Published in final edited form as:
Am J Surg Pathol. 2008 December ; 32(12): 1800–1806. doi:10.1097/PAS.0b013e318181a7ce.

Low-grade Serous Carcinoma of the Ovary Displaying a Macropapillary Pattern of Invasion

Anna Yemelyanova, M.D.[1], **Tsui-Lien Mao, M.D.**[1,3], **Naomi Nakayama, M.D.**[1], **Ie Ming Shih, M.D.,Ph.D.**[1,2], and **Robert J Kurman, M.D.**[1,2]

[1]Department of Pathology, The Johns Hopkins Hospital, Baltimore, Maryland [2]Departments of Gynecology and Obstetrics, The Johns Hopkins Hospital, Baltimore, Maryland [3]Department of Pathology, National Taiwan University Hospital, Taipei, Taiwan

Abstract

Invasive micropapillary serous carcinoma (MPSC) also designated “low-grade serous carcinoma” (LGSC) of the ovary is characterized by small micropapillae that infiltrate underlying tissue (ovarian stroma). On occasion these tumors in addition to the micropapillae contain large macropapillae lined by bland epithelium. In rare cases the entire tumor is composed of macropapillae. In these cases the question of whether this is an invasive carcinoma or an unusual type of adenofibroma has been raised. The goal of this study was to describe this unusual macropapillary pattern of invasion in low-grade serous carcinoma.

Cases of LGSC containing macropapillae were retrieved from the files of the Johns Hopkins Hospital. In addition to a detailed morphologic analysis, the mutational status of *KRAS* and *BRAF* in the macropapillary, noninvasive and invasive MPSC components was analyzed by nucleotide sequencing. There were fourteen cases containing macropapillae (eleven cases of low-grade serous carcinoma, two cases of APST with microinvasion and one case of APST with a focus of LGSC with macropapillae in perivaginal soft tissue). In three cases extraovarian metastases contained macropapillae. Molecular analysis of the primary tumor components (macropapillary, non-invasive and invasive MPSC and/or APST) was performed in seven cases and of a lymph node metastasis with macropapillae in one case. The identical *KRAS* mutation was detected in all of the analyzed components of the primary ovarian tumors in four cases. In one of these cases macropapillae in the lymph node metastasis contained a *KRAS* mutation identical to the primary tumor. The *BRAF* mutation identified in one case was identical in all components of the ovarian tumor. The identical mutations in the macropapillae and the other tumor components in each case indicate that they are clonally related. The finding of macropapillae within lymph nodes supports the interpretation that the macropapillary component is another manifestation of invasion in LGSC. The recognition of this pattern is important, especially in cases when a tumor is composed entirely of macropapillae.

Keywords

ovarian cancer; low grade serous carcinoma; macropapillary serous carcinoma; micropapillary serous carcinoma; serous borderline tumor; atypical proliferative serous tumor

Address correspondence to Anna Yemelyanova, M.D., The Johns Hopkins Hospital, Department of Pathology, 401 North Broadway, Weinberg building, room 2242, Baltimore, MD 21231, phone: (410) 955-3580, fax: (410)614-1287; e-mail: E-mail: ayemely1@jhmi.edu. Dr. Nakayama's current affiliation is Shimane University, Japan.

Micropapillary serous carcinoma (MPSC) was described in 1996 as a variant of a noninvasive serous tumor.[4] It has also been reported as "serous borderline tumor (SBT), micropapillary type". Subsequently, MPSCs were further subdivided into non-invasive and invasive types.[26]. The invasive MPSC is the most common histologic type of low-grade serous carcinoma (LGSC).

The controversy in the nomenclature of low grade serous tumors of the ovary was addressed at The Borderline Ovarian Tumor Workshop, Bethesda, MD 2003.[2] It was concluded the terms "borderline tumor", "tumor of low malignant potential", and "atypical proliferative serous tumor" are equivalent. In this report we use the term "atypical proliferative serous tumor" (APST) and non-invasive micropapillary serous carcinoma (MPSC) for serous borderline tumors with a micropapillary pattern. Several studies suggest that non-invasive tumors with a micropapillary pattern are low-grade carcinomas.[4,17,26] Recently presented preliminary data from a large long term follow up study from MD Anderson Cancer Center comparing APST and non-invasive MPSC to invasive MPSC demonstrated that when the micropapillary component of a non-invasive tumor involves greater than ten percent of the neoplasm, the behavior is the same as that of invasive LGSC.[13]

Molecular genetic studies have reported that low grade serous carcinomas as well as atypical proliferative serous tumors and non-invasive MPSCs have *KRAS* or *BRAF* mutations in about two thirds of the cases and only rarely contain *TP*53 mutations.[12,14,18,20-24] In contrast high grade serous carcinomas have *TP*53 mutations in over 80% of cases, but lack *KRAS* and *BRAF* mutations.[22,24,25] Based on these findings a dualistic model of ovarian carcinogenesis has been proposed. In this model APSTs and non-invasive MPSCs (SBT, micropapillary type) are precursors of invasive low-grade serous carcinomas (invasive MPSCs).[18,19] In contrast, the precursor of high grade serous carcinoma is not well characterized and therefore has been described as arising *de novo*[1,15], however, recent data suggest that high grade serous carcinomas arise from intraepithelial carcinomas within ovarian inclusion cysts or fallopian tube epithelium.[5-8,10,11]

The vast majority of low-grade serous carcinomas display a micropapillary pattern, but some occasionally contain large, "macro" papillae, distributed in a haphazard infiltrative pattern.[9,16] The current study is a clinicopathologic and molecular genetic analysis aimed at characterizing this uncommon pattern of invasion in LGSC and evaluating the relationship of macropapillae to coexistent APST and/or non-invasive and invasive MPSC.

Material and Methods

This study was approved by the Office of Human Subject Research Institutional Review Board of the Johns Hopkins University School of Medicine.

Case selection

Cases of low-grade serous carcinoma and APST containing macropapillae were retrieved from the files of the Department of Pathology of the Johns Hopkins Hospital. These macropapillae are distinctly different from the typical micropapillae of LGSC that contain minimal or no identifiable stroma. They contain more abundant stroma composed of spindle cells. A "macropapilla" was defined as a papillary structure within the invasive component of the tumor, measuring at least 0.3 mm in greatest dimension (Fig. 1c). Occasionally, the stromal core would be absent, probably due to the fact that the psammoma body occupying the core had fallen out during processing, creating this artifact and giving the papillae an "empty" appearance. These "empty" papillae are invariably present along with the ones that have an identifiable stromal core. The stromal core is covered by low-grade epithelium exhibiting serous differentiation with or without ciliated cells. They are present in the ovarian stroma (or extraovarian sites) in

haphazard infiltrative distribution and always at least partially surrounded by a cleft-like space. In this study the smallest percentage of macropapillae observed within the primary tumor was 20%. An arbitrary cut off of 10% can be considered when diagnosing a tumor as having macropapillary features.

Patient age, tumor size and laterality data were obtained from the surgical pathology reports. All the cases were reviewed by two authors (AY and RJK). The presence of macropapillae and micropapillae was recorded, and the percentage of macropapillae estimated. The number of slides of the ovarian tumors ranged from 3 to 24 slides (median/mean 13/12.5 slides). Evidence of extraovarian disease was noted including non-invasive implants and foci of metastatic low-grade serous carcinoma (invasive implants) with particular attention to the presence of a macropapillary pattern.

Molecular genetic analysis

Paraffin blocks from eight cases were available for molecular analysis. These included cases 1, 2, 3, 4, 5, 6, 11, 12 (case numbers refer to the case list in Table 1). 10 um sections were mounted on the membrane Palm slides and stained with hematoxylin and eosin. The epithelium lining of macropapillae was harvested using laser capture microdissection under an inverted microscope by a surgical pathologist (AY). Other components of the ovarian tumors and extraovarian metastases were also obtained by scraping tissue from the corresponding areas of the slide. Genomic DNA was isolated by using a PicoPure DNA extraction kit (Arcturus, Mountain View, CA). The DNA from the tissue obtained by scraping of the tumor areas from the slides was extracted using overnight digestion with proteinase K at 65°C and subsequent heat inactivation of the enzyme at 95°C for 30 minutes or Agencourt FormaPure Kit (Beckman Coulter). Primers used for PCR amplification were : *KRAS* - forward 5′ TAAGGCCTGCTGAAAATGACTG 3′, reverse 5′-TGGTCCTGCACCAGTAATATGC -3′; *BRAF* forward 5′- TGCTTGCTCTGATAGGAAAATGA-3′, reverse 5′-CCACAAATTGGATCCAGACAAC-3′. PCR products were obtained from seven cases (cases 1, 3, 4, 5, 6, 11, 12) (Table 2). Mutational analysis was performed by nucleotide sequencing at the Core Facility of the Johns Hopkins Medical Institution.

Results

The clinicopathologic features of the ovarian tumors are summarized in Table 1. There were eleven cases of low grade serous carcinoma (invasive MPSC) with macropapillary invasive component (Fig. 1) and three cases of an atypical proliferative serous tumor with a macropapillary component. Of the latter three cases, two contained microscopic invasive foci with macropapillae, measuring less than 5 mm in greatest dimension (cases 9 and 14); in one case there were bilateral APSTs without invasion, but a focus of tumor demonstrating a purely macropapillary pattern, identical to those in the ovary in the other cases, was found in perivaginal soft tissue (case 13).

The mean and median sizes of the ovarian tumors were 12.2 cm and 11.8 cm respectively (range 5.5 - 27.0 cm). The ovarian tumors were bilateral in ten cases and unilateral in four. The non-invasive component was APST alone in six cases. Five cases had APST and non-invasive MPSC and one case contained non-invasive MPSC without APST. In two cases the ovarian tumors were composed entirely of pure invasive low-grade serous carcinoma (cases 4 and 12). In three cases (cases 2, 9, and 13) the macropapillary component was the only invasive component present (Fig. 2). One of these (case 9) contained microscopic invasive foci in an APST, largest measuring 3 mm in greatest dimension. In one case of bilateral APSTs , a focus of tumor in perivaginal soft tissue was composed entirely of macropapillae (case 13). The macropapillary component was present in both ovaries in six of ten bilateral tumors. One of these (case 6) contained a microscopic invasive focus, measuring 4 mm in greatest dimension

in one of the ovaries (Fig. 3). The mean/median percent of the macropapillary component was 63/60% (range 20 - 100%). In two of eight cases that were thoroughly staged the tumor was confined to the ovaries. Six cases were FIGO stage III. Extraovarian disease included non-invasive implants in two cases, foci of invasive carcinoma in the peritoneum and omentum in six cases (invasive implants) and lymph node metastasis in three cases. The extraovarian foci contained macropapillae in three cases, including one case (case 1) with lymph node metastasis, in which the tumor replaced the lymph node parenchyma, one case (case 7) in the omentum (Fig. 4), and one in perivaginal soft tissue (case 13). Only the latter (case 13) was composed entirely of macropapillae. The first two cases contained a mixture of macropapillae and micropapillae in metastatic foci.

Molecular analysis was performed in seven cases (Table 2). In four cases, both macropapillary and micropapillary components (non-invasive and invasive) contained an identical *KRAS* mutation, in each case. In one of these cases (case 1) the *KRAS* mutation identical to the ovarian tumor components was present in the macropapillae in the lymph node metastasis. An identical *BRAF* mutation was found in the APST, macropapillary, and invasive micropapillary components in one tumor. Two tumors contained wild type *KRAS* and *BRAF*.

Discussion

The morphological and molecular genetic findings in this study indicate that macropapillae arranged in a haphazard infiltrative pattern are a manifestation of invasion in low grade serous carcinomas. Usually, the macropapillae are intimately admixed with micropapillae. Tumors composed entirely of macropapillae are rare, but important because the minimal cytologic atypia and low mitotic index can lead to a benign interpretation. It would have been of interest to analyze the behavior of tumors composed solely of macropapillae but, they are extremely rare, and we were unable to collect a sufficient number of cases to determine their biologic behavior.

The tumors in this study demonstrate a spectrum of morphologic findings similar to those described in micropapillary serous carcinoma, including the presence of microscopic foci of invasion that measure less than 5 mm, frankly invasive carcinoma and extraovarian metastases.[3,4,26] Macropapillary serous carcinoma generally is associated with its putative precursor lesion APST and non-invasive micropapillary serous carcinoma. In one case of bilateral ovarian APSTs a focus of invasive macropapillary serous carcinoma was found in perivaginal soft tissue. The relationship of this focus to the ovarian neoplasm is not entirely clear. Although the ovarian tumor was adequately sampled (14 sections from a 10 cm tumor), it is still possible that a focus of invasive carcinoma was present in the unsampled areas and therefore the perivaginal lesion could represent a metastasis from the ovary.

In one case the ovarian tumor was composed entirely of macropapillae whereas the metastasis in the lymph nodes and omentum were composed of typical MPCS without macropapillae. There are three possible explanations for this discordant finding. First, this could simply represent variation in the morphologic manifestation of the same clonal process. Second, inadequate sampling of the ovarian tumor may have failed to detect a micropapillary component. Third, the ovarian and peritoneal tumors may have been independent primaries. Unfortunately, we were unable to perform molecular analysis to confirm either of these possibilities.

The presence of an identical *KRAS* or *BRAF* mutation in the non-invasive components in addition to the invasive micropapillary and macropapillary components indicates that they share a common lineage. Mutations that were found in tumors containing macropapillae

involved the same loci (*KRAS* - codon 12, and *BRAF* - codon 600), that have been previously described in APSTs and MPSCs. [20,22-24]

Tumors containing macropapillae were found in extraovarian sites, specifically lymph nodes and omentum. In one case the macropapillae in a lymph node contained the identical mutation as the primary tumor indicating that this was indeed a metastasis from the ovarian neoplasm.

Macropapillae are more often observed in combination with invasive MPSC within the ovary and extraovarian metastases, but occasionally it is the only pattern of invasion. When this occurs, these neoplasms can be potentially misinterpreted as a serous adenofibroma.

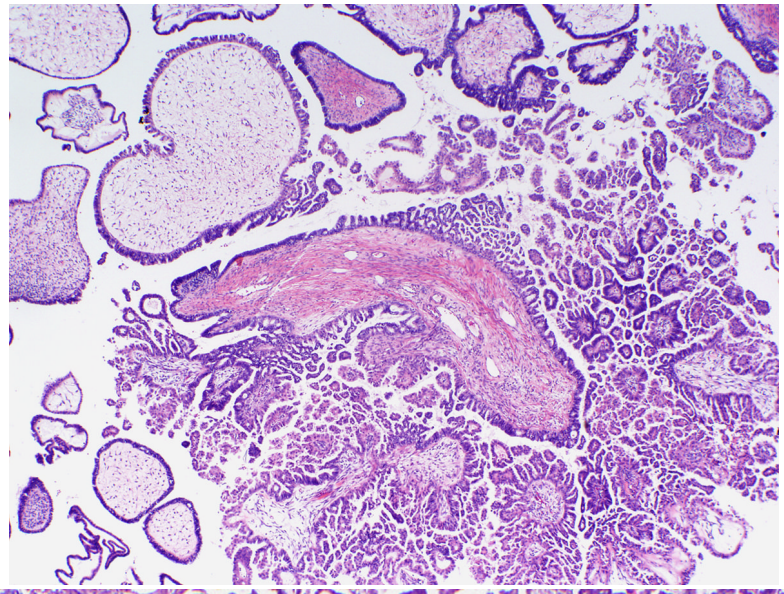
Acknowledgements

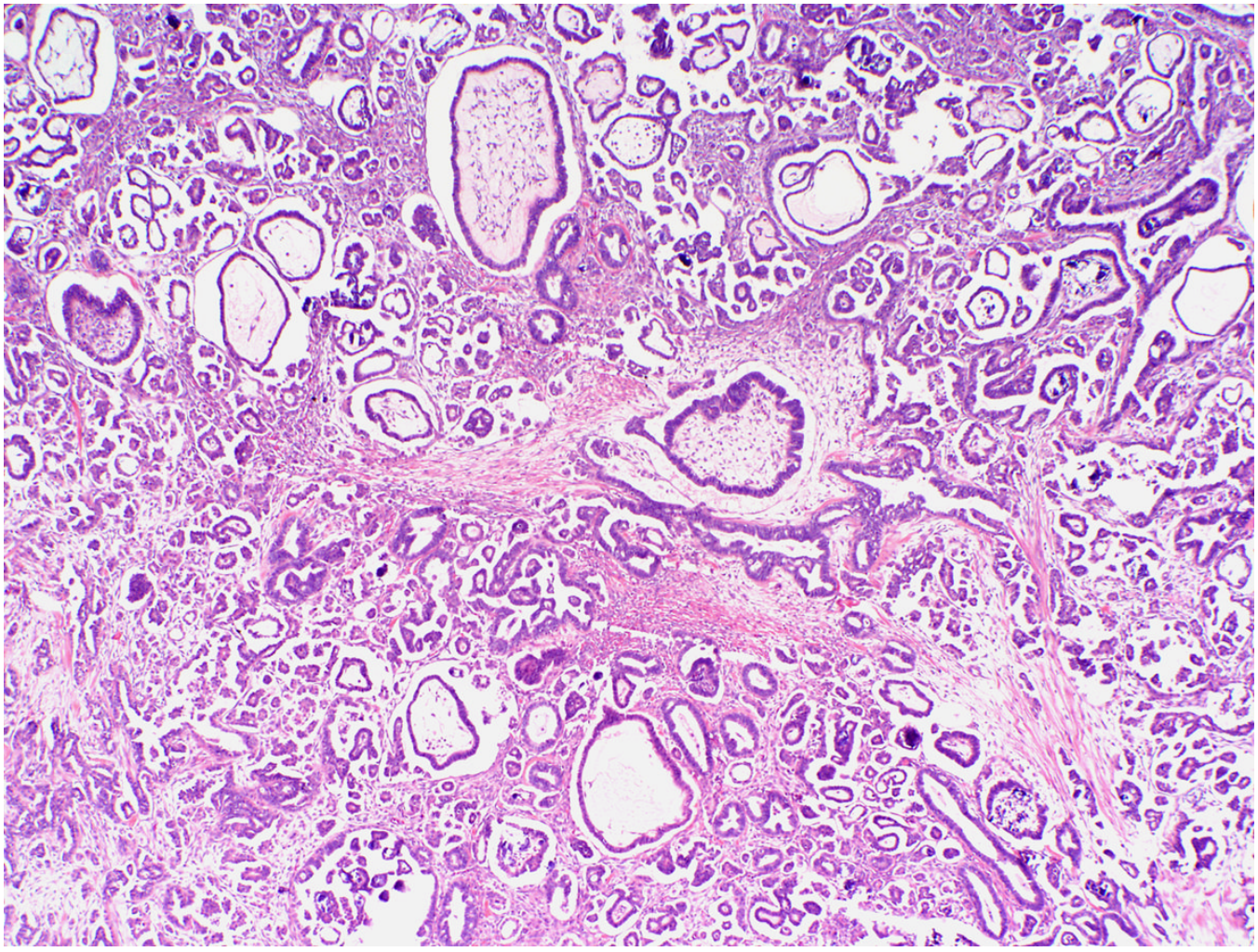
The authors thank Dr. Saeid Movahedi for contributing two cases for this study and providing paraffin blocks for molecular analysis. This study was supported in part by NIH/NCI RO1 CA116184.

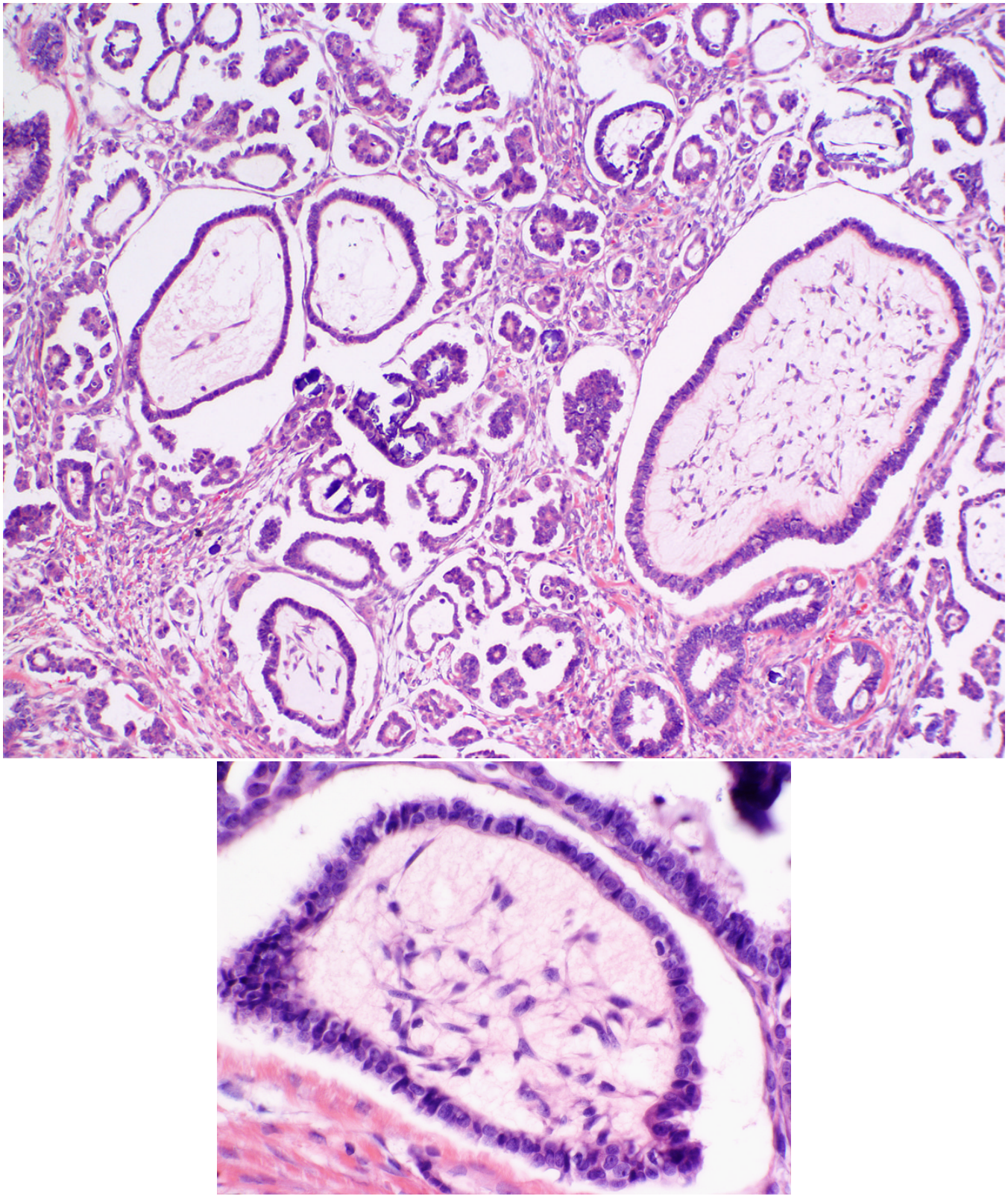
References

1. Bell DA, Scully RE. Early de novo ovarian carcinoma. A study of fourteen cases. Cancer 1994;73:1859–1864. [PubMed: 8137211]
2. Bell DA, Longacre TA, Prat J, et al. Serous borderline (low malignant potential, atypical proliferative) ovarian tumors: workshop perspectives. Hum Pathol 2004;35:934–948. [PubMed: 15297961]
3. Bell KA, Smith Sehdev AE, Kurman RJ. Refined diagnostic criteria for implants associated with ovarian atypical proliferative serous tumors (borderline) and micropapillary serous carcinomas. Am J Surg Pathol 2001;25:419–432. [PubMed: 11257616]
4. Burks RT, Sherman ME, Kurman RJ. Micropapillary serous carcinoma of the ovary. A distinctive low-grade carcinoma related to serous borderline tumors. Am J Surg Pathol 1996;20:1319–1330. [PubMed: 8898836]
5. Crum CP, Drapkin R, Kindelberger D, et al. Lessons from BRCA: the tubal fimbria emerges as an origin for pelvic serous cancer. Clin Med Res 2007;5:35–44. [PubMed: 17456833]
6. Crum CP, Drapkin R, Miron A, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. Curr Opin Obstet Gynecol 2007;19:3–9. [PubMed: 17218844]
7. Folkins A, Nucci MR, et al. Serous carcinogenesis in the fallopian tube: a descriptive classification. Int J Gynecol Pathol 2008;27:1–9. [PubMed: 18156967]
8. Kindelberger DW, Lee Y, Miron A, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. Am J Surg Pathol 2007;31:161–169. [PubMed: 17255760]
9. Kurman, RJ. Blaustein's Pathology of female genital tract. Springer-Verlag; New-York, NY: 2002.
10. Lee Y, Medeiros F, Kindelberger D, et al. Advances in the recognition of tubal intraepithelial carcinoma: applications to cancer screening and the pathogenesis of ovarian cancer. Adv Anat Pathol 2006;13:1–7. [PubMed: 16462151]
11. Lee Y, Miron A, Drapkin R, et al. A candidate precursor to serous carcinoma that originates in the distal fallopian tube. J Pathol 2007;211:26–35. [PubMed: 17117391]
12. Mayr D, Hirschmann A, Lohrs U, et al. KRAS and BRAF mutations in ovarian tumors: a comprehensive study of invasive carcinomas, borderline tumors and extraovarian implants. Gynecol Oncol 2006;103:883–887. [PubMed: 16806438]
13. Roma AA, Malpica A, Deavers MT, et al. Ovarian serous borderline tumors with a predominant micropapillary pattern are aggressive neoplams with an increased risk for low grade serous carcinoma. Mod Pathol 2008;1(supplement 1):221A.
14. Russell SE, McCluggage WG. A multistep model for ovarian tumorigenesis: the value of mutation analysis in the KRAS and BRAF genes. J Pathol 2004;203:617–619. [PubMed: 15141374]
15. Scully RE. Pathology of ovarian cancer precursors. J Cell Biochem Suppl 1995;23:208–218. [PubMed: 8747398]

16. Scully, RE.; Young, RH.; Clement, PB. Tumors of the ovary and Maldeveloped gonads, Fallopian tube, and Broad ligament. Armed Forces Institute of Pathology; Washington, DC: 1998.
17. Seidman JD, Kurman RJ. Subclassification of serous borderline tumors of the ovary into benign and malignant types. A clinicopathologic study of 65 advanced stage cases. Am J Surg Pathol 1996;20:1331–1345. [PubMed: 8898837]
18. Shih I, Kurman RJ. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. Am J Pathol 2004;164:1511–1518. [PubMed: 15111296]
19. Shih I, Kurman RJ. Molecular pathogenesis of ovarian borderline tumors: new insights and old challenges. Clin Cancer Res 2005;11:7273–7279. [PubMed: 16243797]
20. Sieben NL, Macropoulos P, Roemen GM, et al. In ovarian neoplasms, BRAF, but not KRAS, mutations are restricted to low-grade serous tumours. J Pathol 2004;202:336–340. [PubMed: 14991899]
21. Sieben NL, Roemen GM, Oosting J, et al. Clonal analysis favours a monoclonal origin for serous borderline tumours with peritoneal implants. J Pathol 2006;210:405–411. [PubMed: 17096315]
22. Singer G, Kurman RJ, Chang HW, et al. Diverse tumorigenic pathways in ovarian serous carcinoma. Am J Pathol 2002;160:1223–1228. [PubMed: 11943707]
23. Singer G, Oldt R III, Cohen Y, et al. Mutations in BRAF and KRAS characterize the development of low-grade ovarian serous carcinoma. J Natl Cancer Inst 2003;95:484–486. [PubMed: 12644542]
24. Singer G, Shih I, Truskinovsky A, et al. Mutational analysis of K-ras segregates ovarian serous carcinomas into two types: invasive MPSC (low-grade tumor) and conventional serous carcinoma (high-grade tumor). Int J Gynecol Pathol 2003;22:37–41. [PubMed: 12496696]
25. Singer G, Stohr R, Cope L, et al. Patterns of p53 mutations separate ovarian serous borderline tumors and low- and high-grade carcinomas and provide support for a new model of ovarian carcinogenesis: a mutational analysis with immunohistochemical correlation. Am J Surg Pathol 2005;29:218–224. [PubMed: 15644779]
26. Smith Sehdev AE, Sehdev PS, Kurman RJ. Noninvasive and invasive micropapillary (low-grade) serous carcinoma of the ovary: a clinicopathologic analysis of 135 cases. Am J Surg Pathol 2003;27:725–736. [PubMed: 12766576]







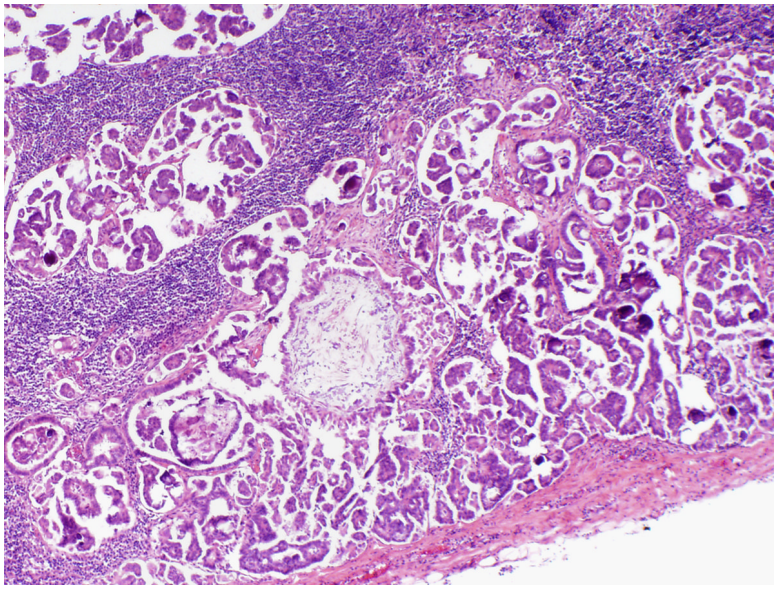
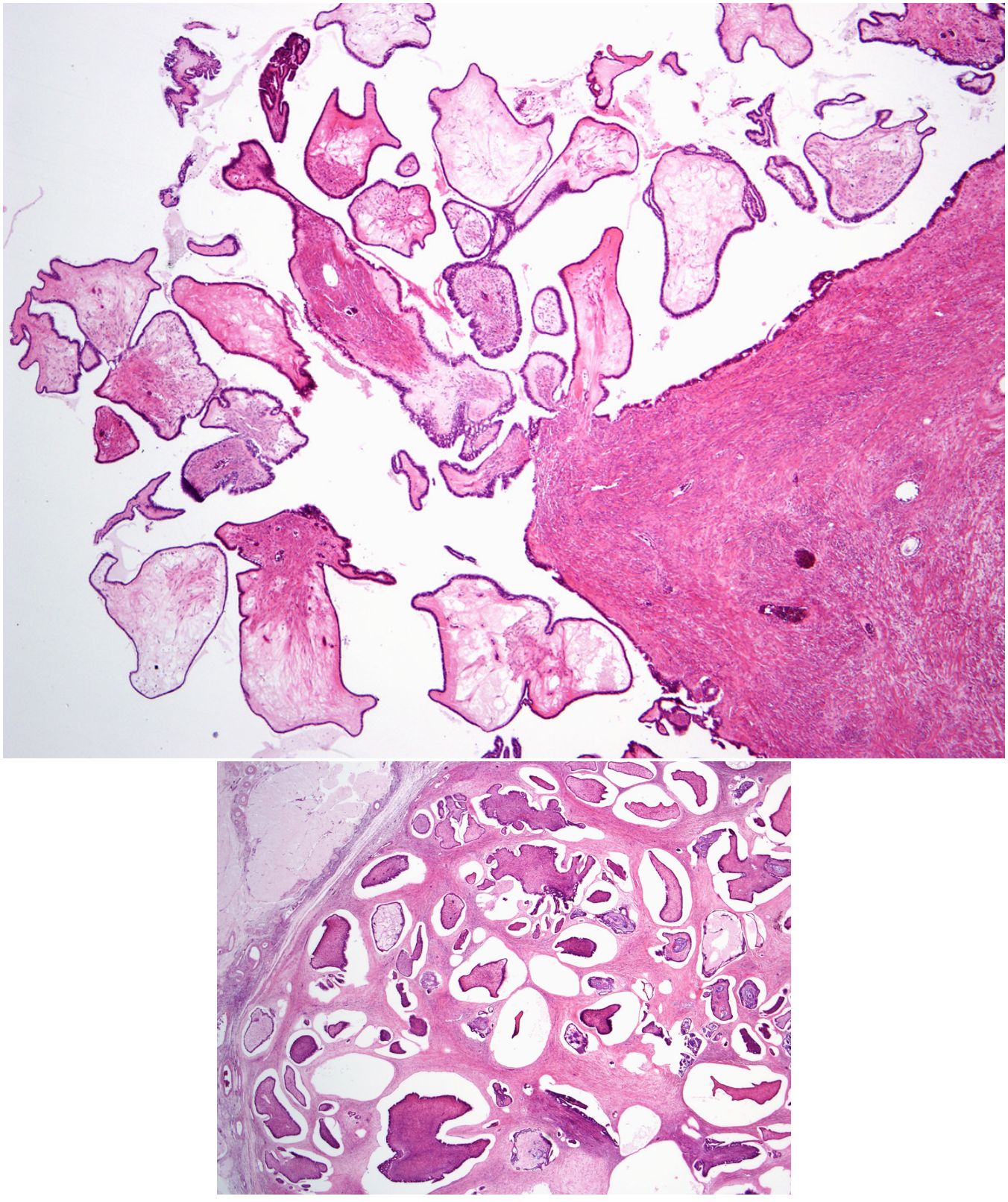


Fig. 1.

Case 1: Ovary with non-invasive low grade serous carcinoma (micropapillary variant of serous borderline tumor) (A) and invasive low grade serous carcinoma comprised of macro- and micropapillae (B). High power magnification showing a macropapilla lined by bland serous-type epithelium (C). Lymph node with metastatic low grade serous carcinoma displaying both macro- and micropapillae (D).



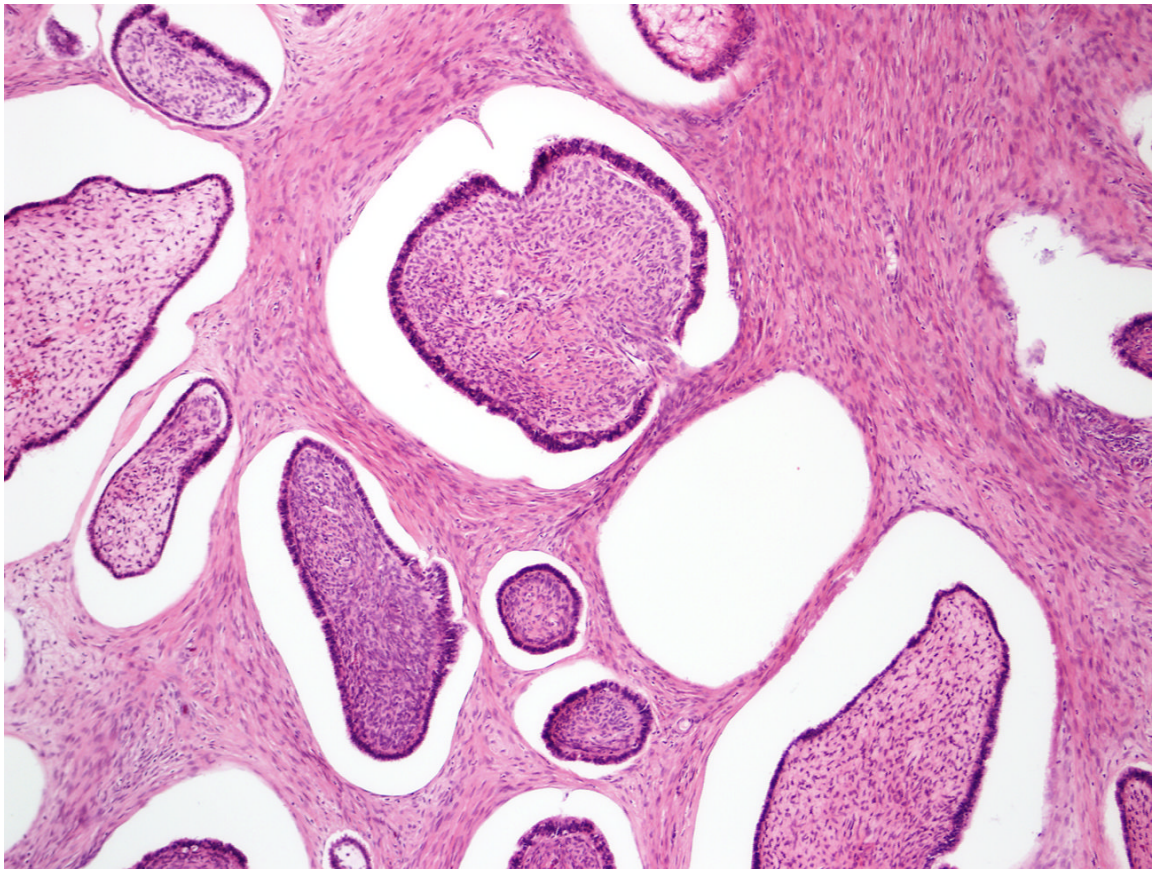
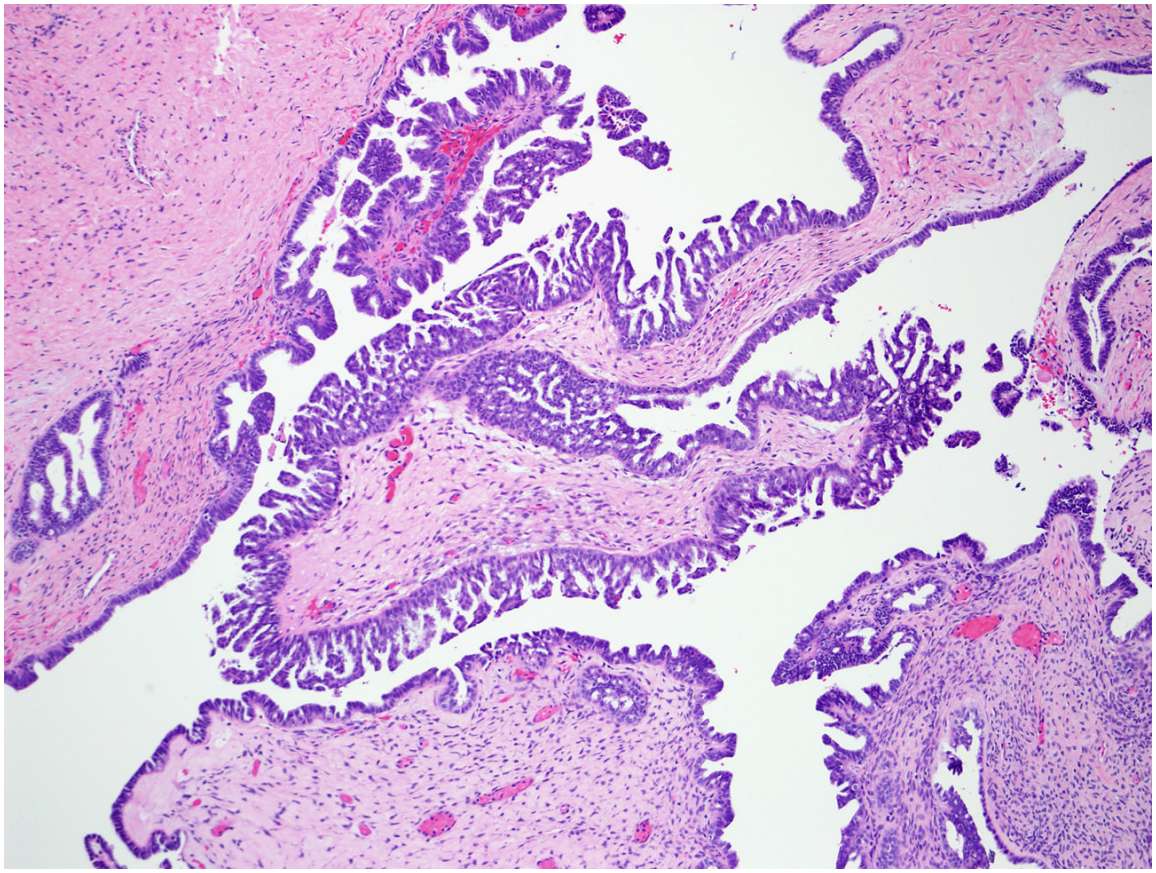
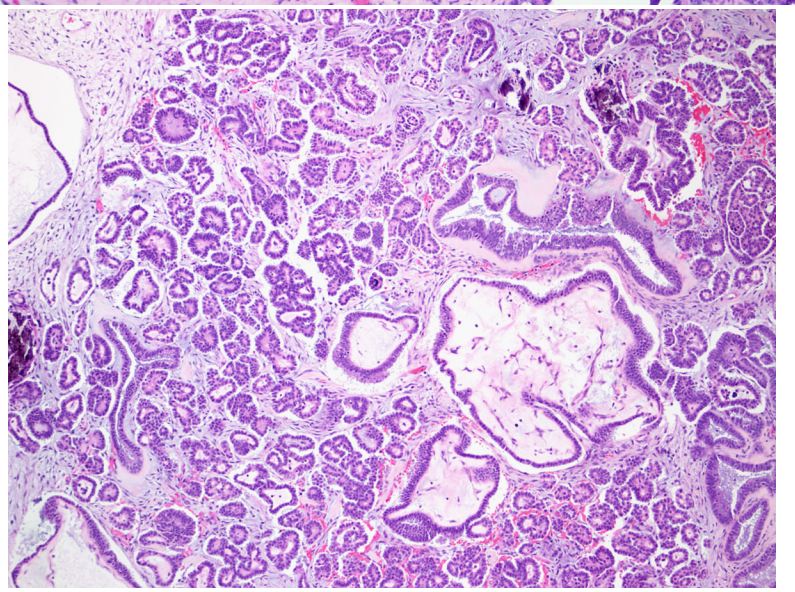


Fig. 2.
Case 2: Ovary with non-invasive component represented by an APST (A). Invasive low grade serous carcinoma composed entirely of macropapillae (B). Higher power magnification with invasive macropapillae in a cleft-like space lined by bland epithelium (C).





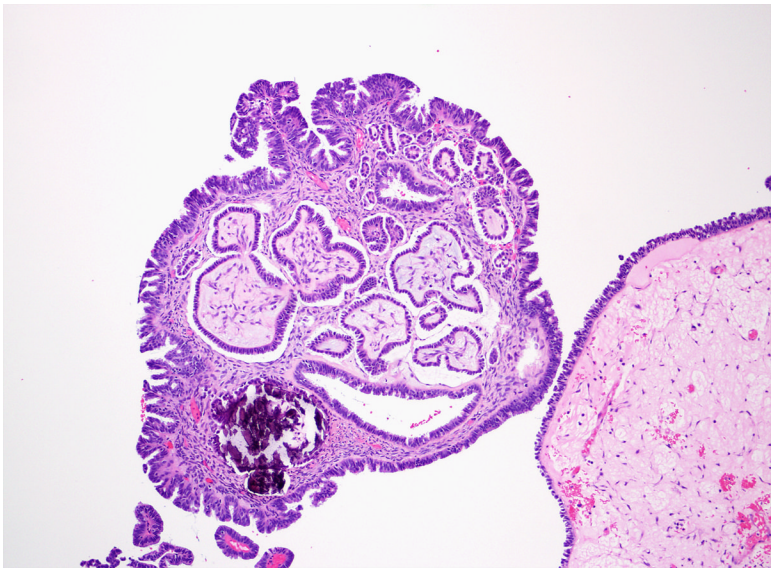


Fig. 3.

Case 6: Atypical proliferative (borderline) ovarian tumor with focal micropapillary pattern (A); Ovary with invasive low grade serous carcinoma displaying predominantly micropapillary pattern with occasional macropapillae (B); Focus of microinvasion containing macropapillae in APST in contralateral ovary (C)

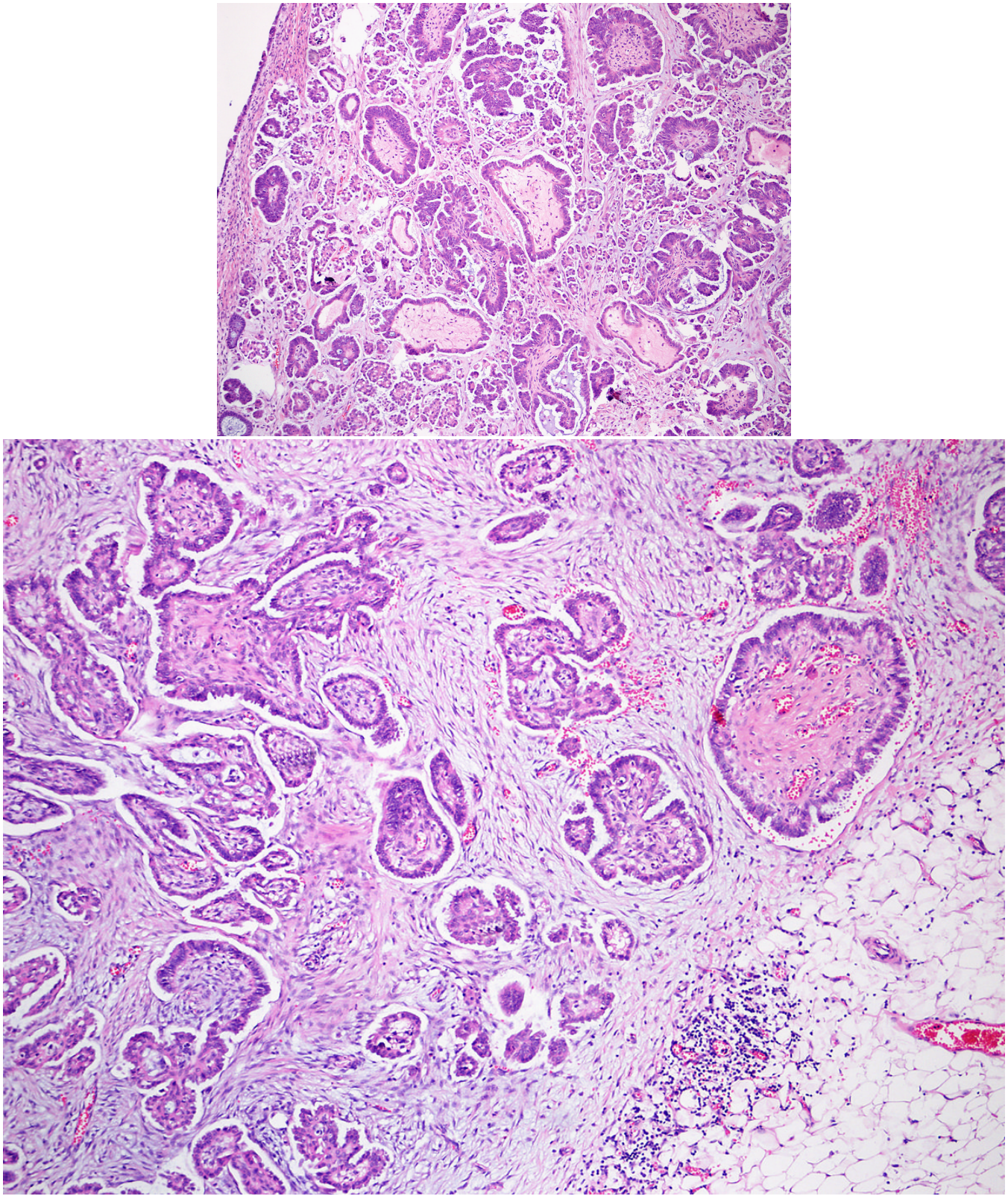


Fig. 4.

Case 7: Ovary with invasive low grade serous carcinoma comprised of a mixture of macro- and micropapillae (A). Omentum with low grade serous carcinoma comprised of a mixture of macro- and micropapillae invading adipose tissue (B).

Table 1

Clinicopathologic features of the ovarian serous tumors with invasive macropapillary pattern.

N	Patient's Age	Ovarian tumor size (cm)	Laterality	Non-inavsive component of the ovarian tumor	Macropapillary invasive epithelial component (%)	Tumor Stage*	Extarovarian disease
1	47	7.0	Bilateral	APST, non-invasive MPSC	40	IIIC	Non-invasive implants, macropapillary and MPSC metastasis in the lymph nodes
2	56	14.0	Bilateral	APST	100	IIIC	MPSC metastasis in the lymph nodes and omentum
3	66	12.0	Unilateral	APST, non-invasive MPSC	60	IA**	Non-invasive implants
4	59	14.0	Bilateral	Not present	90	IIIC	MPSC metastasis in the lymph nodes and omentum
5	85	15.0	Bilateral	APST, non-invasive MPSC	60	IIC**	N/A
6	31	5.5	Bilateral	APST	30	IC	Non-invasive implants
7	44	11.5	Bilateral	Non-invasive MPSC	20	IIIC	Macropapillary and MPSC metastasis in the omentum
8	30	9.0	Unilateral	APST, non-invasive MPSC	60	IC**	N/A
9	62	9.2	Bilateral	APST	100 in microinvasive foci	IC**	N/A
10	79	12.0	Unilateral	APST	50	IA**	N/A
11	79	14.0	Unilateral	APST, non-invasive MPSC	80	IC	Not present
12	60	27.0	Bilateral	Not present	40	IIIC	MPSC metastasis in the omentum and peritoneum
13	28	10.0	Bilateral	APST	N/A	N/A	Macropapillary serous carcinoma in perivaginal soft tissue
14	48	10.2	Bilateral	APST	90 in microinvasive foci	IIIA	MPSC metastasis in the omentum and peritoneum

APST - Atypical proliferative (borderline) serous tumor

MPSC - Micropapillary serous carcinoma

N/A - Not applicable

* ovarian tumor stage according to the Fédération Internationale de Gynécologie et d'Obstétrique

** limitted or incomplete staging

Table 2

Molecular analysis of the invasive and non-invasive components of the ovarian tumors.

Case number*	Tumor components analyzed	Mutational analysis	
		Kras	Braf
Case 1	Non-invasive MPSC, invasive MPSC, MAPSC, lymph node metastasis with macropapillae	Codon 12 GGT → GTT Gly → Val	Wild type
Case 3	Non-invasive MPSC, invasive MPSC, MAPSC	Codon 12 GGT → CGT Gly → Arg	Wild type
Case 4	invasive MPSC, MAPSC	Codon 12 GGT → GAT Gly → Asp	Wild type
Case 5	APST, invasive MPSC, MAPSC	Wild type	Codon 600 GTG → GAG Val → Glu
Case 6	APST, invasive MPSC, MAPSC	Wild type	Wild type
Case 11	APST, invasive MPSC, MAPSC	Wild type	Wild type
Case 12	invasive MPSC, MAPSC	Codon 12 GGT →GAT Gly → Asp	Wild type

APST – Atypical proliferative (borderline) serous tumor

MPSC – Micropapillary serous carcinoma

MAPSC – Invasive macropapillary serous carcinoma

*Case numbers correspond to the case list in table 1.