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CLEAR CELL ADENOCARCINOMAS OF THE OVARY– AN INTERESTING CASE SERIES

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ABSTRACT

Clear cell adenocarcinomas of the ovary account for less than 5% of all ovarian carcinomas (David S P Tan and Stan Kaye, 2007). They constitute approximately 3.7–12.1% of all epithelial ovarian carcinomas. A retrospective study was conducted on all the ovarian carcinomas received in the Department of Pathology, Sri Ramachandra Medical College and Research Institute for the past 3 years. Of the total 53 cases of epithelial ovarian carcinomas, all the Clear Cell Carcinomas (CCC) were identified. The clinico pathological parameters were noted from the case records. The histological and immunohistochemical features were reviewed and analysed. There were four cases of ovarian clear cell carcinomas (7.5%) among all the epithelial tumors. The median age group was 42-65years. Two cases (50%) had associated endometriosis. The slides were reviewed and the characteristic histopathological appearance of large cells with hobnailing and abundant clear cytoplasm was noted. Immunohistochemical workup done in two cases were also reviewed.

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INTRODUCTION

Clear cell carcinoma of the ovary is a rare tumor and accounts for <5%of all ovarian malignancies. Among the epithelial carcinomas of the ovary it constitutes about 3.7-12.1%. In advanced stages they have a poor prognosis compared to other epithelial ovarian tumors. But in early stages they have a comparatively better prognosis (David S P Tan and Stan Kaye, 2007). Histological types like clear cell carcinoma (CCC) and mucinous adenocarcinoma are histological variants which are considered as reliable criteria in predicting the ineffectiveness of chemotherapy (Takano *et al*., 2006). Recent studies have revealed mutations in PIK3CA, ARID1A and loss of PTEN in clear cell adenocarcinomas (Toru Sugiyama *et al*., 2000). Hence identification of these rare tumors is of great importance as they may be potential candidates for targeted therapy since prognosis is good in the early stages and hence early detection of these tumors is helpful for the patient (David S P Tan and Stan Kaye, 2007; Takano *et al*., 2006 and Toru Sugiyama *et al*., 2000).

MATERIALS AND METHODS

This retrospective study consisted of all patients who presented with epithelial ovarian tumors from January 2012 till March 2014 in the Department of Pathology, Sri Ramachandra University & Research Institute. A total of 53 cases of epithelial ovarian carcinomas were reported, among which 4 cases were clear cell carcinoma. The slides were retrieved, reassessed and the diagnosis was confirmed on the basis of histopathological features and immunohistochemical markers. Complete baseline and follow-up data were collected using the hospital records.

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RESULTS

Out of the 53 epithelial malignancies evaluated, 37 cases were serous carcinomas followed by 7cases of endometrioid carcinomas. 4 cases (7.5%) were found to be clear cell carcinoma ovary [Table 1]. The age range of these patients were between 42 – 65 years with a median age of 49.25 years. All the four patients had disease on the right side. Bilaterality was not seen in any of these cases. The mean size of the tumor was 8.2 cm (ranging from 3-18cm). An association with endometriosis was found in 2 out of 4 cases (50%). Radiologically they were visualised as large hypodense lesions with cystic and solid areas (Figure1). Grossly two of the four cases presented as cystic lesions and other two (50%) had cystic and solid components. On hematoxylin and eosin stained sections they were predominantly arranged in a tubular pattern (Figure 2) and had the characteristic hob nailed cells with abundant clear cytoplasm lining the tubules (Figure 3). Immunohistochemical workup for EMA (Figure4), P53, Ki67

Table 1.Table showing the distribution of the epithelial malignancies

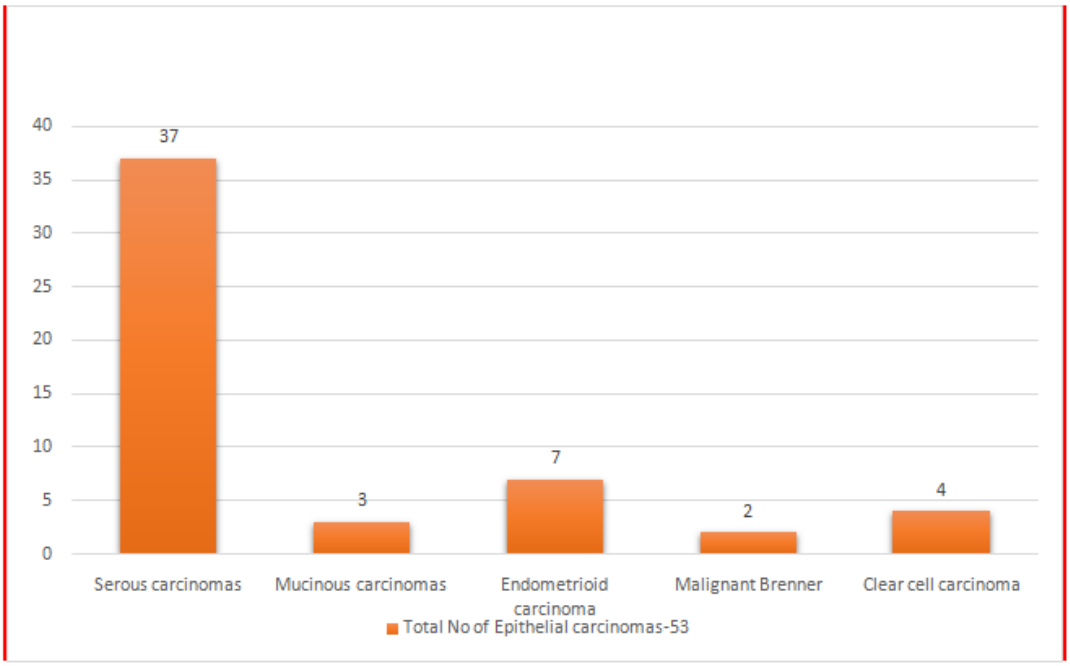

Table 2.Table showing the histopathological profile of the four cases of clear cell carcinomas

S.no	Age	Site	Gross details	Histopathology Diagnosis	Assosiation with Endometriosis	IHC	Follow up
1.	42	Right ovary	Cystic lesion (M)9x6x7.3cm	pT1a Nx cM0 clear cell carcinoma	No	EMA+ P53-focal + Ki67-70%	Chemo Therapy
2.	47	Right ovary	Solid lesion with cystic component (M)12x5x2cm	pT3a Nx Cm0 Clear cell carcinoma	Yes	CD10+ ER,PR,Inhibin,CD 34, CD117-	Chemotherapy
3.	65	Right ovary	Solid lesion with cystic component (M)10x7x5cm	pT3a Nx Cmo Clear cell carcinoma	Yes	Not done	Chemo Therapy
4.	43	Right ovary	Cystic lesion (M)5x3x2cm	pT1a Nx Cmo Clear cell carcinoma	No	Not done	Lost to follow up

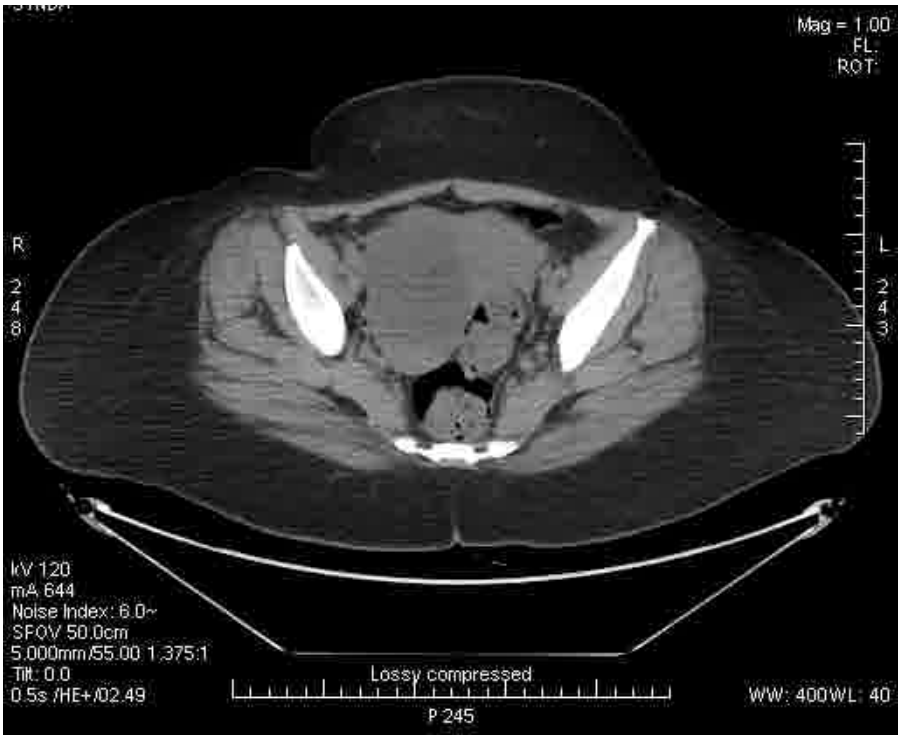

Figure1. Large Hypodense lesion abutting the wall of uterus

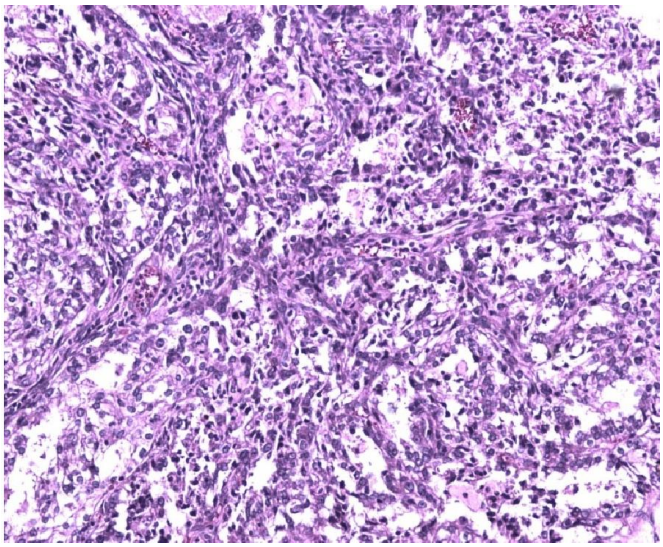

Figure 2. H&E 40x -Tumor cells arranged in a tubular pattern

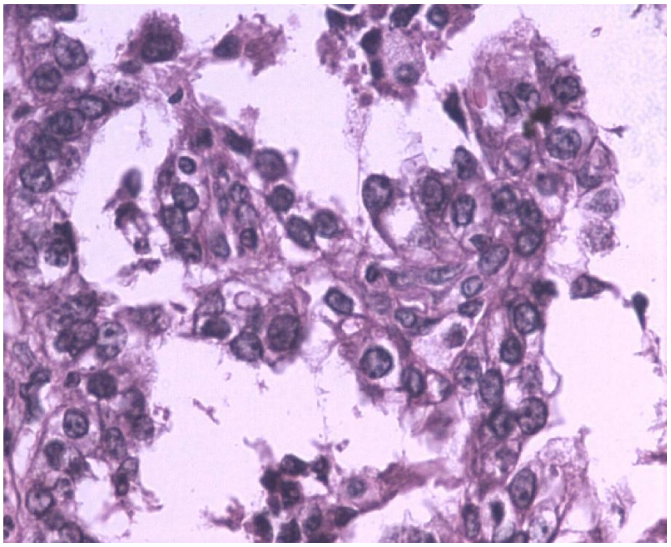

Figure 3. H&E 400x -Tumor cells with Clearing & Hobnailing

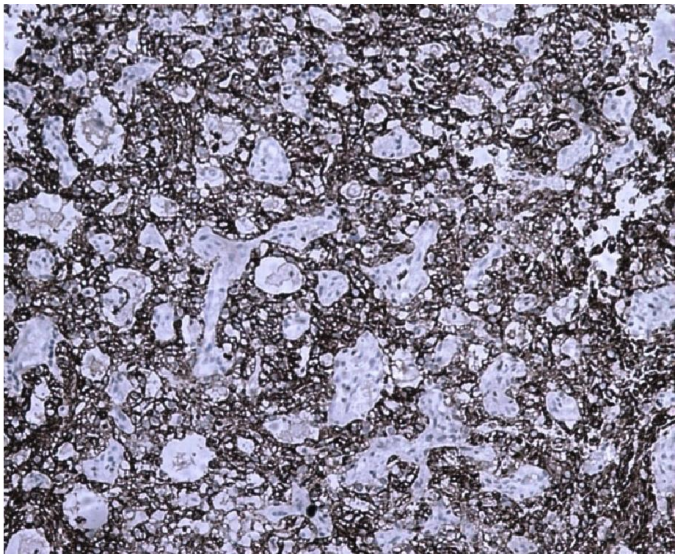

Figure 4. IHC 100x -EMA Positive

was done in one case and CD117,CD10,ER,PR,Inhibin,and CD34 in another case as an ancillary study to rule out the other differentials [Table2]. Metastasis was not seen in any of the cases. Chemotherapy was the main stay of therapy in three cases and follow up of the patient was lost in one case.

DISCUSSION

Clear cell carcinoma was called as mesonephroma in 1939. In 1973 World Health Organisation recognised it as a specific entity. Recent evidence to support the different clinical behaviour of clear cell ovarian carcinomas from other epithelial ovarian carcinomas are that it usually presents as a large pelvic mass, Bilaterallity is very rare, Endometriosis is often associated with it. It is usually accompanied by thromboembolic complications. High frequency of hypercalcemia has been observed (Takano *et al*., 2006; Toru Sugiyama *et al*., 2000 and Chengquan Zhao *et al*., 2011). Our study suggests that clear cell carcinomas of the ovary constitute 4% of epithelial carcinomas which is in concordance with data given in literature (David S P Tan and Stan Kaye, 2007). The mean age group of the patients in our study was 49.25. In a study done by Takano *et al* the mean age group was 52.4yrs (Takano *et al*., 2006). Most of our patients were less than 60 yrs which is considered a poor prognostic factor (David S P Tan and Stan Kaye, 2007). Two out of our four cases were associated with endometriosis.

In a study done by David SP Tan *et al* 25-58% of cases of clear cell carcinomas of the ovary were associated with endometriosis (Toru Sugiyama *et al*., 2000). Two of our cases were Figo stage Ia and other two cases were Figo stage 3a.In a study by M Takano *et al* 13% of their cases were Figo stage Ia, 36% were Figo stage Ic,13% were Figo stage II,31% were Figo stage 111,6% were Figo stage IV (Takano *et al*., 2006). Clear cell ovarian carcinomas are usually high grade tumors. Nulliparity is proposed to be a risk factor for ovarian clear cell adenocarcinoma. Grossly they usually present as a cystic lesion with solid areas. Histopathologically they are composed of large cells that are cuboidal, hob nailed or flattened with abundant clear cytoplasm usually lining tubules and cysts arranged in solid, tubular or glandular patterns. Oncocytic variant of clear cell ovarian carcinoma have also been reported. Immmunohistochemically they stain strongly and diffusely for keratins, epithelial membrane antigen, Leu M1, BAX, P21, cyclin E and B72.3. The differential diagnosis includes germ cell tumours, particularly yolk sac tumour and dysgerminoma.

The poor prognostic factors for ovarian clear cell adenocarcinoma include younger age (<60yrs), advanced stage of presentation, the presence of vascular invasion. The good prognostic factors are the presence of tubulocystic or papillary morphological pattern (David S P Tan and Stan Kaye, 2007; Takano *et al*., 2006). Pathogenesis of ovarian clear cell carcinoma has been proposed that endometriosis is the underlying precursor for the cystic and the adenofibromatous types of clear cell ovarian carcinoma. There are two pathways involved in the pathogenesis of ovarian clear cell carcinoma. One is the endometriotic cyst pathway and the other is the adenofibromatous pathway. In the cystic pathway endometriosis forms an endometriotic cyst which develops atypia and finally turns into clear cell carcinoma. In the adenofibromatous pathway there is a fibromatous reaction along with endometriosis which causes the formation of clear

cell adenofibroma which progresses to borderline clear cell tumor and finally results in the formation of clear cell carcinoma (Chengquan Zhao *et al*., 2011). Clear cell carcinomas have also been found to arise from mucinous lesion. Cases have been reported in which clear cell carcinoma arose from mucinous cystadenoma (Dutt and Berney, 2000).

A lot of work on the molecular aspect of ovarian clear cell carcinomas is under study. The most accepted recent data are as follows: 1) ARID1A mutation is found in 40–57% clear cell carcinoma ovary. The cellular effect is loss of BAF250a, a key component involved in the SWI–SNF chromatin remodelling complex.2) IL6-STAT3-HIF up regulation (IL-6 expression) is seen in 49% cases with the cellular effect of angiogenesis.3) HNF-1b up regulation is almost seen in 100% the cellular mechanism being apoptotic escape.4) TMS/1/ASC methylation (69%). The cellular effect is Apoptotic escape.5) PI3K/AKT/mTOR pathway activation by PTEN loss /PIK3CA mutation /AKT2 amplification.6) PTEN loss (40%), PIK3CA mutation (33%), AKT2 amplification (14%).

The cellular effects are activation of cell cycle progression, Inhibition of apoptosis, Increased cell motility, Impaired homologous recombination (Tan *et al*., 2013). One of the features of ovarian clear cell carcinomas is their tendency to recur. In a study done by M Takano *et al* recurrence was seen in 29% of stage I patients, 30% of stage II patients, 62% of stage III patients, and 73% of stage IV patients (Takano *et al*., 2006). The most common organs to which clear cell carcinomas metastasize are bone, breast and brain (Aalok Kumar *et al*., 2013; Masashi Takano *et al*., 2012; Susana M. Campos and Sue Ghosh, 2010 and Prat, 2012). Recent studies have indicated that inactivation of the PTEN tumor suppressor gene is the early stage of development of clear cell carcinoma ovary (Nakako *et al*., 2000). Early or stage I ovarian clear cell carcinomas have more than 90% 5yr disease free survival (Paul *et al*., 16662).

Conclusion

Clear cell carcinomas of the ovary are rare and histopathology remains the gold standard for indentification of these tumors. Hence prompt and early recognition of these tumors is essential as early stage ovarian clear cell carcinomas have a good prognosis compared to the advanced stages which have poor prognosis

REFERENCES

Aalok Kumar, C. Blake Gilts, Colin Mar. Jennifer Santos, Anna V. Tinker; Patterns of spread of clear cell ovarian cancer: Case report and Case series; *Gynaecologic Oncology Reports* 6 2013: 25–27

Chengquan Zhao, Lee Shu-Fune Wu, Ross Barner. Pathogenesis of Ovarian clear cell adenofibroma, atypical proliferative tumor and carcinoma. *journal of cancer*. 2011; 2:94-106

D S P Tan, R E Miller and S B Kaye; New perspectives on molecular targeted therapy in ovarian clear cell carcinoma. *British Journal of Cancer* 2013; 108:1553–1559.

David S P Tan, Stan Kaye. Ovarian clear cell adenocarcinoma- a continuing enigma. *J Clin Pathol* 2007: 60; 355–360

Dutt, N., D M Berney. Clear cell carcinoma of the ovary arising in a mucinous cystadenoma. *J Clin Pathol* 2000; 53:938–939

Masashi Takano, Hiroshi Tsuda, Toru Sugiama; Clear cell carcinoma of the ovary: Is there a role of histology specific treatment?; *Journal of Experimental & Clinical Cancer Research* 2012; 31:53

Nakako Sato, Hajime Tsunoda, Masato Nishida, Yukio Morishita, Yasuhiko Takimoto, Takeshi Kubo, Masayuki Noguchi; Loss of Heterozygosity on 10q23.3 and Mutation of the Tumor Suppressor Gene PTEN in Benign Endometrial Cyst of the Ovary-Possible Sequence Progression from Benign Endometrial Cyst to Endometrioid Carcinoma and Clear Cell Carcinoma of the Ovary. *Cancer Research* 2000; 60:7052–7056, December

Paul J. Hoskins, Nhu Le, Blake Gilks, Anna Tinker, Jennifer Santos, Frances Wong, and Kenneth D. Swenerton; Low-Stage Ovarian Clear Cell Carcinoma: Population-Based Outcomes in British Columbia, Canada, With Evidence for a Survival Benefit As a Result of Irradiation; *J Clin Oncol* 30:1656-1662.

Prat, J.; New insights into ovarian cancer pathology. *Annals of Oncology* 2012; 20:111- 117.

Susana M. Campos, Sue Ghosh: A Current Review of Targeted Therapeutics for Ovarian Cancer; Volume 2010, Article ID 149362, 11 pages

Takano *et al*. M. Clear cell carcinoma of the ovary- a retrospective multicentre experience of 254 patients with complete surgical staging. *British Journal of Cancer* 2006: 94; 1369–1374.

Toru Sugiyama, M.D, Ph.D.1 Toshiharu Kamura, Junzo Kigawa, Naoki Terakawa, Yoshihiro Kikuchi, Tunekazu Kita, Mitsuaki Suzuki, Ikuo Sato, Kouji Taguchi. Clinical Characteristics of Clear Cell Carcinoma of the Ovary. *Cancer* 2000: 88; 2584–9.

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