# Low Grade Peritoneal Mucinous Carcinomatosis Associated with Human Papilloma Virus Infection: Case Report

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Pseudomyxoma peritonei is a clinical syndrome characterized by peritoneal dissemination of a mucinous tumor with mucinous ascites. The vast majority of the pseudomyxoma peritonei are are associated with mucinous neoplasms of the appendix. We describe a case of pseudomyxoma peritonei associated with mucinous adenocarcinoma of the cervix in a 60-year-old woman. The patient developed low grade mucinous peritoneal carcinomatosis 8 years after hysterectomy for cervical adenocarcinoma. No other primary mucinous tumor was identified and peritoneal carcinomatosis tested positive for high-risk human papilloma virus (HPV), showing both integrated and episomal pattern. HPV has been previously associated with development of cervical carcinomas (both squamous and mucinous) but neither has cervical adenocarcinoma nor HPV been implicated in development of pseudomyxoma peritonei. To the best of our knowledge, this is the first description of HPV-associated malignancy presenting as pseudomyxoma peritonei.

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Pseudomyxoma peritonei is characterized by peritoneal dissemination of mucin-producing neoplasms originating from the appendix, colon, and ovaries (1-3). The vast majority of tumors arise in the appendix. Benign appendiceal neoplasms (adenomas) may lead to the peritoneal dissemination, ie, disseminated peritoneal adenomucinosis, while malignant appendiceal neoplasms may lead to peritoneal mucinous carcinomatosis. Disseminated peritoneal adenomucinosis is characterized by scant mucinous epithelium that displays little or no cellular atypia, abundant mucin production, variable fibrosis, and inflammation. On the other hand, peritoneal mucinous carcinomatosis is characterized by mucin-producing glands and cells that exhibit cytological and architectural atypia characteristic of carcinoma (including signet ring variants). Peritoneal mucinous carcinomas with

intermediate and discordant features are frequently encountered (1,2) and an alternative dichotomous classification has been proposed, classifying the pseudomyxoma peritonei of appendiceal origin into mucinous carcinoma peritonei peritonei-low grade and mucinous carcinoma peritonei-high grade (4).

Adenocarcinomas account for approximately 12% of all cervical cancers (5) and the majority are human papilloma virus (HPV) positive. In fact, HPV infections are equally prevalent in squamous and glandular carcinomas of the cervix (6,7), and high-risk HPV 16 and HPV 18 types are the two most commonly detected HPV types (7). Although ovarian metastasis of an advanced cervical mucinous adenocarcinoma may occur (8), peritoneal dissemination of cervical adenocarcinoma has not been previously described.

## Case report

A 60-year-old woman underwent surgery for a pelvic mass in March of 2003. The symptoms pointed to an ovarian tumor; during the procedure mucinous ascites was discovered and intraoperative diagnosis of pseudomyxoma peritonei was made. Microscopically, the ovarian tumor resembled mucinous intestinal-type borderline tumor. No tumor was found in the contralateral ovary or appendix. The latter was entirely submitted and showed normal histology. Multiple biopsies of the peritoneal surfaces and omentum revealed a low grade mucinous neoplasm, consistent with peritoneal mucinous carcinomatosis. Eight years before, the patient had undergone hysterectomy for a well-differentiated mucinous adenocarcinoma of the cervix, stage pT1b, N0, MX (Figure 1). Comparative histologic and immunophenotypic characterization of the ovarian and cervical adenocarcinomas showed morphologic similarities and identical pattern of keratin expression (diffusely and strongly positive for low molecular weight cytokeratins CK7+ and CK20+). These findings supported the interpretation that the ovarian tumor was a metastasis from the primary endocervical adenocarcinoma.

In December of 2006, three years after the diagnosis of pseudomyxoma peritonei, the patient presented with copious amounts (several liters) of intra-abdominal mucous fluid, for which she underwent second tumor debulking procedure (Figure 2A). Again, no other possible primary source of pseudomyxoma peritonei was identified.

This time, we performed in situ hybridization for HPV (automated in situ hybridization method, Ventana Inform HPV Test, Tucson, AZ, USA) using Family 16 probe cocktail (Ventana). This probe cocktail has an

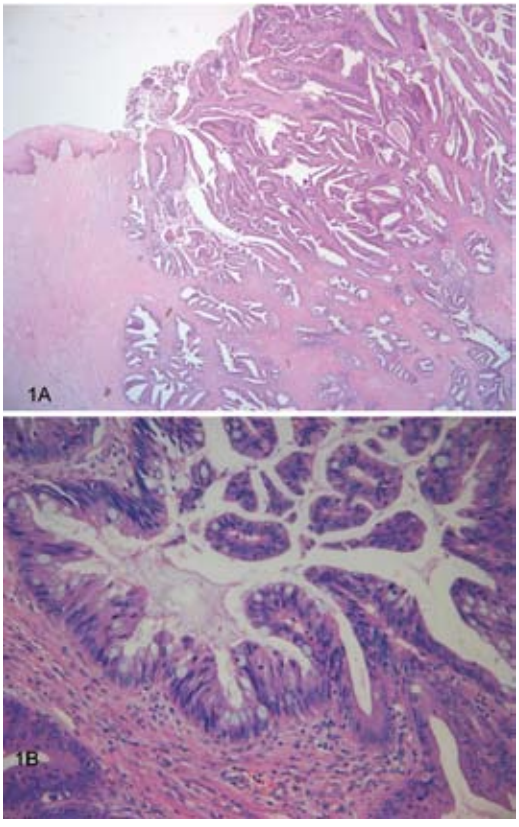


**Figure 1.** (**A**) Cervical adenocarcinoma invades the cervical wall (hematoxylin and eosin stain, ×2). (**B**) Intestinal type mucinous adenocarcinoma of the cervix. The tumor appears well differentiated and contains goblet cells (hematoxylin and eosin, ×20).

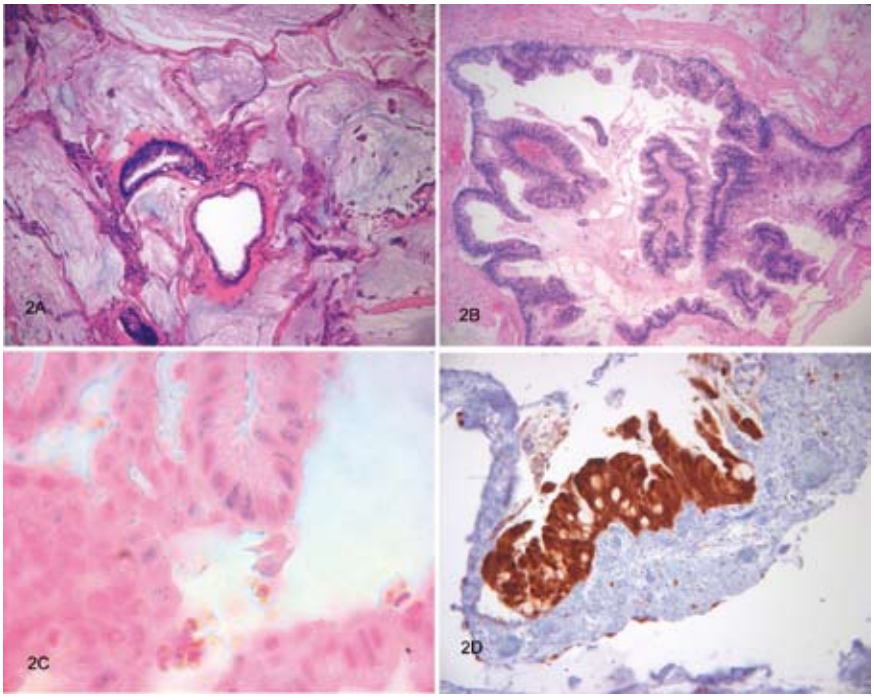


**Figure 2.** (**A, B**) Peritoneal mucinous carcinomatosis, low grade. Low grade mucinous adenocarcinoma of intestinal type exhibiting abundant extracellular mucin and fibrosis (hematoxylin and eosin stain, (**A**) – × 4; (**B**) – × 10). (**C**) Human papilloma virus (HPV) in peritoneal mucinous carcinomatosis. Nuclear dot-like reactivity consistent with an integrated pattern of HPV infection (in situ chromogenic hybridization, ×100). (**D**) Positive p16 immunoreaction. Diffuse strong cytoplasmic and nuclear reactivity (brown) is detected in mucinous epithelium of pseudomyxoma peritonei (immunohistochemistry, ×20).

affinity to HPV genotypes 16, 18, 31, 33, 35, 39, 51, 52, 56, 58, and 66 and it reacted positively with the mucinous epithelium of the peritoneal adenocarcinoma (Figure 2C). The mucinous ascites fluid was also tested for the presence of HPV gene sequences using hybrid capture methodology (Hybrid Capture® 2 technology, Digene Corporation, Gaithersburg, MD, USA), which confirmed the presence of high-risk HPV sequences (testing was performed at ARUP Laboratories, Salt Lake City, UT, USA).

**Table 1.** Immunohistochemical characterization of pseudomyxoma peritonei associated with human papilloma virus – positive mucinous adenocarcinoma of the cervix

| Antibody | Pseudomyxoma peritonei | Cervix | Source, clone |
|---|---|---|---|
| CK7 | positive | positive | DAKO, OV-TL 12/30 |
| CK20 | positive | positive | DAKO, $K_2$20.8 |
| MUC2 | positive | N/E* | Zymed, CCP58 |
| CDX-2 | positive | N/E | Biogenex, CDX2-88 |
| $p16^{ink4a}$ | positive | N/E | Cell Marque, clone 16P04 |

*N/E –Not evaluated due to the unavailability of tissue blocks.

Additional immunohistochemical analysis (Table 1) showed strong and diffuse $p16^{INK4a}$ (Figure 2D), consistent with HPV infection (9).

The patient had a rapid recovery from debulking procedure and is doing well two years after the procedure (stable disease on CT scans). No chemotherapy was given.

## Discussion

The case described in this article demonstrated the association of mucinous tumor of the cervix with pseudomyxoma peritonei. Pseudomyxoma peritonei was first described by Werth (10) in 1884. It is an uncommon disease characterized by abundant extracellular mucin in the peritoneum (gelatinous ascites), reactive fibrosis, neovascularization, and inflammation. It results from multifo-

cal peritoneal, serosal, and omental implants of a mucin-producing neoplasm. Pseudomyxoma peritonei is a broad descriptive term encompassing a wide spectrum of mucinous neoplasms, from benign and borderline to frankly malignant, which are most commonly arising in the appendix, where either the rupture of a distended organ (mucinous cystadenoma) or transmural invasion (mucinous adenocarcinoma) leads to peritoneal dissemination. Disease presents either as disseminated peritoneal adenomucinosis – the benign variant with prolonged course and low mortality or as peritoneal mucinous carcinomatosis – the malignant variant with often rapidly progressive and fatal outcome (1). Given the fact that a proportion of the tumors show histologic features that can combine features of adenomatous and carcinomatous epithelium, some authors proposed a dichotomous classification (low grade vs high grade) based on their experience with outcomes in uniformly treated patients (4).

Pseudomyxoma peritonei arising in organs other than the appendix is extremely rare, particularly after an ovarian source has been excluded by recognition of the common secondary involvement of this organ with a metastasis from appendiceal mucinous primary tumor. Only rare cases of mucinous tumors arising in mature ovarian teratomas have been unequivocally shown to be associated with pseudomyxoma peritonei (3).

Mucinous tumors of the cervix have not, to the best of our knowledge, been associated with the pseudomyxoma peritonei. Several types of invasive cervical mucinous adenocarcinomas are recognized based on histologic appearances including endocervical (including minimal deviation and villoglandular), intestinal, and signet-ring variants (11). In our case, intestinal type was present. The vast majority of cervical adenocarcinomas test positive for high-risk (types 16 and 18) HPV sequences (6,7), and detection of HPV in this patient's pseudomyxoma peritonei was strongly suggestive of a cervical primary source. Immunohistochemical tumor characteristics may be helpful in the identification of the origin of the metastatic tumor. Intestine-specific transcription factor protein CDX-2 expression, found in the current case, has been linked to intestinal mucinous carcinomas. However, aberrant proteins expression is common in malignant tumors and over a half of mucinous ovarian carcinomas express CDX-2 (12); thus CDX2 cannot reliably distinguish between primary ovarian and intestinal adenocarcinoma affecting peritoneum. Furthermore, CDX2 expression has also been described in the intestinal type of cervical adenocarcinomas (13), making clinical correlation and HPV result all more important in the investigation of the origin of pseudomyxoma peritonei in this case. No primary gastrointestinal tumor was found during 2 abdominal surgeries and colonoscopies over a 3-year period, making pseudomyxoma peritonei very unlikely to have developed from an occult mucinous gastrointestinal carcinoma. On the other hand, HPV has been clearly implied in the pathogenesis of cervical adenocarcinomas (6,7). However, HPV sequences have also been recently found in a high proportion of colorectal adenocarcinomas (14) and in normal adjacent mucosa. This is intriguing because, during the laparoscopic hysterectomy for the patient's cervical adenocarcinoma, inadvertent rectal perforation occurred, resulting in repair with transverse loop colostomy. Hence, we cannot exclude a possibility that HPV infection of peritoneum and pseudomyxoma peritonei in this patient resulted from spilling of HPV-infection from rectal/intestinal site.

In conclusion, we have shown for the first time a low grade peritoneal mucinous carcinomatosis containing high-risk-HPV viral sequences, which most likely resulted from metastatic spread of a mucinous adenocarcinoma of

the cervix. Further investigations into the role of HPV in pseudomyxoma peritonei may possibly lead to additional treatment options based on inhibition of E6 and E7 oncogenes (15).


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