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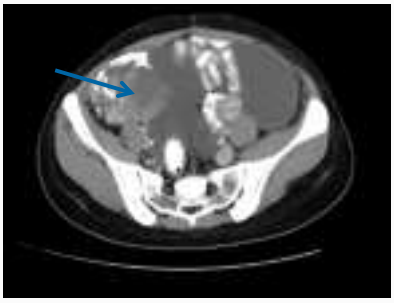
Interesting Case Presentation

Clinical History

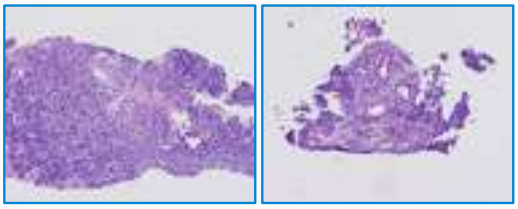
- 34 y/o female, GO
- History of pT3;N1;Mo bilateral invasive, high grade ductal adenocarcinoma, s/p bilateral mastectomy in 2009, and chemoradiation therapy
- ER/PR positive
- *BRCA2* mutation detected
- Currently on Tamoxifen for the last 4 years
- No family history of breast, ovarian, cervical, or colon carcinoma
- Presented in 03/2014 with 5-days of worsening, non-radiating abdominal pain and bloating
- CT scan showed large left adnexal mass and peritoneal carcinomatosis

CT Imaging Summary

- A large left adnexal mass measuring 8.5 x 6.8 x 5.2 cm
- Numerous other soft tissue peritoneal masses suspicious for areas of omental caking/metastasis
- Prominent soft tissue mass in right para-colic gutter measuring 6.1 x 4.5 cm
- Soft tissue mass in the porta hepatis 2.6 x 1.9 cm
- Additional prominent mass within the left lower quadrant measuring 2.3 x 2.2 cm

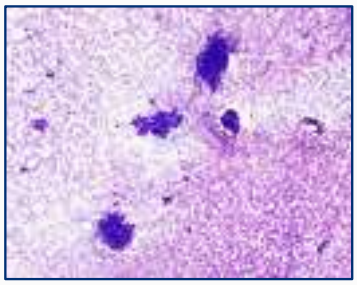


Peritoneum, biopsy

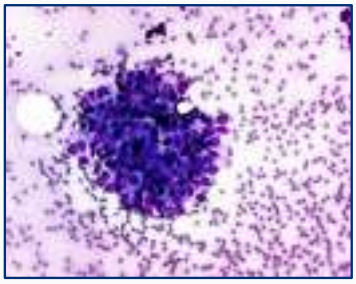


Poorly differentiated malignant neoplasm
Negative for PAX8 and WT1

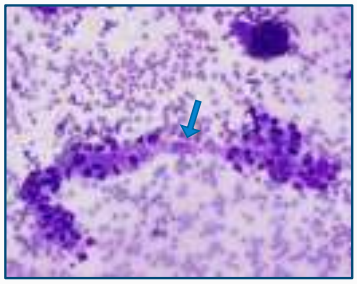
- **Peritoneum, left lower quadrant, 3 cm nodule, (ultrasound-guided fine needle aspiration)**



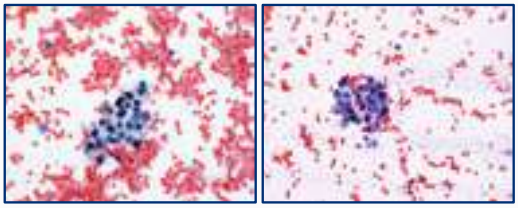
DQ, x100



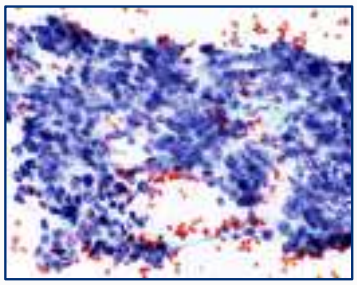
DQ, x400



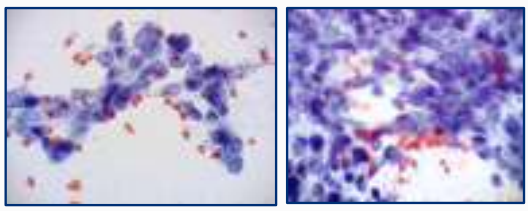
DQ, x400



PAP, x200

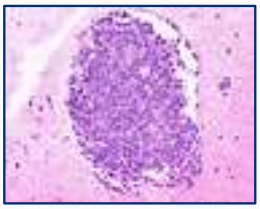


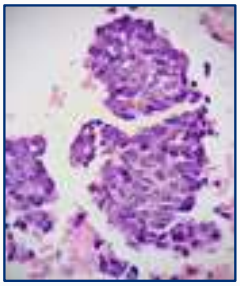
PAP, x400



PAP, x600

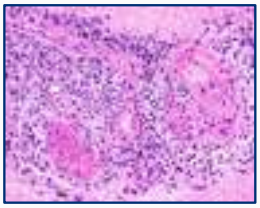
Cell block

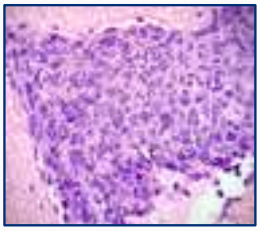




H&E, x200 H&E, x400

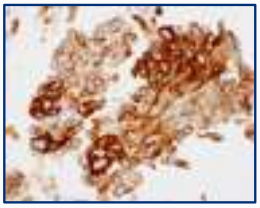
Cell block





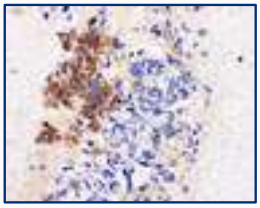
H&E, x200 H&E, x400

Cell Block



CK7 immunostain, x400

Cell Block

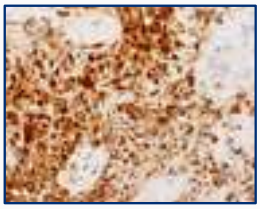


BerEp4 immunostain, x400

Cell Block

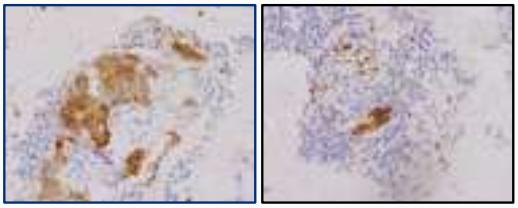
EMA immunostain, x400

Cell Block



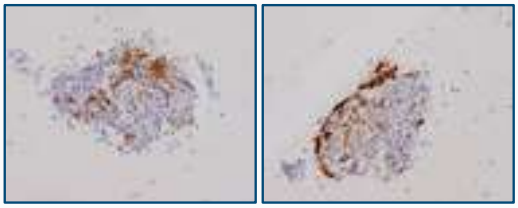
p16 immunostain, x400

Cell Block



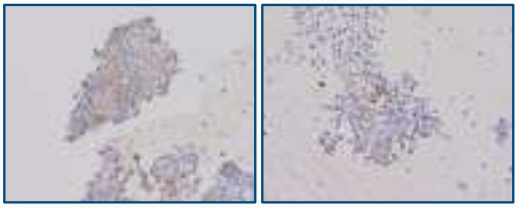
CD10 immunostain, x400

Cell Block



SMA immunostain, x400

Cell Block



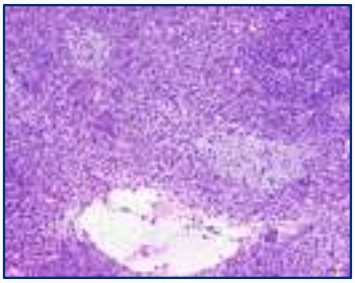
Glypican3 immunostain, x400

Summary of Immunoreactivity

Positive
- CK7
- BerEp4
- EMA
- P16
- Glypican3
- SMA
- CD10

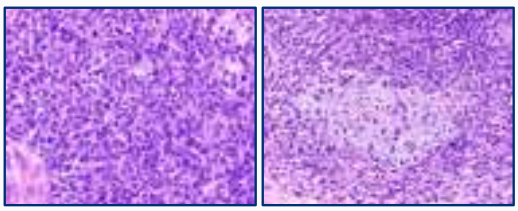
Negative
- PAX8
- WT1
- CK20
- ER/PR
- BRST2
- Chromogranin/Synaptophysin
- S100
- AFP
- OCT4
- Inhibin
- Desmin
- MyoD
- Calretinin

Surgical Pathology-Ovarian Mass



(H&E, x200)

Surgical Pathology-Ovarian Mass



(H&E, x400)

FNA Diagnosis

- Peritoneal nodule, (CT-guided FNA):

Consistent with Malignant Mixed Mesodermal Tumor

Surgical Pathology Diagnosis Summary

- Malignant Mixed Mesodermal (Müllerian) Tumor of the left ovary
- The tumor is present on the ovarian surface as multiple nodules
- The largest nodule measured 0.6 cm
- Metastatic mixed mesodermal tumor, involving small bowel nodule, left pericolic gutter, left pericolic peritoneum, porta hepatis, omentum, and pelvic mass
- Proliferative endometrium
- Histologically unremarkable cervix, myometrium, bilateral fallopian tubes

Carcinosarcoma (Malignant Mixed Müllerian Tumor)

- Malignant Mixed Müllerian Tumor (MMMT) is uncommon, highly aggressive biphasic neoplasm
- Most cases of MMMT, including genital and extragenital location, are described in postmenopausal women older than 60 years
- However, MMMT may occur in relatively younger patients
- In the female genital tract, most cases arise from the endometrium
- Ovaries, fallopian tubes, cervix and vagina are less frequently encountered
- Ovarian MMMT comprise 1 to 4% of ovarian malignancies
- Extragenital primary peritoneal MMMTs are extremely rare

MMMT Histology

- MMTS are composed of carcinomatous and sarcomatous components
- The carcinomatous component can be endometriod, clear cell, serous, or poorly differentiated
- The sarcomatous component can be homologous or heterologous
- The homologous component is composed of native mesenchymal elements of the organ
- The heterologous is composed of nonnative elements (rhabdomyoblastic, osteogenic, chondrobalstic, or lipoblastic)

MMMT, Risk Factors and Pathogenesis

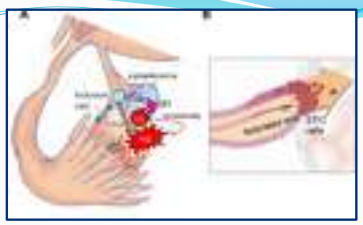
- The youngest patient reported was a 19 y/o female with uterine MMMT associated with Stein-Leventhal syndrome (Chumas et., 1983)
- Risk factors include obesity, nulliparity, exogenous estrogen or long-term tamoxifen use
- Prior pelvic irradiation is considered as risk factor for the development of MMMT with the latent period range 5-35 years (Banik et al., 2012)
- The "combination theory" suggests monoclonal origin of the tumor, with both components arising from the same progenitor
- The "collision theory" suggests polyclonal origin, with two components arising independently

MMMT, Risk Factors and Pathogenesis (Cont.)

- Most authors favor the monoclonal theory of uterine and ovarian MMMT
- Immunostaining for p53 in uterine MMMT is concordant in both components, supporting the monoclonal theory (Buza et al., 2009)
- Buza et al. also found p16 overexpression in both components of uterine MMMT and suggested that alterations of p16-RB pathway play a major role in the pathogenesis
- P53 and p16 markers may have prognostic value and potential therapeutic implications

MMMT, Risk Factors and Pathogenesis (Cont.)

- Kurman and Shih (2010) proposed a unifying theory of the origin and pathogenesis of low-grade and high-grade epithelial ovarian cancer
- Junction between the fimbrial mucosa and the tubal serosa and between the fimbrial mucosa and the ovarian surface epithelium has been implicated in the ovarian carcinogenesis
- Tubal intraepithelial carcinomas (TICs) or serous TIC (STICs) have been identified in the fallopian tubes of prophylactic salpingo-oophorectomies of BRCA mutation carriers in ~90% of cases (Brustmann, 2013)
- Sidman et al. (2011) suggested that "primary peritoneal" high grade serous carcinomas are very likely metastasis from STICs
- Przybycin et al. (2010) speculated that STIC may also play a role in the development of "ovarian" MMMT
- Brustmann (2013) reported the first case of ovarian heterologous MMMT associated with bilateral TIC in a 64 y/o patient



Proposed development of low-grade (LG) and high-grade (HG) serous carcinoma.
A. One mechanism involves normal tubal epithelium that is shed from the fimbria, which implants on the ovary to form an inclusion cyst.
Depending on whether there is a mutation of *KRAS*/*BRAF*/*ERRB2* or *TP53* a low-grade or high-grade serous carcinoma develops respectively.
B. A schematic representation of direct dissemination or shedding of STIC cells onto the ovarian surface where the carcinoma cells ultimately establish a tumor mass that is presumably arising from the ovary.

Kurman RJ and Shih LM. *Am J Surg Pathol.*2010; 34 (3): 433-443

MMMT and *BRCA* Gene Mutations Carriers

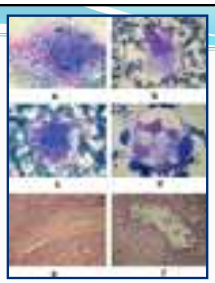
- Johannsson et al. in 1996 reported a case of uterine MMMT in a patient from a breast and ovarian cancer family with a documented germline mutation of *BRCA1*
- A case of ovarian MMMT in a 75 y/o patient with a germline *BRCA2* mutation was reported by Sonoda et al. in 2000
- Clonal loss of the wild-type *BRCA2* allele as well as somatic mutation of the *TP53* gene was evident in both histologic components of the tumor, supporting the "combination theory" of pathogenesis (Sonoda et al, 2000)

MMMT and Tamoxifen

- In 2000 Bergman et al. showed significantly increased risk of developing uterine MMMT or sarcomas compared with matched controls
- In 2002 FDA added the risk factor of sarcoma to warning label of tamoxifen (Goldman et al, 2005)
- Unopposed estrogenic effect of tamoxifen develops proliferative abnormalities both in endometrium and in stroma or stem cells
- The youngest reported patient was a 40 y/o premenopausal, multiparous patient who developed uterine MMMT within 2 years of tamoxifen exposure for Stage 1 breast cancer (Hubalek et al., 2004)

MMMT and FNA Cytology

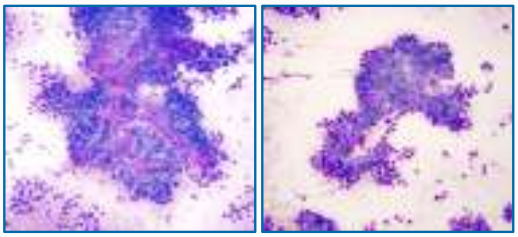
- The majority of the reported cases of MMMT diagnosed on FNA are recurrent or metastatic diseases
- There are rare reports on FNA diagnosis of primary uterine MMMT (Banik et al., 2012)
- There is only one reported case of ovarian MMMT in an elderly women (81 y/o) who underwent FNA during laparotomy (Donat et al., 1994)
- The cytologic findings included well-differentiated papillary adenocarcinoma, sarcomatous cells with wispy cytoplasm, coarsely granular chromatin and eosinophilic nucleoli, and chondrosarcomatous cells (Donat et al., 1994)



(a) Large fragment of stromal material with oval to spindle cells embedded in pinkish matrix; (b) Large multinucleated bizarre giant cells; (c)Malignant cells arranged in gland like fashion; (d)Malignant cells showing moderate nuclear pleomorphism and vacuolated cytoplasm ; (e) Histopathology section showing both malignant mesenchymal cells and fragments of epithelial cells; (f) Histopathology section showing malignant glands along with scattered cells with abundant cytoplasm indicating rhabdomyoblastic differentiation [MGG stain, x440 (a-d); H&E stain, x240 (e-f)].

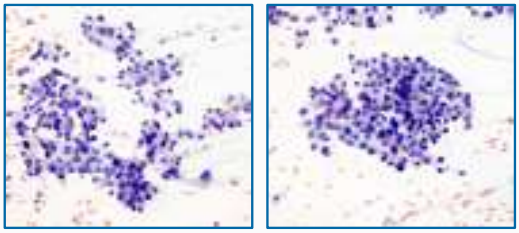
Banik et al. *Diagn Cytopathol.* 2012 Jul;40(7):653-7

Clear Cell Carcinoma



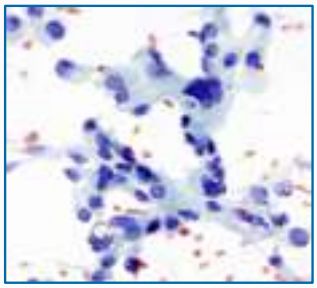
DQ, x200

Clear Cell Carcinoma



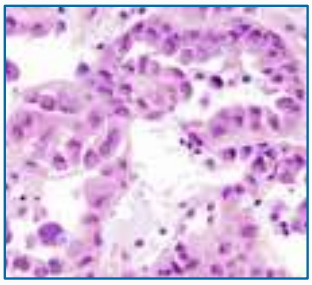
PAP, x400

Clear Cell Carcinoma



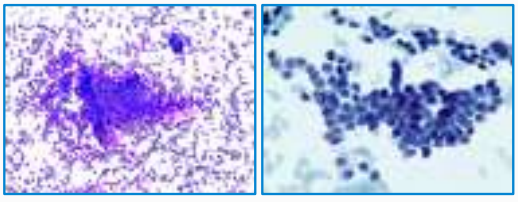
PAP, x400

Clear Cell Carcinoma



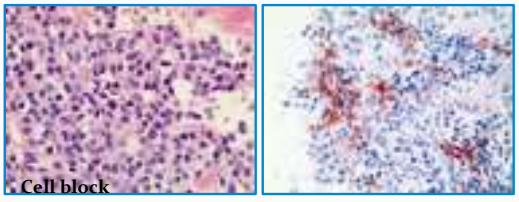
Cell Block

Granulosa Cell Tumor



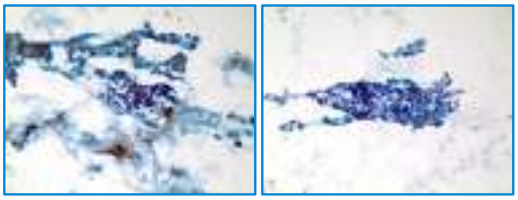
DQ, x200 PAP, x400

Granulosa Cell Tumor



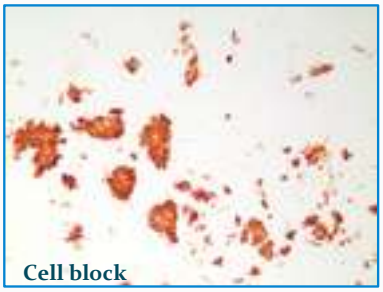
H&E, 400x Inhibin, x400

Ovarian Carcinoid



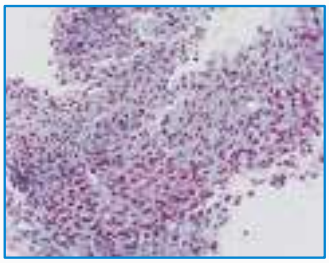
PAP, x200

Ovarian Carcinoid



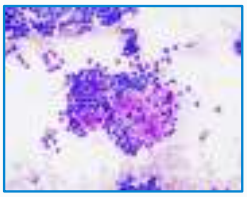
Chromogranin, x200

Endometriod Stromal Sarcoma

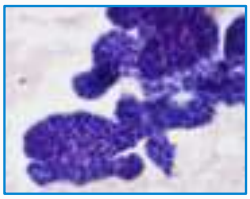


PAP, x400

Mesothelioma

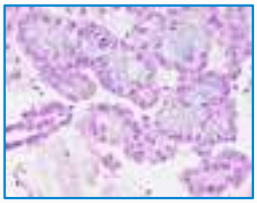


DQ, x200



PAP, x400

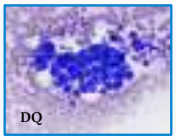
Mesothelioma

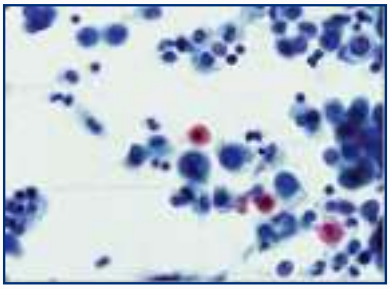


H&E, x400

Calretinin, x400

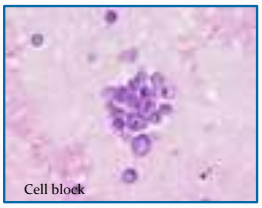
Mesothelioma





Gao L, Reeves W, DeMay RM. ***Cytojournal.*** 2012;9:18

Rhabdomyosarcoma



PAP, x400 **H&E, x400**

Rhabdomyosarcoma

Myogenin, x400 **Desmin, x400**

MMMT and FNA Cytology (Cont.)

- Ovarian MMMT in a young patient with breast carcinoma history has never been reported
- This diagnosis may be challenging in FNA specimens in a patient without prior history of MMMT (Banik et al., 2011)
- If the tumor occurs in relatively younger age, MMMT should be differentiated from various biphasic tumors, e.g. mixed germ cell tumor, granulosa cell tumor, mesothelioma, among others
- PAX8 immunostain can be negative in undifferentiated and sarcomatous components of MMMT (Holmes BJ, Int J Gynecol Pathol. 2014 Jul;33(4):425-31)
- Demonstration of biphasic morphology is required for the diagnosis
- Adequate sampling and utilization of cell blocks for immunostains are crucial for the correct diagnosis

Thank you