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Original Article

Clinical behavior, demographical characteristics, management and pathologic awareness of appendiceal mucinous tumor with review of the literature

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Abstract: Diagnosis other than appendicitis after appendectomies are benign-malign tumors of appendix which the incidence is 0.5-1.1%. The 8% of the appendiceal tumors are presented with mucocele where maligns are 0.5-0.8%. At this study, we analyzed the clinical behavior, demographical characteristics and debated for the pathologic awareness of appendiceal mucinous tumors with treatment modalities. Our study is applied at Department of General Surgery at Gulhane Military Medical Academy (Gulhane Training and Research Hospital). Patients with number of 2250 who had appendectomy between December-2007/November-2015 were evaluated. 23 (1.02%) patients with appendiceal mucinous neoplasm were included into the study. Mean age of the patients were 47.09±18.06 (20-80) years. Gender of the patients were; 14 (60.86%) male, 9 (39.13%) female. Surgeries applied for the patients were; 21 (91.30%) appendectomy, 1 (4.34%) appendectomy with partial caecal resection, 1 (4.34%) explorative laparotomy, appendectomy, segmental ileal resection, end-to-end anastomosis, bridectomy, transverse loop colostomy and 1 (4.34%) TAH+BSO, omentectomty as 2nd step surgery. Histopathologic results were; 15 (65.21%) low-grade mucinous neoplasm, 6 (26.08%) mucinous cystadenoma, 2 (8.69%) mucinous adenocarcinoma. Our study resulted that 4th decade is most common for appendiceal mucinous neoplasms and this entity is more frequent for males. Beside; mucinous neoplasms of the appendix are more frequent than expected with incidence of 1.02%, even more frequent then appendiceal carcinoids as being debated recent days. Appendiceal mucinous neoplasm patients are hard to differentiate preoperatively from non-appendicitis appendiceal pathologies. For this reason, every surgeon must keep in mind that each appendectomy may result with an aggressive tumor and peritoneal carcinomatosis which the management is discussed at the study.

Keywords: Appendiceal mucinous tumor, mucocele, peritoneal carcinomatosis

Introduction

Acute appendicitis is one of the etiologies of acute abdomen, usually presented with abdominal pain. Moreover the non-specific appendicitis, common diagnosis after appendectomies are diverticulitis of appendix, granulomatous appendicitis, other benign and malign tumors of appendix which the incidence is 0.5 to 1.1% [1] which is more common at female gender. The 8% of the appendiceal tumors are presented with mucocele which is the dilatation of appendix by the pressure of secreted intraluminal mucine and may either be malign or benign [2-4]; where maligns are 0.5-0.8 % [1-5]. Management of malign tumors may be much more complicated and required multidisciplinary approach of oncology, general surgery and radiation oncology. The malign tumors of the appendix are adenocarcinomas, neuroendocrine tumors and stromal tumors. Although neuroendocrine tumors are seen more frequent, it is reported that incidence of adenocarcinoma of appendix is increasing. At this study, we analyzed the clinical behavior, demographical characteristics and debated for the pathologic awareness of appendiceal mucinous tumors with treatment modalities of it.

Materials and methods

Study is applied at Department of General Surgery at Gulhane Military Medical Academy,

Table 1. Age, WBC count and hospitalization durations of the patients

Characteristics of the patients	Mean ± SD	Lowest Value	Greatest value
Age (year)	47.09±18.06	20	80
WBC Count (mm^3)	11680±4291	5600	22000
Hospitalization (day)	8.3±6.9	2	26

Table 2. Radiological imaging techniques applied to patients

Radiological Techniques	Applied		Not Applied	
	No	%	No	%
USG	19	82.60	4	17.4
CT	9	39.13	14	60.9
USG+CT	5	21.73	---	-----

Ankara, Turkey (Gulhane Training and Research Hospital). Patents with number of 2250 who had appendectomy because of acute abdomen between December 2007 and November 2015 were evaluated and data analysis was done retrospectively for the study without age and gender limitation. 23 patients with appendiceal mucinous neoplasm according to histopathological examination were included into the study and patients with non-mucinous histopathological diagnosis of the appendix were excluded. Demographic and laboratory findings were statistically evaluated with SPSS v.22 and are discussed due to published literature.

Results

Out of 2250, 23 (1.02%) patients were included to the study for mucinous appendiceal neoplasms. Mean age of the patients were 47.09 ± 18.06 (min: 20, max: 80) years. Gender of the patients were; 14 (60.86%) male and 9 (39.13%) female. Common symptoms of the patients were; abdominal pain 22 (95.65%), loss of appetite 3 (13.04%), dizziness-vomiting 2 (8.69%) and ileus 1 (4.34%). Mean range values of white blood cell (WBC) count and hospitalization durations of the patients are shown at the **Table 1**.

As radiological examination, 9 (39.13%) of the patients were evaluated with abdominal computerized tomography (CT) and 19 (82.60%) of them were evaluated with abdominal ultrasound (USG) which 5 of the patients were evaluated first with USG being inadequate for evaluation and then with abdominal CT as superior technique. Appendix of the 15 (65.21%) patients were evaluated as ≥7 mm where 7 (30.43%) of the patient's appendix were not be able to be visualized by radiological imaging techniques and be evaluated. Appendix of 1 (4.34%) patient was evaluated as 6 mm (**Table 2**).

After the evaluation of the 23 patients for acute abdomen with pre-diagnosis of appendicitis, patients had surgery whom 2 of them had staged surgeries. The surgical techniques applied to patients are shown at the **Table 3**.

Histopathological results of the patients after surgeries were low-grade mucinous neoplasms, mucinous cystadenoma and mucinous adenocarcinoma, which the quantities are shown at **Table 4**. As histopathological results, we also decided to evaluate the serosal defect at mucinous neoplasm diagnosed patients for evaluation of the prognosis. Results of the serosal defects of the appendixes excised are shown at the **Table 5**.

Discussion

Acute appendicitis is one of the most common surgeries applied by the general surgeons [6] and the treatment of acute appendicitis is based on surgery. As the diagnosis of acute appendicitis delays, because of the increased intraluminal pressure, the blood flow of the appendiceal wall decreases and causes necrosis resulting with perforation [7]. The cruciality of the perforation of acute appendicitis other than morbidity and mortality of the gastrointestinal tract perforation is because of the probable malignancy diagnosis of the appendix. The tumor perforation other than the non-specific appendicitis perforation may result with peritoneal carcinomatosis, which is a highly mortal clinical entity. The appendiceal neoplasms presentation, especially the epithelial non-carcinoid ones, may be mucocele which perforation resulting with peritoneal carcinomatosis is more common than others and was first named by Rokitansky on 1850's [8]. To dominate the subject for the readers who may need to look back for the appendiceal tumors, WHO classification of appendiceal neoplasms are shown at the **Table 6**.

Table 3. Operation Techniques applied to patients

Applied Surgeries	No	%
Appendectomy	21	91.30
Appendectomy with partial caecal resection	1	4.34
Explorative laparotomy, appendectomy and segmental ileal resection, end-to-end anastomosis, bridectomy with transverse loop colostomy	1	4.34
Applied Staged Surgeries	**No**	**%**
Not applied	21	91.30
TAH+BSO* with omentectomy	1	4.34
Total colectomy, peritonectomy, splenectomy with HIPEC**	1	4.34

*TAH+BSO: Total abdominal hysterectomy + bilateral salphingo-oophorectomy. **HIPEC: Hyperthermic intraperitoneal chemotherapy.

Table 4. Histopathologic results of the excised appendixes

Histopathological Results	No	%	% for Total Patients
Low grade mucinous neoplasm	15	65.21	0.66
Mucinous Cystadenoma	6	65.21	0.26
Mucinous Adenocarcinoma	2	8.69	0.08

Table 5. Serosal defect situation of the excised appendixes

Serosal Defect of Appendix	No	%
Yes	7	30.43
No	14	60.86
Not evaluated	2	8.89

Mucocele of the appendix is has a huge meaning for the physicians because there is not a histopathological and clinical consensus for this terminology [9, 10]. It may both be used for clinical presentation of the patient or histopathological result of the appendix specimen. Clinical use of the appendiceal mucocele is more common to describe the macroscopic mucinous full filled appendix The histopathological terminology for mucocele of the appendix has subgroups for malignancy potential which there is not a histopathological and clinical classification consensus about the topic as mentioned above [9, 10]. However, as much wide as we can classify the mucocele according to the literature, the subgroups are presented at the **Table 7** [2, 11, 12].

Mucocele is also used to determine only the retention cyst of the appendiceal mucinous neoplasms by the pathologists. The mucinous adenocarcinoma is an invasive malign neoplasm and the most malignant form of mucocele, however a mucocele may only be clinical presentation of a simple retention cyst, which is the most benign form. This mess at the terminology may be considered as one of the biggest problem for appendiceal mucinous neoplasms of the appendix because a report or operation note reported at a center may not correctly direct the physician at another center.

The perforation of mucinous neoplasms of the appendix may result with the spread of the mucine to peritoneal cavity with malign mucine producing cells (if present) causing pseudomyxoma peritonei which was first described by Werth 1884 [13, 14]. Pseudomyxoma peritonei is a radiological term of peritoneal carcinomatosis and may cause one or multiple abdominal organ dysfunction. Re-distribution phenomenon of the mucine producing malign epithelial cells explains the spreading of the tumor in the abdominal cavity which states that the spreading starts locally and progresses with right subdiaphragmatic area, right subhepatic area, left abdominal area, greater omentum, spleen and pelvic cavity as a result of gravity and the drainage pathway of peritoneal fluid [15]. The prognosis of pseudomyxoma peritonei is highly mortal [16] where the source of the mucine or mucine secreting cells is also important for the degree of the mortality. Appendiceal mucocele originated pseudomyxoma peritonei has better survival than others as ovary based ones.

Pre-diagnosis of the mucinous neoplasms of the appendix is difficult because the clinical presentation of the patient is usually with acute abdomen mimicking acute appendicitis and radiological techniques may not be adequate or

Table 6. WHO Classification of Appendix Neoplasms

A. Epithelial tumors
a. Adenoma
1. Tubular
2. Villous
3. Tubulovillous
4. Serrated
b. Carcinoma
1. Adenocarcinoma
2. Mucinous adenocarcinoma
3. Singlet cell carcinoma
4. Small cell carcinoma
5. Undifferential carcinoma
c. Carcinoid
1. EC-cell, serotonin producing tumor
2. L-cell, glucagon-like peptide
3. PP/PYY producing tumor
d. Tubular carcinoid
e. Goblet cell carcinoid (Mucinous carcinoid)
f. Mixed Carcinoid-adenocarcinoma
B. Non-Epithelial tumors
1. Neuroma
2. Lipoma
3. Leiomyoma
4. Gastrointestinal stromal tumor
5. Leiomyosarcoma
6. Kaposi sarcoma
7. Malign lymphoma
8. Metastatic tumor
9. Hyperplastic (metaplastic) polyp

Table 7. Mucocele subgroups

Appendiceal Mucocele
Retention cyst (mucocele)
Mucous hyperplasia
Mucinous cystadenoma
Mucinous neoplasm of unknown malignancy potential
Low grade mucinous neoplasm
Mucinous adenocarcinoma

radiologist may not be experienced enough. For this reason, surgeons must always be in aware about mucinous neoplasms of appendix when the macroscopic view of the appendix is sharply different than normal appendix or appendicitis macroscopic view. Usually more necrotic appendix with a mass like cystic and soft tissue

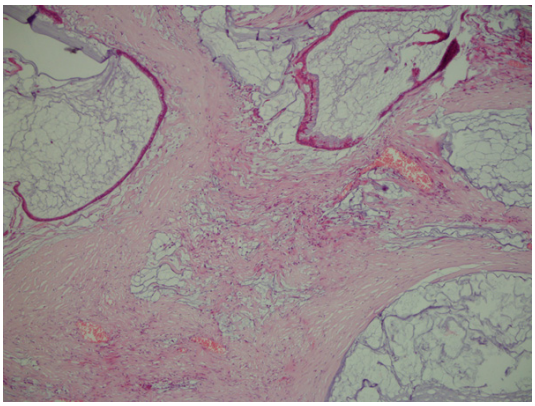

Figure 1. Low-grade mucinous adenocarcinoma of the peritoneum (pseudomyxoma peritonei) is seen in the picture. Mostly acelluler wide mucine lakes and some strands of typical epithelium are located at the surface of them (HE×100).

characteristics, generally bigger in size is more likely to be diagnosed as mucinous neoplasms of appendix (**Figures 1**-**3**). Biggest mucocele reported at the literature is 40.2 cm [17]. In addition, it is vital to differentiate if the epithelial integrity of the appendix has been broken by mucine which is probably be diagnosed after a histopathologic exam for the prediction of the pseudomyxoma peritonei.

As the radiological techniques for the diagnosis of appendiceal mucinous neoplasms are not specific, some of the mucinous neoplasms may be presented with giant cystic formation. These cases are critic for mall-practice at diagnostic biopsy. Fine needle biopsies applied to appendiceal mucinous neoplasms may result with the spread of the mucine to peritoneal cavity, which is also called pseudomyxoma peritonei. For this reason, physicians must also be careful for the cystic abdominal lesions arising from right lower quadrant [9].

The most common pre-diagnosis of appendiceal mucinous neoplasm patients are acute appendicitis as mentioned above and the common surgical approach is appendectomy as a result. However, the surgical strategy may change with the intraoperative or postoperative histopathologic diagnosis of the mucinous neoplasm. Most important key aspect for the surgery of appendiceal mucinous neoplasm is excising the appendix without perforation and leakage of the intraluminal mucine. Otherwise, pseudomyxoma peritonei may be the probable

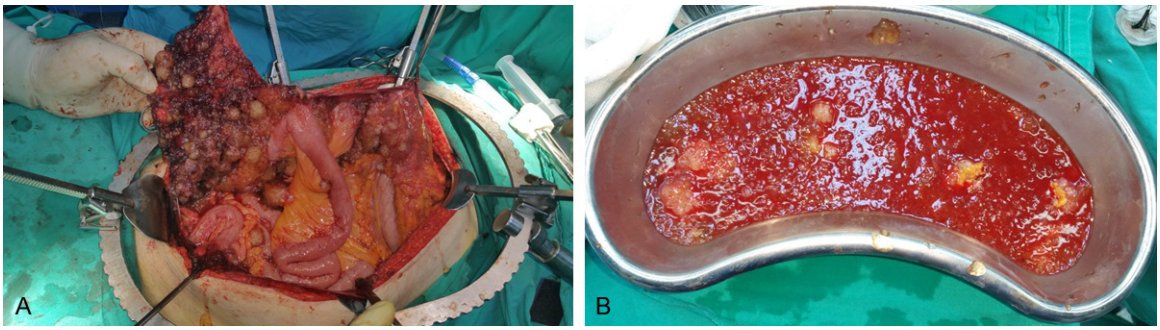

Figure 2. A: Intraoperative view of a pseudomyxoma peritonei of appendix. Wide mucine lakes can be seen all around the abdomen especially at the peritoneum. B: The removed mucine from the abdomen.

Figure 3. The mucine lakes in the abdomen push the intraperitoneal organs so that very few small intestine-colon can be seen at the CT as a result of giant mucine deposits in the abdomen of a pseudomyxoma peritonei patient.

outcome within time [9]. A currently rising debate comes out at this point which is weather laparoscopic resection is suitable or not for the appendiceal mucinous neoplasms. Even it is not contraindicated, laparoscopic approach may result with more risk for perforation but because it is being more commonly applied for routine appendectomy than past, some insists for the laparoscopic resection because of its diagnostic advantage by viewing the abdominal cavity. However still there is no consensus for the subject [18, 19]. At our study, none of the mucinous neoplasms of the appendix were resected with laparoscopic technique.

The surgical approach for the appendiceal neoplasm differs by the histopathological diagnosis, size, localization of the tumor and whether the mucine of the tumor is limited to the wall of appendix or not. If the tumor is found to have invaded the wall of the appendix, staged laparotomies may be needed as right hemicolectomy with complete mesocolic excision (CME) [20]. However if the mucine or the tumor cells are found to have invaded the serosal surface of the appendix, then the risk for pseudomyxoma peritonei increases significantly and right hemicolectomy with CME/cytoreductive surgery (CRS) with HIPEC must be evaluated for the patient. CRS + HIPEC with adjuvant chemotherapy is believed to be the only chance for the patients with macroscopic discharge of the mucine to the peritoneum where most of the guidelines still don't have any suggestions for this approach [21]. Even though, we as our clinical practice manage these patients with this consensus for the treatment. Evaluating the risk of the appendiceal mucinous neoplasm with serosal defect, presence of mucine secreting cells and histopathological grade, staged surgeries with from complementary colonic resection to peritonectomy with CRS + HIPEC and adjuvant chemotherapy are applied to appendiceal malign mucinous neoplasm patients as multidisciplinary treatment approach of general surgery, medical oncology and pathology at our clinic.

One of the most exciting debates for the mucinous neoplasms of the appendix is about the term prophylactic HIPEC that is also debated for gastric adenocarcinomas [22, 23]. Prophylactic HIPEC is suggested specially for perforated malign mucinous tumors and no CRS is suggested as long as the surgical margins are clean and no macroscopic residue tumor is seen [24]. If any residue intraperitoneal tumor can be seen during the staged laparotomies for prophylactic HIPEC, then the case turns out to be curative HIPEC which CRS must be added, which is the major difference from prophylactic HIPEC.

Beside the clinical management and treatment approaches of mucinous tumors of appendix, the demographic characteristics of the patients also carry importance for the survey and potential risk of mucinous appendiceal tumors for the patients suffering from acute abdomen. However, for the demographics of the mucinous tumors of the appendix, there is not much data probably because of the lower incidence and short survey expectation after pseudomyxoma peritonei develops which discourages the surgeon. As examples of demographic studies and the incidence of appendiceal mucinous neoplasms, Ma et al. from China, searched for the histopathological outcomes of the 1492 appendectomies and found out only three adenocarcinomas (0.20%) without pseudomyxoma peritonei, two mucinous cystadenomas (0.13%), one tubulary adenoma (0.06%), one mucinous cystadenocarcinoma (0.06%) and one pseudomyxoma peritonei (0.06%) with total of 8 (0.53%) cases [25]. No treatment modalities and no demographic characteristics as age, gender of the mucinous neoplasms of the appendix patients were discussed separately from the nonspecific appendicitis patients. Beyrouti et al. also discussed the subject with 22 (0.26%) cases from 8373 appendectomies [26]. 22 (0.26%) patients with twelve mucocele (0.14%), 8 mucosal hyperplasia (0.09%) and 2 cystadenoma (0.02%) were evaluated and found 5 (0.05%) pseudomyxoma peritonei cases developed postoperatively, even though none of the patients had the diagnosis of mucinous neoplasm of unknown malignancy potential, low grade mucinous neoplasm or mucinous adenocarcinoma.

According to published studies, the expected mucinous neoplasms of appendix is around 0.2% [27] which at our study it correspond to 1.02% as higher than the expected. Mean expected decades for appendiceal neoplasm except carcinoid of appendix are 5th and 6th decades, however we found the mucinous neoplasms of appendix at our study onsets at mean age of 47, which is 4th decade [2, 27]. Some studies insist on the risk of females are 4 times more than males [2] and some insists of the equal risks for male and female. At our study, we found that the ratio is 2/3 for female/male, which states males are at higher risk. The different results for the risk analysis of gender and age for mucinous neoplasms of appendix may be a result of low incidence of the disease and we believe no statistically significant suggestion or prediction can be made according the results of the risk analysis for gender and age. The reason for us to have higher incidence for male gander and have lower onset age may be a result of our center being a military hospital and us having more younger patients than elder ones and having more male patients than females.

As the final for the discussion, one more subject to point out is the incidence of the mucinous neoplasms and carcinoids of the appendix. Till to present, due to literature, incidence of the carcinoid of appendix is known to be more frequent than the mucinous neoplasms of the appendix [28]. However, recently it is found out that that the mucinous neoplasms are more common than carcinoids [29]. The difference between the incidences of the both entities is unknown whether if it is caused by past misdiagnoses or the increased etiology of the mucinous neoplasms of the appendix causing it to be more common than carcinoids of the appendix. Beside the debate still continuing, our study shows that the incidence of mucinous neoplasms of the appendix is more common the carcinoid tumors of the appendix which we found out 5 (0.22%) cases out of 2250 patients.

Conclusion

As a conclusion of our study, it is hard to discuss the demographic characteristics of the appendiceal mucinous neoplasms because of its low incidence. However according to our study, even the number of patients may not be enough for high powered study results, we found out that 4th decade is most common for appendiceal mucinous neoplasms and this entity is more frequent for males different than other studies. Beside, mucinous neoplasms of the appendix are more frequent than expected with incidence of 1.02%, even more frequent then appendiceal carcinoids. These patients with appendiceal mucinous neoplasms apply to clinics with acute abdomen symptoms and it is hard to evaluate them preoperatively as non-appendicitis appendiceal pathologies. For this reason, every surgeon must keep in mind that each appendectomy may result with an aggressive tumor and peritoneal carcinomatosis. To sum up, all appendectomy patients and their

surgeons must fallow up the histopathological results of the appendectomy specimens and pathologist must alert the surgeon if the appendectomy specimen comes out to be mucinous neoplasms of appendix. This subject is matter of life and medico-legal issues.

Disclosure of conflict of interest

None.

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