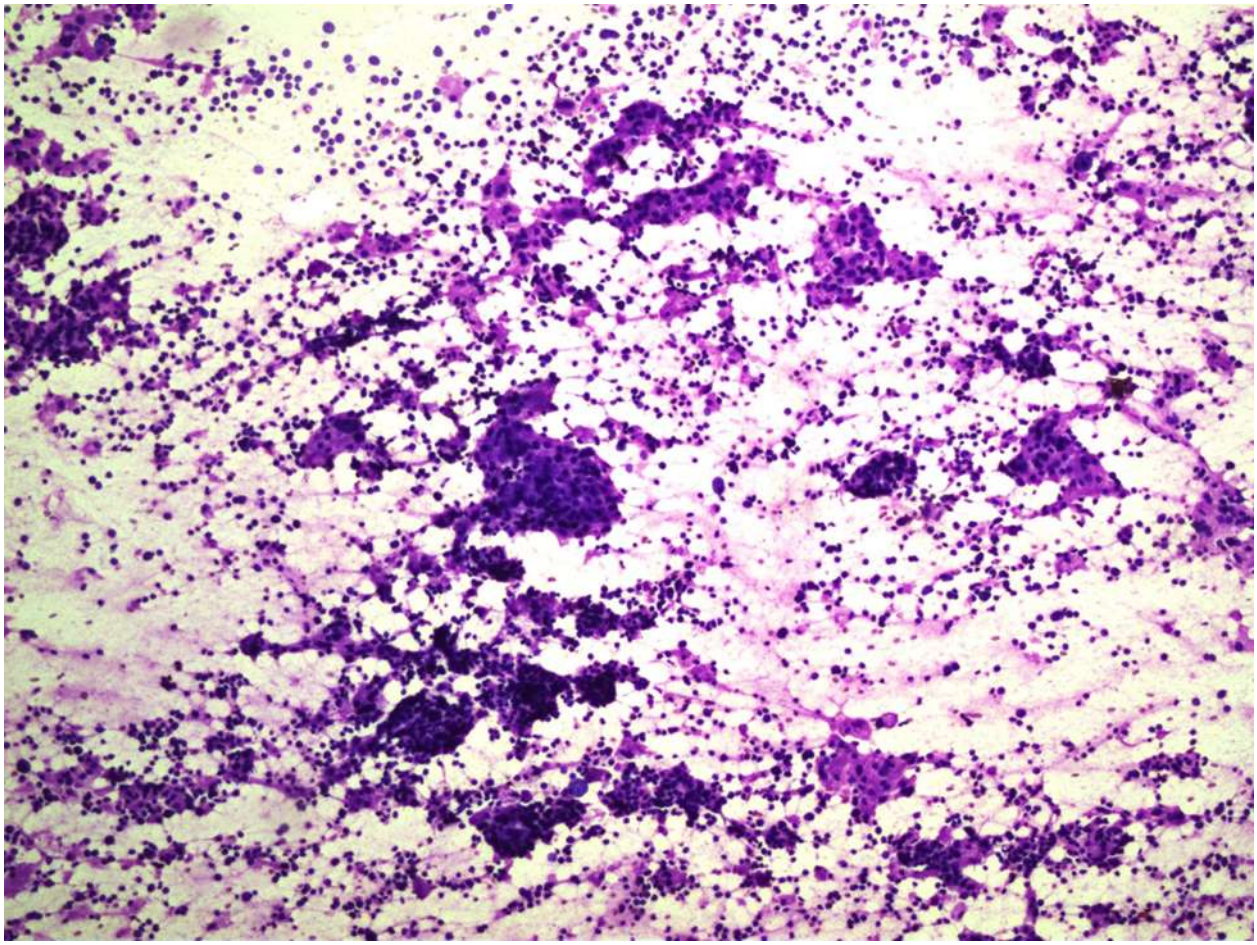
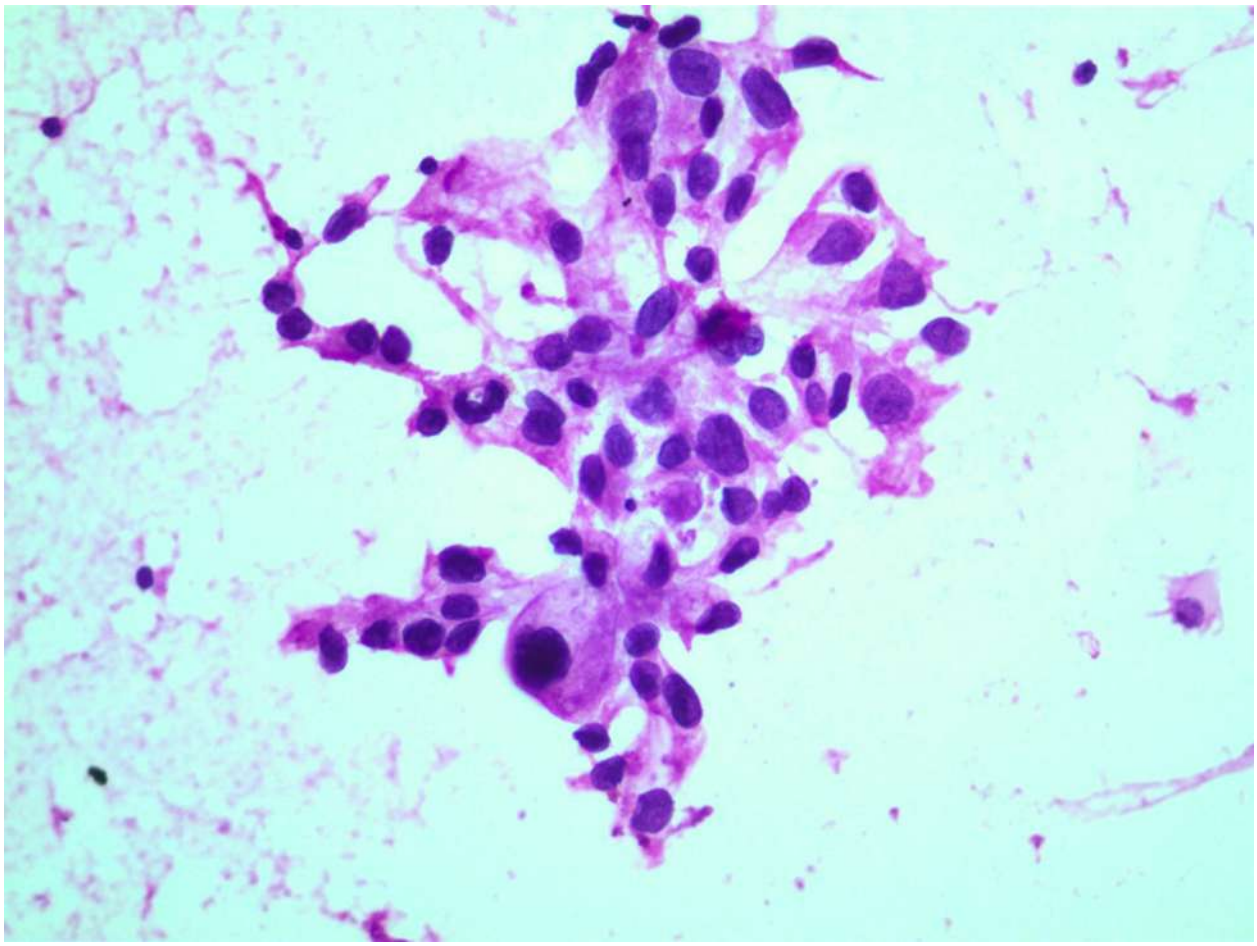
Figure 1: Squash cytology - Cellular smears show tight clusters, loose clusters as well as dispersed epithelial cells. [H&E, X100]



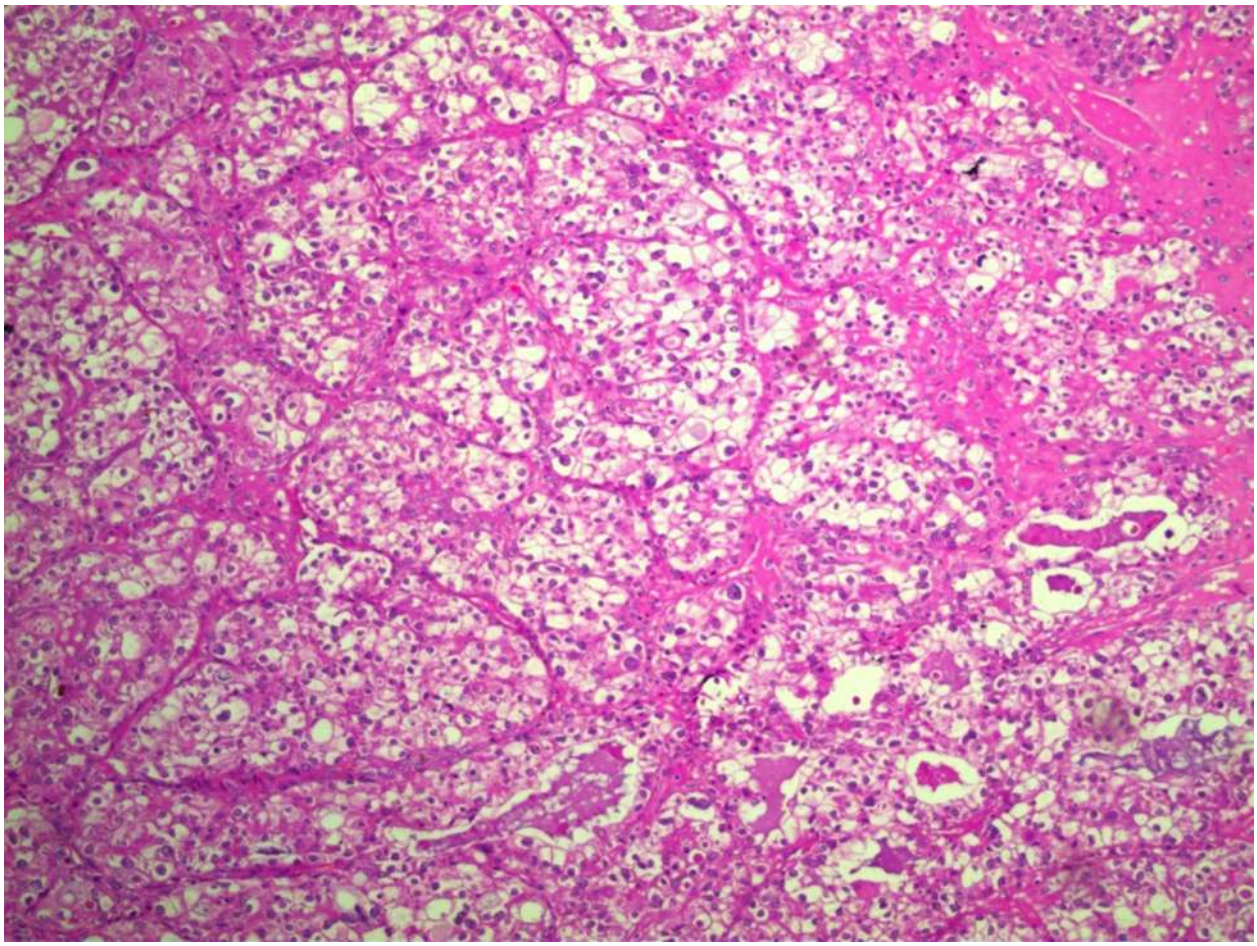
Volume 6, Issue 6; November-December 2023; Page No 81-93

Figure 2: Squash cytology - A papillae of large epithelial cells with individual tumor cells showing central pleomorphic nuclei with fine chromatin and abundant eosinophilic cytoplasm [H&E, X400]



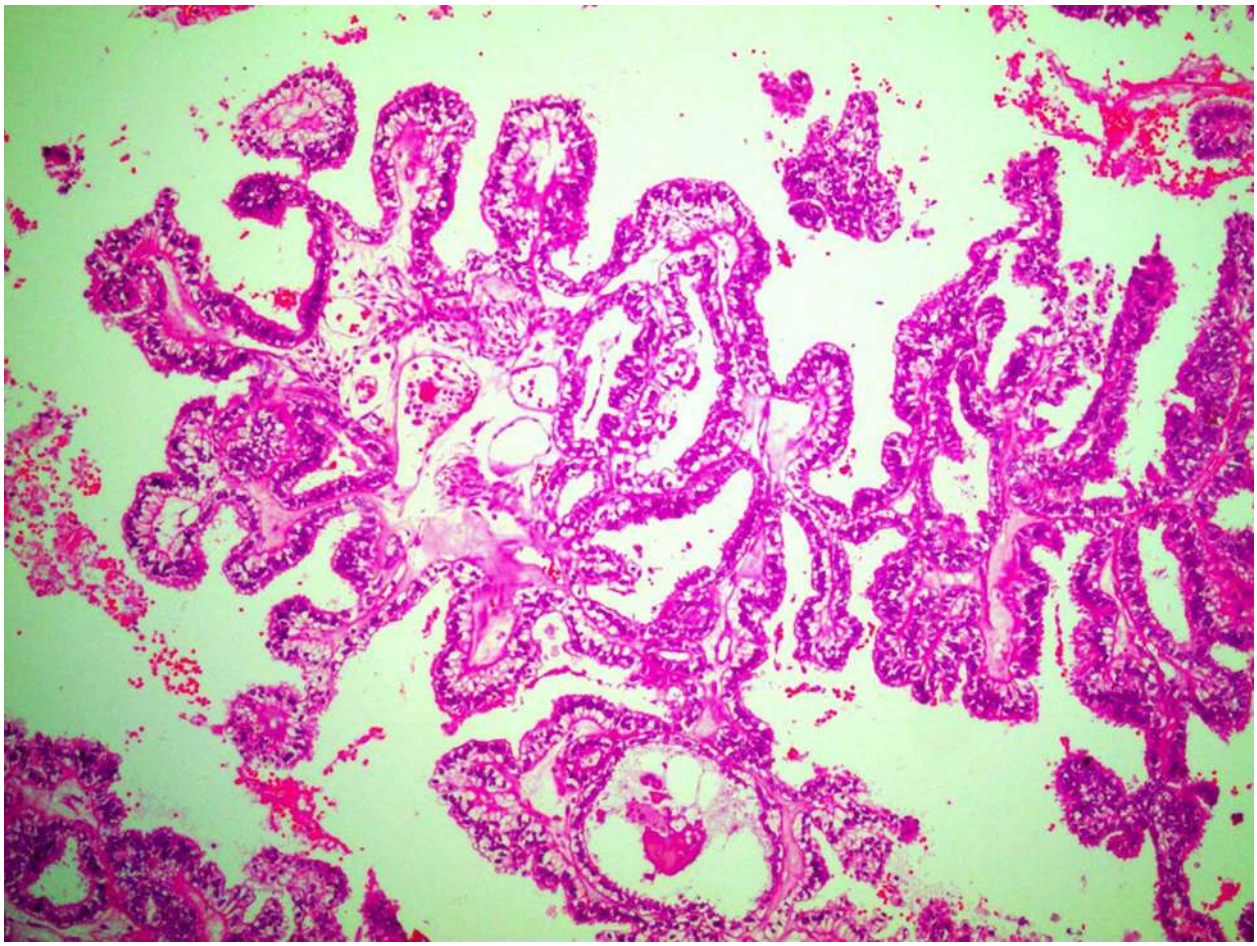
Volume 6, Issue 6; November-December 2023; Page No 81-93

Figure 3a: Tumor exhibiting solid pattern with diffuse sheets of polygonal cells separated by delicate fibro vascular septa showing abundant clear cytoplasm [H&E, X100]



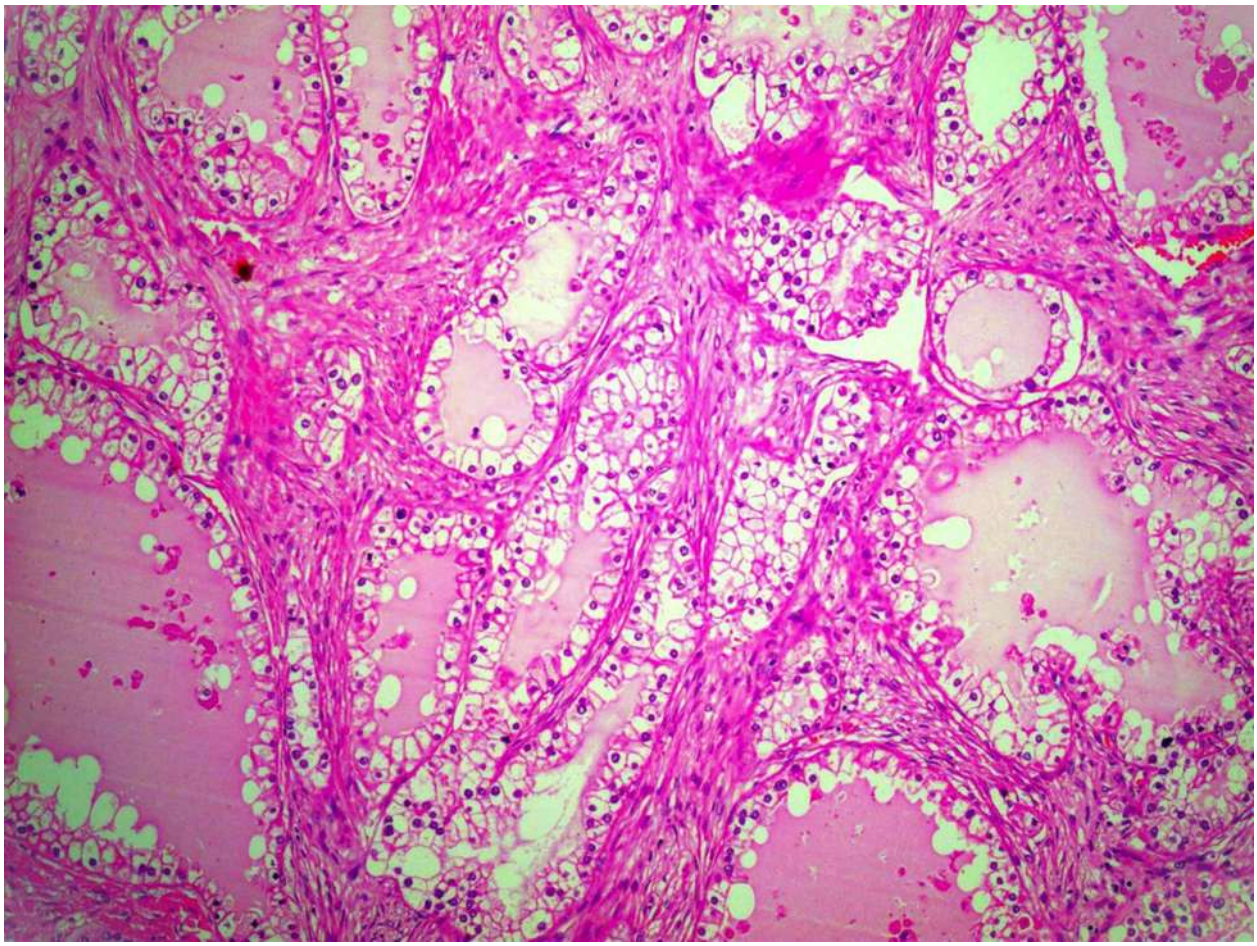
Volume 6, Issue 6; November-December 2023; Page No 81-93

Figure 3b: Tumor exhibiting papillary pattern with nonbranching papillae lined by columnar cells [H&E, X100]



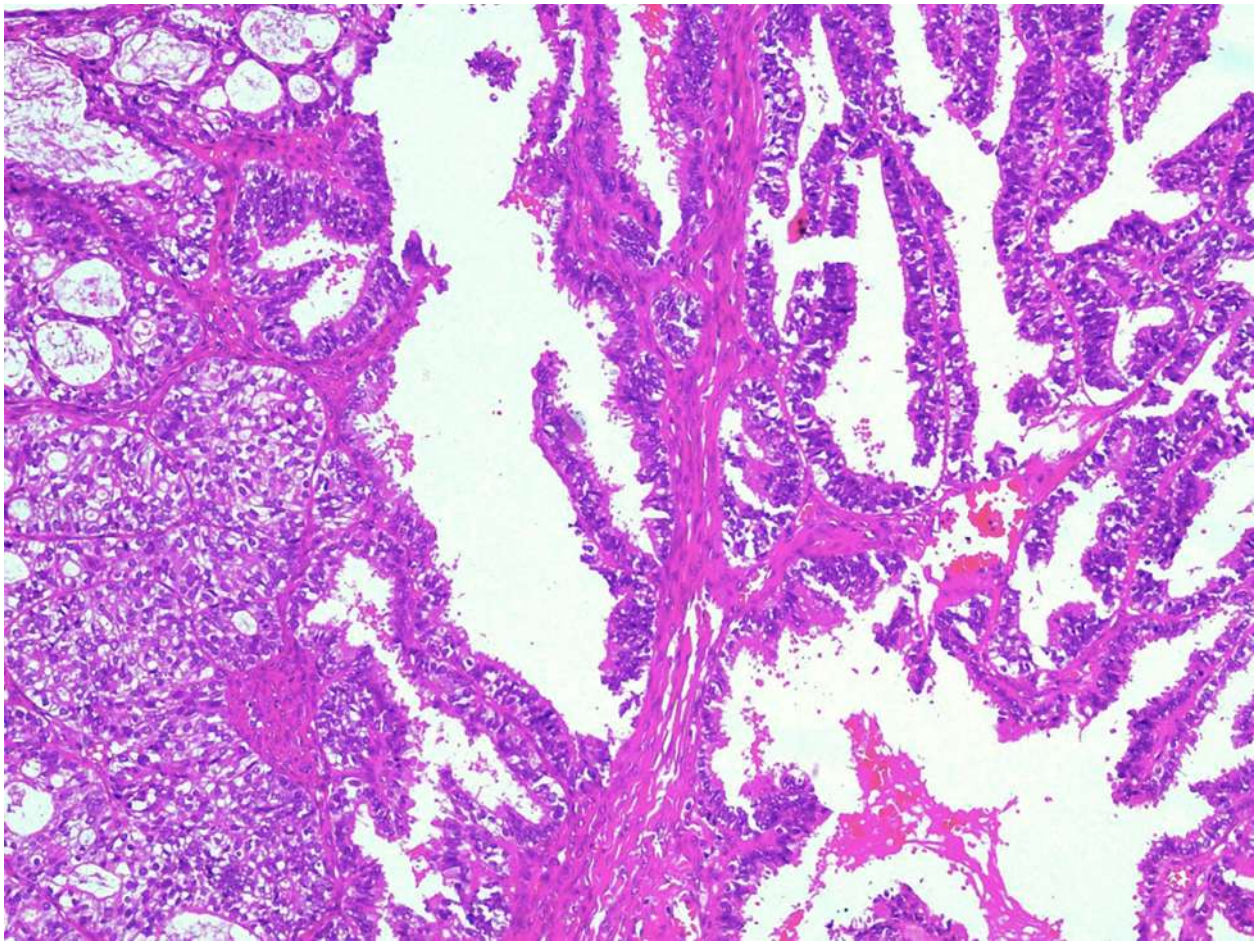
Volume 6, Issue 6; November-December 2023; Page No 81-93

Figure 3c: Tumor exhibiting tubulocystic pattern showing variably sized tubules and cysts, with intraluminal eosinophilic secretions, lined by a single layer of cuboidal or hobnail cells [H&E, X100]



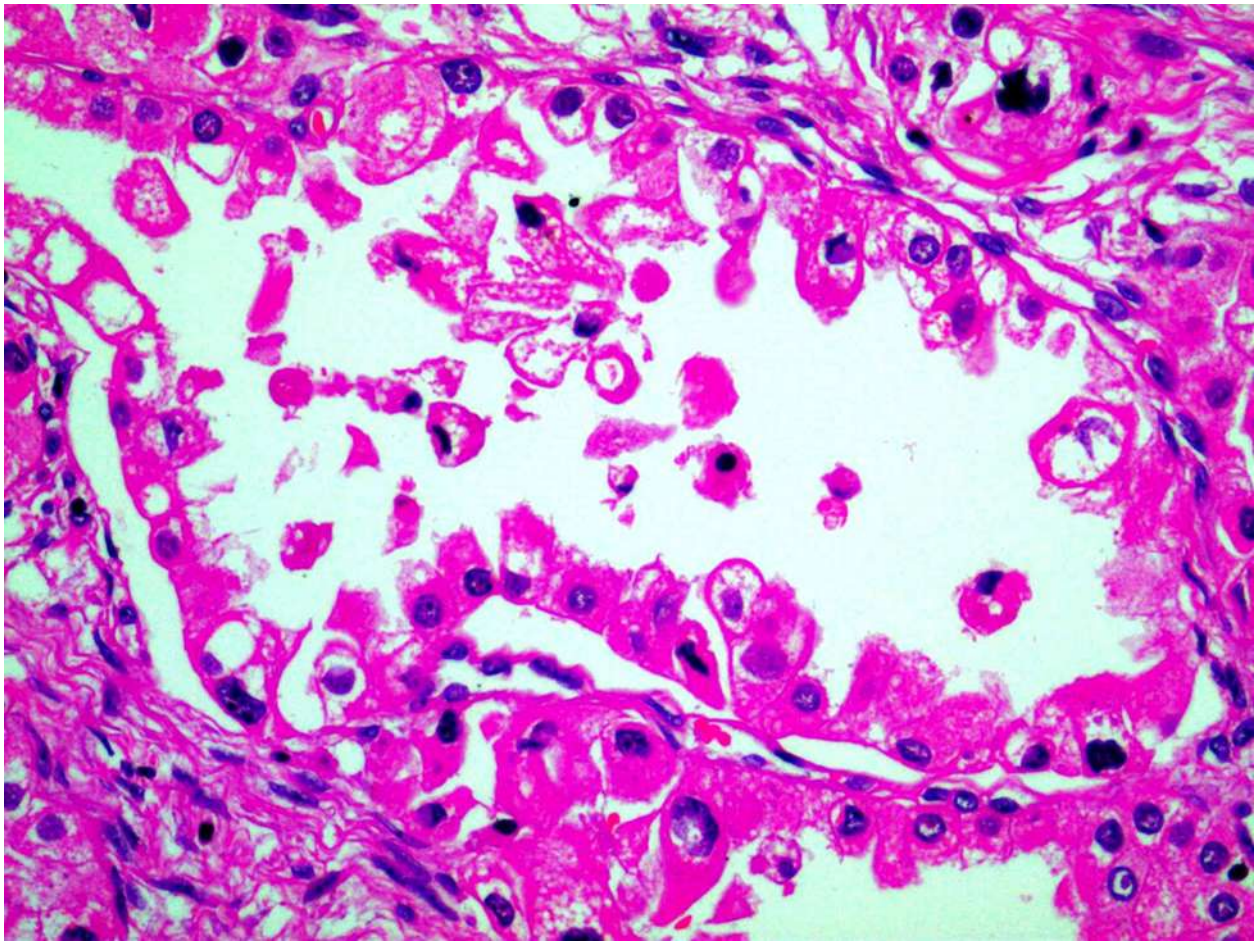
Volume 6, Issue 6; November-December 2023; Page No 81-93

Figure 3d: Tumor exhibiting both tubulocystic (left) and papillary (right) pattern [H&E, X100]



Volume 6, Issue 6; November-December 2023; Page No 81-93

Figure 4: Tumor showing cysts lined by hobnail cells which are large columnar cells with clear to eosinophilic cytoplasm and having hyperchromatic bulbous apical nuclei protruding into the lumen [H&E, X400]



Volume 6, Issue 6; November-December 2023; Page No 81-93