Pseudomyxoma-type Invasion in Gastrointestinal Adenocarcinomas of Endometrium and Cervix: A Report of 2 Cases

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Case Report

Pseudomyxoma-type Invasion in Gastrointestinal Adenocarcinomas of Endometrium and Cervix: A Report of 2 Cases

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Summary: This paper presents a clinicopathologic and immunohistochemical report of 2 gastrointestinal-type tumors, one in the endometrium and the other in the cervix. Both showed extensive invasion into the pelvic structures with acellular mucin, identical to pseudomyxoma but in the absence of appendiceal or ovarian tumors. Case 1 was an 81-yr-old female with a Stage III endometrial gastrointestinal-type adenocarcinoma who had had an endometrial polyp with intestinal metaplasia 4 years previously. Case 2 was a 68-yr-old female with Stage IIIB endocervical gastrointestinal-type adenocarcinoma. Both were associated with a pseudomyxoma type of invasion, which in the endometrial case was transmural through the myometrium, and in the cervical case involved parametria, pelvic floor, and lymph nodes. Immunohistochemically, both tumors had a gastrointestinal phenotype coexpressing cytokeratins 7 and 20, CDX2, villin, MUC2, MUC5AC, and MUC6 and were negative for human papillomavirus, analyzed by real-time polymerase chain reaction. The first case exemplifies intestinal endometrial metaplasia as a precursor lesion of the rare gastrointestinal type of adenocarcinoma and also proves its progression into carcinoma. The second case exemplifies the highly aggressive nature of cervical invasion forming mucin lakes. Extensive pseudomyxoma in the uterus and cervix was associated with high clinical stages with marked lymphovascular invasion and lymph node metastases. **Key Words:** Pseudomyxoma—Endometrium—Cervix—Adenocarcinoma—Intestinal metaplasia.

Pseudomyxoma (PM) peritonei is a lesion defined by the presence of extensive dissecting mucin lakes in the pelvis or abdomen, with or without mucin-secreting cells, usually related to a low-grade mucinous appendiceal tumor (1). Less frequently, PM arises from a mucinous intestinal-type tumor associated with a mature cystic teratoma of the ovary (2). Metastases to the ovary from other mucinous neoplasms with gastrointestinal phenotype can also present as PM.

Endometrial intestinal metaplasia (IM) is an exceptional entity that can be associated with gastrointestinal-type cervical lesions such as pyloric metaplasia (3). In the cervix, gastric-type endocervical growths are not related to human papillomavirus (HPV) (4). In contrast, a substantial proportion of intestinal-type endocervical lesions may be HPV related (5).

In this paper, we report the clinicopathologic and immunohistochemical findings of 2 gastrointestinal-type tumors of the cervix and endometrium with

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characteristic histology and immunophenotype, which determined a hitherto unreported pattern of invasion as PM in the cervix, uterus, and regional lymph nodes.

CASE PRESENTATIONS

Case 1

An 81-yr-old female had abnormal uterine bleeding that was related to an endometrial polyp present in an unremarkable endometrial cavity, which was removed hysteroscopically. Microscopically, the usual-type endometrial polyp showed foci of a surface epithelium with a fully-developed IM with abundant goblet cells (Fig. 1A) that coexpressed cytokeratins 7 and 20 (CK7 and CK20), villin, and CDX2. The patient was discharged but she refused further treatment. Four years later, she presented with severe metrorrhagia due to a uterine mass that required an abdominal hysterectomy with bilateral salpingo-oophorectomy. No other lesions of either the gastrointestinal or female genital tract were found.

Grossly, the resected uterus showed extensive invasion by a $10 \times 4 \times 6$ cm lobulated, partly cystic, mucoid friable mass that extended to the uterine serosa (Fig. 1B). The ovaries, fallopian tubes, and cervix were unremarkable.

Microscopically, the endomyometrium was replaced by abundant extracellular dissecting mucin lakes (Fig. 1C) harboring interspersed, atypical aggregations of columnar cells with eosinophilic or basophilic mucin-laden cytoplasms (Fig. 1D). Acellular mucin lakes also occupied lymphovascular spaces. Neither normal endometrium nor polyps were seen.

Immunohistochemically, neoplastic cells were vimentin, PAX8, and estrogen and progesterone receptors negative, but coexpressed CK7 and CK20. Expression of gastrointestinal differentiation markers such as CDX2, villin, MUC2, MUC5AC, and MUC6 was found. Furthermore, although p16 had strong but patchy nuclear and cytoplasmic expression, real-time polymerase chain reaction performed in using an automated HPV Direct Flow CHIP kit (6) failed to show HPV-DNA sequences.

The final diagnosis was a FIGO Stage IIIA mucinous adenocarcinoma of gastrointestinal type of the endometrium originating from a preexistent IM developing in an endometrial polyp, with massive PM in the myometrium. The patient refused further treatment and is presently lost to follow-up.

Case 2

A 68-yr-old female with a previous diagnosis of invasive ductal carcinoma of the breast treated with chemotherapy and radiotherapy, presented with abnormal uterine bleeding. Magnetic resonance imaging revealed a large cystic mass filling the pelvis and infiltrating the cervix and surrounding structures. Clinical and radiologic studies did not show extrapelvic lesions. A cervical biopsy was performed which revealed a mucinous adenocarcinoma with extensive goblet cell differentiation (Fig. 2A). Radical abdominal hysterectomy with debulking of large mucoid masses in the pelvic floor and lymphadenectomy was performed, followed by neoadjuvant therapy with carboplatin and radiotherapy.

Grossly, an endophytic $3 \times 4 \times 3.5$ cm white mucinous friable mass occupied the entire thickness of the cervix, but respected the uterus and adnexa but not the vaginal cuff, which was focally involved.

Microscopically, the cervix was invaded by confluent, often acellular mucin lakes (Fig. 2B) with occasional floating signet-ring-type cells or bland mucinous glands. Also, hypocellular mucin was seen occupying numerous lymphovascular spaces (Fig. 2C) lined by D2-40 podoplanin-positive endothelial cells as well as 1 regional lymph node (Fig. 2D), where cytokeratins immunostain revealed isolated neoplastic cells. Immunohistochemically, cells expressed pancytokeratin, AE1/AE3, CK7 (focally), CK20 (diffusely), p16 (patchy); mucin markers MUC2, MUC5AC, MUC6; and intestinal phenotype markers villin and CDX2. Estrogen and progesterone receptors were negative thus making an endometrioid phenotype unlikely. Real-time polymerase chain reaction was negative for HPV-DNA sequences. The final diagnosis was a FIGO Stage IIIB mucinous adenocarcinoma of gastrointestinal type of the cervix with extensive PM in the cervix, pelvic floor, and draining lymph nodes. Four months after diagnosis, the patient is alive with disease and is being treated by brachytherapy.

DISCUSSION

Both cases reported here correspond to intestinal-type adenocarcinomas developing in the endometrium and the cervix (7) that were associated with invasion of PM type, a type of invasion identical to that occurring in appendiceal and ovarian teratomas (1,2).

In the first case, IM arose first within the surface epithelium of a polyp, revealing well-defined goblet

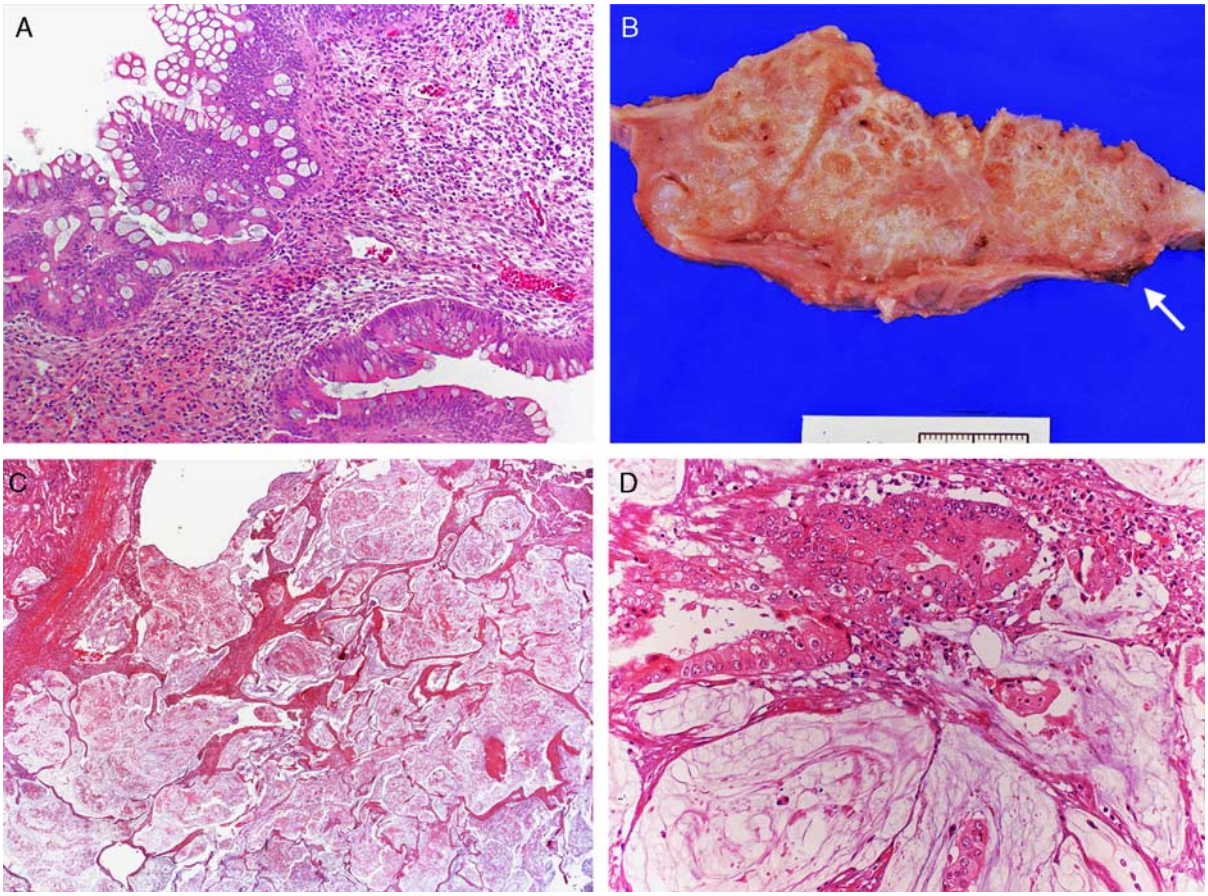

FIG. 1. Case 1, endometrial tumor. (A) Initial hysteroscopic biopsy revealed an endometrial polyp with marked intestinal metaplasia. (B) Transmural invasion by a lobular, septated hypocellular mucinous mass that involves the uterine serosa (arrowhead). (C) Pseudomyxomatous lakes with basophilic contents in the myometrium which at higher magnification revealed isolated atypical glandular formations (D) and loose cells.

and absorptive intestinal-type cells. At that time, the endometrium appeared normal on hysteroscopy. However, only 4 yr later, the patient had an aggressive intestinal-type mucinous adenocarcinoma of the endometrium, exemplifying the short evolution of this type of adenocarcinoma and its relationship with IM. Endometrial IM is an extremely rare condition associated with cervical glandular lesions of intestinal type (3,8), proved to be the precursor of an intestinal-type adenocarcinoma, which shows characteristic pseudomyxomatous invasion of the myometrium. In the present case, neither lesion, IM in the polyp nor adenocarcinoma, had an endometrioid carcinoma phenotype but expressed CDX2, villin, and MUC2, as well as concurrent staining of gastric-type mucins MUC5AC and MUC6, confirming their full gastrointestinal phenotype. Intestinal-type mucinous endometrial carcinoma is equally exceptional, having been reported only twice (9,10). Neither of these previously described cases was associated with PM and in both, diagnoses were based on histologic findings but not on the finding of a gastrointestinal immunophenotype. One was initially found in a high clinical stage (10), similar to our case, thus exhibiting the potential for a high degree of malignancy.

Our second case represents an instance of intestinal-type endocervical adenocarcinoma. It showed a predominant mucinous goblet cell population with mild atypicality and also a full gastrointestinal immunophenotype which, as a PM, also invaded, the cervix, pelvic tissues, and lymph nodes. This type of gastrointestinal-type cervical adenocarcinoma is not related to HPV infection lesions. Both pyloric metaplasia and lobular endocervical gland hyperplasia are closely related conditions (11) and are putative precursors of minimal deviation endocervical adenocarcinoma, a characteristic gastric-type

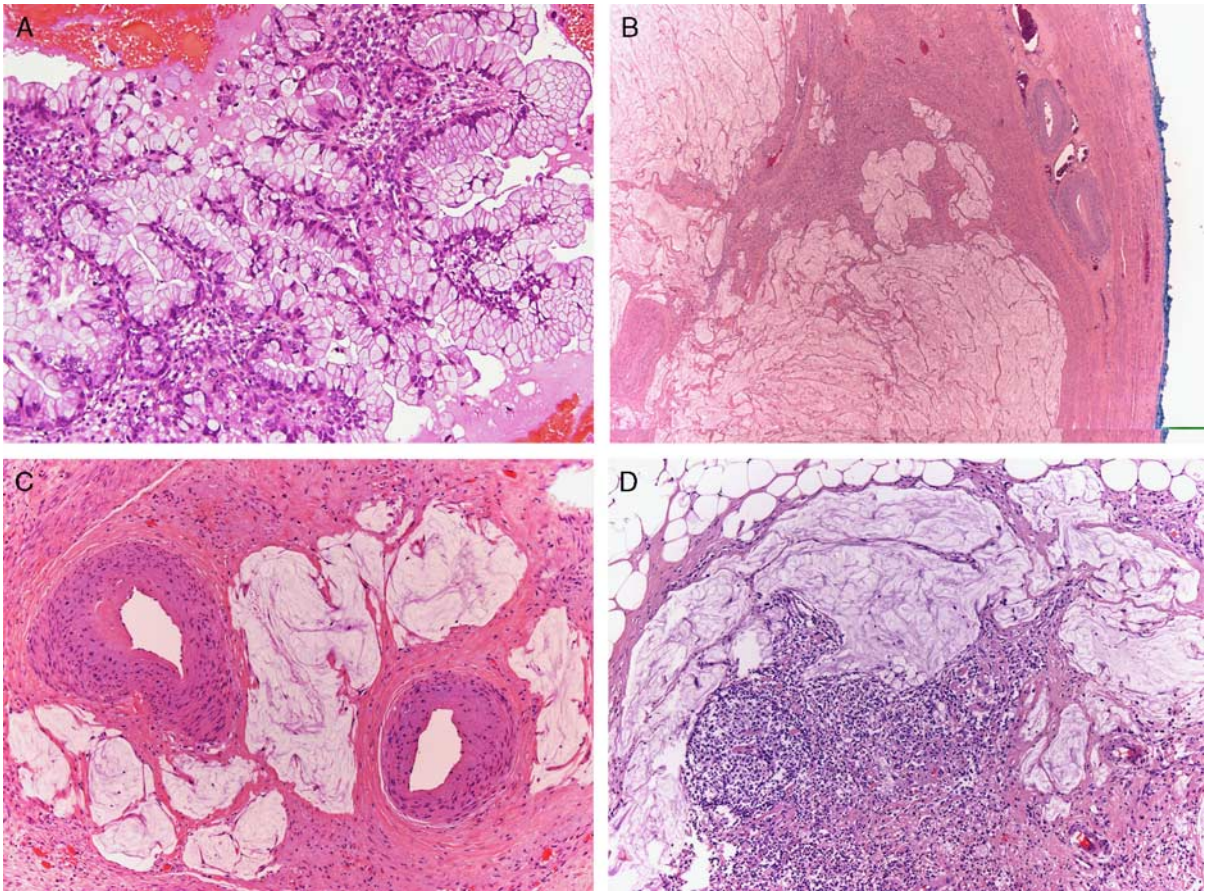

FIG. 2. Case 2, endocervical tumor. (A) Initial biopsy revealed a goblet cell adenocarcinoma. The resected cervix was occupied by pseudomyxoma (B), which also filled perivascular lymph vessels (C) and isolated lymph nodes (D).

adenocarcinoma. Nevertheless, IM of goblet cell type often represents an intestinal variant of cervical glandular intraepithelial neoplasia and, consequently, a large proportion of cases test positive for HPV. However, even if our case corresponded to an adenocarcinoma with an intestinal phenotype, it lacked the presence of HPV.

Both cases were interpreted as gastrointestinal-type tumors invading as a PM. In the cervix a similar pattern of invasion with mucin lakes has been found to be associated with poor survival (12).

PM peritonei is almost invariably associated with low-grade appendiceal tumors and teratoma-associated mucinous tumors of the ovary (1,2,13) and has not been reported in other areas of the female genital tract. Although endometrioid adenocarcinomas of the endometrium with mucinous differentiation are frequent, their association with a PM pattern of invasion has not been previously reported. In the cervix, only 2 instances of a mucinous lesion, named colloid endocervical mucinous adenocarcinoma, have been reported (14,15). One of them (14) was an HPV-positive case associated with a usual-type adenocarcinoma *in situ* and, even if there was a mucin hypersecretion, it lacked CDX2 and MUC2 expression of intestinal neoplasms as well as the lobularly arranged expansive, paucicellular, mucin lakes that characterize PM (14). In the other case (15), HPV status was unknown and the presence of goblet cells was not reported. Thus, although these cases showed mucin hypersecretion as did ours, they were different both in the phenotype and the invasion pattern.

In summary, our first case suggested intestinal endometrial metaplasia as a precursor lesion with a rapid progression to the rare gastrointestinal-type adenocarcinoma. Furthermore, the second case confirms the highly aggressive nature of endocervical adenocarcinomas with a mucin lake type of invasion. Thus, the extensive PM in the corpus uteri and cervix, associated with lymphovascular invasion and lymph

node metastases corresponding to high clinical stages, indicates poor outcome for gastrointestinal-type adenocarcinomas, akin to appendiceal or ovarian tumors with associated PM.

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