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ORIGINAL ARTICLE

Adenocarcinoma of the Appendix Is Rarely Detected by Colonoscopy

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Abstract
Introduction Appendiceal tumors represent a subset of colonic neoplasms that frequently defy early diagnosis only to present at advanced stage with peritoneal metastasis. Data on early detection by colonoscopy is limited to case reports or series. The aim of this study is to determine the diagnostic yield of colonoscopy in detecting appendiceal lesions in patients with appendiceal adenocarcinoma and pseudomyxoma peritonei.
Methods We reviewed clinicopathologic data on 121 consecutive patients with histologically confirmed appendiceal adenocarcinoma with pseudomyxoma peritonei presenting to our institution for intraperitoneal hyperthermic chemotherapy (IPHC) and cytoreductive surgery between February, 1993 and August, 2007, focusing on the colonoscopy findings.
Results Preoperative colonoscopic data were available on 64 patients (average age=51; 52 for IPHC patients). Abnormal findings included seven patients with appendiceal lesions (11%), 12 patients with cecal abnormalities (19%), and 28 patients with polyps (44%). Twenty-three patients (36%) had a normal colonoscopy. Malignancy was documented in two of the 64 (3.1%) patients on preoperative colonoscopy biopsies.
Conclusions Appendiceal abnormalities are infrequently seen on colonoscopy and rarely yield a diagnostic biopsy in patients with appendiceal carcinoma. We found that nearly 42% of patients with carcinoma of the appendix have synchronous colonic polyps, a much higher prevalence than would be expected, supporting a role for a perioperative colonoscopy.

Keywords Appendiceal adenocarcinoma · Pseudomyxoma · Colonoscopy · Intraperitoneal hyperthermic chemotherapy

Introduction

Appendiceal adenocarcinoma is a rare lesion, which is, unfortunately, seldom diagnosed early. Presenting symptoms can include right lower quadrant pain, appendicitis, early satiety, and changes in bowel habits or abdominal distention. It is not unusual for these lesions to be detected incidentally at surgery or by cross-sectional imaging. In the USA, there are 561,000 appendectomies performed annually with approximately 250,000 cases of appendicitis per year.[1] Mucinous distention of the appendix, or mucocele, is present in 0.2–0.3% of appendectomy specimens and may be a premalignant lesion if associated with adenomatous changes. The incidence of appendiceal adenocarcinoma ranges from 0.11–0.80% in appendectomy specimens.[2–5] According to the surveillance, epidemiology and end-results program, the incidence of appendiceal malignancies in the USA is 0.12 cases per 1,000,000 people per year,

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with adenocarcinoma accounting for the largest subset at 37% of total cases.[6] Histologic type predicts extent of disease,[7] with signet-ring cell carcinoma of the appendix having metastases at time of diagnosis in 93% of cases, mucinous adenocarcinoma having metastases at time of diagnosis in 71% of cases, and colonic type adenocarcinoma having metastases at time of diagnosis in 83% of cases.[6]

Pseudomyxoma peritonei is a distinct clinical entity characterized by gelatinous ascites originating from a mucinous appendiceal adenoma or adenocarcinoma. Ronnett et al. found that at least 87% of cases of pseudomyxoma peritonei or mucinous adenocarcinoma with peritoneal involvement were of appendiceal origin.[8] Additionally, Misdraji et al. found that 64% of cases of appendiceal mucinous neoplasms showed evidence of appendiceal rupture and peritoneal spread.[9] We have found that pseudomyxoma is rarely caused by nonappendiceal tumors.

Endoscopic detection of appendiceal adenoma and adenocarcinoma has been reported as case reports and limited case series in the medical literature.[10–20] Ponsky first described the detection of appendiceal mucocele by colonoscopy in 1976 as a yellowish, submucosal, lipoma-like mass.[21] In the largest series to date, Zanati et al. described seven patients with mucinous cystadenoma of the appendix detected on colonoscopy over a 14-year period at a single institution.[16] Lee et al. first described their abnormal colonoscopy findings in a patient with pseudomyxoma peritonei.[22] We are unaware of a large series that adequately describes the preoperative colonoscopic findings in patients presenting with appendiceal adenocarcinoma with pseudomyxoma peritonei. Thus, the aim of this study was to determine the diagnostic yield of colonoscopy in detecting previously diagnosed appendiceal adenocarcinoma with pseudomyxoma peritonei and to characterize the mucosal abnormalities associated with appendiceal adenocarcinoma with pseudomyxoma peritonei.

Methods and Materials

We retrospectively reviewed our experience in 191 patients, from 1993 to 2006, with pseudomyxoma peritonei related to primary appendiceal tumors, who were treated with cytoreductive surgery (CS) and intraperitoneal hyperthermic chemotherapy (IPHC); complete records were available in 121 patients and made up our cohort. Sixty-four patients had a complete colonoscopy either prior to surgery. The initial history and physical, colonoscopy reports, surgical pathology reports, and clinic notes were reviewed for record of colonoscopy performed prior to CS. Reference to prior colonoscopy as normal was deemed to have no appendiceal lesion and no colonic polyps. A total of 64 patients were selected for final review. Colonoscopy report findings of appendiceal lesions, cecal lesions, colonic polyps, and any other mucosal or submucosal defect were compiled. This study was approved by our institutional review board.

Results

Colonoscopy Findings

There were a total of 68 colonoscopies performed on 64 patients prior to IPHC/CS. The indications are summarized in Table 1. The leading indications for performing colonoscopy were new diagnosis of appendiceal adenocarcinoma with pseudomyxoma peritonei (26.6%), cancer of unknown primary source (15.6%), abdominal pain (14.1%), and abdominal mass (10.9%). There were two patients with colonoscopy performed for screening purposes only (3.1%). Indication for colonoscopy was not available in three of the 64 (4.7%) patients.

Patients were defined as having normal colonoscopies if a normal endoscopy report was available and/or if the initial history and physical within our medical record reported on a normal colonoscopy. Colonoscopy reports were available on 54 of the 64 patients (84%) and the initial history and physical was used to report "normal" findings in the remaining ten patients (16%). The average age at time of endoscopy was 51 (range 26–74 years), the average age at time of diagnosis was 50 (range 26–74 years), and the average age at time of IPHC C/S treatment was 52 (range 26–74 years). There were 36 males and 28 females. Colonoscopy was performed for an average of 182 days

Table 1 Indications for Colonoscopy in Patients Presenting for Treatment of Appendiceal Adenocarcinoma with Pseudomyxoma Peritonei

Indication for colonoscopy	Number of cases (%)
Appendiceal adenocarcinoma with pseudomyxoma peritonei	17 (26.6)
Cancer of unknown primary	10 (15.6)
Abdominal pain	9 (14.1)
Abdominal mass	7 (10.9)
Preoperative for IPHC C/S	4 (6.3)
Anemia/rectal bleeding	4 (6.3)
Ascites	3 (4.7)
Unknown indication	3 (4.7)
Weight loss/change in bowel habits	2 (3.1)
Diverticulosis	2 (3.1)
Screening colonoscopy	2 (3.1)
Ulcerative colitis	1 (1.6)

CS cytoreductive surgery, *IPHC* intraperitoneal hyperthermic chemotherapy

(range 1–1447 days, median 79 days) prior to CS/IPHC. Table 2 summarizes colonoscopic findings. In 23 patients, the colonoscopy was entirely normal (36%). Appendiceal lesions were detected in seven patients (11%). Abnormal findings of the cecum, usually a mass effect, were present in 12 patients (19%). Lesions of the appendix and/or cecum were present in 16 patients (25%). Overall, a malignant diagnosis was made on two of the 64 (3.1%) patients on the preoperative colonoscopic biopsies. Table 3 summarizes the clinicopathological findings of patients with abnormalities at the cecum or appendix. Disseminated adenomucinosis of the appendix is classified as a low grade malignant lesion.[7] Colonic polyps were present in 27 patients (42%); only nonhyperplastic polyps were considered significant both within and outside of the cecum. An extrinsic mass in the midascending colon ulcerating through the bowel wall into the lumen was detected concomitantly in one patient (2%). One patient had extensive pancolonic polyps suggestive of familial polyposis (2%).

Surgical Treatments Prior to Colonoscopy

Because many patients presenting for IPHC have prior surgical therapy, we investigated the effect of prior surgery on likelihood of abnormalities being detected with colonoscopy. Prior surgery is defined on a scale of 0–3. Prior surgical score (PSS) of 0 is defined as biopsy only or laparoscopy plus biopsy. PSS of 1 is defined as previous exploratory laparotomy. PSS of 2 is defined as exploratory laparotomy with some resection, usually greater omentectomy or greater omentectomy plus right colectomy. PSS of 3 is defined as extensive surgery with an attempt at complete cytoreduction. PSS was unknown in six patients. There were 16 patients (25%) with PSS of 0, 23 (40%) patients had PSS of 1, 16 (25%) patients had PSS of 2, and three patients had PSS of 3 (5%). The three patients with extensive cytoreduction had normal colonoscopies. Thirty-three of the 64 patients (52%) with colonoscopy prior to IPHC had prior appendectomy.

Forty-four percent of the subset of 16 patients with abnormal findings of the appendiceal orifice and/or cecum had appendectomy prior to colonoscopy. Five of these 16 had PSS of zero, six patients had PSS of 1, and four patients had PSS of 2. PSS was unknown on a single patient.

Table 2 Colonoscopy Results for Patients with Appendiceal Adenocarcinoma with Pseudomyxoma Peritonei

Colonoscopic findings	Number of cases (%)
Normal colonoscopy	23 (36)
Colonic polyps	27 (42)
Appendiceal lesions	7 (11)
Cecal lesions	12 (19)
Invasive ulcerated mass	1 (2)
Pancolonic polyposis	1 (2)

Discussion

We describe the colonoscopic findings of patients presenting to our institution for treatment of appendiceal adenocarcinoma with pseudomyxoma peritonei with intraperitoneal hyperthermic chemotherapy and cytoreductive surgery. This constitutes the single, largest cohort of patients with appendiceal carcinoma in which preoperative colonoscopic data exist. Our series is limited by the inherent limitations and weaknesses seen in retrospective database studies. Specifically, the time between colonoscopy and surgery (either CS or conventional) varied between a few days and 4 years. Further, the clinical impressions of the endoscopists beyond that included in their report were not queried. In addition, our analysis is limited by a highly selected subset of patients with appendiceal carcinoma associated with pseudomyxoma and not just appendiceal adenocarcinomas and as such is not generalizable. However, it is clear that colonoscopy rarely identifies cancer of the appendix, even when it is in an advanced stage.

Standard colonoscopy continues to be the gold-standard study to evaluate colonic mucosa for abnormalities; however, the predilection of appendiceal adenocarcinoma to spread to the peritoneum limits detection of endoluminal disease with colonoscopy. The general consensus of centers caring for patients with appendiceal adenocarcinoma with pseudomyxoma peritonei is that a colonoscopy is inconsequential in these individuals as they typically have stage IV disease. We found that a colonoscopy alone is poor at definitively diagnosing advanced appendiceal adenocarcinoma with peritoneal spread with only 10% of cases showing an appendiceal abnormality and virtually no masses noted intraluminally. Thus, a normal colonoscopy does not predict the absence of an appendiceal adenocarcinoma.

However, we found a high incidence of synchronous colonic polyps, with no synchronous colon cancer. Wolff and Ahmed reported metachronous colonic neoplasm present in 21.4% in patients with benign lesions of the appendix and a single case (4.8%) of metachronous colonic neoplasm in patients with adenocarcinoma of the appendix.[23,24] Colonoscopy is useful in detecting synchronous colonic polyps that may have a higher risk for malignant transformation in this patient population as synchronous colonic neoplasms have been reported in the literature. Nonetheless, the increased incidence of colonic polyps in our cohort (44%) compared to those noted in the age-matched screening population in which adenomas should

Table 3 Appendiceal and Cecal Lesions Detected by Colonoscopy in Patients with Appendiceal Adenocarcinoma with Pseudomyxoma Peritonei

Patient	Age at time of CS	Gender	Initial Chief complaint	Final pathologic diagnosis	Prior appendectomy	Indication for colonoscopy	Site of lesion (A, C, A+C)	Colonoscopic findings	CT findings
1	68	F	Right lower quadrant pain, perforated appendicitis	PMCA of appendix	Yes	Performed prior to IPHC/CS	A	Appendiceal orifice lesion in the lumen	Acute appendicitis; right lower quadrant mass
2	53	M	Right lower quadrant pain, perforated appendicitis	PMCA of appendix	Yes	Screening colonoscopy	A	Colonic mucosa with no abnormalities, benign lymphoid aggregates, small polyp in appendiceal orifice	Appendicitis, 5.6×4.0 cm periappendiceal fluid collection consistent with abscess
3	49	F	Intermittent abdominal pain	PMCA of appendix	Yes	Abdominal pain, evaluate for diverticulosis	A+C	Mild mucosal edema and inflammation at appendiceal orifice	Right lower quadrant mass 3–4 cm
4	32	F	Primary infertility and dysmenorrhea	DPAM of appendix	No	Adenocarcinoma of unknown primary found on laparoscopy with mucinous features	A	Localized area of erythema at appendiceal orifice. Appendiceal orifice appeared bulging with large amount of mucin. Pathology negative for malignancy	None—diagnosis by laparoscopy with evidence of diffuse peritoneal seeding
5	57	M	Unknown	PMCA of appendix	Unknown	Adenocarcinoma of the appendix and malignant ascites	A+C	Cecal deformity. Prominent appendiceal stump. Pathology negative for malignancy	Unknown
6	33	M	Right lower quadrant pain, bloating, right inguinal hernia	DPAM of appendix	Yes	Appendiceal cancer, prior to IPHC/CS	A+C	Small tuft of abnormal nodular tissue at the appendiceal orifice in the cecum. Pathology found focal adenomatous changes with areas of abnormal mucinous glandular epithelium	Right inguinal canal mass/hernia, large mass in region of appendix suggestive of appendiceal mucocele
7	36	M	Vague abdominal discomfort	Peritoneal mucinous adenocarcinoma of appendix	No	Abdominal pain	A	Suggestion of depression of AO from extrinsic compression	Peritoneal carcinomatosis, mass in the appendix, tumor involved extensively the left hemidiaphragm, spleen, right diaphragm, right colon
8	65	M	Inguinal hernia	Peritoneal mucinous adenocarcinoma of appendix	No	Right lower quadrant mass, mucinous tumor	C	4 mm sessile polyp in the cecum	Lesion in the appendix highly suggestive of a large adenoma with low-volume mucin scattered throughout the abdomen

Table 3 (continued)

Patient	Age at time of CS	Gender	Initial Chief complaint	Final pathologic diagnosis	Prior appendectomy	Indication for colonoscopy	Site of lesion (A, C, A+C)	Colonoscopic findings	CT findings
9	54	M	Bloating, lower abdominal pain, cramping	Peritoneal mucinous adenocarcinoma of appendix	Yes	Bloating, lower abdominal pain, cramping	C	Deformed cecum, mucinous exudate from cecum with inflammatory component, appendiceal orifice not well identified, dysplastic rectal polyp. Cecal biopsy found tubulovillous adenoma and adjacent adenocarcinoma could not be excluded, rectal biopsy found hyperplastic polyp	7.2×4.6×6 cm thick walled necrotic, cystic paracecal mass, appendix not identified
10	52	F	Increased abdominal girth, anorexia	Low grade cancer of the appendix	Yes	History of pseudomyxoma peritonei	C	Cecum was deformed, poorly distensible, no mucosal abnormalities	Abdominal ascites, superficial umbilical mass 25×14×28 cm, large cystic mass from pelvis to mid abdomen with pelvic ascites
11	59	F	Postmenopausal vaginal bleeding, free pelvic fluid, and increased CEA	Low grade cancer of the appendix	Yes	Abdominal fluid and increased CEA	C	Four hyperplastic polyps at splenic flexure, cecum, and transverse colon,	2×2.5 cm low attenuation lesion on right paracolic gutter above iliac crest adjacent to associated colon, free abdominal fluid, bulky uterus, intrauterine free fluid
12	27	F	Left upper quadrant abdominal pain	PMCA of appendix	No	Abnormal abdominal CT with thickened cecum	C	Multiple, pedunculated, and sessile, adenomatous polyps (estimated at 30–40) were seen scattered throughout the colon. In addition, there were three polypoidal masses seen: one in the cecum measured about 3 cm, one in the proximal transverse colon (with extensive central ulceration and an irregular surface) measured about 5 cm, and one in the distal sigmoid colon (also with an irregular surface and central ulceration) measured about 3×6 cm	Thickened cecum and irregular stomach wall, abdominal pain, weight loss, bilateral ovarian mass, bilateral adrenal enlargement, right lung nodule

13	43	M	Right lower quadrant abdominal pain for 3 months, developed acute appendicitis	PMCA of appendix	Yes	Follow-up of diagnosis of adenocarcinoma of the appendix	C	There were two small nodules/polyps in the terminal ileum with papillary projections. There was an erythematous irregular mucosa in the cecum. There was a 1–2-cm flat adenoma-like lesion in the sigmoid colon at 35 cm. Pathology found cecal lesion to be invasive moderately differentiated adenocarcinoma	Acute appendicitis
14	58	F	Right-sided abdominal pain, presumed diverticulitis	PMCA of appendix	Yes	Follow-up of diverticulosis	C	Large, friable, ulcerated, sessile mass in the cecum. A single sessile polyp in the ascending colon. A single small polyp in the midsigmoid colon. Large, irregular, pedunculated, polypoid mass in the sigmoid colon 25 cm from the anus. Pathology found lesions to be tubular adenomas	None performed
15	39	M	Right upper quadrant abdominal pain	PMCA of appendix	No	Anemia	C	Mass in the region of the cecum. Pathology found lesion to be suspicious for high-grade dysplasia	Mass in right lower quadrant, soft tissue nodules, question of peritoneal carcinomatosis, multiple low attenuating liver lesions that maybe cysts
16	66	M	Unknown	DPAM of appendix	Unknown	Carcinoma of undetermined origin	C	There was a 5-mm diminutive polyp in the cecum, 5 cm above the ileocecal valve. Pathology found lesion to be tubulovillous adenoma with moderate glandular dysplasia	Unknown

CS cytoreductive surgery, *A* appendiceal, *C* cecal, *A+C* appendiceal and cecal, *IPHC* intraperitoneal hyperthermic chemotherapy, *PMCA* peritoneal mucinous carcinomatosis, *DPAM* disseminated peritoneal adenomucinosis

be detected in ≥25% of men and ≥15% women suggests that these patients are most likely at a higher risk for developing colonic neoplasia.[25] Thus, the value of the colonoscopy is not so much in identifying an appendiceal carcinoma, but, moreover, in detecting colonic neoplasia. Although finding polyps in patients with stage IV disease typically has no effect on long-term survival, most patients with peritoneal dissemination from low-grade appendiceal tumors treated with cytoreductive surgery and IPHC have median survival beyond 5 years. Therefore, colonoscopy and polypectomy may be of value in selected patients being evaluated for surgery.

Conclusion

We examined the yield of colonoscopy in detecting appendiceal adenocarcinoma in a cohort of patients with advanced disease and pseudomyxoma peritonei. There was a low detection rate of 11% for appendiceal abnormalities and 19% for cecal abnormalities. Despite a priori knowledge of the patient's appendiceal carcinoma diagnosis, the endoscopist was able to document malignancy in only 3% of patients on preoperative colonic biopsies. This data represents the largest series of colonoscopic examinations in the literature. We confirm that the likelihood of finding early lesions of the appendix is rare using endoscopic evaluation. Indeed, a negative colonoscopy was commonly present in our cohort with advanced disease, indicating that a negative colonoscopy does not rule out appendiceal primary tumor. There was a higher than expected rate of synchronous colon polyps in our cohort. Colonoscopy should be performed in selected patients diagnosed with appendiceal adenocarcinoma with pseudomyxoma peritonei to evaluate for synchronous premalignant lesions. Endoscopists should be aware that colonoscopy is unlikely to detect advanced appendiceal adenocarcinoma. However, findings of a smooth, submucosal lesion in the cecum near the appendiceal orifice or free-flowing mucin from the appendiceal orifice should raise concern for appendiceal adenocarcinoma.

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