Case Analysis

Low-Grade Appendiceal Mucinous Neoplasm: A Rare Cause of Acute Abdomen

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Key Words
Low-grade appendiceal mucinous neoplasm;
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Purpose. Low-grade appendiceal mucinous neoplasm (LAMN) is a rare type of appendiceal cancer. Patients with LAMN may initially present with acute abdominal pain. Despite the use of CT, ultrasound or colonoscopy, preoperative diagnosis is difficult. In this study, we retrospective analyze cases of LAMN diagnosed in the past 10 years in Chang-Hua Christian Hospital and review the associated literature.
Materials and Methods. This study retrospectively analyzed 15 patients who underwent surgery and was histopathologically confirmed LAMN at Chang-Hua Christian Hospital between January 2000 to August 2011. Patient charts and data on patient demographics; clinical features; ultrasonography (US), colonoscopy and computed tomography (CT) findings; pathology reports; pre-operative diagnosis and operative method were reviewed.
Results. The were 15 cases of LAMN at Chang-Hua Christian Hospital over the past ten years. In our review, there were eight (53.3%) female patients. The median age was 67 years (47-85 years), and the most common presentation was abdominal pain (93.3%). On US in six patients, findings were abdominal cystic mass and cyst wall calcification. The CT finding was well-encapsulated cystic mass in thirteen patients. Appendectomy was performed in ten patients. Right hemicolectomy was performed in five patients, and there was one patient found concomitant colon adenocarcinoma in the specimen.
Conclusion. LAMN is difficult to diagnose before operation. The actual diagnosis is usually made intraoperatively or during histopathologic examination of the excised specimen. Although surgical treatment is straightforward, proper management of the incidentally found lesion requires understanding of the potential complications of widespread peritoneal disease. It should be kept in mind that LAMN may coexist with other neoplasms, and follow-up colonoscopy and pelvic examination is warranted for the high association with other colon and ovarian malignancies.
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Carcinomas of the appendix are rare and have an annual age-adjusted incidence of 0.4 cases per 100,000. Ravi Marudanayagam et al. had analyzed 2660 appendectomy specimens, and 0.6% of them were reported "cystadenoma".[1]

Mucinous cystadenoma of the appendix is an uncommon clinical finding. It is generally termed "mucocele" of the appendix, which simply refers to a cys-

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tic mass filled with mucin in a dilated appendix.[2] However, as it possesses the potential behavior of malignant widespreading, the term "adenoma" has been abandoned. The 4th edition of World Health Organization (WHO) classification had officially introduced "low-grade appendiceal mucinous neoplasm" (LAMN) as the appropriate name.[3]

The presenting clinical signs are variable. Preoperative colonoscopy, ultrasonography (US), and computed tomography (CT) are methods in diagnosing LAMN and distinguishing the mucocele from mimicking diseases. However, the diagnosis is usually made intraoperatively or postoperatively on histopathological examination.[4-6]

As the presenting illness differs, the treatment is not always the same. In this report, we analyzed the cases in our hospital and reviewed related papers for a better understanding of the disease.

Patients and Methods

In Chang-Hua Christian Hospital, each pathologic diagnosis has a code. According to the coding system, we retrospectively searched cases from January 2000 to August 2011. Totally there are fifteen specimens labeled as LAMN. We review these fifteen charts and recorded data including patient demographics, clinical features, US, colonoscopy and CT findings, concomitant diseases, and conditions for which surgery was indicated. Pathology reports, operative and postoperative management, and information on last follow-up were also recorded. In this study, the descriptive variables of standard deviation and median were used.

Results

A total 15 patients were admitted and received surgery as a result of LAMN. The median age was 67 years (47-85 years). Regarding to the clinical signs, 14 of our patients (93.3%) experienced abdominal pain. The pain was mainly located over right-lower quadrant area (n = 10; 71.4%); one patient had paraumbilical pain and two complained of diffuse abdominal pain with no specific location. Other presenting signs included abdominal distention (n = 3), nausea/vomiting (n = 4), and weight loss (n = 1) (Table 1).

During the physical examination, rebound tenderness over the pain site was noted in 9 patients (60.0%). A palpable mass was perceived in one patient. Before operation, abdominal ultrasonography (US) was performed in 6 patients, which revealed a cystic mass with variable internal echogenicity, layered wall, and calcification in the wall. Thirteen patients received abdominal computed tomography (CT), and the tumor was detected as an abdominal cystic mass with

Table 1. Clinical presentation, pre-OP evaluation and suspected diagnosis in patients with LAMN

No	Age	Sex	Clinical Presentation	Pre-OP test	Pre-OP impression
1	66	M	RLQ pain	US, CT	Ruptured diverticulitis
2	47	F	Diffuse abdominal pain, nausea	US	Right adnexl mass
3	74	F	RLQ pain	US	Right ovary torsion
4	76	M	Abdominal distension	US, CT	Intestinal obstruction
5	65	F	RLQ pain	CT	Appendiceal tumor
6	46	F	Peri-umbilical pain, nausea	CT	AA
7	85	M	RLQ pain	CT	Appendiceal tumor
8	77	F	Diffuse abdominal pain	US, CT	AA
9	66	F	RLQ pain,, nausea, vomiting	CT	AA
10	72	M	Vague abdominal pain	Colonoscopy, CT	AA
11	65	M	RLQ pain	US, CT	Ileo-colonic intussuception
12	69	F	RLQ pain, abdominal distension	CT	Appendiceal tumor
13	75	F	RLQ pain	CT	Cecal carcinoma
14	64	M	RLQ pain, nausea, vomiting	CT	AA
15	59	M	RLQ pain, abdominal distension	CT	Intestinal obstruction

M: Male; F: Female; RLQ: Right lower quadrant; US: ultrasonography; CT: computed tomography; AA: Acute appendicitis.

wall calcification situated in the right lower quadrant (Fig. 1).

Eight patients underwent emergent surgery under the impression of acute abdominal conditions (acute appendicitis in 5 cases; right ovarian torsion in 1 patient; ruptured diverticulitis in 1 patient; ileo-colonic intussuception in 1 patient) (Table 2). In three patients, surgery was indicated for appendiceal tumor detected by image pre-operatively. Four of our cases were operated for other indications. One was exploratory laparotomy for suspective adnexal mass; another one was for suspective cecalc cancer; the other two were for adhesiolysis.

Ten patients received appendectomy; one of them also had cecum removed due to gross tumor invasion.

Fig. 1. CT scan shows a cystic mass with mural thickening in the cecum.

Right hemicolectomy was performed in 5 patients. In all patients, histopathological examination of specimens found low-grade appendiceal mucinous neoplasm.

Two patients expired at the 37th and 60th postoperative day respectively. There were no gastrointestinal tract complications, and the enteral feeding could be fully achieved through nasogastric tube. The main cause of death were pneumonia induced by long-term ventilation use. The other 13 patients recovered uneventfully with a median hospital stay of 6.4 days (range: 4-60 days). The 13 survived patients had no evidence of recurrence or metastasis at their last follow-up (median: 50.6 months; range: 6-108 months).

Discussion

Low-grade appendiceal mucinous neoplasm (LAMN) is a rare tumor of the appendix associated with cystic dilatation, to which the more general term of mucocele has been applied (Fig. 2). Mucocele of the appendix denotes an obstructive dilatation of the appendiceal lumen due to abnormal accumulation of mucus, which may be caused by a retention cyst, mucosal hyperplasia, cystadenoma and cystadenocarcinoma.[7,8] Mucocele of the appendix is more frequent in women and is usually observed in patients older than 50 years. In this study, the patients we re-

Table 2. Treatment, accompanying disease and follow-up interval in patients with LAMN

No	Surgery	Accompanying disease	Follow-up (months)
1	Right hemicolectomy	AA, ascending colon diverticula	108
2	Appendectomy + bilateral salpingectomy	Right hydrosalpinx	54
3	Right hemicolectomy	Ischemic colitis	72
4	Open appendectomy	AA	37 days
5	LA	AA	48
6	Appendectomy + cecectomy	Colonic diverticulitis	31
7	LA	–	39
8	Right hemicolectomy	Terminal ileum necrosis	60 days
9	LA	AA	13
10	Right hemicolectomy	Adenocarcinoma of the ascending colon	85
11	Right hemicolectomy	AA	6
12	LA	AA	54
13	Open appendectomy	AA	57
14	LA	AA	46
15	Open appendectomy	AA	41

LA: laparoscopic appendectomy; AA: Acute appendicitis.

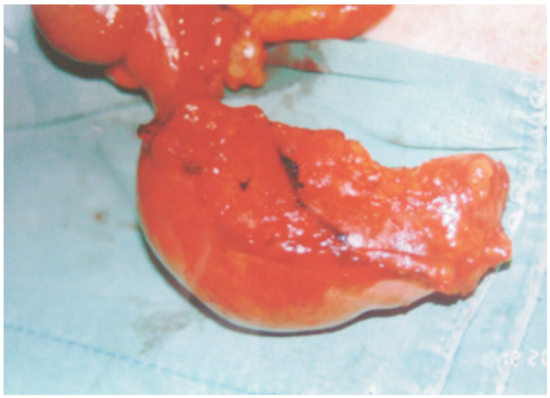

Fig. 2. The specimen was diagnosed as low-grade appendiceal mucinous neoplasm after pathologic exam.

viewed included 8 women and 7 men; the youngest age is 46-year-old.

The most common presenting symptom associated with LAMN has been abdominal pain; however, one-fourth of patients are asymptomatic and are found incidentally. Other symptoms such as bloody stool, intussusception have also been reported.[9]

Without specific symptoms, image studies are usually needed for differential diagnosis. By ultrasound, cystic masses with varying internal echogenicity and a layered wall with calcification may be seen; we found this in 3 patients. The typical findings by computed tomography are well-encapsulated cystic masses with low attenuation. However, if the mucocele ruptures, it may be misdiagnosed as ruptured appendicitis or diverticulitis. Colonoscopy is usually nondiagnostic, as mucosal biopsies will often be normal.[4,5,10]

LAMN generally grow slowly, and tend to produce the clinical picture of low-grade pseudomyxoma peritonei in which spread beyond the peritoneum or nodal metastasis is unusual. Histologically, LAMN may have villous, serrated or undulating morphology, but unlike adenomas, they rest on fibrous tissue rather than lamina propria (Fig. 3). They tend to involve the appendix in a circumferential fashion with atrophy of the underlying lymphoid tissue.[11] Because LAMN can proliferate outside the appendix in a malignant way, producing pseudomyxoma peritonei and even distant metastasis,[12,13] it is inappropriate to regard LAMN as "one kind of adenoma". The term "mucinous cystadenocarcinoma" has been used for well-differentiated mucinous tumor with cystic structures; however, such a diagnosis should be avoided because this neoplasm dose not constitute a separate disease entity.[14] The 4th edition of World Health Organization (WHO) classification asserted "low-grade appendiceal mucinous neoplasm" the appropriate name.

Recently, serrated polyps in the colon have generated interest as the possible precursor lesions of microsatellite instable carcinomas.[19-22] Jass et al.[22] noted that the serration in serrated polyps is the result of accommodation of an enlarged cytoplasmic compartment due to increased secretory mucins. LAMNs often have tall, mucinous epithelium in villous areas and, perhaps because of this, occasionally have serrated glands.[23] Therefore, distinguishing between villous adenomas, serrated adenomas, and even circumferential mucosal hyperplasia in the appendix can sometimes pose a considerable challenge. Others have commented on the morphologic similarity between villous adenomas of the colon and serrated adenomas.[24] In 1999, Szych et al.[25] found frequent K-ras mutations and loss of heterozygosity of chromosome 5q in LAMNs, a pattern similar to colorectal adenomas. Together with their findings, LAMNs arising via the chromosomalinstability pathway of colorectal carcinogenesis was suggested. For this reason, colonoscopy examination was recommended to rule out synchronous colon cancer.

The morbidity/mortality associated with LAMN

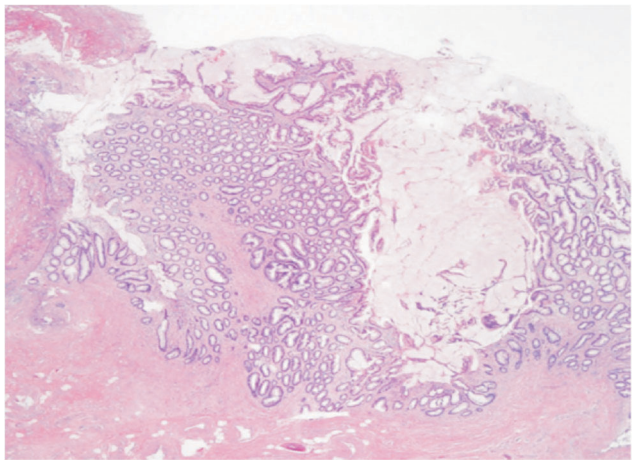

Fig. 3. Low-grade appendiceal mucinous neoplasm. This morphology is smilialr to adenomas, but there is no lamina propia and the neoplastic epithelium rests on fibrous stroma.

stems from rupture and intraperitoneal spread of mucin-producing epithelium, which may cause pseudomyxoma peritonei. As a result, gentle tissue handling during operation cannot be overemphasized.[15] Since there are no evidence in regard to lymphatic or hematogenous spreading of LAMN, if the mass confines in the appendix body without local invasion or cecal involvement, simple appendectomy and mesoappendix excision is considered sufficient treatment.[16] Successful removal of appendiceal mucoceles laparoscopically has been reported.[26,27] In our practice, there were 5 patients (33.3%) had their LAMN removed by laparoscopic appendectomy. For mass involving the cecum or adjacent organs, right hemicolectomy is often required. LAMN is associated with colon and ovarian malignancy.[15-17] In our review, 1 patient had concomitant ascending colon cancer (6.6%). Therefore, intraoperative exploration of the entire gastrointestinal tract and ovaries in females is warranted. All gross peritoneal implants should undergo a biopsy and be removed with grading of the degree of epithelial atypia for prognostic purposes.[18]

Rarity of the tumor and absence of randomized clinical trials preclude the compilation of guidelines for the follow-up practice. CT, US, pelvic exam and colonoscopy are recommended by some authors to detect other colon and ovarian malignancies. During the follow-up period, there was no evidence of disease recurrence or metastasis in our group.[8,11]

Conclusion

Low-grade appendiceal mucinous neoplasm is more frequent in elderly patients and may cause acute abdomen. US, CT and sometimes colonoscopy are helpful in diagnosis. However, actual diagnosis is usually made intraoperatively or during histopathologic examination of the excised specimen. Appendectomy with removal of the mesoappendix or right hemicolectomy is the treatment of choice, depending on the degree of tumor invasion. It may coexist with other neoplasms. Thorough examination of the abdominal and pelvic cavity during surgery is warranted. Follow-up CT, US, or colonoscopy are also recommended.

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病例分析

闌尾低度惡性黏液瘤 — 罕見之急性腹痛原因

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目的　「闌尾低度惡性黏液瘤」是一種十分罕見的闌尾腫瘤。患者可能以急性腹痛為臨床表現。雖然配合電腦斷層、腹部超音波與大腸境的檢查，術前診斷仍有其困難性。在本篇報告中，我們收集彰化基督教醫院近十年來的案例進行分析，並回顧相關之研究文獻。

方法　本研究是採取回溯性分析。案例來自於本院 2000 年 1 月至 2011 年 8 月間經病理檢驗證明為「闌尾低度惡性黏液瘤」之 15 位患者。我們記錄並分析其臨床表現、腹部超音波檢查報告、大腸鏡報告、電腦斷層之發現、病理報告、術前診斷與手術方法。

結果　在十年間本院總共有 15 患者。其中 8 位 (53.3%) 是女性。平均確定診斷之年齡為 67 歲 (47-85 歲)。最常見之臨床表現為腹痛 (93.3%)。其中 6 位接受腹部超音波檢查的患者，發現到腹內有囊狀腫塊，與囊壁鈣化的現象。有 13 位患者接受電腦斷層檢查，影像顯示外膜完整之囊腫。有 10 位患者接受闌尾切除術。有 5 位接受右側結腸切除手術，其中一位患者檢體中同時發現大腸腺癌。

結論　「闌尾低度惡性黏液瘤」在術前不易診斷，其確診往往有賴於手術中直接觀察與手術後之檢體病理分析。儘管手術切除是最直接的治療方法，但仍須小心保持腫瘤之完整性，以避免腫瘤破裂造成黏液瘤細胞擴散。因其可能同時與其他種類的癌症同時存在(如大腸癌或卵巢癌)，術後的檢查如大腸鏡與骨盆檢查是必需的。

關鍵詞　闌尾低度惡性黏液瘤、闌尾腫瘤、急性腹痛。