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Case Report

Same Or Different? Resolution of Diagnostic Difficulty of Two Mixed Cell-Type Tumors in Ovarian Pathology

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ABSTRACT

INTRODUCTION: When confronted by two disease processes, physicians in all disciplines are faced with the question: Are they manifestations of a common etiology, or distinct entities co-occurring? Inherent in this dilemma is whether an aberration from normal is even a disease process at all. Tissue pathology plays a key role in resolving this conundrum. Although diagnoses can be challenging, there are various methodologies used in the field of pathology to ascertain whether two tumors are of the same or different origins.

CASE DESCRIPTION: This case report reviews two patients with large ovarian neoplasms and surgical pathology revealing histopathological features of two distinct types of tumors, presenting the dilemma of "same or different?" A pathological review of one of the cases revealed that the tumor was composed of an uncommon mixture of Brenner tumor and mucinous cystadenoma. The second case's initial pathology revealed a rare thecoma mixed with a more common tumor, serous cystadenoma. The combination of thecoma and serous cystadenoma has only been described in a few isolated case reports. Further pathologic evaluation revealed the second component was a fallopian tube remnant rather than a serous cystadenoma.

DISCUSSION: Although this review is of academic interest and is in the context of benign disease, it is relevant and can be applied to malignant neoplasms as it is important for staging and treatment selection to know if two tumors are considered the same or different.

KEY WORDS: thecoma, adherent fallopian tube, cystadenoma, Brenner tumor

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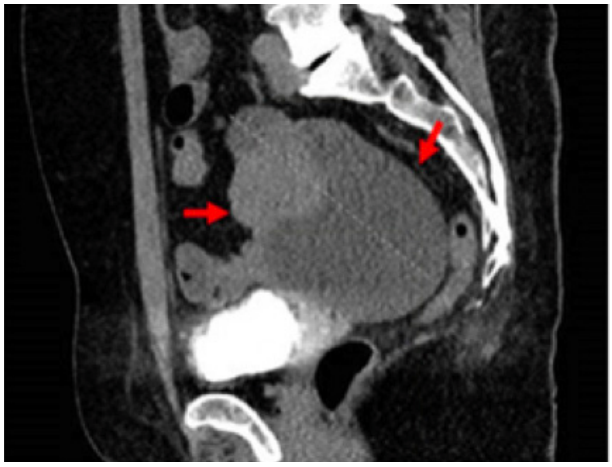
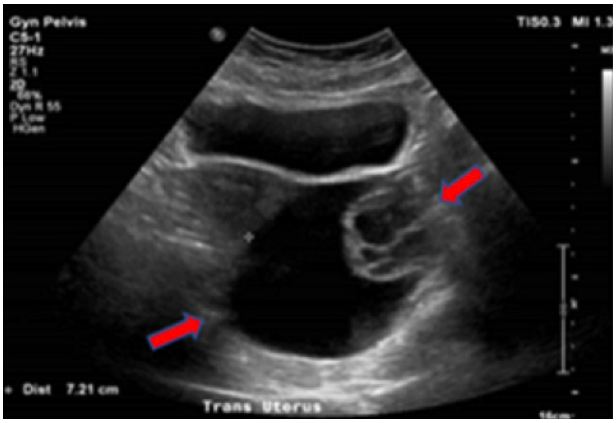
INTRODUCTION

Ovarian tumors are grouped into three discrete subtypes based on their presumed cellular origin: 1. epithelial tumors arising from the ovarian surface, 2. germ cell tumors developing from the resident ova, 3. sex cord-stromal tumors derived from the supporting cells in the ovary.[1] Typically, neoplastic growths from the ovary are derived from one of these tissue lineages and display a homogeneous cell-type population. Less commonly, a mass may contain a heterogeneous population of tissue types. When these divergent cellular elements are intimately admixed histologically within the mass, they are designated as composite, or "hybrid" tumors; when a mass consists of two cell populations that are distinct, but co-existing, they are considered "collision" tumors.[2] Case 1 illustrates the features of a hybrid tumor consisting of a large-sized, mixed mucinous cystadenoma and Brenner tumor. This is a rare, but well-described in literature, neoplastic combination of epithelial elements. In Brenner tumor, the nests of transitional epithelium are typically solid, composed of only urothelial-like cells. However, some tumors develop central cystic spaces lined by gastric foveolar-type mucinous cells. The second neoplastic component seen in this patient's mass is a mucinous cystadenoma. As its name suggests, a mucinous cystadenoma features cystic spaces lined by a monolayer of bland mucinous epithelium. Cystadenomas are the most common benign ovarian lesions. They are classified as mucinous (as in case 1) or serous.[1]

Case 2 features a rare sex cord-stromal tumor, a thecoma, with elements initially assessed to be an epithelial-derived tumor, a serous cystadenoma. While it is rare for an individual tumor to contain multiple epithelial cell types as in case 1, it is exceedingly rare to have a tumor composed of both epithelial and sex-cord elements with only a few documented case reports.[2,3] Thecomas are ovarian

FIGURE 1. Case 1 a. Sagittal CT demonstrating a large adnexal mass with solid and cystic components. b. Ultrasound further demonstrates the complex cystic components.





sex-cord stromal tumors derived from resident thecal cells, which provide structural (theca externa) and hormonal support (theca interna) to the ovarian follicles.

Initial pathologic evaluation of the second case revealed a combination of rare sex cord stromal tumor, a thecoma, and an epithelial derived serous cystadenoma. The combination of a sex cord stromal and epithelial tumor is only documented in a few case reports. Case 2 was postulated to be another example of such a collision tumor. However, after further histological staining, the initially diagnosed cystadenoma was found to be the fimbriated end of the fallopian tube adherent to the thecoma. Therefore, the ovarian neoplasm was not of mixed cell origin.

In the field of surgical pathology, histopathological assessment of the tissue of origin of a neoplasm is critical in determining both prognosis and treatment. Not uncommonly, this can be challenging, especially when a mass is composed of cells of various lineages. Critical to the assessment is whether the neoplasms consists of a single cell type, hybrid cell types, or collided cell types. The work-up performed for these two cases demonstrates the variety of tools that can be utilized when trying to make a diagnosis. These tools include clinical presentation, imaging, clear understanding of basic anatomy and histology, pathologic testing such as immunohistochemistry and molecular testing. A summary of this process is provided in Table 1.

CASE SUMMARIES

CASE 1.

History and Imaging

A 60-year-old post-menopausal woman presented to the emergency department for evaluation of abdominal pain and nausea. Her computed tomographic (CT) scan also showed an incidental complex cystic left ovarian mass. The mass measured 9.1 x 7.8 x 7.0 cm and showed areas with mural nodules, up to 4.2 cm. Figure 1a. Subsequent transvaginal ultrasound confirmed an adnexal mass with solid and cystic components with an endometrial thickness of 6 mm.

Due to concern for a malignant ovarian neoplasm, the patient underwent a laparoscopic hysterectomy and bilateral salpingo-oophorectomy with surgical staging due to concern for malignancy.

Pathology: Gross and Histological Assessment

Gross examination of the uterus, left and right fallopian tubes, and ovaries showed an intact cystic, left ovarian mass attached to the fallopian tube measuring 10.1 x 8.0 X 3.3 cm. The specimen contained cystic areas filled with mucin and a 4.5cm firm, solid, and yellow area. Sections of the mass and other anatomical structures, as well as staging biopsies, were submitted for histopathological assessment.

Microscopic sections of the left ovarian mass showed a tumor within the mesosalpinx, but distinct from the fallopian tube. Histological evaluation of the solid, yellow mass showed nests of transitional epithelium within a background of dense fibrous stroma. These histological findings are consistent with a benign Brenner tumor. Cytologically, the areas of Brenner tumor were composed of cells with round and oval nuclei with nuclear grooves and small, punctate nucleoli with finely granular to vacuolated eosinophilic cytoplasm. Rare mitotic figures are seen. Dense, fibrous stroma surrounds the nests with areas of coarse calcification. The cystic areas of the mass showed a mucinous cell lining, similar to gastric foveolar cells, consistent with an mucinous cystadenoma (MCN). The areas

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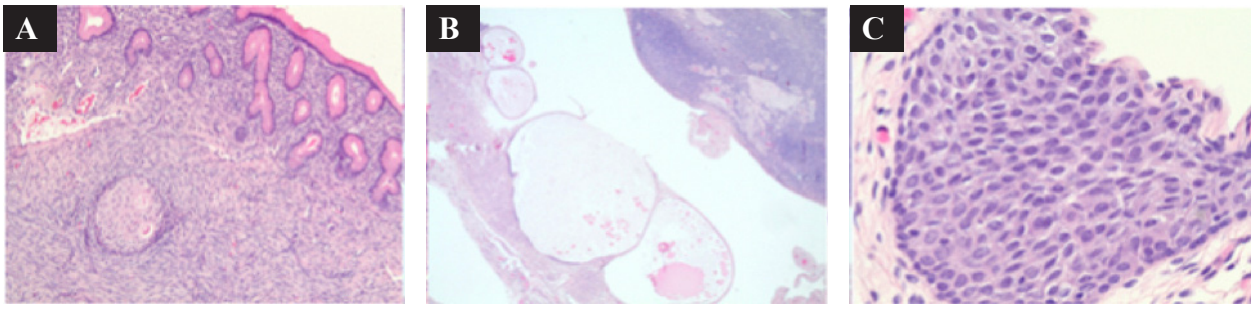
TABLE 1. Algorithms used in Surgical Pathology to Resolve Diagnostic Difficulty of Mixed Cell-Type Tumors in Surgical Pathology.

Work up of Divergent Tissues in Neoplasia	Parameters	Examples	Application in Case 1 and Case 2
Clinical History	Patient age, prior malignancies, genetic, environmental, or iatrogenic risks factors	- Recurrences of a tumor in a patient with a prior malignancy, sometimes even decades later. - One tumor may cause another malignancy, such as ovarian tumor causing endometrial carcinoma. - Risk for multiple malignancies: radiation, immunosuppression obesity, cigarette smoking. genetic syndromes	A negative history for malignancy in each patient in case 1 and 2, made recurrence unlikely. The thecoma in case 2 had estrogenic manifestations that causes endometrial polyps and is, in general, frequently associated with endometrial adenocarcinoma (20%)
Review Imaging	Consider: - number, distribution and size of lesions - borders of the lesion for circumscription vs infilitration - serial imaging for growth rates and support a benign or malignant assessment	If a stable lesion begins to increase in size, consider either a second process, or a malignant transformation	Radiologically the ovarian masses in both Case 1 and Case 2 appeared circumscribed, but the large size in each case made malignancy a consideration
Read the Operative Report	- Review the anatomic structures present. - Consider any operative findings that may not have been sampled for pathological evaluation. - Call surgeon for addition information if needed	The finding of multiple tumors and/or deposits the peritoneum or on the surface of other organs is a reliable sign of malignancy	The information in the operative reports in these cases was reviewed but did not provide additional information for the diagnosis.
Correct Specimen Labeling	Correct patient identification and labeling	Specimen labeling issues occur due to: - Prelabeled specimen collection containers in the procedure area - Failure to perform a second time out post-procedure - Mislabeled tissue cassettes during prosection	Two patient identifiers are used on all pathology specimens, and these were verified in each case. There were no concerns for mix up of tissue
Gross Anatomic Features	Inspect and sample areas of: - any solid areas in a cystic mass - gross color or texture changes - necrosis or hemorrhage - transition point between two processes - interface between normal anatomical structures and pathological areas	- Solid areas within a cystic mass are concerning for malignancy and should be well sampled - A mixture of components grossly suggests a hybrid tumor - Distinct areas juxtaposed with one another suggest a collision tumor - Necrosis and hemorrhage favor malignancy	In case 1, the solid areas within the cystic mass raised concern for malignancy. The elements of the MCN and the Brenner tumor were intimately admixed both grossly and histologically. Transition points between various elements were well sampled in both cases.
Additional Specimen Sampling	Typically, tumors are submitted one section per centimeter of tumor. Submitting additional sections or the entire lesion can provide more information	Sampling areas that appear grossly heterogeneous may reveal distinctive histological patterns. Areas of hemorrhage, necrosis, color variation, or areas with mucoid or gelatinous appearance should be sampled	In case 2, additional sections of the area of interest, the interface between the two putative neoplasms helped define the elements
Review of Literature	Investigate: - the frequency of co-occurrence - methods used to assess divergent elements	Infrequently described combination of tumors may merit additional work up. If case is a novel hybrid or collision tumor, consider contributing the case to the literature in a case report	Case 1 is well described in the literature and more confidence could be made in the diagnosis of a hybrid tumor Case 2 has only very rare reports and was approached with more skepticism
Review of Anatomy and Histology	Review: - the normal resident cells in an organ - the morphology of resident cells in inflammation and repair - common variations from normal	- Inflamed cells often show histological features of malignancy such as nuclear enlargement, prominent nucleoli and mitosis - Benign inclusions, can also mimic neoplasia	In case 1, Walthard Nests are composed of transitional epithelium, and knowing that these are extremely common benign inclusions in the fallopian tubes avoids misdiagnosis as metastatic bladder cancer
Immunohistochemistry	May be used to demonstrate: - tissue origin of the tumor - tissue architecture and neoplastic involvement - various admixed cell types present in tissues - cellular products - can show proliferation rates	Examples of key Immunohistochemical stains: - keratins for epithelial malignancies - vimentin for mesenchymal malignancies - PAX 8 is a typical Mullerian marker in the gynecological tract. - Ki67 demonstrates tissue proliferation rates	In case 2: - immunohistochemical stains for smooth muscle actin highlights the smooth muscle of the fallopian tube - calretinin and inhibin support that the mass is a thecoma
Tumor Clonality Studies	- Next generation sequencing to demonstrate molecular signatures of areas of tumors with divergent histological features - Chromosomal microarrays (high resolution karyotype) - PCR for X chromosome inactivation in female patients	It is critical to assess if two malignant tumors are the same tumor with metastatic spread, or separate primary tumors: - one neoplasm with multiples sites of involvement is staged differently than two distinct primary malignant tumors - even within the same organ, two separate primary malignancies may arise which affects staging - clonality studies can determine if the tumors are the same process, or two separate primary malignancies	In case 1: studies in the literature, used PCR for chromosomal inactivation to examine whether the MCN and Brenner were the same tumor - homogeneous inactivation patterns of the X chromosome in multiple hybrid tumors confirm their clonal relationship

FIGURE 2. Case 1. a. Left ovarian mass with MCN component showing a mucinous cell lining and confluent Brenner Tumor composed of transitional cell nest and dense stroma. b. Right ovary: cystic and solid Walthard nests in mesosalpinx. c. Solid Walthard Nest.



of MCN feature a single-layer columnar epithelium with eosinophilic apical mucin and basally located nuclei without cytological atypia or mitotic activity. The two tumor types are admixed together with nests of the Brenner component in the walls of the mucinous cysts.

Within the contralateral (right) mesosalpingial tissue, in proximity to the rete ovarium, there are multiple cystic and solid spaces lined by transitional epithelium "Walthard nests."

CASE 2.

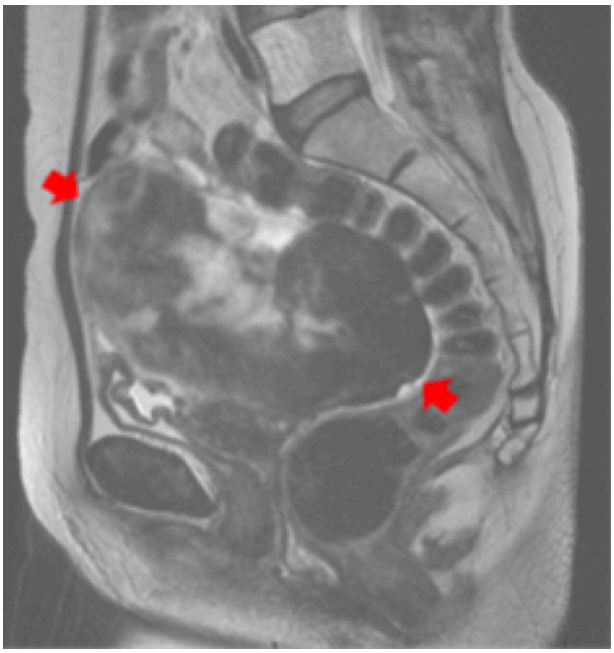
History and Imaging

A 64-year-old female was discovered to have an enlarged uterus on a routine gynecological examination. CT scan showed a large right, well-defined heterogeneous ovarian mass measuring 13.2 x 11.0 x 10.4 cm. Transvaginal ultrasound showed an endometrial thickness of 2 mm. A total abdominal hysterectomy, resection of pelvic mass, and bilateral salpingo-oophorectomy with surgical staging due to concern for malignancy were performed.

Pathology: Gross and Histological Assessment

Gross examination of the uterus, left and right fallopian tubes, and ovaries showed a 12.3 x 10.5 x 9.2 cm mass in the right ovary with an attached fallopian tube. Sectioning of the mass demonstrated homogenous whorled white, focally yellow, firm, rubbery cut surface. The surface of the mass was almost entirely smooth, with a small area of focal polypoid excrescences, 2.0 x 2.0 cm, on the surface. Histologically, sections from the smooth-bordered mass show round spindly cells in a vague storiform pattern. In some areas, these cells had a plump eosinophilic cytoplasm and, in other areas, more pale scant cytoplasm. Immunohistochemistry showed these neoplastic cells to be positive for inhibin and calretinin, consistent with a thecoma, a steroidogenic sex cord-stromal tumor. The area of grossly identified excrescences shows histological

FIGURE 3. Case 2. Sagittal Pelvic T2 weighted MRI scan showing a large, well-defined heterogeneous adnexal mass.



architectural features identical to a typical serous cystadenoma on hematoxylin and eosin-stained sections. There are papillary projections composed of a fibrous stroma lined by tubal-type epithelium lining, showing a single layer of ciliated columnar cells, mucinous cells, and peg cells. Immunohistochemical staining for Smooth Muscle Actin (SMA) was performed to help differentiate between non-pathological fallopian tube and a serous cystadenoma. In the papillary areas, subepithelial smooth muscle is highlighted with SMA, demonstrating that the area was not a tumor, but adherent fallopian tube. Contralateral ovary was benign. A uterine and endocervical poly were noted, both of which were benign.

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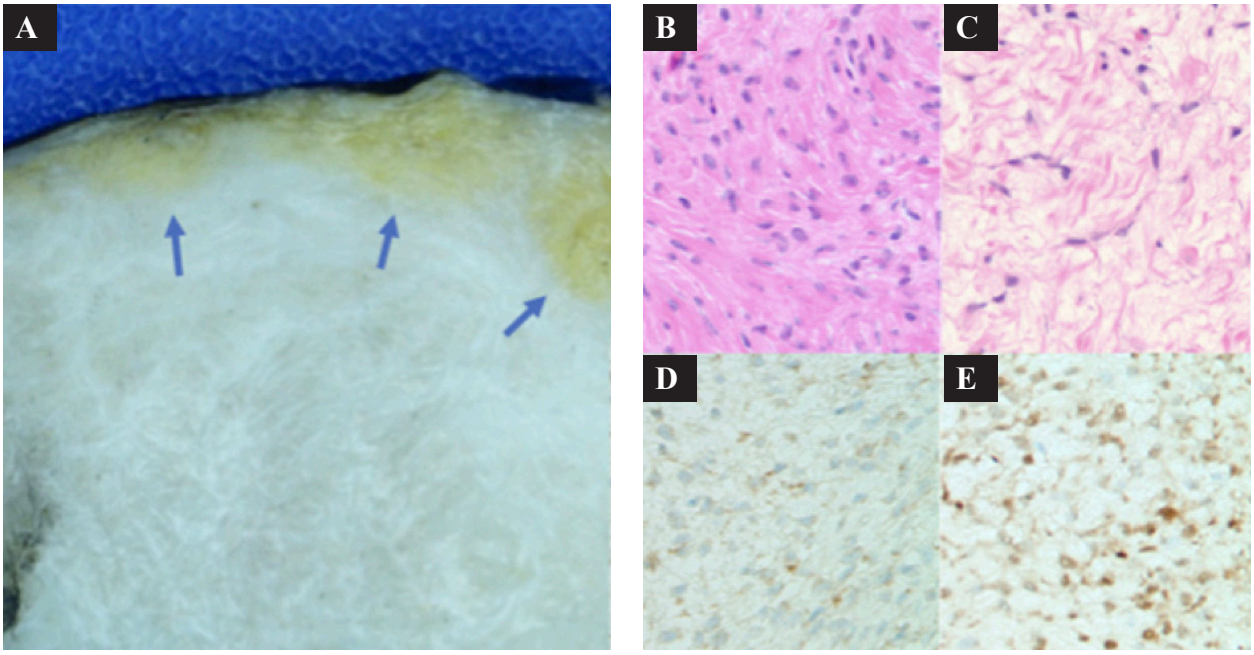
FIGURE 4. Case 2. Thecoma tumor with areas of bland cells in a vaguely storiform pattern. a. Whorled white ovarian mass with focally yellow areas (blue arrows) b. Steroid-rich eosinophilic cytoplasm (H&E). c. Areas with more pale cytoplasm (H&E). d. Positivity for Inhibin A. e. Positivity for Calretinin.



DISCUSSION

The pathologic evaluation of the ovarian neoplasm in case 1 exemplifies the "sameness" due to a hybrid of two cell types derived from a common origin, the Walthard Nest. Case 1 typifies the presentation of an ovarian Brenner tumor: A patient in her early 60s with an incidentally well-circumscribed adnexal mass. Brenner tumors are usually benign, unilateral, and most frequently appear in post-menopausal women.4 Brenner tumors are believed to arise from epithelial tissue in Walthard Nests, which are benign cystic or solid nests of transitional epithelium commonly found in the mesosalpinx and mesovarium.[5-8] Similarly, Brenner tumors feature nests of transitional cells within a fibrous stroma. A common immunohistochemical profile also supports the relationship between Walthard nests and Brenner tumors; both lesions express urothelial markers (GATA3) and are negative for Müllerian markers (PAX8, ER, PR).[4,7]

Mucinous cystadenomas have a frequent association with both Walthard Nests and Brenner tumors.8 It is theorized that the connection between the MCN and Brenner tumor occurs as the Brenner tumor evolves and develops differential growth of the mucinous cystic spaces, with the mucinous epithelial component eventually overtaking the nested urothelial component.[8,9] Case 1 demonstrates this relationship between the Brenner Tumor and MCN as described in the literature. There is a solid and cystic mass measuring 10.1 x 8.0 x 3.3 cm. The solid area measures 4.5 cm in greatest dimension and is composed of a typical solid Brenner tumor. The cystic component, which comprises the majority of the mass, features large, dilated spaces lined by mucinous cells, consistent with a mucinous cystadenoma. Within the walls of the MCN are admixed scattered nests of transitional epithelium. The finding of small pockets of Brenner tumor interspersed throughout the mucinous tumor, without an abrupt transition, supports this theory of evolution. Molecular studies show a consistent pattern of common X chromosome inactivation in both neoplastic components, providing additional evidence of a common origin of the Brenner and MCN in mixed tumors.[9]

The intermingled anatomic distribution, and cytological features, corroborated by numerous cases in the literature demonstrating frequent co-occurrence and common molecular events, overwhelmingly make a case of "sameness" of Brenner tumor and MCN. Synthesis of these data elements concludes that a mass containing both

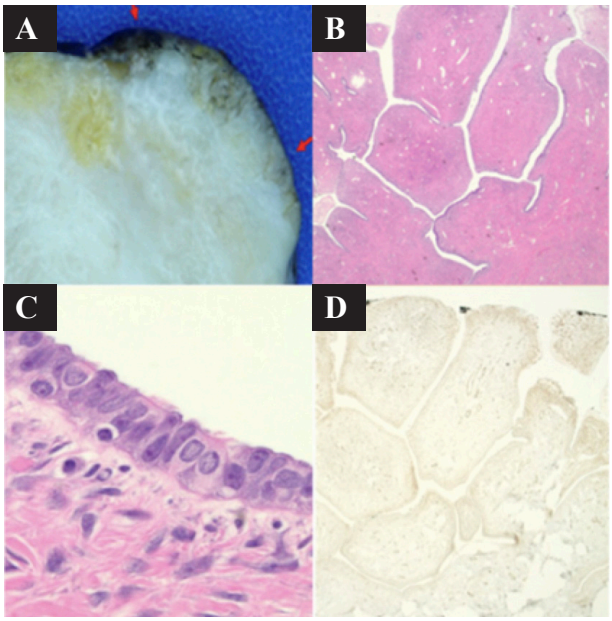


FIGURE 5. Case 2. a. The mass (arrows) has excrescences arising from the otherwise smooth surface. b. Low power image of papillary areas showing architecture characteristic of serous cystadenoma. c. High power columnar cells with cilia, mucinous cells and peg cells in the surface of these areas. d. Smooth muscle actin stain highlights subepithelial smooth muscle (brown areas).

Brenner areas and MCN can be considered a true hybrid tumor in which the two cell populations represent divergent differentiation from a common origin, the Walthard Nest.

In contradistinction, the evaluation of the divergent elements in the ovarian mass in case 2 led to the conclusion that the co-occurrence of the abnormal processes in this case is "different."

Case 2 shows a typical clinical presentation of an ovarian thecoma which presented as an incidentally discovered asymptomatic mass in a post-menopausal woman. Gross and histological studies supported this mass to be a thecoma. Macroscopically, the tumor was a yellow and white lobulated mass, and histologically composed of cells with round to spindled nuclei. In some areas, cells show abundant eosinophilic cytoplasm reminiscent of steroidogenic theca interna cells, and in other areas, more pale grey cytoplasm of the fibroblast-like thecal externa cells. Immunohistochemical studies show positivity for calretinin and inhibin, characteristic of a thecoma.[4]

Confluent with the thecomatous growth, was a second tumor-like area showing excrescences lined by a fallopian tube-type epithelium with ciliated columnar cells, mucinous cells, and peg cells, in keeping with a serous cystadenoma (SCN). Serous cystadenomas are characterized by cysts or papillae lined by cuboidal to columnar cells resembling fallopian tube epithelium with subepithelial fibroblasts.[10]

In Case 2, the smooth-bordered thecoma was closely juxtaposed with the papillary area lined by tubal epithelium. The close relationship, but an abrupt transition, suggested a collision tumor a thecoma, and an SCN. However, reports in the literature describing collision tumors composed of thecoma and serous cystadenoma are vanishingly rare.[2, 3] Due to the paucity of cases in the literature, we reevaluated our initial assessment, including specimen collection and additional tests. In surgical pathology, a thorough examination of the surgical resection specimen can provide vital information to understand unexpected histological findings. Additionally, the procurement of more tissue for histopathological assessment addresses sampling errors in specimen collection. On inspection of the resection specimen, it was noted that, generally, the entire tumor had a smooth-contoured surface, but for a discrete area of papillary projections measuring 2.0 x 2.0 on the surface. The focal nature of the excrescences informed a new hypothesis that perhaps the areas considered to be SCN, may, in truth, be fallopian tube fimbriae adhered to the surface of the tumor.

The challenge in the evaluation of the fallopian tube versus SCN is that they have the same cell lining: They both contain ciliated columnar cells, mucinous cells, and peg cells.[11] A thorough examination of H and E- stained sections of the area in question could not offer a distinction between the fallopian tube and SCN. Additional study of reference texts which provide detailed normal histology of the uterine tube, revealed an important distinction that could distinguish tube from SCN tumor: the presence of smooth muscle in the fallopian tube which is not present in serous cystadenomas nor thecomas.[12,13] Subsequent immunohistochemical studies with Smooth Muscle Actin (SMA) demonstrated the presence of bundles of smooth muscle present under the epithelium, definitively identifying this "tumor" as adherent fallopian tube fimbriae. Previous case reports with thecomas and serous cystadenomas did not report if testing for SMA was performed and this additional step could help further characterize

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the nature and immunohistochemistry of these exceedingly rare tumors by ruling out possible adherent fallopian tube.[2,3] Case 2 illustrates that a mimic for a collision tumor may actually be normal structures that have become adherent to the neoplastic growth. In this regard, case 2 was assessed as "different:" distinct processes, one neoplastic and the other abnormal but non-neoplastic.

Case 2 also illustrates the oncological phenomena in which one tumor can potentially cause another tumor. In case 2, the thecoma is a steroidogenic tumor, and up to 20% percent of patients with this benign tumor will have an associated endometrial carcinoma due to the estrogenic stimulation of the uterine lining.[1] The patient in case 2 did not have endometrial carcinoma, but the benign polyps found in the endometrial cavity were likely a result of the supra-physiological levels of estrogen produced by this tumor.

CONCLUSION

This case series examines two ovarian masses with a variety of cell types and shows the resolution of the assessments. The conclusion in Case 1 of the consideration of "Same or Different?" was that the two lesions Brenner tumor and MCN were part of the same pathological process. In contrast, the work-up of Case 2 revealed the two lesions in the mass were "different:" one, a neoplasm, and the other, a result of local growth of the neoplasm distorting normal anatomical structures.

In a greater scope, these cases highlight that many of the tenets used in clinical medical practice apply to an assessment of the surgical pathology specimen. These cases illustrate how an essential understanding of the nuances of normal histology is critical to accurate surgical pathology evaluation. Case 1 demonstrates other principles used in both surgical pathology and clinical medicine, such as observing the anatomic distribution of lesions to form a hypothesis as well as modern techniques of molecular diagnosis to determine if two lesions are related. The versatile role of immunohistochemistry in histopathological assessment is also demonstrated as a tool to define both architecture (e.g. presence of smooth muscle) and origin of tissues (e.g. use of inhibin and calretinin to show derivation of tumor). In Case 2, we went back to the gross specimen for the collection of additional samples. When an unexpected result occurs, it is critical to reevaluate the preanalytical variables in specimen collection. Similar to clinical medicine, we essentially "reran the test" with an examination of additional histological sections and performed additional tests in parallel, looking for smooth muscle. While these two cases were interesting benign examples of how to assess tumors with divergent elements, these cases illustrate key algorithms in surgical pathology to demonstrate "sameness or differentness" also used in malignant neoplasms in which there may be a significant impact on both staging and treatment selection.

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