APPENDICEAL EPITHELIAL NEOPLASMS AND PSEUDOMYXOMA PERITONEI, A DISTINCT CLINICAL ENTITY WITH DISTINCT TREATMENTS

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Appendiceal epithelial neoplasms account for approximately 1% of all colorectal cancers (1). Therefore in the United States there are approximately 1500 patients with this condition each year. Confusion over proper identification of this entity arises at least in part because of the redundancy of histologic designations associated with the appendiceal epithelial tumors. Table 1 itemizes the many different designations for these malignancies that occur in the literature. Unfortunately, even though the interest in these tumors is broad-based and there are a generous number of publications from prominent institutions that concern this subject, no consensus regarding proper nomenclature for these tumors has occurred.

Table 1. Multiple histologic designations that are used in the literature to describe the primary tumor and peritoneal dissemination of appendiceal epithelial neoplasms

<table>
<thead>
<tr>
<th>Designation</th>
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<tr>
<td>Colloid carcinoma</td>
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<tr>
<td>Goblet cell carcinoma</td>
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<tr>
<td>Cystadenocarcinoma</td>
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<tr>
<td>Mucinous cystadenocarcinoma</td>
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<tr>
<td>Peritoneal mucinous carcinomatosis (PMCA)</td>
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<tr>
<td>Disseminated peritoneal adenomucinosis (DPAM)</td>
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<tr>
<td>Mucinous adenocarcinoma (MACA)</td>
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<td>Low-grade appendiceal mucinous neoplasm (LAMN)</td>
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<tr>
<td>Pseudomyxoma peritonei (PMP)</td>
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<tr>
<td>Pseudomyxoma peritonei syndrome</td>
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<tr>
<td>Pseudomyxoma ovarii</td>
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<tr>
<td>Appendiceal mucinous tumor of uncertain malignant potential</td>
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<tr>
<td>Borderline appendiceal mucinous tumor</td>
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Perhaps the most prominent clinical designation for appendiceal epithelial neoplasms is pseudomyxoma peritonei syndrome. Again, unfortunately this is a poorly understood clinical entity and therefore patients may not receive appropriate treatment. Pseudomyxoma peritonei as originally described by Werth is a group of malignancies whose presentation is characterized by increasing abdominal girth, an omental cake caused by infiltration of this structure by mucinous tumor, and a large volume of mucinous ascites plus mucinous tumor (2). Pseudomyxoma peritonei is a registered rare disease no. 843 by the National Organization of Rare Disorders (3).

In contrast, Sugarbaker and colleagues in working with a large number of cases of pseudomyxoma peritonei recognized that this condition associated with an appendiceal neoplasm present a definite clinical entity which was designated as the pseudomyxoma peritonei syndrome (4). In this disease the primary tumor is an appendiceal adenoma or mucinous adenocarcinoma. The disease progresses as the appendix wall is perforated by the primary tumor and mucus along with mucinous tumor cells are released into the peritoneal cavity. Using the mucus as a vehicle, the epithelial cells distribute themselves in a characteristic fashion around the peritoneal cavity. A very definite clinical entity occurs which can be both clinically and histopathologically distinguished from the other causes of pseudomyxoma peritonei. Mucinous peritoneal neoplasms with dis-
semination from a non-appendiceal primary site always need to be distinguished from the pseudomyxoma peritonei.

Unique clinical features of appendiceal epithelial neoplasms

In the 9th International Classification of Disease (ICD-9) revised in 2004, primary epithelial neoplasms of the appendix are grouped together with colorectal malignancy. In future revisions appendiceal neoplasms should be a distinct clinical entity because there are profound differences in the natural history and pathology of colorectal cancer as compared to appendiceal neoplasms.

Consequently, there are profound differences in the approach to treatment of these two distinct disease processes. Table 2 contrasts the clinical and pathologic features of colorectal cancer and appendiceal neoplasms. The clinical presentation, histology, the extent of tumor invasion, and the great difference in tumor differentiation separate colorectal cancer and appendiceal neoplasms as distinct pathological and clinical diseases.

The age of onset of appendiceal epithelial neoplasms is lower with a mean and median age for initial presentation of 48 years. Although the proportion of patients who have an unruptured mucocelle is not known, approximately 85% of these patients have peritoneal dissemination at the time of their initial presentation. The great majority of the tumors are of a mucinous histopathologic type. Also, a great majority of appendiceal neoplasms, approximately 75%, are minimally invasive so that they layer out on the peritoneal surfaces rather than invade into parietal peritoneum or visceral structures. However, there is a wide spectrum of aggressiveness and some patients will show signet ring morphology or poorly differentiated cancer with dissecting mucus penetrating deeply through the peritoneal layer of structures of the abdomen and pelvis. Because they usually present with peritoneal dissemination, even the most minimally aggressive of these malignancies should be regarded as a uniformly fatal condition sometimes over several decades unless special treatments are initiated.

Clinical and histopathological definition of the pseudomyxoma peritonei syndrome

Confusion still exists regarding the clinical entity, “pseudomyxoma peritonei”. Ronnett in 1995 described it as a poorly understood condition characterized by mucinous ascites and mucinous implants diffusely involving peritoneal surfaces. It is a slowly progressive disease characterized by recurrences after attempts at surgical removal. Most pathologists continue to use pseudomyxoma peritonei to refer to a spectrum of neoplastic conditions that lead to an extensive mucus accumulation within the abdomen and pelvis (5).

In contrast to the poorly defined clinical entity, pseudomyxoma peritonei, the pseudomyxoma peritonei syndrome has been defined and its distinct clinical and pathological features studied (4). The pseudomyxoma peritonei syndrome includes a large majority of the appendiceal epithelial neoplasms that have disseminated beyond the primary site (tab. 3). First and foremost, a mucinous epithelial malignancy of the appendix is the primary site for this syndrome. Because of the thin wall and narrow lumen of the appendix, even a small histologically benign appearing neoplasm is capable of rupturing the wall of the appendix so that mucus and the epithelial cells contained within

<table>
<thead>
<tr>
<th>Feature</th>
<th>Colon</th>
<th>Appendix</th>
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<tr>
<td>Mean age of onset (years)</td>
<td>68</td>
<td>48</td>
</tr>
<tr>
<td>Peritoneal dissemination at onset of disease</td>
<td>10%</td>
<td>85%</td>
</tr>
<tr>
<td>Adenocarcinoma histology</td>
<td>85%</td>
<td>10%</td>
</tr>
<tr>
<td>Mucinous histologic type</td>
<td>10-15%</td>
<td>90%</td>
</tr>
<tr>
<td>Minimally invasive</td>
<td>1%</td>
<td>75%</td>
</tr>
<tr>
<td>Signet ring adenocarcinoma</td>
<td>1/1000</td>
<td>1/10</td>
</tr>
<tr>
<td>Adenocarcinoid</td>
<td>0%</td>
<td>2,5%</td>
</tr>
<tr>
<td>Differentiation of adenocarcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>well-differentiated</td>
<td>10%</td>
<td>80%</td>
</tr>
<tr>
<td>moderately differentiated</td>
<td>80%</td>
<td>10%</td>
</tr>
<tr>
<td>poorly differentiated</td>
<td>10%</td>
<td>10%</td>
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the mucus are disseminated into the free peritoneal cavity. Very often, the primary tumor that ruptures is a mucocele (fig. 1). The mucinous tumor distends the wall of the appendix oftentimes causing poorly defined symptoms over several years prior to diagnosis of the syndrome. Either through invasion of the appendiceal wall by dissecting mucus or through continued high intraluminal pressure the wall of the appendix is transgressed by the tumor. This often occurs at the tip of the appendix which then opens up producing a cone-shaped source for continued production of mucus and neoplastic cells.

In some patients the primary appendiceal tumor is more invasive and will cause near complete destruction of the primary anatomic site of the disease. In these patients a mucinous cancer forms a crater at the base of the cecum and ileocecal valve region with layering of mucinous cancer over the entire right colon and terminal ileum (fig. 2).

Photomicrographs of the primary tumor will usually show a mucocele which has neoplastic changes of the epithelial lining of the appendix. Study of the degree of differentiation of this primary tumor (dysplastic or malignant mucocele) can provide the pathologist with important information regarding the aggressiveness of the peritoneal surface component of the disease. However, caution must be exercised in that “discordant features” have been reportedly; in this condition the histologic type of the primary tumor and that of the peritoneal surface malignancy are not the same (5).

A controversy still exists regarding the spectrum of histology of the appendiceal neoplasm that should be included within the pseudomyxoma peritonei syndrome. This author believes that all appendiceal epithelial neoplasms that produce copious mucus including the peritoneal mucinous adenocarcinomas should all be included. Intestinal type adenocarcinoma (non-mucinous) of the appendix with peritoneal dissemination is not included as pseudomyxoma peritonei syndrome.

There are some definite clinical conditions that should not be included as the pseudomyxoma peritonei syndrome (tab. 4). Mucinous carcinomatosis from malignancy other than the appendix that results in a copious mucus ascites should not be designated as pseudomyxoma peritonei syndrome. This would include stomach tumors, mucinous colorectal cancers and small bowel cancers, urachal tumors, cy-
stic mucinous tumors of the pancreas or those of the gallbladder. Also, mucinous neoplasms primary in the ovary should not be categorized as pseudomyxoma peritonei syndrome. Confusion regarding the primary site of cystic ovarian tumors may occur unless the appendix is resected and carefully studied (6, 7). In order to be included in the designation pseudomyxoma peritonei syndrome, the tumor must arise from within the appendix (fig. 3).

Gross pathology of appendiceal epithelial neoplasms

The position of the appendiceal neoplasm within the appendix may have important implications for understanding this disease. The appendiceal malignancies that occur at the orifice of the appendix are usually high-grade intestinal type cancers that behave very similar to colon cancer in their patterns of local extension and dissemination. Consequently, these mucinous neoplasms at the base of the appendix tend to be more aggressive than those that are located at the tip of the appendix. Figure 4 illustrates the mechanism of initial symptoms in cancers located at the base of the appendix. Gonzalez and Sugarbaker, in a study of appendiceal epithelial neoplasms with positive lymph nodes, found 15 of 25 patients (60%) had an initial symptom of acute appendicitis (8). Appendicitis was the initial symptom of 112 of 476 patients (24%) with negative lymph nodes or no lymph nodes detected within the specimen. This was a significant difference in the presentation of lymph node positive and lymph node negative appendiceal neoplasms (p=0.0006).

Appendiceal epithelial neoplasms that occur at the tip of the appendix usually produced symptoms that occurred as a result of mucinous ascites accumulating within the abdomen and pelvis (fig. 5). This symptomatology could
be increasing abdominal girth seen in 23% of patients or new onset hernia seen in 14% of patients. Another symptom seen in 30% of women (20% of both males and females) was an ovarian cystic tumor caused by entrapment of adenomatous epithelial cells within a ruptured corpus hemorrhagicum as a site for adherence of tumor cells (9).

The combination of minimally aggressive neoplastic cells producing copious mucinous fluid and arising from an appendiceal epithelial neoplasm results in a distinctive pattern of dissemination within the peritoneal cavity. Observations regarding this unique pattern of dissemination were described by Sugarbaker and later documented by a statistical analysis of tumor distribution within the abdomen and pelvis by Carmignani and coworkers (10, 11). These authors suggested that physical principles and fluid hydrodynamics predominate in controlling the distribution of the mucinous neoplasms. Tumor accumulation by gravity is into the pelvic and right retrohepatic space. Tumor accumulation within a structure that has the capacity for peritoneal fluid resorption occurs at the greater omentum, lesser omentum, omental appendages, and lymphatic lacunae beneath the right and left hemidiaphragms. Mucinous neoplastic cells recirculating within the peritoneal cavity may become caught within intraperitoneal cul-de-sacs such as the rectovesicle and rectouterine space, omental bursa and subpyloric space, lacunae created by the ligament of Treitz, left paracolic sulcus and inguinal canal.

In contrast to these sites for mucinous neoplasm accumulation some peritoneal surfaces remain clear of tumor accumulation. The movement by peristalsis of the bowel, especially near continuous peristalsis of the small bowel, spares these structures (fig. 6). Portions of the bowel less mobile because of a lack of mesentery are less spared. The antrum of the stomach and the ileocecal valve region are fixed to the retroperitoneum, and the rectosigmoid colon is fixed within the pelvis causing greater volumes of mucinous neoplasm to accumulate. Tumor that does accumulate on small bowel is often polyloid in nature reflecting the fact that the adenomatous cells have been frequently moved so that a stalk is created (fig. 7) (12).

These patterns of neoplastic progression that control the gross pathology in-vivo can be demonstrated by computerized tomograms of the abdomen and pelvis. In fig. 8 the large accumulation of mucin and mucinous tumor within the pelvis is demonstrated. The large volume tumor migrates into the pelvis as a result of the forces of gravity. In fig. 9 the accumulation of tumor beneath the right and left hemidiaphragm is illustrated. A layering of mucinous tumor and mucinous tumor nodules forms a coating of the diaphragmatic surface of the liver. Also, the diaphragmatic surface of the spleen shows a similar distortion. Another site for copious fluid resorption is the greater omentum. In fig. 10 the greater omentum is infiltrated by a massive tumor accumulation.

Fig. 6. Structures, such as the greater omentum, which absorb peritoneal fluid draw mucinous neoplastic cells into the structure. The omental cake, the hallmark of the pseudomyxoma peritonei syndrome, may result. Sparing of mucinous neoplasm from accumulation on the small bowel surface is evident.

Fig. 7. The pseudomyxoma peritonei polyp results from an accumulation of neoplastic cells on a mobile surface such as the small bowel.
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The small bowel beneath is compartmentalized by the greater omentum plus mucinous ascites and has been spared of large volume disease.

Figure 11 illustrates that tumor accumulation can occur in dependent sites other than the pelvis. The subpyloric space is the most dependent space within the lesser abdominal sac. It forms a cul-de-sac whose borders are the anterior surface of the pancreas and the posterior aspect of the antrum of the stomach (13). Tumor cells enter through the foramen of Winslow and accumulate within this space.

One additional determinate of in-vivo gross pathology needs to be clarified. The surgical management of this disease can have a profound effect upon the distribution of progressive disease within the abdomen and pelvis. These free-floating mucinous tumor cells will become attached to a raw (sticky) tissue surface, implant at that site and progress. This is referred to as tumor cell entrapment. One example is the ruptured Graafian follicle (corpus hemorrhagicum) that causes mucinous neoplastic cells to adhere to the ovary. This accounts for the frequent occurrence of large cystic ovarian masses as a presenting feature of women with this disease. These tumor cells will also attach at sites of a surgical wound such as a laparoscopic trocar site, a right colectomy resection.
site, or traumatized peritoneal surfaces as a result of handling of a small bowel by the surgeon. Figure 12 shows tumor accumulation deep in the pelvis in and around the metal clips that mark the anatomic site of a surgical procedure to remove the uterus and ovaries. Although gross disease was removed, tumor has implanted and progressed at the hysterectomy resection site. Figure 13 shows the small bowel and small bowel mesentery in a patient who has had extensive prior debulking procedures. The redistribution of the mucinous tumor away from the small bowel and its mesentery has disappeared. There is now a uniform distribution of tumor throughout the mid-abdomen so that the small bowel is no longer compartmentalized but rather entrapped within masses of mucinous tumor.

Histomorphology of appendiceal epithelial neoplasms

In the past, appendiceal epithelial neoplasms with peritoneal dissemination have been regarded as a lethal condition. However, a great variation in the survival of this group of patients has been observed. Figure 14 shows a composite graph of the survival of these mucinous appendiceal malignancies at 3 prominent institutions in the United States. The Memorial Sloan-Kettering Cancer Center, the Massachusetts General Hospital, and the Mayo Clinic in Rochester reported the long-term follow-up of their patients. Only a small number of patients are cured of this process even though the median survival is between 5 and 10 years. Few, if any, patients are alive at 20 years (14, 15, 16).

Ronnett and colleagues studied the histomorphology of mucinous appendiceal neoplasms and greatly clarified the differences in survival to be expected in this disease process where there is a wide spectrum of aggressive versus non-aggressive neoplasms (5). In the Ronnett data all patients were treated in a uniform manner with cytoreductive surgery and perioperative intraperitoneal chemotherapy. They separated the mucinous appendiceal neoplasms into three groups: the least aggressive neoplasms were designated disseminated peritoneal adenomucinosis (DPAM), the more aggressive were designated peritoneal mucino-
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Yan and colleagues further classified the PMCA group into well-differentiated, moderately differentiated, and poorly differentiated cancer (17). When survival was assessed using the Ronnett criteria and a uniform treatment plan, these subtypes of mucinous appendiceal neoplasms were associated with statistically different survival (fig. 15).

The histomorphologic description of the subtypes of mucinous appendiceal tumors was based on both architectural and cytologic features. DPAM was characterized by multifocal mucinous tumors adherent to but not invading into visceral and parietal peritoneal surfaces. Microscopically, the peritoneal lesions contained scant histologically benign mucinous epithelium with abundant extracellular cytoplasm. Cells were in a single layer surrounding pools or globules of mucin. There was no loss of cellular polarity and no atypia. An intense hyalinizing fibrotic reaction that separated pools of mucin was an important histologic feature of this lesion (fig. 16 and 17).

PMCA was characterized by invasive peritoneal lesions composed of abundant epithelium with glandular or signet-ring cell morphology with sufficient architectural complexity and cytological atypia to warrant a diagnosis of mucinous adenocarcinoma. Mucinous adenocarcinomas were further separated into three

Fig. 15. Survival distribution by the Ronnett Criteria for histologic subtypes of mucinous appendiceal neoplasms. These patients were all treated by cytoreductive surgery plus perioperative intraperitoneal chemotherapy (from Reference 5 with permission)

Fig. 16. Disseminated peritoneal adenomucinosis (DPAM) as a subtype of mucinous appendiceal neoplasm (H+E x 10)

Fig. 17. High power view of disseminated peritoneal adenomucinosis (DPAM) (H+E x 100)
grades by evaluating epithelial content of the tumors in order to more completely describe a histological progression. In the well-differentiated PMCA the mucinous adenocarcinoma was composed of predominantly single layer of tubular glands. The tumor cells were well-polarized similar to epithelium of an adenoma. Atypia of the tumor was present and an invasive component was identified (fig. 18).

Moderately differentiated mucinous adenocarcinoma showed characteristics between well- and poorly-differentiated adenocarcinoma. It was composed of solid sheets of malignant cells admixed with glandular formations. The polarity of the tumor cells was minimal or absent. Poorly differentiated mucinous adenocarcinoma was composed of highly irregular glandular structures or lacked glandular differentiation. The polarity of the cancer cells had disappeared completely. In some cases, signet-ring cells were seen (fig. 19).

Ronnett described a third subtype of mucinous appendiceal neoplasm. The hybrid appendiceal mucinous tumors included foci of mucinous carcinomatosis within a background of DPAM histomorphology (5). These two different histologies were present within the same case material. The hybrid tumors predominantly demonstrate histologic features of adenomucinosis; focal areas of less than 5% of the fields of view of adenocarcinoma are identified in order to be categorized as hybrid (fig. 20).

Caveats in the use of histological subtypes of mucinous appendiceal tumors

The Ronnett criteria for assessing prognosis in this group of patients has been of great help in predicting the outcome following cytoreductive surgery with intraperitoneal chemotherapy. However, problems remain in the use of this histological system as a prognostic indicator. First, discordant features occur indicating a lack of consistency between the histopathology of the primary appendiceal neoplasm and the peritoneal surface malignancy. In the original Ronnett et al. report, there were 3 cases with DPAM primary tumors and PMCA noted in the peritoneal surface lesions. There were 109 patients in this study for a 2.8% rate of discordance (5). In the study by Young et al. from the Massachusetts General Hospital, the-

Fig. 18. Peritoneal mucinous carcinoma (PMCA) of the well-differentiated subtype (H+E x 400)

Fig. 19. Peritoneal mucinous carcinoma (PMCA) which is poorly differentiated and shows signet ring cells (H+E x 400)

Fig. 20. Hybrid subtype of mucinous appendiceal neoplasm which shows a focus of well-differentiated adenocarcinoma surrounded by disseminated peritoneal adenomucinosis (H+E x 100)
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there were 3 patients with low-grade appendiceal mucinous neoplasms (LAMN) as a primary tumor and mucinous appendiceal cancer (MACA) in the peritoneal lesions. There were 107 patients in the study showing a 2.9% incidence of discordance (16). In the study of Yan et al., 2 cases showed DPAM in the primary appendiceal cancer with PMCA in the peritoneal lesions. Four cases showed PMCA in the primary lesion and DPAM in the peritoneal lesions. There were 46 patients in this study for a 13% incidence of discordance (17). The anatomic site to determine prognosis has not been clarified by any of the groups describing the discordant features.

Sugarbaker and colleagues studied the histologic appearance of surface tumors in patients with mucinous carcinomatosis. They determined that the 5-fluorouracil and mitomycin C given intraperitoneally induced marked changes in the histological appearance of the carcinomatosis. This finding was limited to the most superficial approximately 2 mm of the peritoneal surface. It suggested a marked change in tumor histology caused by the intraperitoneal chemotherapy (fig. 21) (18).

A third clinical caveat in assessing prognosis from the histologic subtypes concerns the transitions seen from less aggressive to more invasive histologic types over time and associated with multiple surgical interventions. Yan and colleagues determined that 68% of 19 patients who failed reoperative treatment of their appendiceal neoplasm demonstrated transition from a less aggressive to a more aggressive histologic subtype (17). Apparently, a continued genetic change can occur in these mucinous neoplasms if the treatment fails to completely eradicate the disease and a further progression of the cancer is allowed to occur.

Mohamed and colleagues showed that some patients who repeatedly showed DPAM histology may succumb to a rapidly progressive peritoneal surface disease despite this benign appearing histology. They studied 11 of 500 cases (2.2%) who had a rapidly fatal progression of DPAM subtype of mucinous appendiceal malignancy. These patients went on to die despite multiple reoperations and multiple attempts to arrest the disease by combinations of cytoreductive surgery combined with intraperitoneal chemotherapy. Although the histologic appearance suggested an indolent disease process, the clinical course was rapidly fatal (19).

CONCLUSIONS

Despite its small size and apparent lack of gastrointestinal function, the appendix has a significant cancerous predisposition. The cancer types and patterns of disease dissemination are varied; differences in patterns of dissemination and mucinous epithelial tumor subtypes demand a knowledgeable and experienced approach to the management of this disease. Appendiceal mucinous neoplasms should be considered a distinct disease with a unique natural history. Although much progress has been made, greater knowledge regarding the gross and microscopic pathology of this disease and the surgical implications of these findings are needed.

REFERENCES


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