Significance of Proximal Margin Involvement in Low-Grade Appendiceal Mucinous Neoplasms

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● Context.—Appendiceal adenomas and low-grade appendiceal mucinous neoplasms (LAMNs) confined to the appendix are cured by appendectomy. However, involvement of the proximal margin raises concern for residual disease. Some patients with a positive margin at appendectomy undergo cecal resection to eliminate a perceived risk for tumor recurrence or dissemination, although that likelihood is assumed rather than demonstrated.

● Objective.—To determine whether involvement of the proximal appendiceal resection margin by adenoma or LAMN is a risk factor for local development of recurrence or pseudomyxoma peritonei.

● Design.—Appendiceal adenomas and LAMNs confined to the appendix were considered for the study if they showed neoplasia or dissecting mucin at the proximal margin. The presence or absence of residual tumor in cecal resections was determined. Follow-up data were obtained from clinical records.

Low-grade appendiceal mucinous tumors include those that are confined to the mucosa and that are classified as adenomas and those that display pushing or expansile invasion and can disseminate in the peritoneal cavity as pseudomyxoma peritonei, for which the term low-grade appendiceal mucinous neoplasm (LAMN) was proposed and adopted by the World Health Organization. In the latter group, the risk of developing pseudomyxoma peritonei is most clearly related to extension of mucin or epithelial cells beyond the appendiceal serosa. The presence of acellular mucin in the right lower quadrant confers a low risk of recurrence, whereas mucin with mucinous epithelial cells in the right lower quadrant confers a high risk of recurrence.

Assessment of surgical margins is an integral part of pathologic tumor evaluation, and the evaluation of an appendix with an adenoma or LAMN includes reporting on the status of the margin. An involved margin would be a rational basis for a cecectomy given the assumption that it indicates a possibility that residual disease remains in the appendiceal stump or cecum that can lead to disease recurrence or dissemination. In fact, several authors recommend additional surgery for patients with appendiceal mucinous neoplasia at the proximal margin, but these suggestions are based largely on assumptions of what an involved margin signifies. In reality, the significance of proximal margin involvement by an appendiceal adenoma or a LAMN that is otherwise confined to the appendix is not clear and data to guide management of these patients are lacking. Therefore, we undertook this study to determine whether a positive margin in the setting of an appendiceal adenoma or LAMN confined to the appendix requires surgical resection of the cecum, or whether a conservative approach can be justified.

METHODS

Identification of Cases

The pathology archives of 3 institutions were searched to identify appendectomy specimens containing LAMNs and appendiceal

Results.—Sixteen patients (14 female, 2 male) with LAMN (n = 15) or adenoma (n = 1) and an involved proximal resection margin were identified, including 9 with neoplastic epithelium within the lumen and 7 with acellular mucin in the appendiceal wall at the margin. Six patients underwent cecal resection and the others were nonsurgically followed. No cecal resection had residual neoplasia. No patient developed recurrence or pseudomyxoma peritonei (mean follow-up, 4.7 years).

Conclusions.—In patients with LAMNs confined to the appendix, involvement of the appendectomy margin by neoplastic epithelium or acellular mucin does not predict recurrence of disease, even without further surgery. A conservative approach to managing these patients can be justified.

Summary of Pathologic Findings and Clinical Follow-up for Cases With Margin Involvement by Low-Grade Appendiceal Mucinous Neoplasm (LAMN) or Appendiceal Adenoma

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, y/Sex</th>
<th>Diagnosis</th>
<th>Pattern of Margin Involvement</th>
<th>Subsequent Resection</th>
<th>Follow-up Interval, y</th>
<th>Method of Follow-up</th>
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<tbody>
<tr>
<td>1</td>
<td>36/f</td>
<td>LAMN</td>
<td>Neoplastic epithelium</td>
<td>Cecum</td>
<td>3.5</td>
<td>Abdominal CT and colonoscopy</td>
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<td>Neoplastic epithelium</td>
<td>Cecum</td>
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<tr>
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<td>Adenoma</td>
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<tr>
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<td>Dissecting acellular mucin</td>
<td>Ileocecum</td>
<td>Recent</td>
<td>Recent case</td>
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<tr>
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<td>Dissecting acellular mucin</td>
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<td>8.6</td>
<td>Abdominal CT and colonoscopy</td>
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</tbody>
</table>

Abbreviation: CT, computed tomography.

adenomas that were diagnosed between January 1990 and March 2014. The surgical pathology reports were reviewed to identify cases with either neoplastic epithelium at the resection margin or acellular mucin at the resection margin. Cases that showed only denuded mucosa at the margin or only scant acellular mucin in the lumen were excluded. Also excluded were cases with peripendimural mucin, periappendiceal mucinous epithelium, or overtly malignant cytologic features (ie, invasive adenocarcinoma), as it is likely that these features would confound the impact of margin status on clinical outcome. The study protocol was approved by the institutional review board at the Massachusetts General Hospital, Boston.

Pathology Review

Hematoxylin and eosin–stained sections were available for review in 14 cases and these cases were evaluated by 3 study pathologists to confirm the diagnoses. The presence of high-grade dysplasia, if any, was noted. Subsequent materials were also reviewed when patients received further surgery, in order to confirm the presence or absence of residual disease. The slides could not be obtained for review in 2 cases, for which the status of resection margins was established based on review of prior surgical pathology reports.

Patient Outcomes

Medical records of all study patients were evaluated for clinical follow-up. All available clinical and imaging records were reviewed to determine whether any patient developed local recurrence or disseminated peritoneal disease (ie, pseudomyxoma peritonei). The follow-up period was calculated as the time from appendectomy to the time of the last available abdominal computed tomography, last colonoscopy, or last laparoscopic or open procedure, or the last available clinical note that documented the clinical history and physical examination. We included patients with at least 1 year follow-up or who underwent additional surgical resection.

RESULTS

The study group included 16 patients (14 women and 2 men) with a mean age of 55 years (range 28–85 years) at appendectomy (Table). The tumors were classified as LAMNs (Figure 1) in 15 cases and appendiceal adenoma in 1 case. Nine cases were classified as having a positive margin based on the presence of neoplastic epithelium lining the appendiceal lumen at the surgical resection margin (Figure 2). Seven of the LAMN cases showed no neoplastic epithelium at the margin, but had dissecting acellular mucin at the margin (Figure 3).

Six patients underwent a second surgical procedure, 4 of whom had mucinous epithelium at the margin and 2 with acellular mucin at the margin. None of these patients had residual neoplasm in the resection specimen. One patient (case 1) had a small pool of acellular mucin in the cecal cuff. The other 10 patients were followed nonsurgically. There was no significant difference between the 2 groups in terms of patient age or the type of involved margin. None of the patients experienced disease recurrence or developed pseudomyxoma peritonei. The follow-up interval ranged from less than a year in a single recent case to 11.7 years (mean 4.7 years; median 3.5 years).

COMMENT

Tumor involvement of a surgical resection margin is considered to be an indication for additional treatment or additional surgery in many organ systems. Certainly some appendiceal neoplasms, including endocrine tumors, goblet cell carcinoid tumors, conventional adenocarcinomas, and high-grade mucinous neoplasms, are managed in this fashion, as complete resection and pathologic staging of regional lymph nodes are important for tumor staging and subsequent management. However, low-grade appendiceal mucinous tumors infrequently involve lymph nodes, even when they have spread to the peritoneum, and thus the role of right hemicolectomy in patients with disseminated peritoneal disease (ie, pseudomyxoma peritonei) is not clear. In fact, some studies have shown that right hemicolectomy can have a negative survival advantage in the setting of pseudomyxoma peritonei, and should only be carried out at the time of complete cytoreduction and intraperitoneal chemotherapy, as success of the latter may be impaired by adhesions created by prior colonic surgery.

Low-grade appendiceal mucinous neoplasms with acellular mucin in the right lower quadrant are at low and high risk, respectively, for dissemination in the peritoneal cavity, and that risk is not clearly modified by the status of the surgical resection margin.
ceal mucin and neoplastic epithelial cells in the right lower quadrant as well as tumor present at the surgical resection margin. That patient subsequently underwent a colectomy procedure and the resection specimen did not contain residual tumor. However, the patient developed disseminated peritoneal disease 41 months later, indicating that additional surgery did not eliminate the risk for disease recurrence. However, the status of the margin may be one factor in the management of these patients, because patients with epithelial cells outside the appendix but confined to the right lower quadrant may undergo additional surgery and/or heated intraperitoneal chemotherapy, and at that time, the possibility of residual disease in the cecum can be addressed. The benefit of further surgery to achieve a clear margin for appendiceal adenomas and LAMNs in patients who otherwise would not require surgery is less clear, although several groups recommend this practice. Indeed, some authors base their classification of appendiceal mucinous neoplasms on the status of the proximal surgical margin. Pai et al classified mucinous tumors that are cured by appendectomy as adenomas, provided they have a negative resection margin. Presumably, then, tumors with a positive margin should be classified in their system as low-grade mucinous neoplasms of low malignant potential or, according to an earlier review on appendiceal neoplasia by the same authors, as mucinous tumors of uncertain malignant potential. They caution that, given its prognostic implications, the surgical margin must be completely evaluated, even though those implications are assumed rather than proved.

There are no clear guidelines regarding appropriate management of patients with appendiceal adenomas or LAMNs who have positive surgical margins on their appendectomy specimens, particularly when the tumors are confined within the serosa. None of the 10 patients in this series who underwent appendectomy alone developed recurrent disease, despite the presence of a positive surgical resection margin. Six of our patients underwent additional surgery, 4 of whom had neoplastic epithelium at the margin. None of these patients had residual neoplastic epithelium in subsequent surgical material. One of these patients did have acellular mucin in the subsequent cecal cuff resection specimen, but interestingly, this individual’s appendectomy margin was involved by neoplastic epithelium in the lumen, without dissecting mucin. One possible explanation is that the cecal mucin originated from surgical manipulation during appendectomy that resulted in mechanical extrusion of mucin into the cecal wall. However, it may also represent discontinuous mucin extrusion from the neoplasm. There are at least 4 other reports in the literature describing cases of low-grade appendiceal neoplasms with positive appendectomy margins with no additional tumor in resection specimens. A possible explanation for this consistent finding is that many appendectomies have a stapled resection margin, and the tissue designated as the margin is in fact not the true surgical margin. Although very rarely villous adenomas extend into the cecum, this

Figure 1. Low-grade appendiceal mucinous neoplasm. The appendiceal lumen is lined by a villous proliferation of mildly atypical mucinous epithelial cells (hematoxylin-eosin, original magnification ×200).

Figure 2. Margin involvement by low-grade appendiceal mucinous neoplasm (LAMN). At the resection margin, the appendiceal lumen is lined by a single layer of mucinous epithelial cells with mildly atypical, pseudostratified, and hyperchromatic nuclei, consistent with involvement by LAMN (hematoxylin-eosin, original magnification ×100).

Figure 3. Dissecting mucin at the margin. At the resection margin, the mucosa lining the appendiceal lumen (left) is hyperplastic with crypts showing superficial serration and lymphoid tissue, but does not show features of low-grade appendiceal mucinous neoplasm. Rather, a pool of acellular mucin with dystrophic calcifications is present in the submucosa (right) (hematoxylin-eosin, original magnification ×10).
unlikely possibility can be excluded with colonoscopic examination, as has been suggested by others.12

We conclude that in patients with LAMNs confined to the appendix, without extrusion of mucin or mucinous neoplasia beyond the appendiceal serosa, involvement of the appendectomy margin by either neoplastic epithelium or acellular mucin is not associated with disease recurrence or peritoneal dissemination. These observations suggest that nonsurgical modalities, including colonoscopy and radiographic studies, are a reasonable option for the management of these patients. We recognize that, given the assumption that an involved margin denotes the presence of residual tumor and its attendant risk for recurrence or dissemination, some might find it unacceptable to recommend conservative follow-up rather than cecectomy. However, in our series, most patients did not have additional surgery, evidence that conservative follow-up is already an option for some patients. Our data provide justification for that approach. Furthermore, none of the cecal resection specimens in our series or in the literature had residual neoplasia, refuting the assumption that a positive margin necessarily indicates disease left behind in the patient. Although we understand that a limitation of this study is the small number of cases, we encourage others to report their experience with this patient group in order to accumulate data upon which to base reasonable treatment recommendations.

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References