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Case Report

Invasive Micropapillary Carcinoma of the Uterine Cervix

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Abstract
We herein present a case of uterine cervical invasive micropapillary carcinoma (IMPC) in a 35-year-old woman. She had neither specific symptoms nor any previous gynecological history. A cervical punch biopsy revealed a high-grade squamous intraepithelial lesion and concurrent intestinal-type mucinous carcinoma. Based on the preoperative diagnosis of endocervical adenocarcinoma, she underwent radical hysterectomy with bilateral salpingo-oophorectomy and bilateral pelvic lymph node dissection. Grossly, there was an ovoid, slightly elevated mass with surface nodularity in the lower endocervix, measuring 10 × 8 mm. Histologically, the tumor consisted predominantly of tufts of tumor cells arranged in micropapillary structures devoid of fibrovascular cores and surrounded by clear, empty, lacunar spaces between tumor cell nests and stroma. The IMPC component comprised 90% of the entire tumor volume. The greatest dimension and stromal invasion depth of the IMPC were 8 and 3 mm, respectively (FIGO stage IA2). Immunostaining revealed that mucin 1 (MUC1) surrounded each micropapillary structure, indicating the reverse epithelial polarity of the glandular cells. MUC1 was localized predominantly in the stroma-facing surface of the cell clusters, accentuating the outlines of the micropapillary structures by forming a distinct, characteristic band on this surface. In addition, targeted sequencing analysis of the IMPC revealed a missense *PIK3CA* mutation (c.1633G>A). In summary, we present the clinicopathological characteristics of cervical IMPC. We demonstrate for the first time that IMPC of the uterine cervix harbors a pathogenic missense mutation in *PIK3CA*. Further investigations using larger cohorts of patients are necessary to confirm these findings.

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Introduction

The term invasive micropapillary carcinoma (IMPC) was first proposed by Siriaunkgul and Tavassoli [1] in the breast. IMPC is a rare variant of adenocarcinoma, exhibiting a distinct morphological pattern that consists of small, morula-like nests of malignant tumor cells typically lacking central fibrovascular support, with surrounding clear cleft-like or lacunar stromal spaces [2, 3]. These characteristic morphological features were subsequently identified in carcinomas of other organs, such as the salivary gland, thyroid, lung, gastrointestinal tract, pancreatobiliary tract, urinary bladder, and ovary, and the IMPC terminology was applied to those tumors.

IMPC of the uterine cervix is a very rare condition. To the best of our knowledge, only 55 cases of uterine cervical IMPC have been documented in the English literature [2, 4–7]. Alvarado-Cabrero et al. [7] recently reported the largest case series of 44 cervical IMPCs. Stewart et al. [2] reported the results of the clinicopathological analysis of 8 IMPCs. Each of the remaining 3 cases was published as an individual case report [4–6].

In this report, we describe the detailed histological characteristics and immunophenotype of a cervical IMPC case, the molecular characteristics of which we investigated by performing targeted sequencing. This comprehensive analysis of cervical IMPC will improve the current understanding of this rare disease and offer insight to pathologists faced with diagnostic decisions.

Case Presentation

A 35-year-old woman was referred to our institution because of abnormal cervicovaginal cytology results. At a local clinic, she was diagnosed with a high-grade squamous intraepithelial lesion and a high-risk HPV type 16 infection. A cervical punch biopsy was performed at the local clinic, and the biopsied specimen was interpreted as a concurrent intestinal-type mucinous carcinoma and high-grade squamous intraepithelial lesion. An abdominopelvic magnetic resonance imaging scan revealed no mass-like lesion in the cervix. Neither lymph node enlargement, peritoneal seeding, nor hematogenous metastasis in the abdomen or pelvis was noted. She received a radical hysterectomy with a bilateral salpingo-oophorectomy and bilateral pelvic lymph node dissection. Gross and histopathological examination were performed, and a board-certified pathologist specializing in gynecological oncology made a final pathological diagnosis.

Grossly, there was an ovoid, slightly elevated mass with surface nodularity in the lower endocervix, measuring 10 × 8 mm (Fig. 1A). The bilateral parametria and endomyometrium did not show any pathological abnormality, and the uterine serosa was smooth and glistening. The bilateral ovaries and salpinges were also unremarkable. Histologically, the tumor measured 8 mm in the maximum horizontal dimension. The maximum depth of stromal invasion was 3 mm. The micropapillary component comprised approximately 90% of the entire tumor volume, and the intestinal-type mucinous carcinoma and adenocarcinoma in situ components comprised approximately 10% (Fig. 1B). The micropapillary component consisted of tumor cells arranged in small tight micropapillary nests surrounded by cleft-like, lacunar spaces (Fig. 1C). The intervening stroma exhibited an extensive fibromyxoid desmoplastic response that was associated with lymphoplasmacytic infiltrates (Fig. 1D). The intestinal-type mucinous carcinoma component displayed dilated and enlarged glands exhibiting cribriform and papillary architectural patterns. The pseudostratified epithelium possessed enlarged, elongated, and hyperchromatic nuclei (Fig. 1E). Numerous intracytoplasmic mucins were observed (Fig. 1F), and many of the tumor cells exhibited a goblet cell-like morphology.

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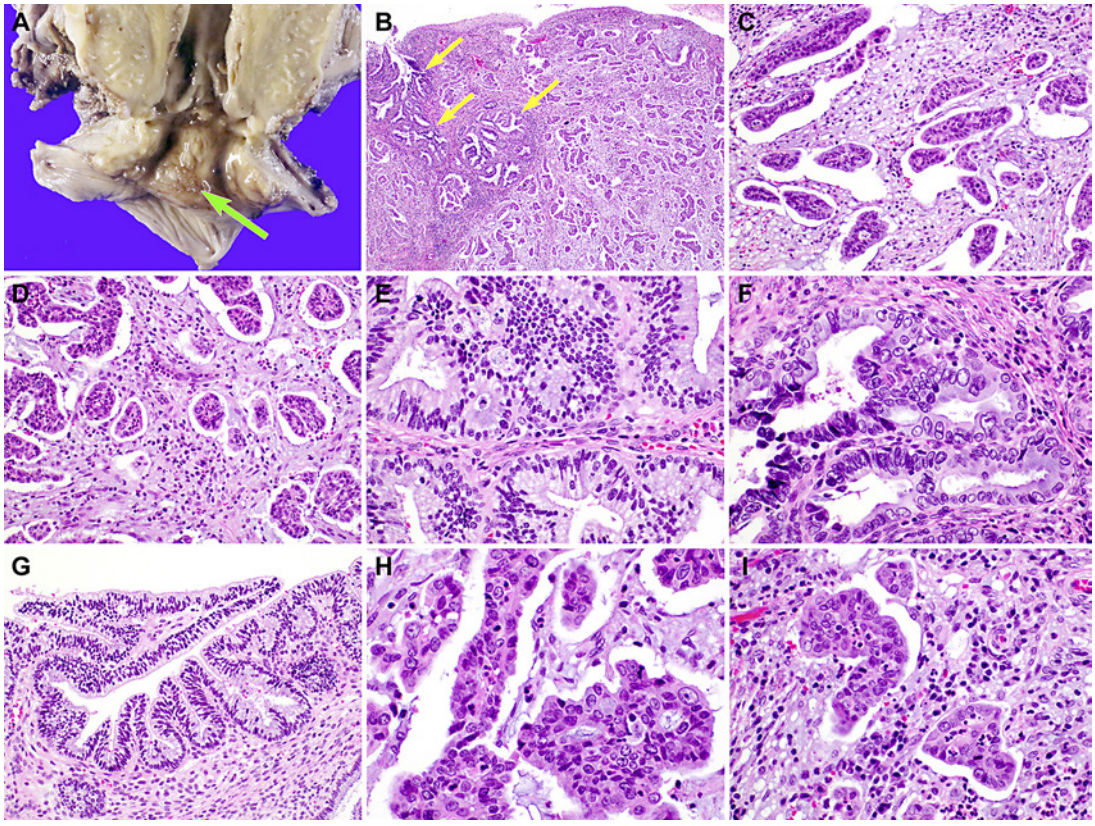

Fig. 1. Pathological features of invasive micropapillary carcinoma of the uterine cervix. **A** Grossly, an ovoid, slightly elevated mass with surface nodularity measuring 10 × 8 mm was visible in the lower endocervix (long green arrow). **B** Histologically, the tumor tissue exhibited a micropapillary component (90%) and a mucinous carcinoma component (10%) (yellow arrows). **C** The micropapillary component consisted of tumor cells arranged in small micropapillary nests surrounded by cleft-like, empty spaces. **D** The intervening stroma exhibited mixed inflammatory infiltrates with extensive fibromyxoid desmoplastic responses. **E** The intestinal-type mucinous carcinoma component displayed complex and cribriform architectural patterns. **F** In each gland, pseudostratified epithelial cells showed enlarged, elongated, and hyperchromatic nuclei and intracytoplasmic mucin. **G** Adenocarcinoma in situ was present at the periphery of the tumor. **H** The tumor cells of the micropapillary component possessed atypical nuclei with moderate-to-severe pleomorphism and conspicuous nucleoli. The cytoplasm appeared moderate in amount and pale to eosinophilic, with occasional intracytoplasmic mucins. **I** Numerous intraepithelial neutrophilic infiltrates were visible. Staining method: **B–I**, hematoxylin and eosin staining. Magnification: **B**, ×40; **C**, **D**, ×100; **E**, ×200; **F**, ×400; **G**, ×100; **H**, **I**, ×400.

Lymphovascular invasion (LVI) was absent. At the periphery of the tumor, several areas showing endocervical adenocarcinoma in situ were present (Fig. 1G). The individual tumor cells possessed atypical nuclei with moderate-to-severe pleomorphism and conspicuous nucleoli (Fig. 1H). The cytoplasm was moderate in amount and pale to eosinophilic. Numerous intraepithelial neutrophilic infiltrates were identified (Fig. 1I). In several foci, atypical mitotic figures and apoptotic bodies were noted. High-grade squamous intraepithelial lesions, which were observed in the biopsied specimen, were not identified in the hysterectomy specimen. The bilateral parametria, uterine body, and bilateral adnexae showed no pathological abnormalities. The patient was diagnosed as having FIGO [8] stage IA2 IMPC.

All tumor cells displayed p16 block positivity (Fig. 2A, B) and wild-type p53 immunostaining patterns. Mucin 1 (MUC1) characteristically surrounded the micropapillae, indicating

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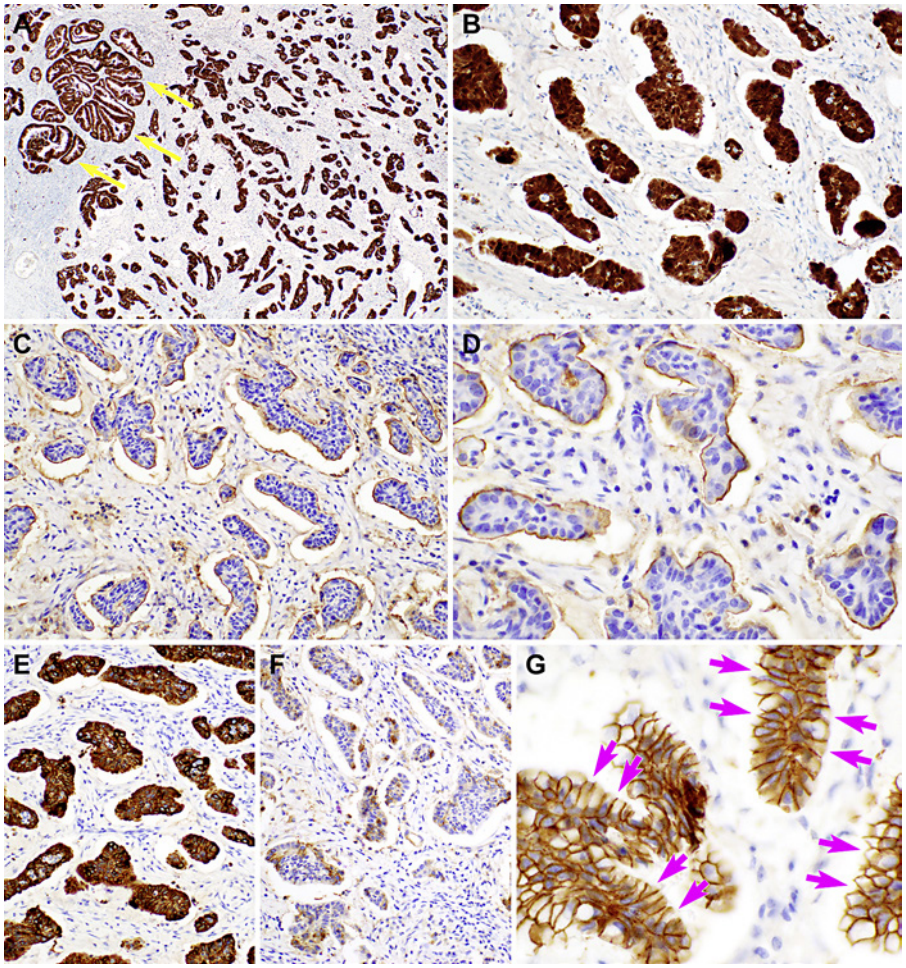

Fig. 2. Immunophenotype of invasive micropapillary carcinoma of the uterine cervix. **A**, **B** The tumor cells in both the mucinous carcinoma (left upper corner; long yellow arrows) and micropapillary carcinoma (right two-thirds) components diffusely and strongly expressed p16 in their nuclei (block positivity). **C**, **D** Mucin 1 (MUC1) immunostaining revealed that MUC1 surrounded each micropapillary structure, exhibiting the reverse epithelial polarity of the glandular cells. MUC1 was localized predominantly in the stroma-facing surface of the cell clusters, accentuating the outlines of the micropapillary structures by forming a distinct band on this surface. **E** Diffuse and strong membranous cytokeratin 7 immunoreactivity was observed. **F** Carcinoembryonic antigen expression was focal and patchy. **G** E-cadherin expression was noted in the intercellular junction but absent from the cell membrane facing the stroma (short pink arrows). Staining method: **A–G**, polymer method. Magnification: **A**, ×40; **B**, **C**, ×100; **D**, ×200; **E**, **F**, ×100; **G**, ×400.

the inverted epithelial polarity of the glandular cells (Fig. 2C, D). MUC1 expression was predominantly located in the stroma-facing surface of the cell clusters, accentuating the outlines of the micropapillary structures by forming a distinct band on this surface. Almost all of the tumor cells exhibited diffuse and strong cytokeratin 7 expression (Fig. 2E). The carcinoembryonic antigen reacted focally with the cytoplasm of some tumor cells (Fig. 2F). Loss of E-cadherin expression was observed in the stroma-facing cell membrane, whereas along the intercellular junction, E-cadherin expression was preserved (Fig. 2G). An elevated Ki-67 labeling index was observed. The tumor cells were negative for estrogen and progesterone receptors.

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Table 1. Targeted sequencing results

Gene	Mutation type	Sequence change	Predicted effect	Allele frequency	Clinical significance
PIK3CA	Missense	c.1633G>A	p.Glu545Lys	17.27%	Pathogenic
PMS2	Missense	c.472A>T	p.Ser158Cys	55.4%	Variant of unknown significance
CREBBP	Missense	c.1132C>T	p.Arg378Trp	48.87%	Variant of unknown significance

Targeted sequencing analysis was performed using an Oncomine Cancer Research Panel (Thermo Fisher Scientific, Waltham, MA, USA), Ion 540 Kit-Chef (Thermo Fisher Scientific), and Ion S5 Chef system (Thermo Fisher Scientific). Table 1 summarizes the single nucleotide variations detected. We found that the IMPC harbored a pathogenic missense mutation in *PIK3CA* (c.1633G>A; p.Glu545Lys). Neither copy number alteration nor fusion was detected.

Discussion

Irrespective of location, the presence of a micropapillary component has been documented as one of the most important factors that determines clinical behavior and outcome [9, 10]. In agreement with reports that a micropapillary pattern is associated with an aggressive clinical course of adenocarcinoma in many different organs, IMPC of the uterine cervix has been reported to frequently exhibit extensive LVI and be classified as an advanced stage at the time of diagnosis [2, 5, 7]. In a recent case series of 44 cervical IMPCs reported by Alvarado-Cabrero et al. [7], LVI was detected in all cases (100.0%), and lymph node metastases were present in 41 of the 44 cases (93.2%). The authors also observed that the nodal metastatic tumors typically retained a prominent micropapillary morphology. Similarly, in one of the 8 cases of cervical IMPC reported by Stewart et al. [2], all of the metastatic lesions exhibited a micropapillary pattern, whereas a micropapillary pattern was just a minor component of the primary cervical lesion. These results emphasize the importance of the micropapillary component as a significant adverse pathological factor. Furthermore, Alvarado-Cabrero et al. [7] documented that 70% of patients developed recurrent diseases or distant metastases and that 47.7% of patients with available follow-up data died of IMPC. Taken together, previous studies have shown that a micropapillary component in endocervical adenocarcinoma is associated with aggressive behavior that results in an advanced stage, recurrence, and metastasis.

In our case, however, the cervical IMPC measured 8 and 3 mm in the maximum horizontal dimension and stromal invasion depth, respectively, corresponding to the FIGO stage IA2. Neither parametrial extension, nor lymph node metastasis, nor LVI was identified. Given the popular notion that FIGO stage is the strongest prognostic factor in adenocarcinoma of the uterine cervix, our patient, who received standard surgical treatment (radical hysterectomy with bilateral salpingo-oophorectomy and bilateral pelvic lymph node dissection), is expected to have a favorable prognosis, similar to that of stage IA2 cervical carcinoma patients [11]. It has been reported that between 95 and 98% of women with stage IA2 cervical carcinoma survived beyond 5 years after diagnosis with standard surgery. Since the postoperative follow-up duration is only 4 months, long-term observation is necessary to thoroughly evaluate the clinical outcome of our patient.

Although there is no clear explanation for the pathogenetic mechanism of the micropapillary pattern in endocervical adenocarcinoma, we can deduce its morphogenesis through several studies about IMPCs in other organs. The histological features of IMPC in other

anatomical sites are very similar to those described in endocervical adenocarcinoma, and the reverse epithelial polarity of the former has been confirmed immunohistochemically, particularly via MUC1 expression [12]. MUC1 immunostaining normally highlights the apical cell border, but in IMPC, it accentuates the outlines of the micropapillary units by forming a distinct band on the surface [2, 5, 13]. Nassar et al. [13] reported that while MUC1 usually highlights apical, intracytoplasmic, or intercellular areas in conventional adenocarcinomas, its expression is limited to the external aspect of the cells in IMPC, supporting the reversal of cell orientation as evidence of the morphogenesis and pathogenesis of IMPC. Moreover, whereas E-cadherin is preserved along the intercellular junction between tumor cells of IMPC, it exhibits a loss of expression in the stroma-facing cell membrane, and this finding is similar to those of previous mammary IMPC studies. As E-cadherin is a representative cell adhesion protein, this result also confirms the reverse epithelial polarity of IMPC. One can hypothesize that the reverse in polarization facilitates the secretion by the tumor cells of molecules (namely metalloproteinases) responsible for stromal and vascular invasion, permitting easier dissemination of the tumor cell clusters. This concept is further supported by the observation that the micropapillary component is usually present at the invasive front of the tumor.

In this study, we identified pathogenic mutations in cervical IMPC for the first time. Targeted sequencing analysis revealed that IMPC harbored a pathogenic missense *PIK3CA* mutation. The molecular mechanisms associated with micropapillary morphology remain unclear. In mammary IMPC, thus far, genomic analysis has failed to identify specific, consistent alterations. Some previous studies have suggested a possible correlation between micropapillary morphology and epithelial-mesenchymal transition, and it has also been proposed that micropapillary differentiation represents a phenomenon similar to that of poorly differentiated clusters in colorectal and mammary IMPCs. Genetic abnormalities in IMPC have been investigated in the breast; Thor et al. [14] observed that mammary IMPCs demonstrate chromosomal aberrations involving multiple chromosomes. They speculated that 8p loss, detected in all 16 examined cases, might contain one or more genes whose loss is responsible for the IMPC phenotype or its aggressive behavior. Gruel et al. [15] also found numerous mutations in mammary IMPCs. The most commonly mutated genes are *TP53*, *DNAH9*, and *PIK3CA*. Interestingly, genes involved in ciliogenesis (*DNAH9*, *BBS12*, and *BBS9*), cytoskeleton organization (*UBR4*, *PTPN21*, and *ZFYUE26*), and cell polarity (*FMN2* and *SEC63*) have also been found to have mutations in mammary IMPC. Based on these data, it seems possible that the demonstration of distinct genetic alterations in IMPCs may have potential future implications regarding the use of targeted therapies for patients with advanced-stage or recurrent disease.

The differential diagnoses for adenocarcinoma with a micropapillary pattern in the uterine cervix include IMPC, serous carcinoma from elsewhere in the female genital tract, and metastatic lesions from extragenital IMPC. Considering that most patients with IMPC have advanced-stage disease at presentation, it is important for pathologists to determine the origin of the tumor, since treatment can differ significantly depending on the primary site. In addition to clinical information, immunostaining can be helpful in identifying the tumor origin. In distinguishing cervical IMPC from serous carcinoma originating from the uterine body or tubo-ovarian region, immunostaining for p16, p53, and Wilms tumor 1 can be helpful, but the clinical setting, gross finding, and presence of a precursor lesion must be prioritized. Extragenital IMPC that involves the cervix secondarily is very rare and therefore difficult for pathologists to recognize, particularly due to the lack of clinical information. A combination of clinicopathological correlation, immunostaining for GATA-binding protein 3 (for a breast or urothelial origin), thyroid transcription factor 1 (for a lung origin), gross cystic disease fluid protein 15 (for a breast or salivary gland origin), caudal type homeobox 2 (for a colorectal origin), and HPV status will be useful in determining the origin.

Conclusion

We investigated a case of IMPC in the uterine cervix that was determined to be a rare but distinct variant of endocervical adenocarcinoma. In contrast to the previously reported aggressive behavior of IMPC, our patient was diagnosed as having FIGO stage IA2 IMPC without LVI and lymph node metastasis. Based on the fact that FIGO stage is the strongest prognostic factor in endocervical adenocarcinoma and that our patient received standard surgical treatment, the patient is expected to have a favorable prognosis. Long-term observation is necessary to evaluate her clinical outcome. In addition, we demonstrated for the first time the molecular characteristics of cervical IMPC, which includes a missense *PIK3CA* mutation. Further investigations using larger cohorts of patients are necessary to confirm these findings.

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Statement of Ethics

Written informed consent for publication was obtained from the patient. This study (2020-07-043) was reviewed and approved by the Institutional Review Board of Samsung Medical Center (Seoul, Republic of Korea).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Hyun Hee Koh: conceptualization, data analysis, and manuscript drafting; Hyunjin Kim: data collection and manuscript editing; Sujin Park: manuscript editing; Sung-Im Do: conceptualization, manuscript editing, and funding acquisition; Hyun-Soo Kim: conceptualization, manuscript drafting, manuscript editing, funding acquisition, and supervision. All authors read and approved the final manuscript.

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