NYU Langone Health

DEPARTMENT OF PATHOLOGY

Case of the Week

Gynecologic Pathology: Clear cell carcinoma of Ovary

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History

The patient is a 48 year-old woman who 4 months previously had undergone hysterectomy and salpingooophorectomy. She now presents with 3 enlarged supraclavicular lymph nodes. FNA was performed.

Images from prior hysterectomy resection:

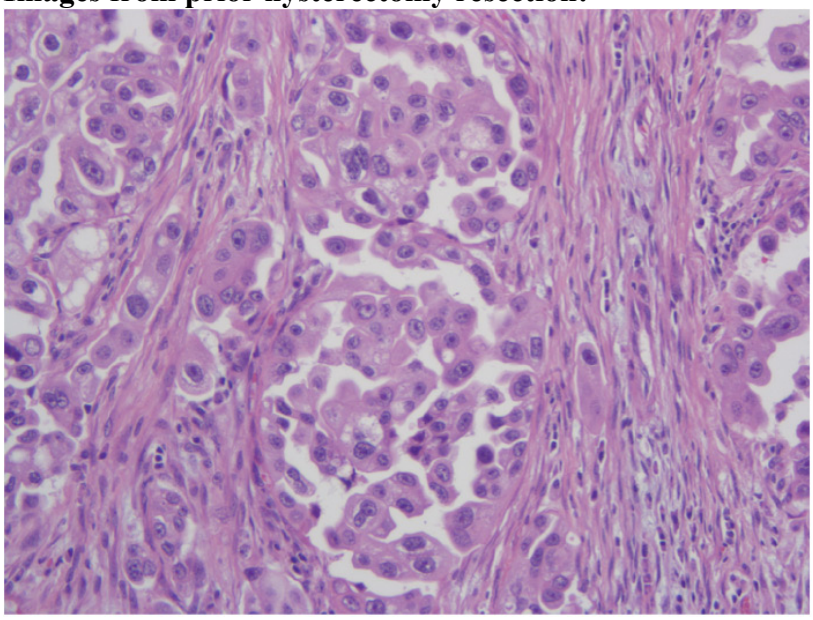

Fig 1.

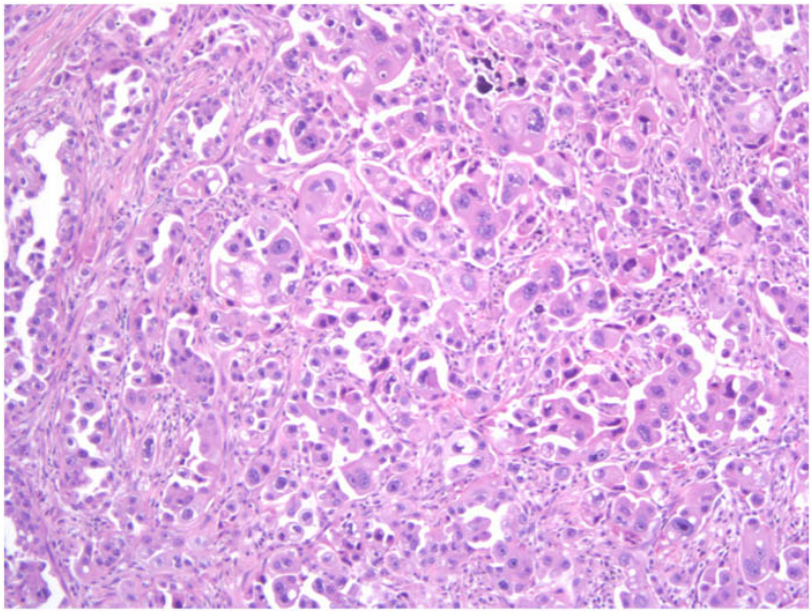

Fig 2.

Figure 1 and 2

Fig. 1 and 2: Clear cell carcinoma of the ovary with invasive implants into uterine serosal surface and myometrium. Fig. 1: H&E stain, 200x magnification: Representative area of clear cell carcinoma with classic hobnail appearance, invading into the uterine serosal surface. Fig. 2: H&E stain, 100x magnification: Area of serous differentiation with marked nuclear

pleomorphism and abundant eosinophilic cytoplasm. This area showed positive reactivity for p53, supporting serous differentiation.

FNA cytology images:

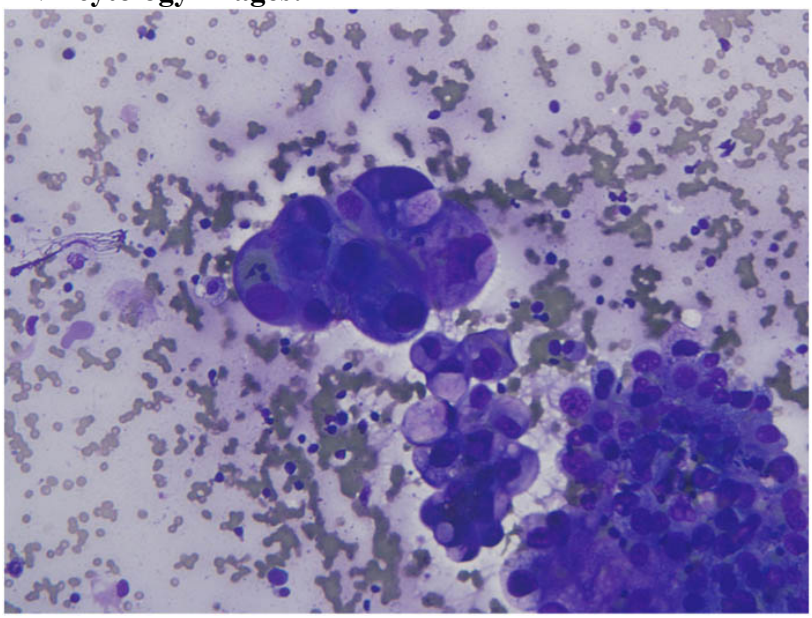

Fig 3.

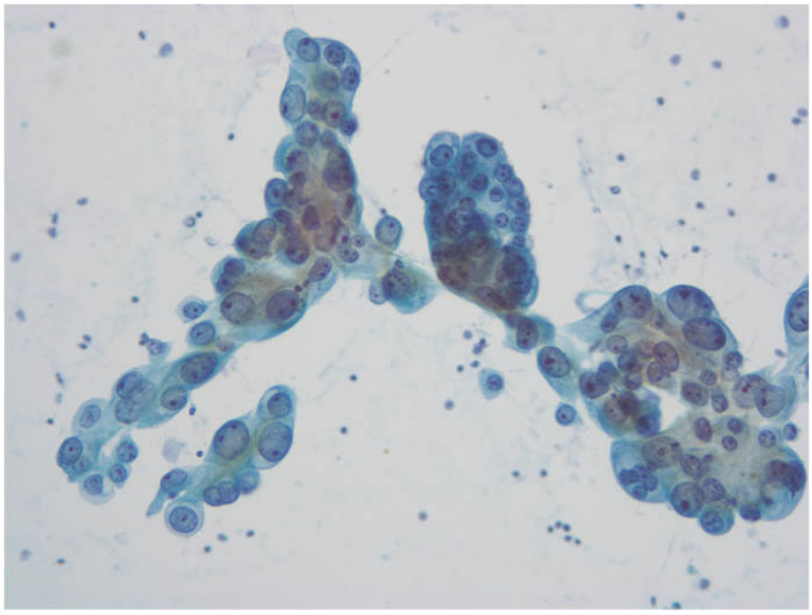

Fig 4.

Figure 3 and 4

Fig. 3 and 4: FNA from supraclavicular lymph node. Fig. 3: Diff Quik Stain, 200x magnification: The FNA smear from the supraclavicular lymph node shows two populations of

tumor cells: the large cohesive cluster of tumor cells showing similar marked nuclear pleomorphism of the serous component and second component of clear cell carcinoma with smaller cuboidal shaped nuclei with vacuolated cytoplasm. Fig 4. Papanicolaou stain, 200x magnification: Dual population of larger pleomorphic serous component (right side) and smaller cluster of cuboidal clear cell carcinoma (center).

Diagnosis

Clear cell carcinoma of Ovary

Discussion

Microscopic findings
Clear cell carcinomas display several different patterns which often occur together. These include papillary, tubulocystic, and solid. The solid pattern of clear cell carcinoma is characterized by sheets of polyhedral cells with abundant, clear cytoplasm separated by fibrovascular septae or dense fibrotic stroma. The papillary pattern is characterized by papillae that can be fibrotic or hyalinized. The tubulocystic pattern is characterized by tubules and cysts of varying size. The majority of tumors display combination of all of these patterns. The cells with clear cytoplasm contain glycogen and at times intracytoplasmic mucinous inclusions. In the tubulocystic and papillary patterns, the cells often have a hobnail appearance, with the nucleus protruding from the papillae, tubule or cyst into the lumen.

Immunohistochemistry
Clear cell ovarian carcinomas stain positive for HNF-1 β and pax8 (Tsuchiya et al). WT1, estrogen receptor, progesterone receptor and p53 are generally negative. Napsin A was recently reported to be expressed in clear cell carcinoma (Yamashita et al.); our case showed positive staining for this marker.

p53 is positive in most high grade serous carcinomas (Chisea-Voterro et al.). For our case, there was p53 staining in the poorly differentiated component (areas with large pleomorphic nuclei), indicating that there is a serous component to this tumor.

Mutations
ARID1A and PIK3CA mutations have recently been identified in ovarian clear cell carcinoma (Yamamoto, S. et al.) ARID1A is a tumor-supressor gene and its mutation in ovarian clear cell carcinoma is associated with loss of protein expression. PIK3CA gene encodes the catalytic subunit p110a of phosphatidylinositol-3 kinases (PI3K). Its activating mutation often coexists with loss of ARID1A protein expression. Additionally, patients under the age of 53 with clear cell ovarian carcinomas are at a clinically significant risk for loss of mismatch repair (MMR) protein expression and Lynch Syndrome; in such patients, IHC should be done for MMR abnormalities.

Association with endometriosis
Several studies have linked endometriosis to an increased risk of ovarian cancer, particularly endometrioid and clear cell types (Brinton et al., Ogawa et al.). The question of whether endometriosis-associated ovarian cancers are associated with a better overall prognosis is controversial since the studies addressing this question are conflicting (Orezzoli, J. et al. and Yamamoto, S. et al vs. Goff, B. et al and Cuff and Longacre).

Management
Primary treatment of ovarian clear cell carcinoma and clear cell carcinoma of the uterus involves surgery with a total abdominal hysterectomy, bilateral salpingooophorectomy and omentectomy. Lymphadenectomy adds important prognostic information (Glasspool and McNeish). Unlike high-grade serous carcinomas, ovarian clear cell carcinoma is known to be less responsive to traditional types of ovarian cancer chemotherapies (DeLair et al.). Since upregulation of the PIK3/AKT/mTOR pathway, particularly through mutations of PIK3CA and inactivation of PTEN, is involved in tumorigenesis of clear cell carcinoma, clinical trials for inhibitors of PI3-kinase/mTOR pathway have recently been started (Jin, Y., et al.)

References

Brinton, L. et al. Cancer risk after a hospital discharge diagnosis of endometriosis. Am J Obstet Gynecol. 1997. 176:572–579.

Chisea-Voterro, A. et al. Immunohistochemical overexpression of p16 and p53 in uterine serous carcinoma and ovarian high-grade serous carcinoma. Int J Gynecol Pathol. 2007. 26: 328-333.

Cuff, J, Longacre, T. Endometriosis does not confer improved prognosis in ovarian carcinoma of uniform cell type. Am J Surg Pathol. 2012. 36(5):688-95.

DeLair, D. et al. HNF-1β in ovarian carcinomas with serous and clear cell change. Int J Gynecol Pathol. 2013. 32(6):541-6.

Glasspool, R. and McNeish, I. Clear cell carcinoma of ovary and uterus. Curr Oncol Rep. 2013. 15(6):566-72.

Goff, B. et al. Clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy in stage III disease. Gynecol Oncol. 1996. 60:412–417.

Jin, Y., et al. The target therapy of ovarian clear cell carcinoma. Onco Targets Ther. 2014. 7:1647–1652.

Ogawa, S. et al. Ovarian endometriosis associated with ovarian carcinoma: a clinicopathological and immunohistochemical study. Gynecol Oncol. 2000. 77:298–304.

Orezzoli, J. et al. Prognostic implication of endometriosis in clear cell carcinoma of the ovary. Gynecol Oncol. 2008. 110:336–344.

Tsuchiya, A. et al. Expression Profiling in Ovarian Clear Cell Carcinoma: Identification of Hepatocyte Nuclear Factor-1β as a Molecular Marker and a Possible Molecular Target for Therapy of Ovarian Clear Cell Carcinoma. Am J Pathol. 2003. 163(6): 2503–2512.

Yamamoto, S. et al. Loss of ARID1A protein expression occurs as an early event in ovarian clear-cell carcinoma development and frequently coexists with PIK3CA mutations. Mod Pathol. 2012. 25(4):615-24.

Yamamoto, S. et al. Clear cell adenocarcinoma associated with clear cell adenofibromatous components: a subgroup of ovarian clear cell adenocarcinoma with distinct clinicopathologic characteristics. Am J Surg Pathol. 2007. 31(7):999-1006.

Yamashita, Y. et al. Napsin A is a specific marker for ovarian clear cell adenocarcinoma. Mod Pathol. 2015. 28(1):111-7.

Vierkoetter, K. et al. Lynch Syndrome in patients with clear cell and endometrioid cancers of the ovary. Gynecol Oncol. 2014 135(1):81-4.

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