MALIGNANT TUMORS OF THE APPENDIX: EVALUATION OF 6748 APPENDECTOMY CASES

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Abstract: Objective: Appendiceal neoplasms are usually diagnosed incidentally after appendectomy for the treatment of acute appendicitis. This study aimed to present incidental malignancy cases that we detected retrospectively by examining our appendectomy results.

Materials and Methods: 6748 appendectomy cases performed in Van Research and Training Hospital, Department of Surgery, Turkey, between January 2016 and January 2020, were retrospectively analyzed. After histopathological analysis, 22 patients were found to have low-grade appendiceal mucinous neoplasia (LAMN) and appendiceal neuroendocrine tumors (NET). The complete data of the patients were recorded, including the demographic, laboratory, imaging, and histopathological data.

Results: The median age of 22 patients included in the study was 39 years (18-72 years), and 14 (63.6%) were women. Malignancy was suspected in only 4 (18%) patients during exploration. Histologically, the tumor was located distally in 19 (83.4%) patients and was located at the base of the appendix in 3 patients. Histopathological analysis; resulted as grade 1 NET in 15 patients, LAMN in 5 patients, grade 2 NET in 1 patient, and mixed type (mucinous + neuroendocrine tumor) in 1 patient. The Median follow-up time was 45.5 months (range: 26-53). During the follow-up, one of our patients who underwent right hemicolectomy due to the tumor at the surgical margin was diagnosed with pseudomyxoma peritonei.

Conclusion: Appendiceal neoplasms are often diagnosed in the results of postoperative pathological examinations. In patients with suspected malignancy during the perioperative examination, it is crucial to carefully examine intra-abdominal organs and avoid surgical margin positivity. Malignancy risks should always be kept in mind in non-routine appendix appearances.

Keywords: appendix, appendiceal, malignancy, tumor.

INTRODUCTION

Appendiceal neoplasms are usually seen after appendectomy for acute appendicitis (1). It is uncommon to diagnose it before or during surgery. Although appendectomy for acute appendicitis is generally an adequate treatment for most of these neoplasms, surgeons cannot offer different surgical options without definitive pathological results (2). Depending on the histopathology, size, and surgical margin of the tumor, appendectomy or right hemicolectomy are surgical treatment options. Adenocarcinomas, mucinous neoplasms, and neuroendocrine tumors (NET) are types of primary appendix neoplasm histopathology. NET is the most common type of these neoplasms (3).

MATERIALS and METHODS

Between January 2016 and January 2020, 6748 appendectomies were performed, with the diagnosis of acute appendicitis at Van Research and Training Hospital, Department of Surgery, Turkey. Patients who underwent appendectomy for a reason other than acute appendicitis were excluded from the study. These medical records were evaluated retrospectively. After histopathological analysis of appendectomy specimens, 22 patients were found to have low-grade mucinous neoplasia and appendiceal neuroendocrine tumors. A retrospective database including gender, age, preoperative radiological diagnosis, symptom duration, intraoperative surgical findings, histopathological type of tumors, tumor grades, diameters, and localizations were obtained. All patients were invited to check the wound site at the postoperative 1st week and the pathology report on the 15th day. If the pre-

malignant lesion was detected in the pathology report, the patient was called for a 1st and 6th months post-operative control. Total colonoscopy was performed for suspected synchronous colorectal cancers in cases with appendiceal neoplasia.

Statistical analyzes

All statistical analyzes were performed using SPSS software version 22 for Windows (SPSS Inc., Chicago, IL, USA), and the results were considered statistically significant if $P < 0.05$. Continuous variables were expressed as median (range), and categorical variables were expressed as frequency (percentage).

Approval was obtained from the ethics committee of our center for a retrospective study (2020/20 – 08.10.2020).

RESULTS

The data of 6748 surgical patients diagnosed with acute appendicitis were retrospectively analyzed, 22 patients were found to have appendix neoplasms (0.32%). The median age of these 22 patients was 39 years (range, 18-72 years), and 14 (63.6%) were female. All patients presented with clinical and radiological appendicitis. The median symptom duration was 2 (1-3) days. Twenty patients had localized pain (right lower quadrant), two patients had pain in all four quadrants of the abdomen.

Tenderness and rebound were detected in the right lower quadrant in all patients. As radiological imaging, ultrasonography (USG) in 10 patients, computed tomography (CT) in 11 patients, and both methods were used in 1 patient. The median appendix diameter was 10 (7-36) mm in preoperative imaging.

Malignancy was suspected in 4 (18%) patients during exploration. The mean appendix diameter in the preoperative examinations of these four patients was 28.5 ± 11.8 mm. Imaging tests showed an increase in the diameter of the appendix, which was significant in terms of suspicion of malignancy in the perioperative

Figure 1. Appendectomy specimen with multiple lymphadenopathies in the mesoappendix

examination. At the same time, there was a statistical correlation between histological tumor size and malignant appearance in perioperative control (Figure 1). The histological median tumor diameter in the entire group was 0.65 cm (range: 0.2–7 cm). While the mean tumor diameter of the patients suspected of tumor on exploration was 48.2 ± 23.93 mm, it was 8.56 ± 6.69 mm in the others.

Histologically, the tumor was located distally in 19 (83.4%) patients and at the base of the appendix in 3 patients. Histopathological tumor size and surgical margin positivity were unrelated. The surgical margin was positive in 2 patients with radix located, and radix location was significant in terms of the risk of surgical margin positivity. Although it has been determined that radix located tumors are statistically significant in terms of malignant appearance on exploration, it may be thought that the mean diameter of these neoplasms being larger than those located distally may contribute to this result. A right hemicolectomy was performed in patients with positive surgical margins.

Table 1. Histopathological features of tumors

	Neuroendocrine tumor	Mucinous neoplasia	Mixt type tumor
Total patient number	16	5	1
Sex (Female)	8	3	1
Localisation (Proximal)	1	2	No
Mesoappendix invasion	8	1	1
Lenfovacular invasion	2	1	1
Pseudomiksoma peritonei	No	No	1

Figure 2. The villi of an appendiceal mucinous adenoma are lined by pseudostratified nuclei with mild hyperchromasia (X400 Hematoxylin and eosin)

Histopathological analysis; It resulted as grade 1 neuroendocrine tumor in 15 patients, low-grade mucinous neoplasia in 5 patients (Figure 2), grade 2 neuroendocrine tumor in 1 patient, and mixed type (mucinous + neuroendocrine tumor) in 1 patient (Table 1). All Grade 1 NETs were located distally. Therefore, there was a statistically significant relationship between histopathology and tumor location. Due to its distal location and small histological tumor size, no perioperative malignancy was suspected in any grade 1 NET case.

Mesoappendix invasion was detected in 10 patients (45.5%). Median mitotic index and Ki67 levels were 1 (0-4) and 1 (1-10), respectively.

Open appendectomy was performed in 16 patients and laparoscopic appendectomy in 6 patients. In the preoperative imaging, the patient with an appendix diameter of 36 mm had a conversion from laparoscopy to open (Figure 3). Only mesoappendix invasion did not require re-operation in any of our patients.

The Median follow-up time was 45.5 months (range: 26-53). During the follow-up, one of our patients who underwent right hemicolectomy due to tumor positivity at the surgical margin was diagnosed with pseudomyxoma peritonei. The patient, who is on oncology follow-up, is in the postoperative 19th month. Surgical complications and mortality were not observed in any of our patients during our follow-up.

DISCUSSION

Appendix tumors are rare and usually asymptomatic. They are detected incidentally, either during

Figure 3. The patient with an appendix diameter of 36 mm had a conversion from laparoscopy to open. The black arrow shows the edematous appendix tissue

surgery or after a pathological examination of a resected appendix sample. The most common type of appendix cancer is neuroendocrine tumors that make up about 60% of all appendix tumors. The incidence of appendix NET in patients undergoing appendectomy is 0.30% -2.27% (4). Barut et al. in their study, 12 (0.43%) NET cases were found in 2778 patients (2). In our series, there was a 0.23% appendix NET rate which was lower than the literature, and all operated patients presented with symptoms of acute appendicitis. None of these patients showed signs of carcinoid syndrome.

Appendix NETs are more common in women than in men (5). Similar to this study, 56.2% of our patients were also women. Most NETs are located at the tip of the appendix. Most of the cases are smaller than 1 cm, the malignant potential is directly related to tumor size, and metastasis is extremely rare in tumors smaller than 1 cm (6). In our patient group, the median tumor diameter was 0.65 cm (range: 0.2-7 cm) and was localized at the tip of the appendix in 83.4%.

Neuroendocrine tumors, appendectomy alone is a sufficient treatment if the tumor size is less than 1 cm. A right hemicolectomy is recommended for tumors > 2 cm. However, the optimal treatment of 1-2 cm tumors is still controversial (5). In our case series, appendectomy was considered an adequate treatment for neuroendocrine tumors. Raoof et al. reported that the probability of nodal metastasis was 2.7% in tumors smaller than 1 cm, 31.0% in tumors with a diameter of 1.1-2.0 cm, and 64% in tumors > 2 cm, and they suspected that the number of lymph nodes was a prognostic factor for well-differentiated neuroendocrine tumors (3). In our

series, 2 of the neuroendocrine tumors were 26 and 60 mm and the others were smaller than 12 mm; Ki-67 index rates were between 1-2% and mitosis numbers between 0-2. We performed a right hemicolectomy in cases with neuroendocrine tumors larger than 2 cm due to the positive surgical margins.

Surgeons generally do not recognize appendix tumors, especially neuroendocrine tumors, and preoperative radiological examination may not be effective in their diagnosis. In our series, malignancy was suspected in only 4 (18%) patients perioperatively. Two of these patients were NETs. Some authors recommend studying frozen if in doubt (7). However, this is generally not possible because appendix tumors usually present as acute appendicitis (8). Therefore if there is no pathological symptom in the radiological diagnosis or during the surgery, appendectomy is sufficient, and the patients do not need additional treatment.

Colorectal cancers may be associated with appendix neuroendocrine tumors. Bucher et al. reported that 14% of appendiceal neoplasms have synchronous colon cancer (9). We performed a colonoscopy on our patients at the 6th week postoperatively, but we did not encounter any synchronous colorectal cancer in any of our patients.

Mucinous neoplasms of the appendix are rare, and an estimated 3500 cases are diagnosed each year in the United States (10). Appendix mucinous lesions (both benign and neoplastic) have a mild female predominance and are usually diagnosed in patients in their 50s and 60s (11). In our series, we encountered 5 cases of appendix low-grade mucinous neoplasia (LAMN). Our patients were compatible with the literature in terms of age and gender.

The risk of appendiceal mucinous neoplasms is higher in patients presenting with complicated appendicitis than in the general population. In a study involving 17 patients who underwent interval appendectomy for complicated appendicitis, five patients were found to have mucinous neoplasms (12). None of our patients had complicated appendicitis. Since mucinous cystic neoplasms are highly associated with colon and ovarian malignancies, the postoperative follow-up of our cases was performed using computed tomography, ultrasonography, and colonoscopy (13). However, no additional malignancy was observed during follow-up.

Although appendectomy is sufficient in cases with limited LAMN in the appendix, a right hemicolectomy can be planned if a positive surgical margin exists. Some authors advocate removing the mesoappendix with a sample so regional lymph nodes can be analyzed (14). Similarly, if a right hemicolectomy is performed for a negative resection margin, it should

follow oncological principles with high ligation of the ileocolic pedicle of origin. However, more extensive lymphadenectomy or routine right hemicolectomy, performed only to increase lymph node yield, is not required for LAMNs or high-grade appendix mucinous neoplasms (HAMNs) of the appendix (15).

Since rupture of the appendix mucinous lesion may cause peritoneal spreading of neoplastic cells, one must carefully resect the lesion during surgery (16). The appendix should be taken out of the abdomen with the help of a bag. If the lesion is ruptured but the rupture is surrounded by a wall, a right hemicolectomy may be considered if the surgeon thinks that it can provide a macroscopically clean surgical border. However, more extensive surgery aimed at clearing the widespread peritoneal mucinous spread (cytoreductive surgery) should only be performed by surgeons with extensive experience in peritoneal malignancies after the final pathology has returned. Therefore, in non-specialized centers, initial surgery (localized) for a ruptured appendix mucinous lesion should be limited to appendectomy/right hemicolectomy, careful examination of the abdominal cavity, and biopsy of any suspected peritoneal lesions.

Recognition of perioperative tumor cases is a warning for the surgeon in terms of obtaining a clean surgical margin. Withfield et al. surgeons suggested that elderly patients with symptomatic acute appendicitis for a long time should be careful if there is a mass-like image (8). In our study, approximately one-fifth of the tumor group was over the age of 50, and their symptomatology was limited to a few days. We think that imaging and surgical findings are as important as pathology results when deciding on appendiceal tumors.

CONCLUSION

Although appendiceal neoplasms are uncommon, they often present as acute appendicitis. Preoperative diagnosis is difficult in patients with appendiceal neoplasia. Therefore when a mass formation is seen during exploration, a methodical perioperative examination should be performed with the suspicion of metastatic disease. Appendectomy will be sufficient in most cases. Incorrect and hasty diagnoses can result in inappropriate surgical treatment.

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Ethical approval: The approval for the study was obtained from the Non-Interventional Clinical Research Ethics Committee of Van Research and Training Hospital (2020/20 – 08.10.2020).

Sažetak

MALIGNI TUMORI SLEPOG CREVA: EVALUACIJA 6748 SLUČAJEVA

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Cilj: Karcinom slepog creva se obično dijagnostikuje slučajno, nakon apendektomije kod lečenja akutne upale slepog creva. Ova studija imala je za cilj da predstavi slučajne maligne slučajeve koje smo otkrili retrospektivno ispitivanjem naših rezultata apendektomije.

Materijali i metode: Retrospektivno je analizirano 6748 slučajeva apendektomije izvedenih u bolnici Van Research and Training, Odeljenje za hirurgiju, Turska, u periodu od januara 2016. do januara 2020. godine. Nakon histopatološke analize, za 22 pacijenta je utvrđeno da imaju mucinozni karcinom niskog stepena (LAMN) i neuroendokrine tumore (NET). Kompletni podaci pacijenata su zabeleženi, uključujući i demografske, laboratorijske, imidžing, i histopatološke podatke.

Rezultati: Prosečna starost 22 pacijenta uključena u studiju bila je 39 godina (18-72 godine), a 14 (63,6%) su bile žene. Sumnjalo se na zloćudnost kod samo 4 (18%) pacijenta tokom eksplorativne laparo-

tomije. Histološki, tumor je lociran distalno kod 19 (83,4%) pacijenata i bio je lociran pri bazi slepog creva kod 3 pacijenta. Histopatološkom analizom je dokazan gradus 1 NET kod 15 pacijenata, LAMN kod 5 pacijenata, gradus 2 NET kod 1 pacijenta i mešoviti tip (mucinozni + neuroendokrini tumor) kod 1 pacijenta. Srednje vreme praćenja bilo je 45,5 meseci (raspon: 26-53). Tokom praćenja, jednom od naših pacijenata koji je podvrgnut desnoj hemikolektomiji zbog tumora na hirurškoj ivici dijagnostikovao je pseudomiksom peritoneuma.

Zaključak: Karcinom slepog creva se najčešće dijagnostikuje u toku postoperativnih patoloških pregleda preparata. Kod pacijenata kod kojih se sumnja na malignost tokom perioperativnog ispitivanja, od ključne je važnosti pažljivo pregledati intraabdominalne organe i izbeći pozitivnu hiruršku marginu. Rizik od maligniteta uvek treba imati na umu pri nerutinim pregledima slepog creva.

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