Case Report

A rare histomorphological coexistence of clear cell carcinoma and mucinous cystadenoma of the ovary in a young female with brief review of literature

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Abstract

Concomitant clear cell carcinoma of the ovary and mucinous cystadenoma of the ovary in the absence of endometriosis are rare entities with very few cases cited in the literature. They pose diagnostic challenge as the differential diagnosis spans from germ cell tumor, sex cord stromal tumor, and other surface epithelial tumors. The various types of tumors have different prognosis and varied treatment protocols. The presence of advanced stage and paraneoplastic syndrome has been associated with poor prognosis. We present a case of a 35-year-old female who presented with complaints of abdominal distension and discomfort for the past 2 months. The patient underwent right-sided oophorectomy in 2016 which was diagnosed as mucinous cystadenoma. The radiological evaluation revealed an enlarged left ovary with solid cystic areas. CA-125 was marginally raised. Oophorectomy with hysterectomy was done. Histopathology showed an unusual combination of clear cell carcinoma with mucinous cystadenoma. There was no endometriosis although omental metastasis was noted. The finding was confirmed on immunohistochemistry. The occurrence of clear cell carcinoma with mucinous cystadenoma in the absence of endometriosis is extremely uncommon with very few literature studies available.

Keywords: Clear cell carcinoma, endometriosis, hepatocyte nuclear factor-1 beta, immunohistochemistry, mucinous cystadenoma, napsin A

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INTRODUCTION

Clear cell carcinoma was first described in 1939 by Schiller.[1] Clear cell carcinoma is relatively a rare tumor comprising 2.4% of all ovarian epithelial neoplasms.[2] Most clear cell tumors are malignant, but benign and borderline clear cell tumors also occur. They are usually occur at 55 years of age.[3] They are known to be the most common ovarian epithelial tumor associated with paraneoplastic hypercalcemia.[4] They have unfavorable histological type and poor prognosis. Stated below is a present case of a young female having rare coexistence of clear cell carcinoma of the ovary with mucinous cystadenoma with brief review of literature.

CASE REPORT

A 35-year-old female presented with abdominal pain and distension. Her history revealed right-sided oophorectomy

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which was done 2 years back, diagnosed as mucinous cystadenoma. The present contrast-enhanced computed tomographic (CECT) findings showed a left ovarian mass measuring 5 cm × 3.5 cm × 2.5 cm with solid cystic areas and suspicious mitotic activity. CEA and CA-125 were marginally raised (69 μg/ml). It was decided to perform hysterectomy with unilateral salpingo-oophorectomy and omentectomy.

On gross examination, left ovary showed intact capsule with nodular outer surface. The cut surface was solid cystic. The solid area was gray-white and necrotic. The cyst was smooth walled and filled with mucinous fluid. On histopathological examination, tumor cells were found to be arranged in the tubulocystic and papillary pattern. Cells have abundant clear-to-fine granular cytoplasm with irregular chromatin and inconspicuous nucleoli. A focus of mucinous cystadenoma was seen away from the tumor with normal ovarian stroma in between, but no evidence of endometriosis was identified [Figure 1]. Necrosis along with lymphovascular and perineural invasion was seen. Mucicarmine and PAS stain showed intraluminal and apical membrane staining, but no intracytoplasmic staining was seen. Immunohistochemical profile showed expression of CK, CK7, napsin A, and EMA in the tumor cells and immunonegative for glypican, SALL4, RCC, P53, WT1, and ER [Figures 2 and 3]. On the basis of morphology and immunohistochemistry, diagnosis of clear cell carcinoma was made. Omentum also showed metastatic carcinoma. Tumor cells were also present in the outer wall of the myometrium, cervix, and left fallopian tube. Hence, the patient was diagnosed with T3 staging.

DISCUSSION

Clear cell carcinoma is a rare ovarian epithelial neoplasm. Initially, it was thought to be mesonephric in origin; however, due to ultrastructural similarities with Mullerian epithelium, its epithelial origin is now established.

The mean age of presentation is 55 years in clear cell carcinoma.[3] In previously reported cases of clear cell carcinoma with mucinous lesion by Dutt and Berney,[5] Uddin *et al*.,[6] Wani and Notohara,[7] and Nakamura *et al*.,[8] older age group ranging between 47 and57 years has been associated with these tumors. However, the present case is unique as it was diagnosed at a very young age of 35 years. Similarly, the literature studies have documented large-sized tumors with size 10–30 cm, whereas in our study, the tumor size is 5 cm.

The most common differentials to be kept in mind are yolk sac tumor, metastatic clear cell RCC, and serous adenocarcinoma ovary. Others differentials are dysgerminoma, Krukenberg tumor, and struma ovarii. Differentiating histomorphological features and immunohistochemistry are demonstrated in Table 1.

On immunohistochemical studies, clear cell carcinoma shows positive staining for CK, CK7, EMA, napsin A, PAX8, BerEP4, and vimentin, while ER, PR, WT1, and P53 are usually negative. Hepatocyte nuclear factor-1 beta (HNF-1B) emerged as a sensitive marker for clear cell carcinoma showed nuclear positivity in more than 80% of clear cell carcinomas.[10,11] As HNF-1B was unavailable at our setup, we did not use it.

Napsin A is another sensitive and specific marker for distinguishing ovarian clear cell tumors from other ovarian tumors. It is also not observed in the normal surface epithelium of the ovary, epithelia of the fallopian tubes, squamous epithelium, endocervical epithelium, or endometrium of the uterus and hence is a useful marker.[12]

Associations between clear cell carcinoma and mucinous lesions without endometriosis are very rare. In a rare case published by Dutt and Berney[5] in 2000, they showed a large clear cell carcinoma of the ovary blending imperceptibly with cyst lined by benign mucinous epithelium without evidence of endometriosis. It suggested the origin of clear cell carcinoma in the background of mucinous cystadenoma. However, it was criticized by McCluggage, as they suggested that the mucinous areas represented mucinous metaplasia of the endometriotic cyst of the ovary and not a true mucinous cystadenoma. Later on, Uddin *et al*.[6] in 2007 reported a case where there were

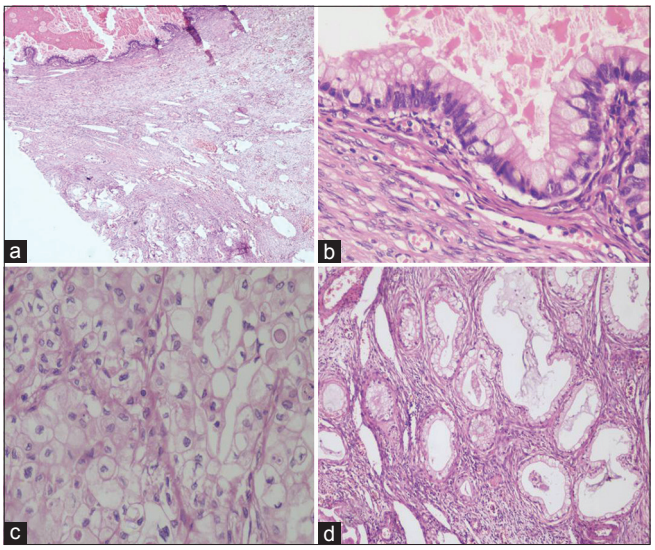

Figure 1: Clear cell carcinoma with mucinous cystadenoma - (a) Ovarian tissue showing clear cell carcinoma with mucinous cystadenoma (H and E, ×10). (b) Area exhibiting lining epithelium of mucinous cystadenoma (×40). (c) Clear cell carcinoma consisting of polygonal cells with clear cytoplasm (×40). (d) Clear cell carcinoma shows tubulocystic patterns (H and E, ×40)

Table 1: Differential diagnosis of clear cell carcinoma of ovary with differentiating histomorphological and immunohistochemistry features

	Yolk sac tumor	Metastatic clear cell RCC	Serous adenocarcinoma ovary	Dysgerminoma	Krukenberg tumor	Struma ovarii
Differentiating hematoxylin and eosin features	Nuclei and papillae of yolk sac tumor are more primitive and lack hyalinized eosinophilic cores in loose edematous background; presence of Schiller-Duval bodies often present in yolk sac tumor is absent in clear cell carcinoma	Do not exhibit hobnail , Typically associated with prominent sinusoidal vascular framework	Irregular thick papillae, More prominent cellular stratification, budding, marked nuclear pleomorphism, high mitotic rate	Cells are not polyhedral, almost always contain lymphocytes	Mucin laden signet ring cells of Krukenberg tumor (clear cell cytoplasm contain glycogen, a feature that can be demonstrated with PAS stain) An intracytoplasmic mucin stain (negative in clear cell carcinoma)	Absence of cytologic atypia and hobnailing
IHC -Immunopositive	AFP, SALL-4, GP-3, HNF-1B (occasionally)	PAX-8, RCC	WT-1, ER, P53	SALL-4, OCT-3/4, PLAP, D2-40, CK7, and EMA focal positive	CK20, CDX-2, GCDFP-15	TTF-1, thyroglobulin
IHC - Immunonegative	EMA, CK7, Leu-M1[9]	CK7, CA-125	HNF-1B	PAX-8, HNF-1B	CK7, CA-125	HNF-1B, napsin-A

IHC: Immunohistochemistry, RCC: Renal cell carcinoma, PAS: Periodic acid-Schiff, HNF-1B: Hepatocyte nuclear factor-1 beta

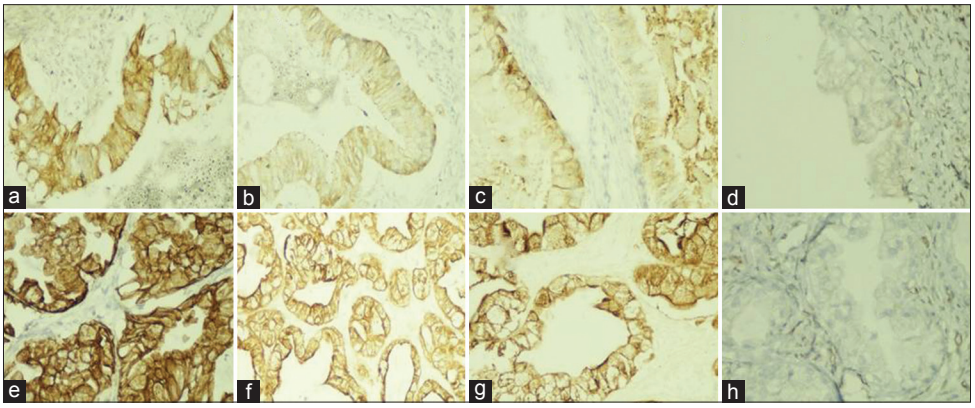

Figure 2: Immunohistochemical study for (a-d) mucinous cystadenoma and (e-g) clear cell carcinoma. Mucinous cystadenoma cells are positive for CK (a), CK7 (b), and EMA (c) and immunonegative for WT1 (d). Clear cell carcinoma cells are immunopositive for CK (e), CK7 (f), and EMA (g) and immunonegative for WT1 (h)

separate foci of mucinous cystadenoma and endometriosis coexisting with areas of clear cell carcinoma. There was no continuity between the areas of endometriosis and mucinous cystadenoma. This finding was supported the study by Dutt and Berney that clear cell carcinoma may arise from mucinous cystadenoma. In 2009, Wani and Notohara[7] also showed, in their case report, the presence of ovarian clear cell carcinoma arising in a mucinous cystadenoma in the absence of demonstrable endometriosis. Apart from this, Allende *et al*.[9] in 2010 also published a case of mural nodules of clear cell carcinoma in an intestinal-type mucinous borderline tumor of the ovary without endometriosis. The studies cited above give ample literature support to belief that clear cell carcinoma arises in the background of mucinous lesion.

Among the various genetic mutations associated with clear cell carcinoma ovary, the most common is *ARID1A* mutation (46%–57%).[13] PIK3CA-activating mutation and PTEN mutation are also seen in these cases. High-grade serous carcinomas are differentiated from clear cell carcinoma by the presence of TP53 mutation mainly and along with BRCA-1, BRCA-2 NOTCH 3, and AKT mutations.

As compared to other epithelial malignancies of the ovary, clear cell carcinoma has unfavorable prognosis in advanced stages and poor response to platinum-based chemotherapy. The case stated above is unique rarity of clear cell carcinoma along with mucinous cyst adenoma in the ovary arising without endometriosis in a young female with small tumor size. The poor prognosis of the tumor carries extremely important for a pathologist to recognize this entity so that appropriate and early treatment is given to the patient.

CONCLUSION

Clear cell carcinoma is very rare to coexist with mucinous cyst adenoma. Most of the cases arise in the background of endometriosis. However, due to limitation of number

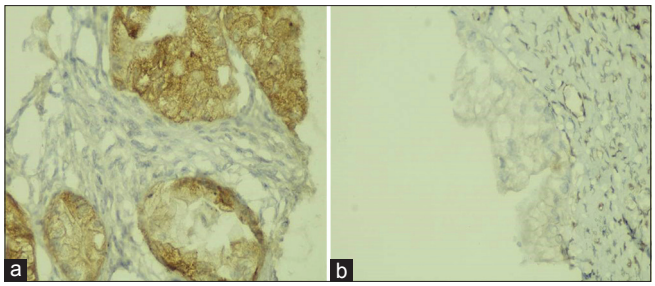

Figure 3: Immunohistochemical study for (a) clear cell carcinoma and (b) mucinous cystadenoma. Clear cell carcinoma showing immunopositivity for napsin A (a). Mucinous cystadenoma showing immunonegativity for napsin A (b)

of reported cases, the origin of clear cell carcinoma from mucinous cystadenoma or endometriosis is not yet proven. The above-stated case also supports this as the clear cell carcinoma and mucinous cystadenoma were coexisting in the ovarian tissue without endometriosis. Clear cell carcinoma has poor response to platinum-based chemotherapy as compared to other epithelial malignancies of the ovary. Prognosis becomes worse as disease progresses into advanced stages.

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Conflicts of interest

There are no conflicts of interest.

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