Research Article

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Seromucinous borderline tumor-associated high-grade ovarian cancers.

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ABSTRACT

We present 6 high grade ovarian carcinomas that were associated with seromucinous borderline tumors. Patients ranged in age from 26 to 66 years. All cancers appeared as solid regions within otherwise paucicystic tumors that measured from 4.2 cm to 14.0 cm in greatest dimension. Five of the 6 tumors were bilateral, and endometriosis was seen in 4 of the tumors. Clinical data, with follow up periods ranging from 0 to 40 months, was available for all patients. Four patients died of their disease and two had recurrent disease at the time of this review.

All tumors exhibited a low-grade carcinoma component, which is consistent with ovarian cancers developing in a progressive adenoma to carcinoma sequence (so-called type I ovarian cancers). Two of the associated low-grade/borderline tumors had focal serous characteristics with WT1+ epithelial cell clustering. High-grade tumors exhibited an array of cell types expressing endometrioid, undifferentiated, serous, clear cell, and mucinous features that were at times mixed within the same tumor.

Five cancers were focally WT1+; two showed admixed low-grade serous features and one showed a high-grade serous adenocarcinoma with transitional features. Two cancers had mucinous features (one with focal CK20 and CDX2 immunohistochemical staining and one only with focal CDX2 immunohistochemical staining). All the high-grade tumors showed a mutated-pattern of p53 nuclear staining with >75% 2-3+ staining.

We conclude that seromucinous borderline tumors need to be extensively sampled. Cyst wall membrane rolls are important to evaluate since they may reveal persisting endometriosis and solid regions most likely harbor a high-grade tumor. Identifying high-grade cancer within a seromucinous borderline tumor is important because, although seromucinous borderline tumors and their oft-associated low-grade endometrioid cancers have favorable outcomes, tumors harboring a high-grade component are aggressive and may eventuate in patient death.

INTRODUCTION

Seromucinous tumors are defined as epithelial tumors composed of two or more Mullerian cell types. "Seromucinous" serves as an alternative name for endocervical-like mucinous, mixed epithelial, or mixed Mullerian epithelial tumor. Grossly, unlike pure, generally multiloculated, intestinal-type mucinous tumors, seromucinous tumors are unilocular or paucilocular. Usually, endocervical-type columnar cells with abundant intracytoplasmic mucin line the tumor surface, but there also may be a variable admixture of ciliated, endometrioid, and eosinophilic cells. Less commonly, foci of transitional cells, squamous cells, clear or hobnail cells, and (very rarely) intestinal-type mucinous cells may be seen. By convention, seromucinous tumors consist of two or more of these cell types, with each cell type representing >10% of the tumor, although, the typical seromucinous tumor is composed mainly of endocervical-type epithelium. [1]

Borderline seromucinous tumors commonly arise in association with endometriosis and may be bilateral in up to 40% of cases. They are typically unilocular or paucilocular. They exhibit a panoply of epithelial cell types that reflect the metaplastic potential of Mullerian epithelium. Nuclear features are typically low-grade, as is the mitotic activity. The stromal cores typically exhibit the tripartite branched configuration resembling borderline and low-grade serous tumors, are often edematous, and characteristically infiltrated by PMN neutrophils and, less commonly, eosinophils. Seromucinous carcinomas are now conventionally classified as endometrioid cancers.

MATERIAL AND METHODS

We report 6 seromucinous borderline tumors associated with high-grade ovarian carcinomas. At least one tumor section (and tumor-cyst membrane role) was examined for each one cm of greatest tumor dimension. All cases showed well fixed, adequate diagnostic tumor.

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Tumor immunohistochemistry was performed on a selected high-grade tumor block. Because of variable numbers of heterogeneous cell types, we report Cytokeratin 7 (CK7), Cytokeratin 20 (CK20), CDX2, Napsin-A, PAX8, and WT1 as "+" when at least 5% of tumor cells within a representative section stain.

Estrogen Receptor α (ERα), Progesterone Receptor (PgR), and p53 were evaluated in the strongest staining low power field using a 4x-lens (surface area ~ 20 mm2). ASCO/CAP ERα and PgR Guideline Recommendations were used for hormone receptor reporting (i.e., positive, or negative). A sample was "+" for ERα or PgR if ≥ 1% of tumor cell nuclei were immunoreactive and "-" if < 1% of tumor cell nuclei were immunoreactive (only if there was evidence that the sample could express ERα or PgR with positive intrinsic controls, usually in retained ovarian stroma). [2] P53 is known to show various immunohistochemical staining patterns, but in this study, all high-grade tumors showed a mutated staining pattern with strong and uniform nuclear decoration in the high-grade tumor component. [3] We reported PTEN based on "all or none" staining (using on-slide EIN control tissue) as having either a deleted (-) or wild-type (+) pattern. For MMR staining, immunohistochemical nuclear decoration for MLH1, MSH2, MSH6 and PMS2 was evaluated, and any staining of tumor cell nuclei was reported as positive, with inflammatory and other benign cells serving as good positive internal controls.

Clinical data was reviewed, and patient anonymity was preserved. Collected data were limited to patient age, tumor FIGO stage, types of adjuvant therapy, months followed, and clinical outcome.

RESULTS

Table 1. Patient data

Case	Age at diagnosis (years)	FIGO stage	Adjuvant therapy	Months follow up	Outcome
1	61	IIIC	Yes	40	Dead of disease
2	65	IIIC	Yes	7	Dead of disease
3	66	IB	No	0	Perioperative death
4	36	IV	Yes	21	Dead of disease
5	26	IC3	Yes	36	Alive with disease
6	49	IC1	Yes	5	Alive with disease

Follow up was available for all cancers with follow up periods ranging from 0 to 40 months. Two individuals with stage IC1 and IC3 cancers, whose follow up was, respectively, 5 and 36 months, were alive with disease at the time of this review and were receiving adjuvant therapy. Agents used in the treatment of cancers included: alkylating agents (carboplatin, oral cyclophosphamide), antimetabolites (gemcitabine), anthracyclines (doxorubicin), plant alkaloid taxanes (paclitaxel, docetaxel), anti-angiogenic agents (Avastin), antineoplastic anti-HER2 monoclonal antibody (pertuzumab), and an immunotherapy drug (Keytruda).

Table 2. Histopathological data

Case	Size of right/left ovary (cm)	Lymph nodes	Endo metriosis	Borderline SM tumor	Low-grade cancer	High-grade cancer
1	14/3.5	0	-	+	EM	UNDIFF
2	6/4.2	0	+	+	EM	EM
3	14/7.5	0	+	+	EM	EM
4	8.7/10.5	1 of 5	-	+	EM and SER	EM/MUC/CCC
5	5.5/8.5	0 of 8	+	+	EM and MUC	EM/MUC
6	7.5	0 of 4	+	+	EM and SER	SEROUS

EM, Endometrioid carcinoma; UNDIFF, Undifferentiated carcinoma; MUC, Mucinous carcinoma; CCC, Clear cell carcinoma; SER, Serous carcinoma

Five cancers were bilateral. Tumors ranged in size from 3.5 to 14 cm. All the tumors were paucicystic and exhibited, as their inclusion criteria for this study, a borderline seromucinous component. Invasive cancers had a panoply of tumor components including endometrioid, undifferentiated, mucinous, clear cell carcinoma (whose component was simultaneously ERα, PgR, and WT1 negative and Napsin-A positive), and WT1+ serous carcinoma of both low-

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grade (with micropapillary features) and high-grade (with a solid/transitional growth pattern) types. Two tumors (cases 4 and 5) showed foci of intestinal-type mucinous carcinoma. Case 5 had foci of CK20 positive cells and cases 4 and 5 had foci of CDX2 positive cells. Endometriosis, with various forms of Mullerian epithelial metaplasia was seen, principally in the cyst components of 4 cases. Examples of the high-grade cancers are illustrated in FIGURES 1 through 4.

FIGURE 1. High grade endometrioid carcinoma and undifferentiated carcinoma as seen in cases 2 and 1, respectively.

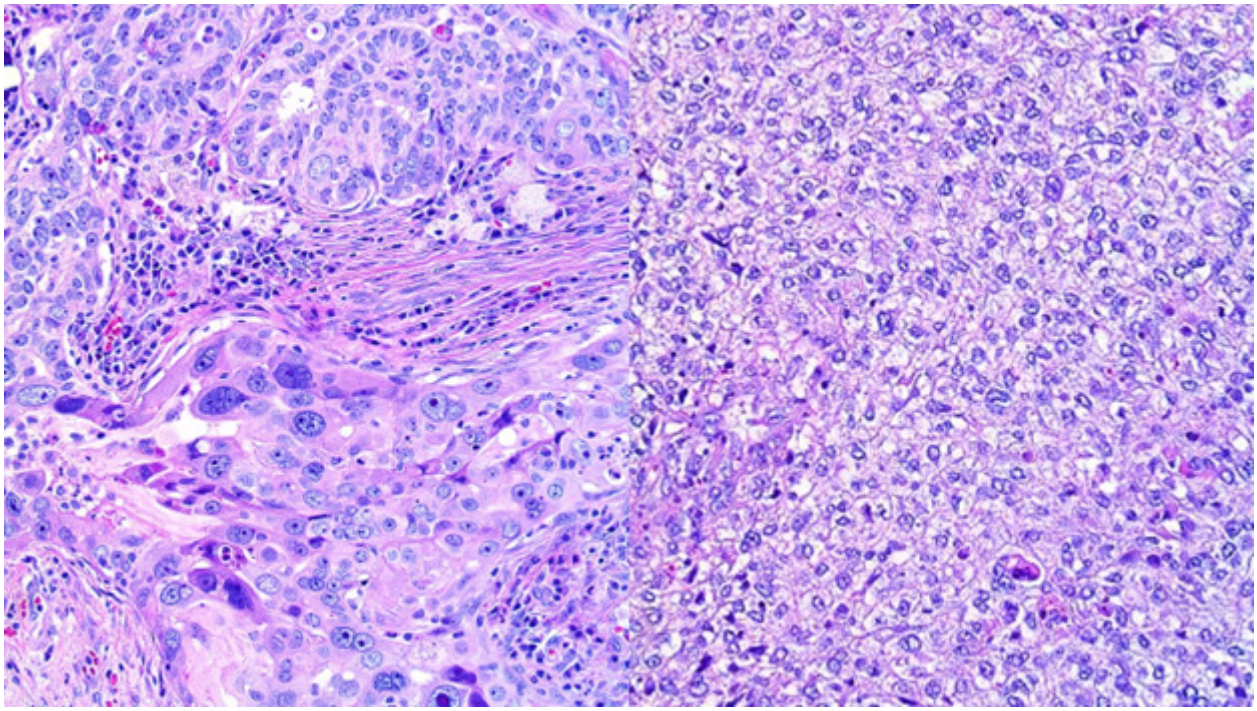

FIGURE 2. Mucinous carcinoma with intestinal features as seen in a portion of case 5.

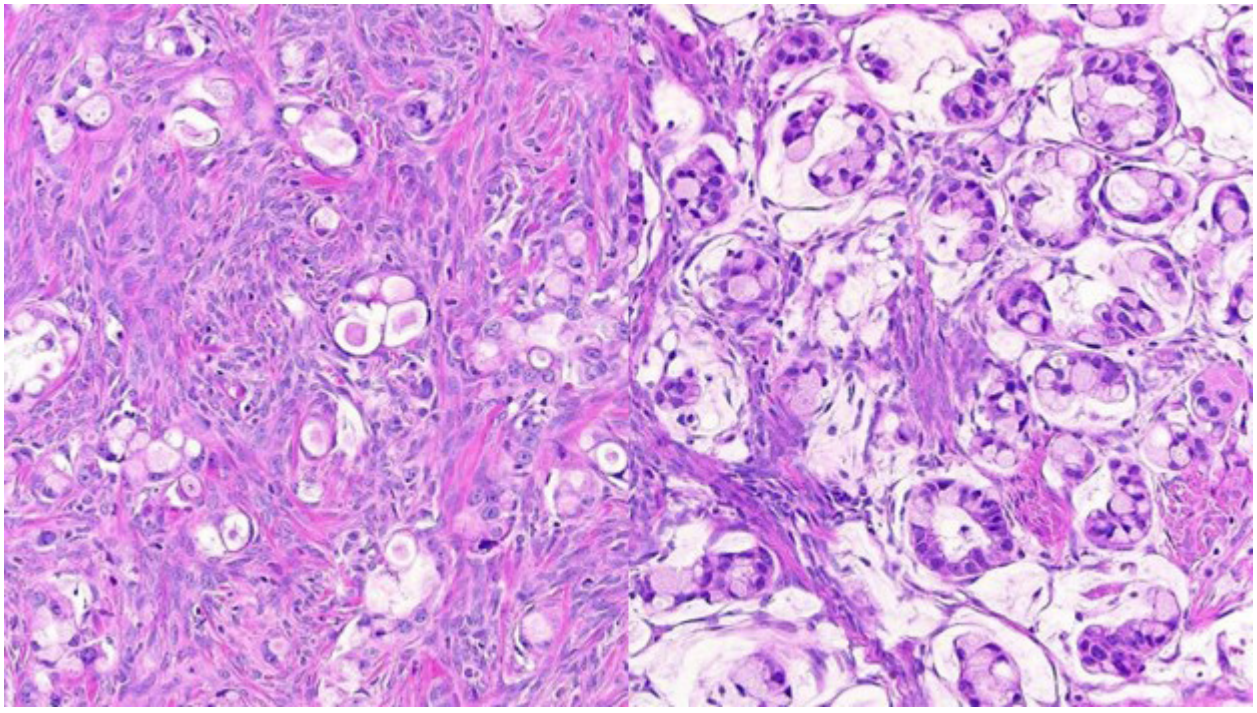

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FIGURE 3. Clear cell carcinoma as seen in a portion of case 4.

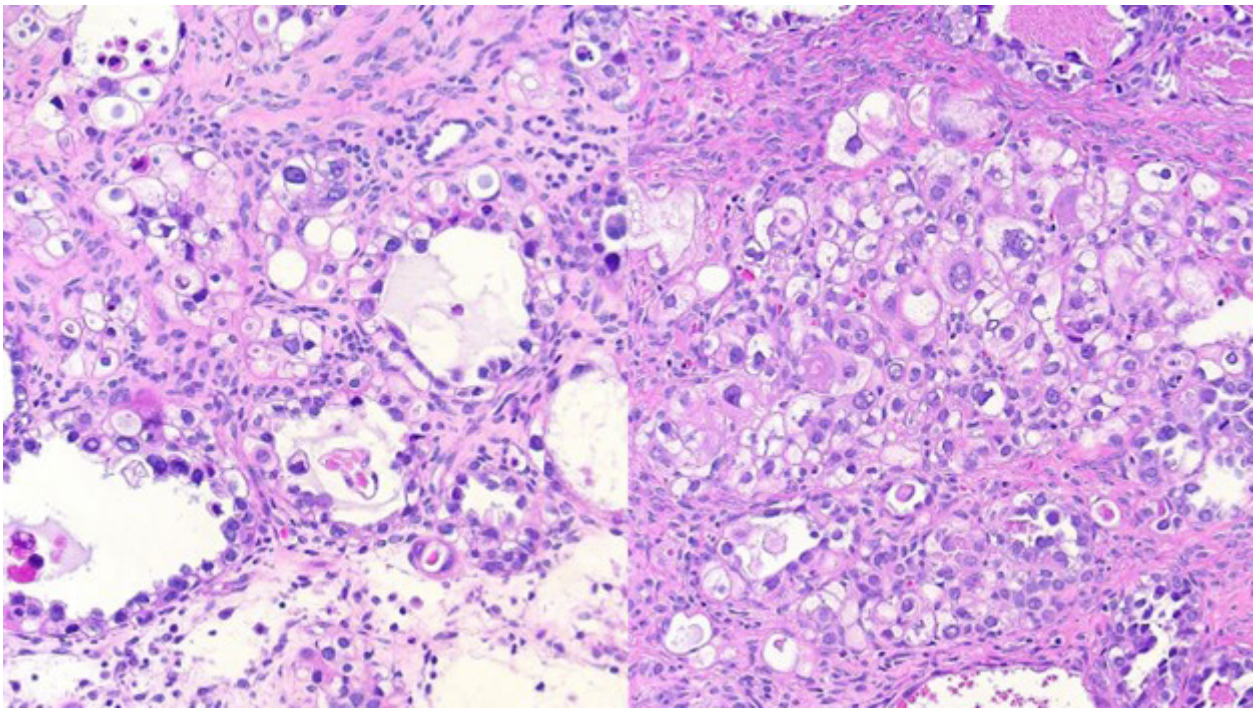

FIGURE 4. Low-grade serous carcinoma in situ (micropapillary serous carcinoma); and high-grade serous carcinoma with a transitional cell pattern as seen in case 6. Both low-grade and high-grade tumor components were WT1+.

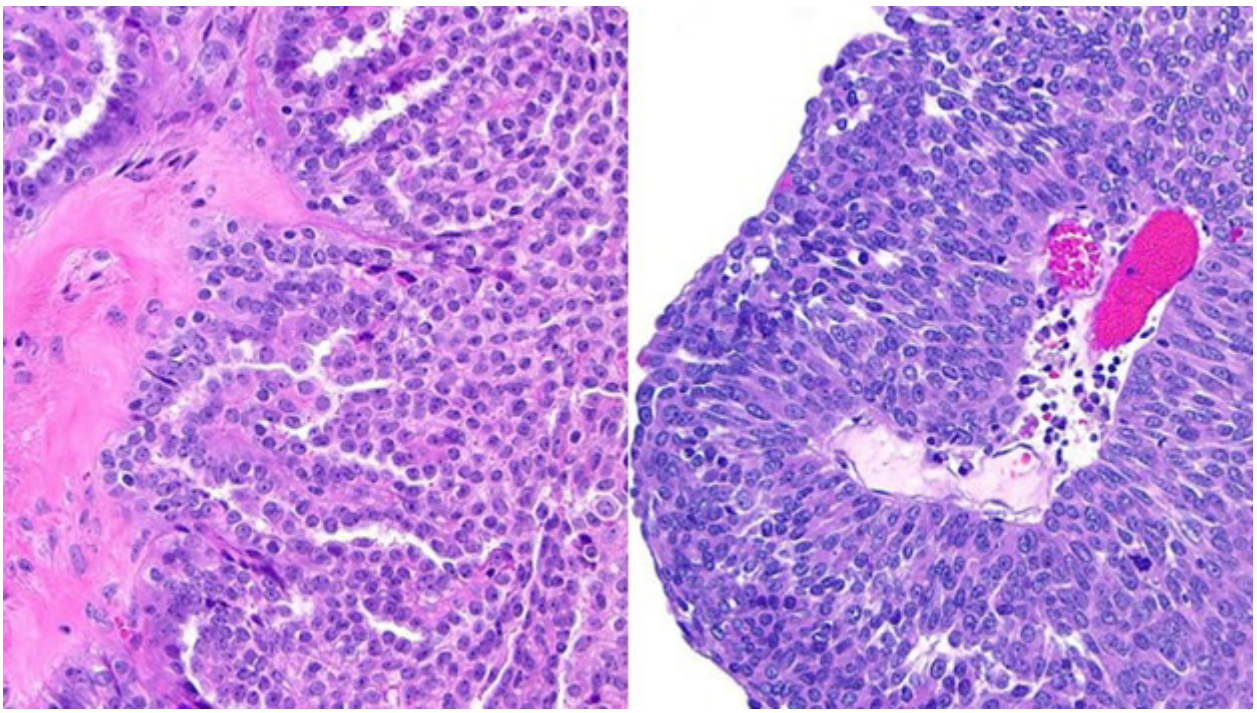

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Table 3. Immunohistochemical data

Case	CK7	CK20	CDX2	PAX8	WT1	ER	PgR	p53 mutation	PTEN staining	MSI*
1	+			+	+	+	+	+	+	Low
2	+			+	+			+	+	Low
3	+			+				+	-	Low
4	+		+	+	+	+		+	+	Low
5	+	+	+	+				+	+	Low
6	+			+	+			+	+	Low

*MLH1, MSH2, MSH6, PMS2; LOW = Positive staining for all nuclear proteins

Immunohistochemical stains were performed on a selected (typically, one) block from each of the tumors' high-grade portions. Immunohistochemical staining was considered "+" when at least 5% of cells stained. All cancers showed at least limited immunopositivity for CK7, PAX8, MLH1, MSH2, MSH6 and PMS2 (consistent with Mullerian epithelial MSI-low cancers). Staining for CK20 was seen in case 5 (that was also thought to show intestinal-type differentiation). CDX2 was positive in cases 4 and 5.

WT1 was positive in cases 1, 2 4, and 6; and cases 4 and 6 showed focal serous-type morphology with an admixture of WT1+ micropapillary features. In addition, case 6 exhibited an isolated focus of poorly differentiated high-grade carcinoma with WT1+ "transitional cell" morphology that was interpreted as serous carcinoma.

The high-grade tumor of Case 1 was positive for ERα and PgR, whereas that of case 4 was positive for ERα but negative for PgR. The high-grade components of all cases showed mutated type p53 staining with uniform strong nuclear decoration. One high-grade carcinoma with endometrioid morphology showed deleted-pattern PTEN staining, whereas the remaining tumors showed wild-type PTEN staining.

In addition to an endometrioid carcinoma component, Case 4 also showed foci of CDX2+ mucinous tumor and a clear cell carcinoma component (that selectively stained ERα-, PgR-, WT1- and Napsin-A+). A membrane roll from case 4 showed a region of benign/atypical endometriosis with clear-cell hobnail change that was also WT1- and Napsin-A+ but retained ERα and PgR immunohistochemical staining.

DISCUSSION

Ovarian seromucinous tumors were formally introduced into the WHO pathology lexicon in 2014. [4] Six years later, invasive seromucinous tumors were reclassified as endometrioid carcinomas. [5]

Historically, in 1988 Rutgers and Scully reported, in the journal, Cancer, on 30 borderline tumors that were lined by mucinous epithelium approximating that of the endocervix with papillae that were architecturally like those of serous borderline tumors. Forty percent of the tumors were synchronously bilateral and 30% were associated with endometriosis. Four were complicated by peritoneal implants, one by both peritoneal implants and lymph node metastasis and one by lymph node metastasis alone. Affected individuals were followed for an average of 3.7 years. In two cases, tumors developed in the conserved contralateral ovarian tissue; but no deaths occurred. The authors observed that these tumors exhibited important clinical and pathologic differences from intestinal mucinous borderline tumors but displayed many similarities to mixed-epithelial borderline tumors of Mullerian epithelial type. [6]

One month later, the same authors reported (in the same journal) 36 borderline tumors with papillae architecturally like those of serous tumors but lined by more than one Mullerian cell type. Twenty-two percent of the tumors were bilateral; all were ovary-confined; and 53% were endometriosis-associated. Thirty-four patients were followed for a mean interval of 4.8 years. Tumor developed in the contralateral ovary in one patient 2 years after unilateral salpingo-oophorectomy. Three patients had pelvic recurrences between 7 months and 3 years; again, none died. As with their Mullerian mucinous papillary cystadenomas of borderline malignancy, these tumors differed clinically and pathologically from intestinal-type mucinous borderline tumors, but were like Mullerian mucinous borderline tumors and, to a lesser extent, to serous borderline tumors. [7]

What unified these tumors was their shared papillary architecture resembling that of a serous borderline tumor. What separated them was that tumors of the first instance showed endocervical-type, mucin-producing columnar cells, and those of the second instance showed two or more Mullerian-type epithelial cells. The Mullerian cell types included serous-, mucinous-, endometrioid-, and squamous-type cells as well as "indifferent cells" with abundant eosinophilic cytoplasm. The two tumor types were, in the end, united into the single WHO taxonomic entity of seromucinous tumor. [4]

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Seromucinous tumors included benign, borderline, and (previously recognized) uncommon malignant neoplasms that are often bilateral, often associated with endometriosis, include a variety of Mullerian-type epithelial cells, and show endocervical but not pure gastrointestinal mucinous differentiation.

Taylor and McCluggage provided a detailed account of so-called seromucinous carcinoma morphology. Most tumors showed predominant papillary architecture with lesser glandular, microglandular, and solid growth. The essential feature was an admixture of cell types. Most cases had endocervical-like mucinous cells; in some tumors there was a predominant endometrioid component; and other cell types, present in varying proportions, encompassed hobnail and clear, eosinophilic, squamous, and occasional signet-ring cells. Most cases exhibited infiltrates of PMN neutrophils, an observation that some experts have come to accept as the mark of seromucinous tumors. [8] Endometriosis and seromucinous borderline tumor, demonstrative of an adenoma-to-carcinoma neoplastic evolution, was present in the same ovary in several cases. [9]

The 2014 WHO classification adopted seromucinous ovarian tumors as a new category, distinct from mucinous tumors showing gastrointestinal differentiation. [4] These tumors were characterized by frequent association with endometriosis and bilaterality, microscopic appearance of papillary architecture, and admixture of a variety of Mullerian-type epithelium. They were deemed to be endometriosis-related ovarian neoplasms, along with endometrioid and clear cell tumors, indeed recent molecular studies have suggested that seromucinous tumor can be considered as a variant of endometrioid tumor, hence their reclassification as endometrioid carcinomas in the 2020 WHO lexicon of ovarian tumors. [5]

The range of the epithelial morphologies of seromucinous tumors reflects the capability of Mullerian epithelium to undergo metaplasia, which may be thought of as the end-differentiation of a unipotent progenitor cell. Nicolae et al. recognize endometrial metaplasia as "...a morphologically heterogeneous group of proliferations and differentiations found in eutopic and ectopic endometria". Mullerian epithelial tissue, including endometriosis, has the capacity, through its progenitor cells, to undergo various differentiations into various types of epithelia; and continuous endometrial growth permits multiple occasions for genetic changes, presenting an opportunity for a tissue to invoke the many potentials of its progenitor cell. [10] To appreciate the metaplastic changes of the ectopic endometrium of endometriosis (and its related neoplasms), it is worthwhile to review some of the metaplastic changes common to Mullerian epithelium. In this regard, we specifically address cilia, transitional cell metaplasia, intestinal mucinous metaplasia, clear cell changes, and eosinophilic changes.

Cilia. Cilia are a common feature of Mullerian epithelia and are integral components of the surface epithelium of late proliferative endometrium and of fallopian tube lining cells. The ubiquitous presence of cilia in the cervix, isthmus uteri and normal proliferative endometrium suggests that ciliated cells may be functional accommodations and are not always metaplastic in nature. For example, the surface of late proliferative endometrium is carpeted by ciliated cells that may serve to move spermatozoa in the direction of the fallopian tube. On the other hand, "ciliated cell hyperplasia" describes the condition when most cells of surface epithelium, including endometrial glands, are prominently replaced by ciliated cells (as seen with prolonged unopposed exposure to estrogens). Unlike "ciliated cell hyperplasia", "tubal metaplasia" (a term often loosely used interchangeably with "ciliated cell hyperplasia") requires the presence of the three cell types that constitute tubal epithelium (ciliated, secretory, and intercalary cells) along with WT1+ nuclear decoration of its epithelium.

Mullerian epithelium is proficient in functional and hormonally driven ciliagenesis, or it can differentiate into fallopian tube epithelium. Notably, normal surface endometrial ciliated cells and those seen in endometrial endocrine hyperplasia and carcinoma are WT1- whereas ciliated fallopian tube cells are WT1+ (and reflect the predominant cell population of serous tumors). Both Mullerian-epithelial-derived WT1- and WT1+ ciliated cells may be seen in endometriosis and in seromucinous ovarian tumors. FIGURES 5 and 6.

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FIGURE 5. Endometriosis with ciliated cells and WT1- nuclei, consistent with ciliated cell hyperplasia.

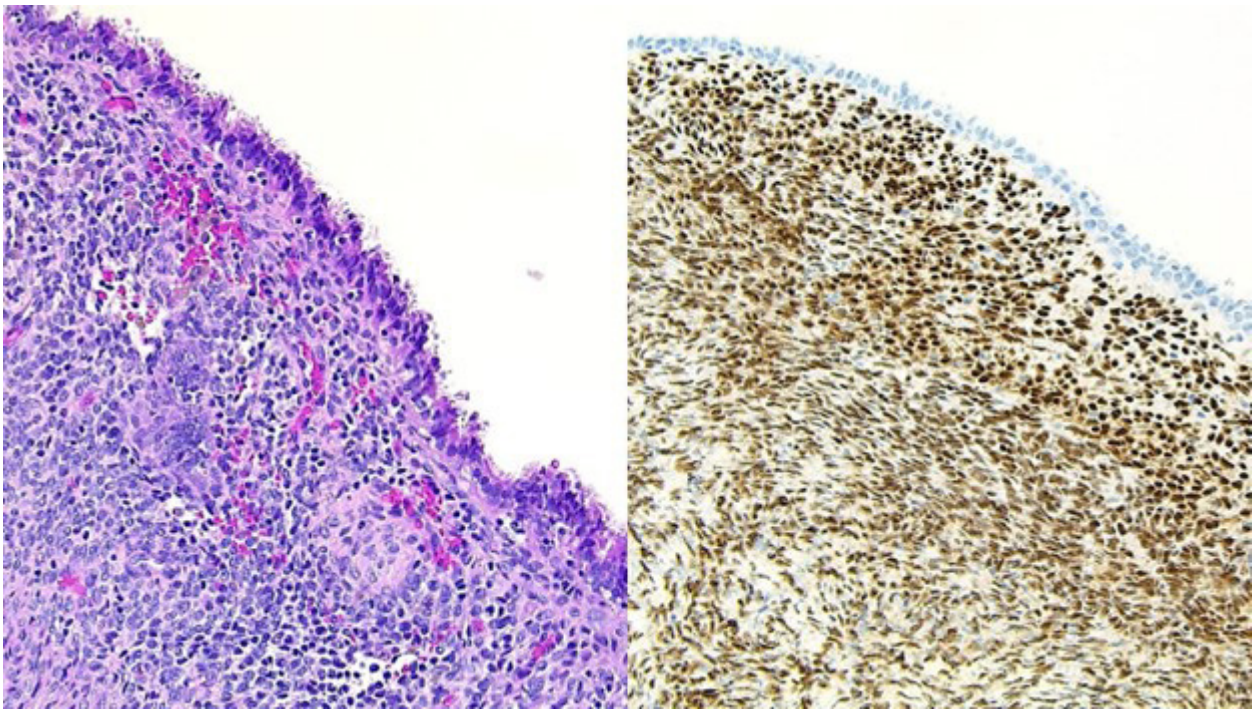
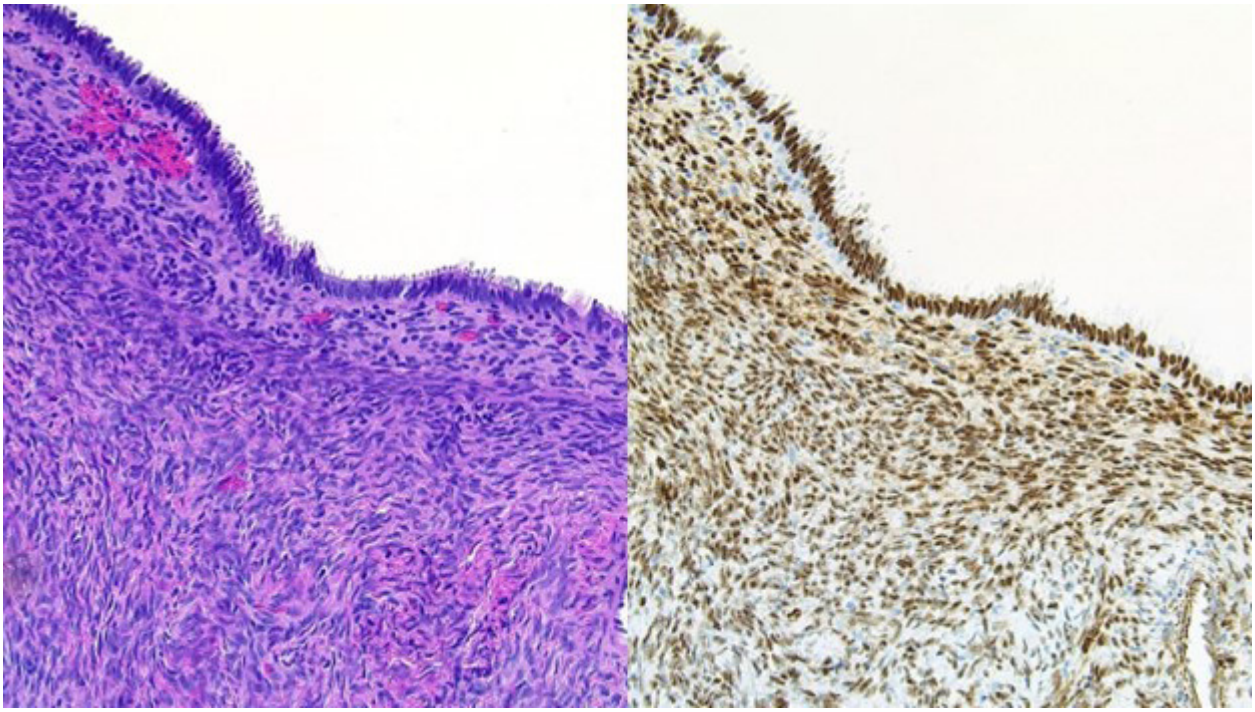


FIGURE 6. Endometriosis with ciliated cells and WT1+ nuclei, consistent with tubal metaplasia.



Brenner tumors. Brenner tumors show transitional-like epithelium resembling that of Walthard nest epithelium and they may at times show intestinal-type mucinous cells and these tumors have been proposed as precursors to intestinal-type mucinous ovarian tumors. Some experts feel that (in contrast to serous, endometrioid, and clear cell tumors) since intestinal mucinous tumors do not express ERα or PgR, they are non-Mullerian-derived (parenthetically, clear cell carcinomas are also ERα and PgR negative). Rather, they postulate that non-germ cell mucinous tumors develop from Brenner tumors, which are in turn derived from nests of transitional epithelium at or near the tubal-peritoneal junction where Mullerian-derived tubal epithelium is in

close contact with the mesothelium of the tubal serosa and ovarian surface epithelium. [11]

It has been shown that fallopian fimbriae, endowed with a Mullerian epithelial lining, may undergo an alteration in which the normal tubal epithelium is replaced by metaplastic cells resembling benign transitional (urothelial) cells resembling those of the urinary bladder. Rabban et al. stated that transitional cell metaplasia is under-recognized in the tubal fimbriae, although it has been reported as present in about 25% of risk reducing salpingo oophorectomy specimens where it involves the edges or base of the fimbrial plicae; and, as with Walthard nests, transitional cell metaplasia of fallopian tube origin shows uniform nuclei with pale chromatin, nuclear grooves, and abundant cytoplasm. [12]

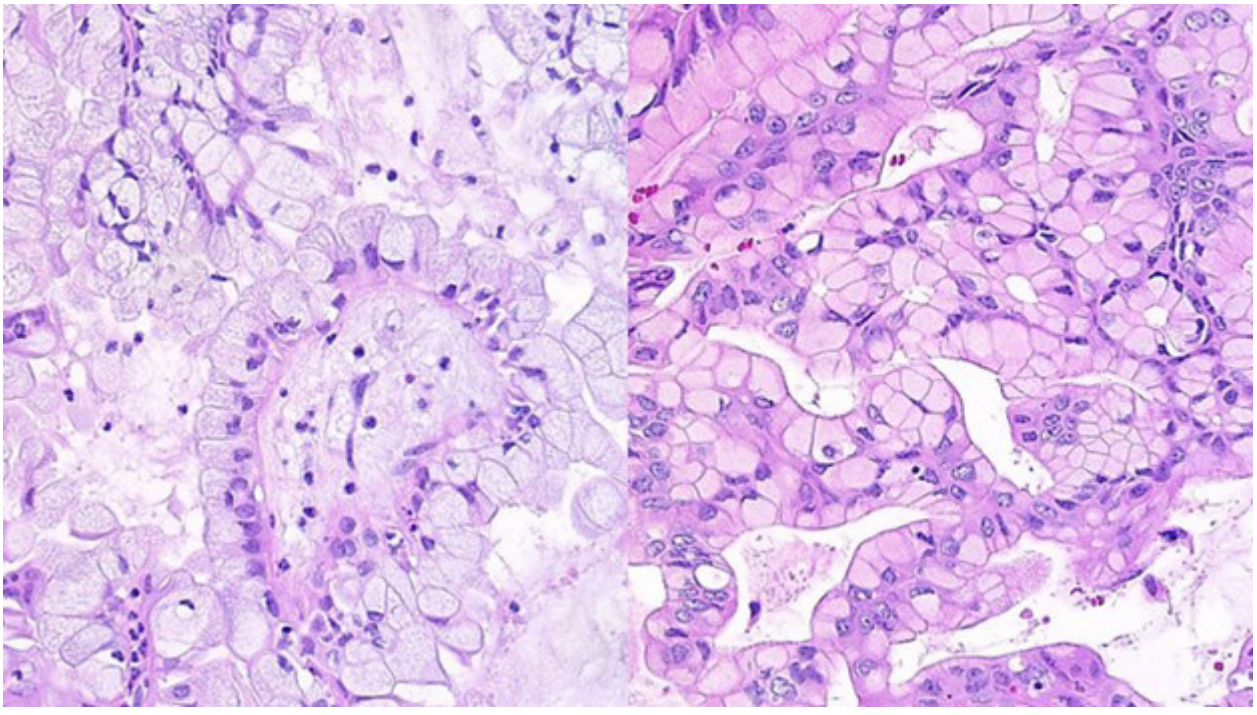
Cytologically and histologically, transitional cell metaplasia of the uterine cervix resembles Walthard nest epithelium—and the uterine cervix is uninfluenced by any connection with the mesothelium. Cervical transitional cell metaplasia involves ectocervix, transformation zone, endocervix, and vagina—all regions that are proximal to or derived from Mullerian epithelium. [13], [14]

We posit that the Walthard nest/Brenner tumor alternative to mucinous ovarian tumors, although probably correct, may not be a proposal that excludes Mullerian epithelial participation, since the Walthard nest, along with fallopian tube and cervical transitional cell metaplasia are of Mullerian origin.

Intestinal mucinous metaplasia. Intestinal mucinous metaplasia is seen throughout the female genital tract and is not limited to Brenner tumors; and, as with fallopian tube transitional metaplasia, mucinous metaplasia of fallopian tube epithelium is a known phenomenon. Wong et al reported on mucinous metaplasia of the fallopian tube, and, in their study, 11 of 23 individuals showed mucinous change in the fallopian tubes in the absence of gynecologic, appendiceal, or pelvic tumors. The mucinous change in these patients was interpreted to represent a metaplasia and their fallopian tubes often showed other benign changes including chronic inflammation, and other metaplastic changes including transitional metaplasia and clear cell changes. [15]

We hypothesize that intestinal metaplasia, as an expression of Mullerian epithelial metaplasia, may also be seen in seromucinous tumors and that the metaplastic cells are likewise of Mullerian origin. Endometrial intestinal mucinous metaplasia can be regarded as one of the many manifestations of Mullerian stem cell differentiation and it has been described in cases of appendiceal endometriosis, where it has been confused with low-grade appendiceal mucinous neoplasia. [16], [17], [18] FIGURE 7.

FIGURE 7. Two borderline seromucinous tumors. The one illustrated in the left image shows basophilic endocervical-type mucinous metaplasia and the one illustrated in the right image shows more eosinophilic and glassier intestinal-type mucinous metaplasia that resembles either pancreatic duct or gastric foveolar epithelium.



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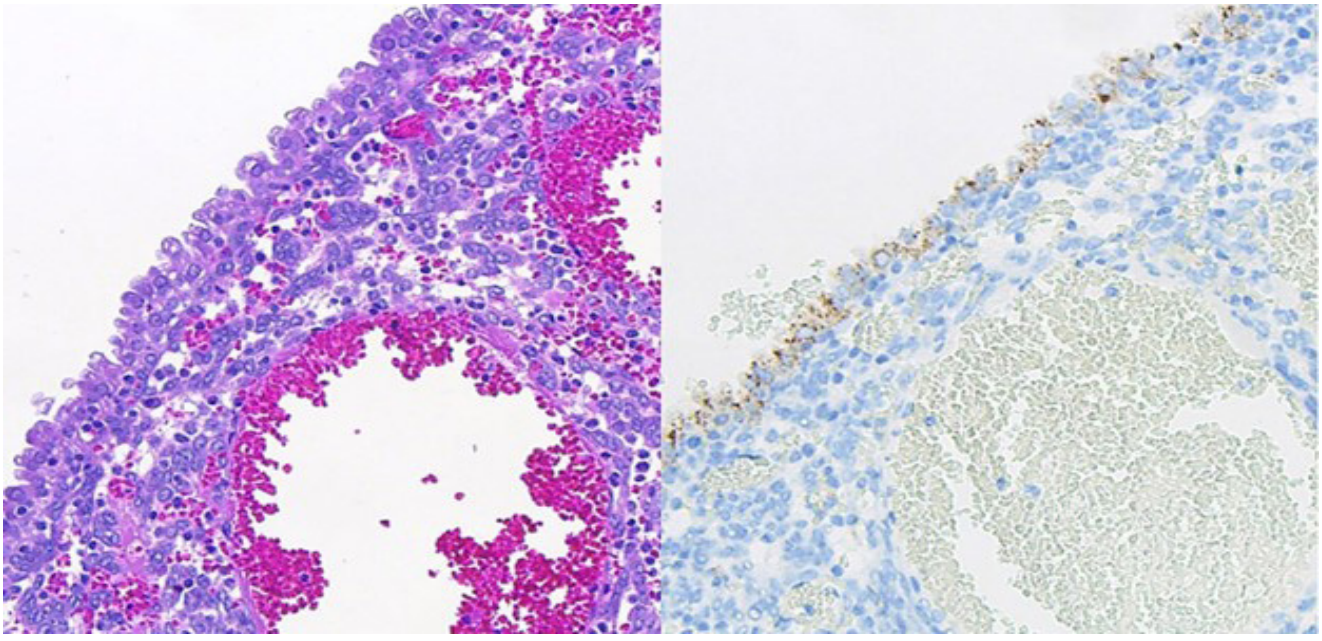
Misdraji et al. described 6 cases of appendiceal or cecal endometriosis with intestinal metaplasia that grossly and microscopically mimicked appendiceal mucinous tumors [19]; and, in a paper by Mitchell et al., one can see images of immunohistochemical staining showing CK7 positivity limited to endometriotic epithelium, CK20 positivity limited to intestinal-type epithelium, CD10 positivity of endometriotic stroma on which both endometriotic and intestinal-type epithelia rest and CD10 positive endometriotic stroma that surrounds intestinal-type glands. In this paper, ERα decorates the nuclei of endometriotic epithelium and stroma, but not those of intestinal-metaplastic epithelium. [18] Moreover, Nicolae et al. described two cases of endometrial intestinal metaplasia, one involving an endometrial polyp, characterized by the presence of intestinal-type epithelium containing goblet and neuroendocrine cells that stained positive with CK20, CDX2, chromogranin, and villin with one case showing concomitant intestinal and pyloric metaplasia in the endocervix. [20] Intestinal mucinous metaplasia may be seen in otherwise unremarkable endocervical glands [21] and the glands of lobular endocervical glandular hyperplasia look like gastric pyloric glands. [22] McCluggage et al. demonstrated that intestinal-type cervical adenocarcinoma in situ and adenocarcinoma exhibit a partial enteric immunophenotype with consistent expression of CDX2. In their study, although CK20 was always negative in usual-type adenocarcinomas in situ, 5 of 6 usual-type adenocarcinomas exhibited CK20 immunoreactivity and all their intestinal-type adenocarcinomas were CK20 positive and CDX2 was diffusely expressed in all cases of intestinal-type adenocarcinoma in situ. The authors speculated that since all their cases of intestinal-type adenocarcinoma in situ were associated with foci of usual-type adenocarcinoma in situ, that intestinal type neoplasia develops from usual type neoplasia because of a metaplastic process. The findings of their study provide further evidence of the ability of Mullerian epithelium to differentiate along intestinal lines. [23]

In an immunohistochemical analysis of a large series of cervical and vaginal gastric-type adenocarcinomas, Carleton et al. documented positive immunohistochemical staining for, among other things, CK7, PAX8, CK20 and CDX2; and most cases were simultaneously negative for ERα and PgR. [24] Mullerian-derived cells throughout the female genital tract may show intestinal differentiation; and, as with endocervical and endometrial adenocarcinomas, primary ovarian mucinous tumors may express markers in common with gastric, intestinal, and pancreatobiliary epithelial cells. [25], [26]

Clear cell like hobnail change. In endometriosis and in seromucinous tumors we have found that some forms of hobnail change are like the change seen after endometrial curettage for abnormal bleeding where the surface and/or glandular epithelia are replaced by teardrop-shaped cells and appear reminiscent of the cells seen with Arias-Stella phenomenon, clear cell carcinoma or the detached eosinophilic cells of a serous adenocarcinoma. In gestational and puerperal endometria hobnail change represents an Arias-Stella phenomenon. Similarly, it can be found in Mirena coil endometria. [10] In these instances, and in endometriosis associated with seromucinous tumors, we have seen positive cytoplasmic immunohistochemical staining for Napsin-A and P504S and negative WT1 staining, as reported with clear cell adenoma and clear cell carcinoma (but generally associated with retained ERα and PgR nuclear decoration). FIGURE 8.

FIGURE 8. Endometriosis with Napsin-A positive clear cell changes as seen in case 4. A portion of the high-grade carcinoma associated with this change was a clear cell carcinoma.



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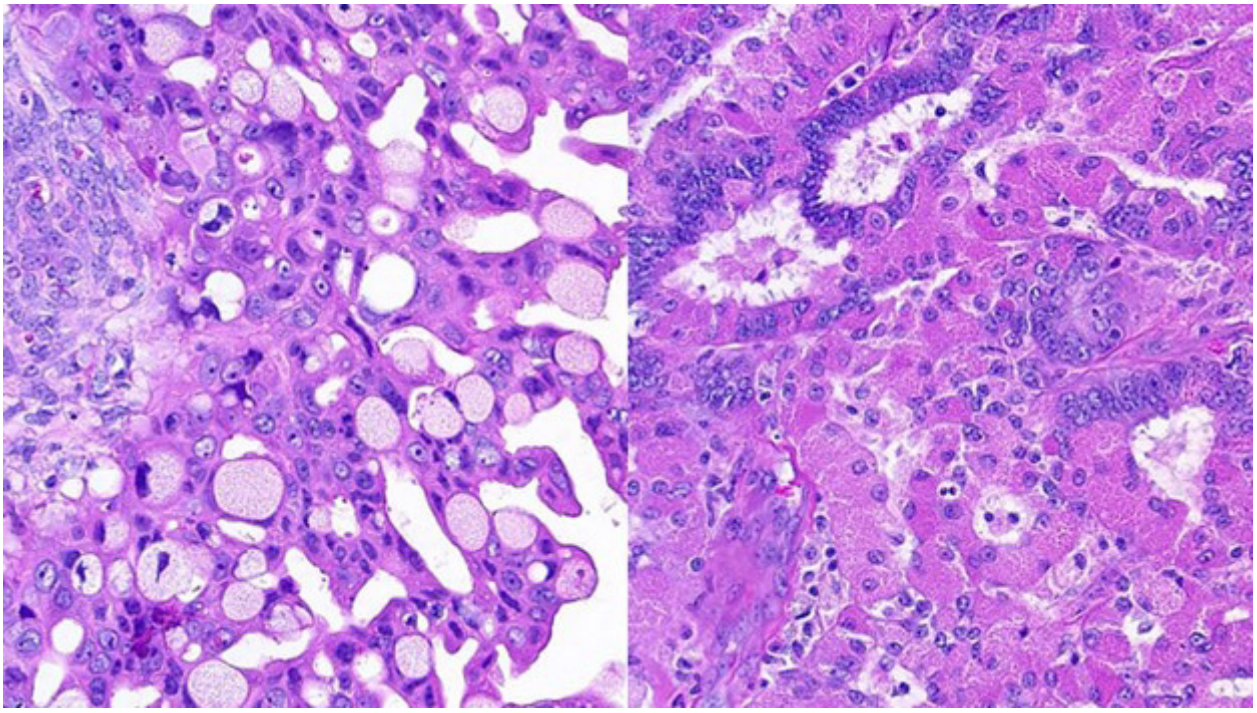
Eosinophilic changes. Oxyphilic, oncocytic and eosinophilic changes are all terminologies that have the non-specific histological feature of eosinophilia. The nature of these eosinophilic cells is poorly understood. Some can be a form of immature mucinous metaplasia, others, a surface degenerative change. [10] For example, in the case of serous borderline tumor, some eosinophilic cells, although appearing in the context of increased cellular proliferation, do not affect tumor aggressiveness and may represent cells in senescence; and, in ARID1A deleted seromucinous tumors, eosinophilic cells retain ARID1A expression in contrast to the rest of the epithelial cells, further supporting their classification as nonproliferating senescent cells. [27] Also, cells resembling the mitochondrion-rich oxyphilic variants of ovarian endometrioid carcinoma can also occur in the context of seromucinous carcinoma. [28], [29] FIGURE 9.

FIGURE 9. Eosinophilic changes may represent degenerative cell changes as illustrated in the left image or they may be associated with oncocytic changes as in the low-grade endometrioid carcinoma that is illustrated in the right image.



The assortment of epithelial morphologies seen with seromucinous tumors reflects the broad range of epithelial metaplastic changes seen with ovarian endometriosis. For example, Fukunaga and Ushigome evaluated 315 consecutive cases of ovarian endometriosis. Two hundred seventy-five were not associated with atypia or malignancy. Epithelial metaplasia was observed in 162 (63%) cases. Ciliated cell and eosinophilic metaplasia were the commonest (44%, respectively), followed by hobnail (13%) and mucinous (4%) types. In their four cases of "Mullerian mucinous borderline tumors", ovarian endometriosis with mucinous metaplasia adjoined the tumor and the authors speculated that the development of the borderline tumors may be contingent on mucinous metaplasia in ovarian endometriosis. [30] Indeed, this close relationship with endometriosis, as with endometrioid and clear cell tumors, has led experts to christen seromucinous tumors "mixed Mullerian tumors" [31]; hence including them among the endometriosis related ovarian neoplasms. [8]

Unlike pure intestinal mucinous tumors, seromucinous tumors show unilocular or paucilocular cysts with thickened cyst walls that display papillary projections on their inner surface and typically lack mural nodules (as are often seen with pure intestinal-type tumors). Cyst contents vary and can be hemorrhagic (resembling the cyst contents of endometriosis), serous, mucinous, or mucopurulent (due to the frequent presence of PMN neutrophils). A shared feature with atypical proliferative serous tumors is the papillary structure with its hierarchical branching and bulbous and edematous to sclerotic stroma. What differs is the lining cells that are composed of varied Mullerian epithelial cells (the commonest being endocervical-type mucinous, ciliated, endometrioid, and indifferent eosinophilic cells). [1] FIGURE 10.

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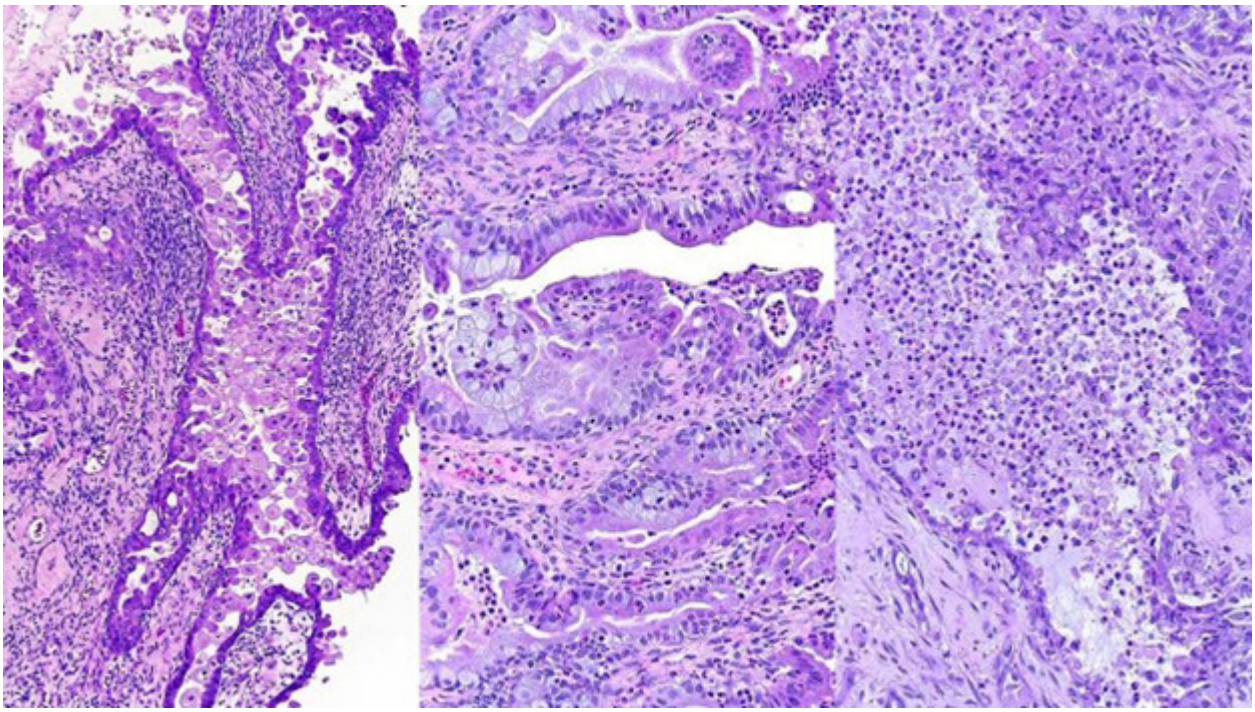
FIGURE 10. Seromucinous tumors commonly show tripartite papillary branches, endocervical type mucinous epithelium and mucopurulent material due to the presence of polymorphonuclear leukocytes.



Taylor and McCluggage's series of 19 ovarian seromucinous carcinomas is the only published series with a substantial number of cancer cases. [9] As with our cases, histological features were highly variable both within and between individual tumors with a characteristic feature being an admixture of cell types. In their series, endometriosis was identified in the same ovary in 10 cases, and in 10 there was a component of seromucinous borderline tumor. Most tumors were grade 1 or 2 according to the FIGO grading system for endometrioid carcinomas. Immunohistochemically, there was consistent positive staining with CK7, ERα, PgR, CA125, PAX8, and CA19.9. WT1 was usually negative, and CK20 and CDX2 were negative in all cases tested. Our series had 6 tumors with high-grade components, all with p53 mutation-pattern immunohistochemical staining in the high-grade component; and, among these high-grade neoplasms we discovered tumors with combinations of endometrioid, clear cell, serous (previously illustrated), and mucinous morphology.

Unusual, often aberrant staining patterns may be seen in endometriosis related ovarian neoplasms. Some are negative for the Mullerian epithelial markers CK7, PAX8, CA125, and ERα, either individually or in combination. These markers are often assumed to be positive in almost all endometriosis related ovarian neoplasms, but, as McCluggage has observed, this is not the case. In addition (and reported among our cases), CK20, CDX2, and WT1 may be positive in endometriosis related ovarian neoplasms. McCluggage states that it has been his experience that WT1 is especially likely to be positive in ovarian low-grade endometrioid carcinomas, and this may result in misdiagnosis as a serous carcinoma; likewise, positive staining with CK20 and CDX2, together with negative staining with Mullerian markers has been known to afford the erroneous diagnosis of a metastatic colorectal adenocarcinoma within the ovary. [32]

McCluggage observed that immunohistochemically, seromucinous borderline tumors were usually positive for CK7, ERα, PgR, CA125, and PAX8. They were typically negative, but sometimes focally positive, for WT1, whereas they were usually (but as we observe, not always) negative for CK20 and CDX2. [32] Taylor and McCluggage described the immunohistochemical staining of seromucinous tumors and found CK7 (17/17 cases), estrogen receptor protein (16/16 cases), progesterone receptor protein (6/7 cases), CA125 (15/15 cases), PAX8 (8/8 cases), monoclonal CEA (8/13 cases), and CA19.9 (8/9 cases) staining; and, less commonly, WT1 (2/13 cases) staining. [9]

Despite their name, seromucinous tumors are not "mucinous" in the purely intestinal sense of the word. Purely intestinal mucinous tumors are not commonly associated with endometriosis. Similarly, seromucinous tumors are not purely serous. Although fallopian tube epithelium is both Mullerian and serous, the absent to limited expression of WT1 in seromucinous tumors does not support a one-on-one connection to purely serous neoplasms. Additionally, a high proportion of seromucinous tumors lose ARID1A (BAF250a) expression and that contrasts with usual serous tumors, which do not. [31]

From a practical standpoint, one of the important contrasting features with purely serous tumors is that seromucinous tumors lack strong and uniform nuclear decoration with WT1 (that effectively defines the serous group of tumors) and one of the significant contrasting features with purely intestinal mucinous tumors is their infrequent decoration with CK20. CDX2 cannot be used as a CK20 surrogate since nuclear β-catenin and CDX2 may be expressed in seromucinous tumors with squamous differentiation and morular metaplasia; and nuclear β-catenin and CDX2 expression (a phenomenon that is well established in endometrial cancers) identifies good prognosis ovarian endometrioid cancers. [33] To summarize, uniform and strong WT1 or uniform and strong CK20 staining militates against the diagnosis of seromucinous/endometrioid tumor. In contrast, except for high-grade seromucinous-associated carcinomas, our experience has been that all borderline seromucinous tumors uniformly express hormone receptors. On the other hand, neither ERα nor PgR was expressed in 30 atypical proliferative intestinal mucinous tumors or in 11 invasive intestinal mucinous carcinomas studied by Vang et al. [34] To be sure, these features do not militate against purely serous or purely intestinal-mucinous tumors being Mullerian-derived, rather they argue for their unique and separate classification apart from the seromucinous group of tumors in the taxonomic hierarchy of ovarian epithelial tumors.

Nakamura et al. described a bilateral FIGO IB ovarian tumor with an admixture of seromucinous borderline tumor and clear cell carcinoma. Both their patient's ovaries showed endometriosis and bilateral multicystic tumors with exophytic papillary growths lined by tall columnar mucinous or cuboidal ciliated serous cells as well as cells with eosinophilic cytoplasm. PMN neutrophil infiltration was present. Clear cell carcinomas were found in both ovaries. [35] In their paper, the authors recognized Wani and Notohara's report of a clear cell carcinoma that had arisen within a benign mucinous tumor [36] in which a unilocular cyst without a solid mass showed a histologic continuum between the clear cell and mucinous components. One of our high-grade tumors had an ERα-, PgR-, and WT-1-, Napsin-A+, and p53 mutated clear cell carcinoma component along with WT1+ serous and CDX2+ mucinous components.

Okumura et. al. reported a 53-year-old Japanese woman with anaplastic carcinoma that was present within a cystic ovarian seromucinous tumor of borderline malignancy. She had FIGO IIIB disease, and accordingly she received 6 cycles of adjuvant paclitaxel and carboplatin chemotherapy and was reported as alive without disease at 3 years. [37] Of interest, the authors noted that ovarian mucinous borderline malignancy in Japan encompasses 38% of intestinal, 36% of seromucinous, and 26% of mixed types; whereas 90% of ovarian mucinous borderline malignancies in Western countries are of intestinal type, adding yet another ovarian epithelial cancer to ovarian clear cell carcinoma that appears to display geographic and racial group differences among Asian women and western women.

According to a recent comprehensive review by Nagamine and Mikami [1], seromucinous carcinoma is rare with, at the time of their publication, fewer than 40 cases reported in the English literature. Outspoken seromucinous carcinoma shares many gross and microscopic features with its borderline counterpart including papillary projections and an admixture of various Mullerian cell types. It regularly shows an adenoma-to-carcinoma spectrum with an admixture of benign, borderline, low-grade malignant and even high-grade malignant features. The malignant tumor may show high-grade cytologic atypia and architectural complexity with cribriform, solid, transitional, and even anaplastic growth patterns. Tumor invasion may be expansile or destructive.

CONCLUSION

A recent study by Hu et al, comprising a review of 12 cases of seromucinous carcinoma, showed that, in a matched cohort, the prognosis of ovarian seromucinous carcinoma was closer to that of ovarian mucinous carcinoma than that of ovarian endometrioid carcinoma, and the authors suggested that retaining "seromucinous carcinoma" as a distinct taxonomic entity deserves a second look. [38] We conclude that the subtyping of Mullerian epithelial tumors is useful only if it predicts type-specific outcomes—in short, it must make a difference to be a difference. The action of different initiators, of diverse niches, of dissimilar HOX gene assignments, of a progressive adenoma-to-carcinoma sequences as opposed to the abrupt action of a driver-gene mutation (specifying progressive as opposed to abrupt tumorigenesis) can all cause a "common cell of origin"—in this case, the Mullerian epithelial cell—to be assigned different developmental pathways that eventuate in dissimilar tumor types, presentations, and prognoses. What is important is recognizing that seromucinous tumors can, most likely by way of an adenoma-to-carcinoma sequence, result in high-grade tumors; and, when they do, they can behave aggressively and eventuate in patient death.

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