Abstract. Background/Aim: We describe a rare case of ovarian mesonephric-like adenocarcinoma (MLA) involving the fimbra and mimicking serous tubal intraepithelial carcinoma (STIC). Case Report: A 47-year-old woman presented with a 4.4-cm left ovarian mass. Histologically, the ovarian tumor showed papillary and solid architecture, severe nuclear pleomorphism, and increased mitotic activity. Some microscopic foci where the tumor cells spread horizontally along the fimbral surface epithelium were noted, compatible with STIC. We initially considered the ovarian tumor to be high-grade serous carcinoma accompanied by a fimbral STIC. However, immunostaining revealed nuclear immunoreactivity for paired box 2 and GATA-binding protein 3, but lacked expression of Wilms tumor 1. A thorough slide review and additional immunostaining revealed architectural diversity, densely eosinophilic intraluminal secretions, and lack of hormone receptor expression, supporting the diagnosis of MLA. Conclusion: Microscopic intraepithelial metastases of the MLA to the fimbra mimic STIC. We recommend ancillary tests, such as immunostaining, in patients with ovarian tumors whenever possible, particularly for those with differential diagnosis of MLA and high-grade serous carcinoma.

Ovarian carcinoma is the deadliest gynecological malignancy, accounting for more than 14,000 deaths each year (1). High-grade serous carcinoma (HGSC) is the most prevalent and aggressive subtype of ovarian carcinoma, accounting for 70% of ovarian carcinoma-related deaths. The fallopian tube has recently emerged as an important site of origin not only for tubo-ovarian HGSC in patients with germline mutation of breast cancer 1 (BRCA1) or BRCA2, but also as a source of peritoneal HGSC (2). A thorough histological examination of resected ovaries and fallopian tubes has led researchers to focus on investigating the carcinogenesis of tubo-ovarian HGSC from the fallopian tube. Increasing evidence suggests that the distal part of the fallopian tube, particularly the fimbra, is the origin of tubo-ovarian and peritoneal HGSCs, and serous tubal intraepithelial carcinoma (STIC) is the precursor lesion (3). STIC is morphologically characterized by the proliferation of non-ciliated epithelium, showing stratification, loss of polarity, severe nuclear pleomorphism, conspicuous nucleoli, and increased mitotic activity (1, 4). In addition to these histological criteria, more than 90% of STICs harbor mutations of tumor protein 53 (TP53), resulting in aberrant expression of p53 on immunostaining. Therefore, the lesions typically demonstrate either p53 overexpression (indicating missense mutations) or complete absence of p53 staining (indicating nonsense or frameshift mutations) (5).
Mesonephric adenocarcinoma (MA) is a rare malignant tumor thought to arise from the embryonic remnants of the mesonephric tubules and ducts, and comprises less than 1% of all gynecological malignancies (6). MA exhibits a variety of histological growth patterns, including tubular, ductal, papillary, solid, spindle, retiform, sex cord-like, and comedo necrosis-like (7-13). The small tubular and ductal structures contain eosinophilic intraluminal secretions. MA typically arises in the uterine cervix or vagina, but several cases arising in the upper female genital tract have also been reported (14, 15). Even though they share the same histological features and immunophenotypes with MA, their association with mesonephric remnants has not been firmly established (6, 14). Within this context, MA of the uterine corpus or adnexa is referred to in the literature as a mesonephric-like adenocarcinoma (MLA).

MLA of the ovary is a rare but distinct subtype of ovarian carcinoma (15). It has been newly included in the fifth edition of the World Health Organization Classification of Female Genital Tumors (5). We recently encountered a rare case of ovarian MLA mimicking HGSC accompanied by multifocal STICs involving the fimbrial surface. The presence of fimbrial STIC-like lesions, together with dominant papillary and solid growth patterns and high-grade nuclear atypia of the ovarian tumor, led to an initial diagnosis of ovarian HGSC. However, the unexpected immunostaining results prompted the re-examination of slides, additional immunostaining, and targeted sequencing analyses. This report aimed to provide a thorough clinicopathological description of ovarian MLA showing multifocal tubal intraepithelial metastases (IEMs), as well as its immunophenotype and genetic features. Pathologists play an important role in making appropriate therapeutic plans for patients by accurately determining the histological subtype. Our comprehensive clinicopathological and molecular analyses can help improve the understanding of this rare condition and assist pathologists in making an accurate diagnosis.

Case Report

The Institutional Review Board (Samsung Medical Center, Seoul, Republic of Korea) granted permission for this study (2021-06-137) to be published on the condition that no patient-identifiable data should be included. Written informed consent for publication was not required by the Institutional Review Board as this study did not include data that could potentially or clearly identify the patient.

A 47-year-old woman presented with a pelvic mass detected on a computed tomography scan that was performed in a different hospital. She underwent total hysterectomy for uterine adenomyosis 4 years ago. Physical examination revealed a non-mobile, non-tender, left pelvic mass.

Magnetic resonance imaging revealed a multinodular, mixed solid and cystic mass in the left ovary measuring 4.4 cm, which appeared to invade the left proximal ureter, causing hydronephrosis of the left kidney. No definite seeding nodule was observed in the abdominal and pelvic peritoneum but a small amount of ascites with mild diffuse peritoneal thickening was noted. A few enlarged lymph nodes, measuring up to 5.6 cm, were detected in the left para-aortic and retrocrural areas, all of which raised suspicion of metastatic lymphadenopathy. Consistent with these findings, positron-emission tomography/computed tomography images revealed an intensely hypermetabolic mass in the left ovary and left para-aortic areas. Hypermetabolic lymph nodes were also noted in the bilateral retrocrural, left mediastinal, and bilateral supraclavicular areas. The preoperative serum cancer antigen 125 level was elevated (206.7 U/ml). As the preoperative clinical impression was ovarian carcinoma, primary debulking surgery, including left salpingo-oophorectomy, bilateral pelvic lymphadenectomy, para-aortic lymphadenectomy, total omentectomy, peritonectomy, and intraoperative peritoneal washing cytology, were performed.

Histologically, the ovarian mass presented as a well-circumscribed, partially encapsulated, round, solid tumor (Figure 1A). The tumor consisted of a central irregular-shaped area undergoing hyaline and hydropic degeneration, and a peripheral hypercellular zone showing tumor cell sheets and haphazardly infiltrating the fibrous stroma. Diverse growth patterns were observed, including irregularly-shaped solid masses of tumor cells with slit-like spaces, papillary and micropapillary structures, and large, cribriform, and pseudopodendrioid glands (Figure 1B). Distorted, angulated glands also destructively infiltrated the myxoid stroma (Figure 1C). Slit-like glandular spaces contained inflammatory cells and necrotic debris (Figure 1D). The amount of intervening stroma was minimal. Most of the tumor cells demonstrated high-grade nuclear atypia, including enlargement, hyperchromasia, severe pleomorphism, increased mitotic activity (Figure 1E), conspicuous nucleoli, and occasional atypical mitoses (Figure 1F). These histological features were consistent with those of ovarian HGSC. In addition, the tip and edge of the fimbrial plica showed multiple microscopic foci, showing a significant increase in epithelial thickness compared with the adjacent epithelium (Figure 2A). The thickened epithelium exhibited irregular stacking of enlarged and hyperchromatic nuclei, loss of polarity, and atypical mitoses, while the adjacent normal tubal epithelium was arranged as a single layer of ciliated low-columnar cells with bland-appearing nuclei (Figure 2B). Transition points were evident between the normal and neoplastic epithelium. The subepithelial stroma was unremarkable, without evidence of invasion. We also observed architectural complexity with small, detached, and...
micropapillary clusters, as well as fusion of the micropapillae and focal cribriform appearance (Figure 2C). The presence of architectural abnormalities and a degree of nuclear atypia similar to that of the ovarian tumor led to the diagnosis of STIC. The tumor cells involving the ovarian surface had a similar growth pattern - a partial replacement of the ovarian surface mesothelium by the neoplastic epithelium with abrupt transition points (Figure 2E and F). Several microscopic foci of peritoneal metastases appeared as well-circumscribed tissue plaques, giving the impression that these were plastered on the peritoneal surface (Figure 2G and I). Their cytological features were the same as those of fimbrial lesions. Coexisting ovarian invasive carcinoma, tubal intraepithelial carcinoma horizontally spreading on the fimbrial surface, and multifocal peritoneal involvement were highly suggestive of HGSC accompanied by STIC.

Immunostaining was performed to confirm our diagnosis, as previously described (16-28). A panel of antibodies against Wilms tumor 1 (WT1), p53, estrogen receptor (ER), paired box 8 (PAX8), PAX2, GATA-binding protein 3 (GATA3), and P16 was used. Contrary to our expectations, the ovarian tumor showed a complete lack of WT1 expression (Figure 3A) and patchy nuclear p53 immunoreactivity with weak-to-moderate staining intensity (wild-type p53 expression pattern; Figure 3B), neither result was compatible with HGSC. ER expression was not observed (Figure 3C). Instead, cells were diffusely positive for PAX8, PAX2, and GATA3 (Figure 3D), with moderate to strong staining intensity. In all foci considered initially as STICs, we observed the same immunophenotype as that of the ovarian tumor. The tumor cells spreading along the epithelium of the fimbrial surface expressed PAX2 (Figure 3E) and GATA3, but not WT1 (Figure 3F and G). The fimbrial tumor cells displayed patchy P16 expression (Figure 3H) and wild-type p53 immunoreactivity pattern (Figure 3I and J).

Due to the unexpected immunostaining results, all hematoxylin and eosin-stained slides were thoroughly reviewed. Several foci demonstrated compactly aggregated small tubular structures in areas initially considered as those showing solid architecture. Moreover, densely eosinophilic
intraluminal secretions were occasionally noted within the tubular and ductal structures (Figure 4A-D). These histological features suggested the possibility of MLA. The intraoperative washing cytology specimen showed variable-sized papillary tufts and irregular-shaped three-dimensional cellular clusters (Figure 4E-G). High-grade nuclear atypia observed under high-power magnification seemed to be characteristic of HGSC (Figure 4H-K). However, the small tubular lumina (Figure 4H and I) and deeply stained substances (Figure 4J and K), which were similar to those identified in hematoxylin and eosin-stained histology slides, supported the possibility of MLA rather than HGSC.
We performed additional immunostaining for progesterone receptor (PR), phosphatase and tensin homolog deleted on chromosome 10 (PTEN), mutL homolog 1 (MLH1), human postmeiotic segregation increased 2 (PMS2), mutS homolog 2 (MSH2), and mutS homolog 6 (MSH6). PR expression was not observed. The expression status of PAX2 and GATA3 was confirmed in the other tumor sections. No significant difference was observed in the intensity and proportion of PAX2 and GATA3 staining among the different tumor areas. PTEN, MLH1, PMS2, MSH2, and MSH6 were preserved in the cytoplasm of tumor cells. Targeted sequencing was also conducted, as previously described (12, 24, 29-32). No pathogenic mutations were identified in the well-known hot spots of TP53 exons. No mutations affecting the splice sites or introns of TP53 were detected. Instead, both the ovarian and fimbrial tumors harbored the same pathogenic v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRA5) mutation (c.35G>T; p.Gly12Val).

The patient received postoperative chemotherapy using a combination of paclitaxel-carboplatin. After the third treatment cycle (3 months postoperatively), abdominal pain occurred. Computed tomography revealed obstructive ileus with a distinct transition point in the terminal ileum. No
measurable seeding lesions were observed. The patient completed six cycles of chemotherapy after the symptoms improved. At 11 months postoperatively, the patient is currently alive without any evidence of disease.

**Discussion**

We describe a case of ovarian MLA with multifocal microscopic involvement of the fimbrial surface. The patient presented with a 4.4-cm solid and cystic ovarian mass with multiple enlarged para-aortic lymph nodes. Histologically, the well-circumscribed ovarian tumor consisted of papillary and micropapillary growth patterns, solid sheets of tumor cells with slit-like spaces, and endometrioid-like glandular proliferation with cribiform architecture. The tumor cell nuclei demonstrated high-grade atypia and occasional mitosis. The tubal lesions consisted of atypical stratified epithelium horizontally spreading along the fimbrial surface and possessing hyperchromatic and pleomorphic nuclei. Their nuclei also showed loss of polarity, severe pleomorphism, increased mitotic activity, and atypical mitotic figures. These histological features prompted the
diagnosis of HGSC accompanied by STIC. However, the complete absence of WT1 immunoreactivity and wild-type p53 expression pattern did not support the diagnosis of either HGSC or STIC. Instead, diverse architectural patterns and positive expressions of both mesonephric markers, PAX2 and GATA3, raised the possibility of STIC. A thorough microscopic review with additional immunostaining aided the final diagnosis of MLA based on the presence of small tubular aggregates with hyaline-like eosinophilic intraluminal secretions and lack of hormone receptor expression. Although the presence of severe nuclear pleomorphism and high mitotic rate were not compatible with the features of a typical MLA, we had previously found that these high-grade cytological features can be identified in a small subset of MLAs (32). The presence of ovarian and tubal lesions harboring pathogenic KRAS mutations, but not TP53 mutations, further confirmed the diagnosis of MLA.

STIC, which is observed in 60% of patients with tubo-ovarian and peritoneal HGSC (5), has been accepted as the earliest pathological manifestation of most HGSCs (33). The presence of occult, non-mass-forming HGSCs (34, 35) or dysplastic epithelial changes (36) in the fallopian tubes of known BRCA1 mutation carriers who underwent prophylactic bilateral salpingo-oophorectomy implies that the fallopian tubes are the anatomical site of origin of HGSC. Concurrent HGSC and STIC, incidentally discovered in patients not known to be at high risk, also provides further evidence supporting the tubal origin of HGSC. Gilks et al. reported that 21 incidental tubal HGSCs were accompanied by STIC and that most of them were confined to the fallopian tube (35). Moreover, according to the recently introduced criteria for assigning the origin of tubo-ovarian HGSC (37), the primary site should be assigned as being tubal if the STIC lesion or HGSC invades the fallopian tube, or when part or all of the tubes are inseparably incorporated within a tubo-ovarian mass. Detection of identical somatic TP53 mutations in STICs and concurrent HGSCs also supports the clonal relationship between the two lesions (38).

However, not all tubal intraepithelial carcinomas originate from the fallopian tube. Recent studies have documented that tubal IEMs of non-gynecological origin can mimic STIC. Rabban et al. investigated 100 patients with non-gynecological carcinomas that metastasized to the fallopian tubes (39). Approximately half of the patients had fimbrial involvement, and 29% had tubal mucosal involvement. The most common site of metastasis was the colorectum, followed by the upper gastrointestinal and pancreaticobiliary tracts, appendix, and breasts. The growth patterns varied from flattened to stratified, exophytic, and pseudoinvasive. High-grade nuclear atypia was observed in approximately two-thirds of the patients with tubal mucosal growth. These tumors mimicked the morphological features of STIC or HGSC, including unilaterality, fimbrial location, severe nuclear pleomorphism, and increased mitotic activity. Reyes et al. also reported eight patients with human papillomavirus-associated endocervical adenocarcinoma with tubal metastasis (40). Seven out of the eight tumors were unilateral, while six had microscopically colonized within the tubal epithelium. These epithelial-limited lesions showed papillary tufting and slit-like spaces, simulating STIC and HGSC, and led to diagnostic confusion. However, the presence of stratified, tall, hyperchromatic nuclei with easily identifiable apical mitoses and apoptotic bodies, and positivity for human papillomavirus upon in situ hybridization support the diagnosis of metastatic endocervical adenocarcinoma. Similarly, we previously reported five patients with endometrial, cervical, and colorectal carcinomas with tubal IEMs (8). We found that the characteristic histological features of STIC, including cellular crowding with papillary configuration and nuclear stratification, loss of polarity, and high-grade nuclear atypia, were also observed in those with epithelial-limited metastasis, indicating that careful consideration of clinical history and the use of immunostaining are critical in making an accurate diagnosis. Taken together, not all tubal intraepithelial carcinomas are of tubal origin. Although uncommon, it is possible for metastases of both gynecological and non-gynecological malignancies to grow within the mucosa of the fallopian tube and create a potential diagnostic pitfall. The intraepithelial growth of a tumor in the fallopian tube is not pathognomonic of the primary tubal origin of the tumor.

It is difficult to distinguish tubal IEM of ovarian MLAs from HGSC based on the morphological features alone. Destructive stromal invasion, papillary and solid architecture, severe nuclear pleomorphism throughout the entire tumor, and the presence of psammomatous microcalcifications are useful diagnostic features of HGSC. In contrast, the classic morphological pattern of MLA, that is, closely aggregated back-to-back tubules lined by cuboidal cells with low-to-intermediate-grade nuclear atypia and containing densely eosinophilic intraluminal secretions, supports the diagnosis of MLA. Interestingly, this case showed overlapping morphological features of ovarian HGSC and MLA, which posed a diagnostic challenge. We previously demonstrated that severe nuclear pleomorphism with increased mitotic activity is an uncommon but possible histological presentation in a small subset of patients with MLAs (32). Conversely, HGSC can have eosinophilic intraluminal substances similar to those of MLA, but these are irregular, shattered materials that do not have the same shape as that of the lumen. MLAs have deeply eosinophilic, hyaline- or colloid-like secretions, which typically appear bright pink on hematoxylin and eosin staining and are similar to those observed in benign mesonephric lesions or thyroid follicles (24, 32). Moreover, the intraluminal secretions of MLA usually conform to the contours of the glands in which they are found. Nevertheless, intraluminal secretions are neither specific nor pathognomonic for HGSC or MLA. Given that
both HGSC and MLA exhibit papillary and glandular architecture with high-grade nuclear atypia, they should be included in the differential diagnosis of uterine tumors exhibiting various growth patterns.

Immunostaining for a panel of antibodies can be useful in distinguishing MLA with tubal IEM from HGSC accompanied by STIC. Ovarian MLA shares an immunophenotype with cervical MA, which is different from that of ovarian HGSC (15, 41-43). The MLA cells show either complete negativity or focal to weak positivity for hormone receptors, lack of WT1 expression, or wild-type p53 immunostaining pattern, while being positive for mesonephric markers, PAX2 and GATA3 (8, 41, 43). A previous study reported that ovarian MLA exhibit nuclear immunoreactivity for thyroid transcription factor-1 (43). In contrast, HGSC typically reacts diffusely and intensely for WT1 protein. They exhibit aberrant p53 expression as well as positivity for ER and PR, with variable staining intensities and proportions. In our case, the tumor lacked immunoreactivity for WT1, ER and PR, and showed a wild-type p53 immunostaining pattern, which excluded the possibility of HGSC. The diffuse positivity for PAX2, a protein associated with the development of the Wolffian system, is typical of mesonephric tumors (41), and GATA3, the best marker for MA and MLA with high sensitivity and specificity (43), supported the diagnosis of MLA. In addition, pathogenic KRAS mutations were observed, but not TP53 mutations. For patients with high-grade ovarian carcinoma showing morphological features of both HGSC and MLA, targeted sequencing can help confirm the presence of characteristic mutations for each particular subtype.

In summary, we describe a rare case of ovarian MLA with multifocal microscopic fimbrial involvement. The invasive ovarian tumor exhibited dominant papillary and solid architecture and high-grade nuclear atypia, compatible with HGSC. The fimbria was infiltrated with tumor cells that spread along the surface epithelium, but did not invade the subepithelial stroma, and displayed the same cytological features as those of the ovarian lesion, compatible with STIC. Based on these histological features, this case was initially considered as ovarian HGSC associated with STIC. However, immunostaining results revealed that the ovarian and tubal lesions were negative for WT1 and ER, which are characteristic markers of HGSC and STIC, and positive for PAX2 and GATA3, which are mesonephric markers. In addition, targeted sequencing analysis revealed that the tumor harbored a pathogenic KRAS mutation, a characteristic genetic alteration of MLA, but none of the pathogenic TP53 mutations. Ovarian MLA can also show intraepithelial spread along the fimbrial surface; in this case, the features of MLA appeared very similar to those of STIC. Since MLA can present various architectural patterns, it can mimic HGSC, the most common ovarian carcinoma, especially when it presents as an ovarian tumor with papillary and solid architecture. However, observation of the various growth patterns and the small tubules containing eosinophilic intraluminal secretions through a thorough microscopic examination can lead to the diagnosis of MLA. In addition, further verification can be done by performing additional immunostaining and targeted sequencing to confirm the immunophenotype and molecular features of MLA.

Conflicts of Interest
None of the Authors have any conflicts of interest or financial ties to declare regarding this study.

Authors’ Contributions
All Authors made substantial contributions to the conception and design of the study; the acquisition, analysis, and interpretation of the data; drafting of the article; critical revision of the article for important intellectual content; and the final approval of the version to be published.

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