



Mucinous Neoplasms of the Appendix: Our Clinical Experience and Review of the Literature

Apendiks Musinöz Neoplazmları: Klinik Deneyimimiz ve Literatürün Gözden Geçirilmesi

© Gökhan Demiral¹, © Muhammed Kadri Çolakoğlu¹, © Süleyman Kalcan¹, © Ali Özdemir², © Ahmet Pergel¹

¹Recep Tayyip Erdoğan University Faculty of Medicine, Department of General Surgery, Rize, Turkey

²Recep Tayyip Erdoğan University Training and Research Hospital, Clinic of General Surgery, Rize, Turkey

ABSTRACT

Aim: Neoplastic lesions of the appendix are very rare and most of them are incidentally detected during appendectomy. In this study, we aimed to evaluate the clinicopathological features and applied treatments of the patients who were operated in our clinic and diagnosed as appendiceal mucinous tumor (ApMT) in the light of the literature.

Method: The data and appendectomy specimens of the patients who were operated in our clinic between January 2011 and December 2016 and who were diagnosed as ApMT were retrospectively evaluated. Age, gender, clinical findings, diagnostic methods, histopathological diagnosis and subsequent treatments were evaluated.

Results: Six of the patients were male and four were female. The mean age was 48.6 years (range, 28-85). Nine patients were operated for acute abdomen and one patient was operated electively. Ultrasonography was performed in four patients and computed tomography was performed in six patients preoperatively. Pathological examination revealed simple mucocele in eight patients, mucinous adenoma in one patient and mucinous cystadenoma in one patient. Two patients had appendiceal diverticulum and two patients had diverticulitis associated with acute appendicitis, two patients had appendix perforation and three patients had periappendicular abscess. All patients underwent appendectomy for ApMT.

Conclusion: ApMT is a rare tumor of the appendix that may be benign or malignant. Patients may present with symptoms of acute appendicitis as well as unspecific symptoms. Although preoperative diagnosis is difficult, it helps to minimize complications. Care should be taken to prevent appendix rupture and peritoneal mucus contamination during surgery.

Keywords: Mucocele, appendicitis, appendectomy, pseudomyxoma peritonei

ÖZ

Amaç: Apendiks neoplastik lezyonları oldukça nadir görülen ve çoğunluğu apendektomi esnasında insidental olarak saptanan lezyonlardır. Bu çalışmada kliniğimizde opere edilen ve apendiks musinöz tümör (ApMT) tanısı konulan olguların klinikopatolojik olarak incelenerek uygulanan tedavilerin literatür eşliğinde değerlendirilmesi amaçlandı.

Yöntem: Ocak 2011-Aralık 2016 tarihleri arasında kliniğimizde opere edilen ve ApMT tanısı konulan hasta dosyası ve apendektomi piyeslerine ait sonuçlar retrospektif olarak incelendi. Hastaların yaş, cinsiyet, klinik bulgular, tanı yöntemleri, histopatolojik tanı ve sonraki tedavileri değerlendirildi.

Bulgular: Hastaların 6'sı erkek, 4'ü kadın olup yaş ortalaması 48,6 (28-85 aralığında) idi. Dokuz hasta akut batın bulguları ile ve 1 hasta elektif olarak opere edilmiş idi. Tanısal yöntem olarak 4 hastada ultrasonografi ve 6 hastada bilgisayarlı tomografi uygulanmış idi. Patolojik değerlendirmede 8 hastada basit mukosel, 1 hastada musinöz adenom ve 1 hastada musinöz kistadenom mevcut idi. İki hastada akut apandisit eşlik eden apandiks divertikülü ve iki hastada divertikülit; iki hastada apendiks perforasyonu; üç hastada ise periapendiküler apse mevcut idi. Tüm hastalarda ApMT için apendektomi işlemi uygulanmış idi.

Sonuç: ApMT apendiks benign veya malign olabilen nadir bir tümördür. Hastalar akut apandisit bulguları yanı sıra belirgin olmayan semptomlar ile başvurabilir. Preoperatif tanı zor olmasına rağmen komplikasyonları en aza indirmede yardımcıdır. Cerrahi esnasında apendiks rüptürünü ve peritoneal mukus kontaminasyonunu önlemek için dikkatli olunmalıdır.

Anahtar Kelimeler: Mukosel, apandisit, apendektomi, psödomiksoma peritonei



Address for Correspondence/Yazışma Adresi: Gökhan Demiral MD,

Recep Tayyip Erdoğan University Faculty of Medicine, Department of General Surgery, Rize, Turkey

Phone: +90 535 291 93 9 E-mail: drgokhandemiral@yahoo.com ORCID ID: orcid.org/0000-0003-2807-5437

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Introduction

The neoplastic lesions of the appendix (NLA) are very rare and the majority of them are incidentally noticed during appendectomy. Although NLA are seen at approximately 1%, it is accepted that the rate of unpredictable pathological anomalies is up to 5%, especially due to unexamined lesions.¹ Appendiceal mucinous tumors (ApMT), also called appendiceal mucocele, are rare NLA and are found incidentally during surgery, routine radiological evaluations or colonoscopic examination. Accumulation of mucoid material within the lumen of the appendix leads to obstructive enlargement of the appendix.² ApMT are more common in women and over the age of 50, and they constitute 8% of NLA and 0.3-0.7% of all appendix pathologies.^{3,4} They have four histopathological subtypes namely simple or retention mucoceles, mucoceles with local or diffuse villous hyperplastic epithelium, mucinous adenoma/cystadenoma and malignant mucinous cystadenocarcinomas. Clinical findings include right lower quadrant pain, palpable mass in the right lower quadrant, colic pain in case of obstruction or invagination, gastrointestinal bleeding, anemia, genitourinary symptoms, acute abdomen, and sepsis in case of rupture of the cyst. Because the findings are nonspecific, they are rarely diagnosed during radiological, sonographic, or endoscopic procedures.^{3,4} On the other hand, most cases are asymptomatic until diagnosis is made intraoperatively or during postoperative histopathological examination.⁴ The recommended treatment for ApMT is surgery and the surgical method should be determined according to tumor size, the presence of local or diffuse peritoneal mucus, appendix perforation, surgical margin status and histological type of tumor.⁵ Appendectomy is sufficient in benign ApMT, and cecum resection or right hemicolectomy is recommended in the presence of spread to neighboring bowel segments, regional lymphadenopathy, pseudomyxoma peritonei (PMP) or malignancy.⁵ In this study, we aimed to evaluate the clinicopathological examination of the patients who were operated in our clinic and diagnosed as ApMT in the light of the literature.

Materials and Methods

The medical records and the results of appendectomy specimens of ten patients who underwent emergency surgery with the diagnosis of acute appendicitis or elective surgery with other diagnoses in our clinic between January 2011 and December 2016 were retrospectively analyzed. Informed consent was obtained from all patients in the study. Age, gender, clinical findings, diagnostic methods, histopathological diagnoses and subsequent treatments were evaluated.

Results

Six of the patients were male and four were female. The mean age was 48.6 years (range, 28-85). Physical examination records revealed right lower quadrant pain and direct rebound findings on physical examination in nine patients. One patient was electively operated. Ultrasonography (US) was performed in four patients and computed tomography (CT) was performed in six patients as a diagnostic method, and both diagnostic methods were used in one patient who was operated electively. Pathological examination revealed simple mucocele in eight patients, mucinous adenoma in one patient and mucinous cystadenoma in one patient. One of the patients with simple mucocele was consulted to general surgery clinic due to periappendicular adhesions while undergoing total abdominal hysterectomy + bilateral salpingo-oophorectomy for endometrial adenocarcinoma, and she had appendectomy. The patient with detected mucinous cyst adenoma was operated for acute abdomen and right ovarian hemorrhagic cyst adenoma rupture was detected. Two patients had appendiceal diverticulum and two patients had diverticulitis associated with acute appendicitis, two patients had diverticulitis, two patients had appendix perforation and three patients had periappendicular abscess. Open appendectomy was performed in all patients (Tables 1, 2).

Discussion

ApMT, which is rarely reported in the literature and is usually incidentally detected, is more common between the ages of 50 and 69 years, although it occurs at any stage of life.^{6,7} Regarding the gender distribution, there are

Table 1. Demographic data of patients

| | |
|---------------------------|---|
| Mean age (years) | 48.6 (range, 28-85) |
| Gender | 6 M, 4 F |
| Type of admission | Acute abdomen (9) Elective surgery (1) |
| Diagnostic method | US (4)/CT (6) CT/US (1) |
| Pathological diagnosis | Simple mucocele (8) Mucinous adenoma (1) Mucinous cystadenoma (1) |
| Accompanying | |
| Appendix diverticulum (n) | 2 |
| Abscess, perforation | 2/2 |
| Surgical procedure | Appendectomy (10) |

M: Male, F: Female, CT: Computed tomography, US: Ultrasonography

Table 2. Gender, age, pathologic diagnosis, clinical diagnosis, surgical procedure and accompanying findings of the patients

| Patient ID | Gender | Age | Pathologic diagnosis | Clinical diagnosis | Surgical procedure | Accompanying findings |
|------------|--------|-----|----------------------|--|---|-------------------------|
| 1 | M | 40 | Simple mucocele | Acute appendicitis | Open appendectomy | - |
| 2 | F | 70 | Mucinous adenoma | Perforated appendicitis | Open appendectomy | - |
| 3 | F | 85 | Simple mucocele | Acute appendicitis | Open appendectomy | - |
| 4 | M | 62 | Simple mucocele | Perforated appendicitis | Open appendectomy | Abscess, diverticulum |
| 5 | M | 60 | Simple mucocele | Acute appendicitis | Open appendectomy | Abscess, diverticulitis |
| 6 | M | 28 | Simple mucocele | Acute appendicitis | Open appendectomy | Abscess, diverticulitis |
| 7 | M | 28 | Simple mucocele | Acute appendicitis | Open appendectomy | Abscess, diverticulum |
| 8 | M | 29 | Simple mucocele | Acute appendicitis | Open appendectomy | - |
| 9 | F | 43 | Mucinous cystadenoma | Hemorrhagic serous ovarian cystadenoma | Open appendectomy/right ovarian cyst excision | - |
| 10 | F | 41 | Simple mucocele | Endometrial adenocarcinoma | TAH/BSO/open appendectomy | - |

F: Female, M: Male, ID: Identify, TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo oferectomy

inconsistencies in the literature, and some studies report a higher incidence in women, while others report a similar incidence in both genders.^{5,7} In our study, the mean age of the patients was 48.6 years (range, 28-85) and was close to the lower limit of the age range reported in the literature. The male-female ratio was 2/3 and a total of three male patients had simple mucocele detected in 20s. ApMT are divided into 4 pathological types according to their epithelial characteristics:

- Simple or retention mucoceles; they are usually caused by obstruction of the root of the appendix with fecalitis or inflammatory adhesion. It is characterized by normal epithelial structure and slight luminal dilatation up to 1 cm.
- Mucoceles containing local or diffuse villous hyperplastic epithelium; luminal dilatation is mild and constitutes 5-25% of mucoceles.
- Mucinous adenoma/cystadenoma; is the most common group and constitutes 63-84% of the cases. This group usually has some degree of epithelial atypia and villous adenomatous changes. There is significant distention in the lumen (up to 6 cm). It is benign and does not carry a risk of recurrence.
- Malignant mucinous cystadenocarcinomas; constitute 11-20% of the cases. Glandular stromal invasion, desmoplastic reaction and/or the presence of epithelial cells in peritoneal implants are observed. Luminal dilatation is very high.⁸

Most patients with ApMT are asymptomatic and may exhibit different clinical findings.⁹ Acute or chronic pain in the right iliac fossa is the most common symptom. Sometimes a palpable mass may be detected on physical examination.⁴ The symptoms observed in the presence of malignant mucocele are weight loss, general condition disorder and presence of intraabdominal masses; however, acute pain in the right iliac fossa is more common in benign mucoceles.⁶ In our study, nine patients showed clinical findings of acute appendicitis at admission and one of them had mucinous cyst adenoma associated with right ovarian cyst rupture. Mucinous cystadenoma is located in the benign part of the pathological spectrum and does not carry a risk of recurrence. Mucinous cystadenocarcinoma with stromal invasion and intraperitoneal spread is similar to ovarian mucinous cystadenocarcinoma with high lymph node involvement and liver metastasis and low survival rate.⁹ In our study, simple mucocele was detected in eight patients, mucinous adenoma in one patient and cyst adenoma in one patient. No mucinous cystadenocarcinoma was detected. One case was operated electively for endometrial adenocarcinoma and concurrent appendiceal simple mucocele was detected. Advances in diagnostic methods, especially in abdominal US and CT, have increased the possibility of preoperative diagnosis of mucoceles.⁶ Cysts of different echogenicities can be identified in relation to the amount of mucus on US.

Multiple echogenic foci in the dilated appendix may reveal multiple echogenic layers that give the appearance of onionskin layers that may be pathognomonic for the mucocele.¹⁰ In the US, an appendix with a diameter of 15 mm and above has a sensitivity of 83% and a specificity of 92% for mucocele.¹¹ On the other hand, appendiceal mucocele is a round, thin-walled cystic mass with a capsular structure in CT. Calcification is detected in 50% of the cases and the presence of nodules in the mucocele wall suggests cyst adenocarcinoma.¹² Malignancy is rarely detected under 2 cm. In addition, cystadenoma/cystadenocarcinoma is detected more frequently in large mucoceles (6 cm or more) and a higher rate (20%) of perforation is observed.¹³ The presence of acid on CT is a nonspecific finding and may be observed in PMP. Since the mucin-producing cells in PMP are weakly adhesive, they can easily be displaced by peristaltic movements and adhere to immobile areas. Douglas/rectovesical pouch, right and left subphrenic areas, and liver and spleen surfaces are the most common sites.¹⁴ Colonoscopy should also be performed preoperatively to exclude the presence of colorectal neoplasia in all patients with suspected appendiceal mucocele.¹⁵ Colonoscopy shows a “volcano sign” in which the appendix orifice is located in the middle of a prominent bump surrounded by a normal mucosa or a yellowish lipoma-like submucosal mass.¹⁶ Mucosal biopsies are usually reported as normal.¹⁵ Biochemical tests may also be used in the diagnosis of ApMT. High levels of carcinoembryonic antigen (CEA) may be seen in cystadenocarcinomas, but this antigen is not routinely evaluated in ApMT because the CEA levels in cystadenomas are rarely high. Preoperative evaluation may include tumor markers such as alpha-fetoprotein and carcinoma antigen 19-9 as well as CEA.¹⁷ In our study, US was performed in four patients and CT was performed in five patients who underwent emergency surgery, and the imaging findings were reported consistent with acute appendicitis. ApMT was not suspected preoperatively in any patients, and therefore colonoscopy was not performed and tumor markers were not examined. Right hemicolectomy is often performed in the treatment of suspected malignancy in preoperative imaging or when malignant mucocele is detected during frozen examination.⁵ Although right hemicolectomy is the standard treatment modality in malignant ApMT, recent studies suggest that the presence of a mucocele with a solid surgical margin is an indicator of good prognosis and disease-free survival.⁷ Gonzalez-Moreno and Sugarbaker¹⁸ reported in 501 patients with appendiceal epithelial neoplasia that right hemicolectomy was not superior to appendectomy in terms of survival. However, the authors suggested that right hemicolectomy is required

in the presence of need for complete excision of a primary tumor or complete cytoreduction, lymph node involvement revealed by histopathological examination of the appendix or ileocolic lymph nodes, and the presence of a non-mucinous neoplasia identified by histopathological examination. The choice of open or laparoscopic surgery in ApMT is controversial.¹⁹ Laparotomy is the best option if the mass is large and resection is difficult. On the other hand, laparoscopic methods have become popular in the last decade and many authors have suggested that laparoscopic method is a safe choice in ApMT surgery.⁵ However, since the distribution of mucus or epithelial cells in the peritoneal space is associated with poor prognosis, rupture and peritoneal contamination should be avoided. For this purpose, the appendix should be pulled to a minimum during laparoscopy, low levels of pneumoperitoneum pressure should be provided and the bag should be used when removing the excised material.⁵ In addition, the presence of any mucinous fluid in the abdomen should be carefully examined. There is consensus that appendectomy is sufficient in the treatment of non-ruptured benign appendix mucoceles.²⁰ In our study, all patients underwent open appendectomy. Since no malignancy was reported pathologically, the surgical procedure was satisfactory. Two cases where the appendix was ruptured during surgery were at 26th and 28th months and are still being followed up. Follow-up was not recommended in other cases. PMP occurs only in a small proportion of mucinous neoplasms. It is characterized by peritoneal spread and implant formation due to iatrogenic or spontaneous rupture of mucocele during appendectomy or due to mucinous cystadenoma/cystadenocarcinoma.⁵ Although clinically more severe, it has a slowly progressive course, often accompanied by nonspecific abdominal symptoms. The most common symptom is acute or chronic pain in the right lower quadrant.²¹ The disease is progressive in both cases when the ruptured primary mass and mucinous cells spreading along the peritoneal surfaces are benign or malignant. Since PMP usually develops as a complication of ovarian and appendix masses, PMP should be suspected in the history of appendectomy.²¹ Although ovaries were considered to be the most common primary organ in the past, recent studies based on immunohistochemical analysis and molecular biology have shown that ovary is a rare source of PMP and that lesions previously called “ovarian borderline mucinous tumors” are typically metastatic lesions of the appendix.²¹ PMP treatment varies due to the rarity of the disease and slow progression of the disease.²² Current treatment strategies of PMP include careful monitoring and continuous observation; enlarged cytoreductive surgery alone or with

hyperthermic intraoperative peritoneal chemotherapy and early postoperative intraperitoneal chemotherapy.¹⁹ In a study based on Sugarbaker's peritonectomy procedure, cytoreductive surgery with intraperitoneal hyperthermic perfusion allowed complete removal and this combined treatment proved its efficacy in terms of increased long-term survival and better regional control of the disease.²³ However, other studies support that fluorouracil-based adjuvant systemic chemotherapy should be the standard treatment for appendix-related PMP patients.²⁴ When surgery is not required immediately, patients can be monitored with CT scans, tumor markers, laboratory tests and physical symptoms, and the time of surgery can be planned. Since the risk of developing colonic adenocarcinoma in these patients is 6 times higher than in the general population, patients should be followed by colonoscopy.²⁵ In addition, screening of solid organs, such as kidney and lung, should be performed in malignant ApMT cases. No PMP was detected in any patient in our study. In conclusion, ApMT is a rare tumor of the appendix that can be benign or malignant. Patients may present with signs of acute appendicitis as well as non-significant symptoms. Although preoperative diagnosis is difficult, it is highly helpful in determining the correct treatment method and minimizing intraoperative and postoperative complications. Ultrasound and CT may be helpful in preoperative diagnosis: however, sometimes it is accompanied by colon cancer and may be detected incidentally during colonoscopy. ApMT treatment is open or laparoscopic appendectomy. Treatment options for malignancy include right hemicolectomy. Since PMP is a feared complication, appendix rupture and peritoneal mucus contamination should be avoided during surgery.

Ethics

Ethics Committee Approval: The study was approved by the Recep Tayyip Erdoğan University Faculty of Medicine Clinical Research Ethics Committee (approval number: 2019/21).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.D., M.K.Ç., A.P., Concept: G.D., S.K. Design: S.K., A.Ö., Data Collection or Processing: M.K.Ç., A.P., Analysis or Interpretation: G.D., A.P., Literature Search: G.D., A.Ö., Writing: G.D.

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