

Clinical Pathological Analysis of Appendiceal Neoplasms From 4800 Appendectomy Specimens

Massood Hosseinzadeh¹; Mohammad Hossein Anbardar²; Mohammad Mohammadian-panah¹; Behrooz Ilkhanizadeh^{3,*}

¹Colorectal Research Center, Shiraz University of Medical Sciences, Shiraz, IR Iran

²Department of Pathology, Shiraz University of Medical Sciences, Shiraz, IR Iran

³Department of Pathology, Urmia University of Medical Sciences, Urmia, IR Iran

*Corresponding author: Behrooz Ilkhanizadeh, Associate Professor of Pathology, Urmia University of Medical Sciences, Urmia, IR Iran. Tel: +98-9143419194, Fax: +98-7112330724, E-mail: ilkhanib@gmail.com

Received: October 28, 2014; Accepted: October 30, 2014

Background: Appendiceal Neoplasms are relatively uncommon. Although Carcinoid tumor is the most prevalent tumor of appendix, mucinous tumors and metastatic tumors can also be identified in appendectomy specimens after careful pathologic examination.

Objectives: The main goal of this study is the evaluation of appendectomy specimens for appendiceal neoplasms and subsequent subtyping of those tumors.

Materials and Methods: Retrospective assessment of 4800 appendectomy specimens, performed from 2010 to 2014, was done. The specimens were collected from Namazee and Faghihi hospitals, affiliated to Shiraz University of Medical Sciences. The clinical and histopathologic data were collected and analyzed by satisfactory statistical methods.

Results: The age of patients was 32 years with a male to female ratio of 3:1. The overall incidence of appendiceal neoplasms was 86 in 4800 specimens (1.8%). The most common neoplasm was carcinoid tumor. Others reported tumors were mucinous cyst adenoma, mucocele, mucinous adenocarcinoma, leukemic infiltration, and a case of appendiceal involvement by bladder transitional cell carcinoma.

Conclusions: Although appendiceal tumors are not as prevalent as colon cancer, careful examination of appendectomy specimens can identify neoplastic processes. Beyond carcinoid tumors and mucinous neoplasms, leukemia lymphoma and other metastatic tumors can involve the appendix.

Keywords:Appendix; Appendiceal Neoplasm; Classification

1. Background

The appendix is the most frequent site for developing carcinoid tumors, i.e., tumors with endocrine differentiation that span a wide range of morphologic variety (1). Adenocarcinomas of the appendix also show interesting morphologic variations from those resembling the usual colorectal carcinoma to those arising from a carcinoid or mucinous tumors, which might appear well differentiated and indistinguishable from adenoma and spread widely through the peritoneal cavity (1, 2). The term mucocele is unspecific and its better no to use this term because it tells nothing about the original cause of mucin accumulation while its causes range from a hyperplasia to malignant neoplastic processes. Therefore, mucocele is not an entity and few authors use it at present (3). The majority of mucinous tumors of appendix are benign, i.e., mucinous cystadenomas. These types of tumors are lined by tall columnar mucin containing epithelial cells with atypical changes. Some of these tumors might arise from previous hyperplastic polyps (4). The malignant counterpart, namely, mucinous cystadenocarcinoma, might have similar or even the same microscopic features. There are

two criteria for malignancy: 1) invasion of the wall of appendix by atypical glands and 2) identification of neoplastic epithelial cells in the peritoneal cavity (5). Two recent nomenclature proposals for mucinous neoplasms of appendix might simplify the classification of these tumors. One classification, suggested by Misdraji et al. is as follows: 1) Low grade mucinous neoplasms when the cells are well-differentiated and noninvasive and 2) mucinous adenocarcinoma, when cells are highly atypical and/or invasive (5). Another classification by Pai et al. suggests the following: 1) mucinous adenoma when tumor is confined to appendix; 2) low grade mucinous neoplasm with low risk of recurrence when a cellular peritoneal deposits are present; 3) low grade mucinous neoplasm with high risk of recurrence have low grade cytological atypia but are accompanied by extra-appendiceal neoplastic epithelium; and 4) mucinous adenocarcinoma when invasion or high grade cytology present. Other common neoplasms of appendix are neuroendocrine tumors, which are sub classified into classic carcinoid tumors and goblet cell carcinoids. They are found in about one of every 300 rou-

tine appendectomies correct. About 70% of these tumors are located at the tip of appendix. Other neoplasms of appendix include GIST, lymphomatous involvement, Kaposi sarcoma, and metastatic tumors (6, 7).

2. Objectives

The study is designed to survey 4800 appendectomy specimens from Namazee and Faghihi hospitals affiliated to Shiraz University of Medical Sciences. Appendiceal tumor prevalence will be identified and then subtyping of these neoplasms will be done.

3. Materials and Methods

A retrospective histopathologic review of appendectomy specimens, which were performed from 2010 to 2014 in Namazee and Faghihi hospitals affiliated to Shiraz University of Medical Sciences, Shiraz, Iran, was conducted. Clinical as well as histopathologic data including macroscopic findings and microscopic examination from hematoxylin and eosin (H and E) staining were collected. The sections were prepared according to a standard procedure and included one longitudinal section from the tip and two circular sections from the center and proximal part of appendix. In the cases with additional gross histopathological abnormalities, especially when a tumoral mass was presented, at least three sections from

mass were added to previous sections and surgical resected margins were embedded. The slide were stained with H and E method and reviewed by one expert pathologist. Any histopathologic findings include inflammatory or neoplastic changes were recorded. In the patients with appendiceal neoplasms, important data including the type of tumor, depth of invasion, lymph vascular invasion, presence of necrosis, degree of cytological atypia, and histopathologic changes of nontumoral parts of appendix were collected. Patients with confirmed appendiceal neoplasms were included. All primary or secondary as well as benign or malignant neoplasms were included. Histopathological reports of neoplasm without available HandE staining were excluded.

Patients were distributed into following subgroups: 1) carcinoid tumor; 2) benign mucinous tumor; 3) mucinous adenocarcinoma; 4) leukemic or lymphomatous involvement; and 5) metastatic tumor.

3.1. Statistical Analysis

All data were collected and analyzed by SPSS version 17 (SPSS Inc., Chicago, IL, USA). The differences between the subgroups was evaluated by one-way ANOVA with subsequent multiple comparison by Pearson's test. Differences between the groups were considered significant if P value was < 0.05 in a two-sided test.

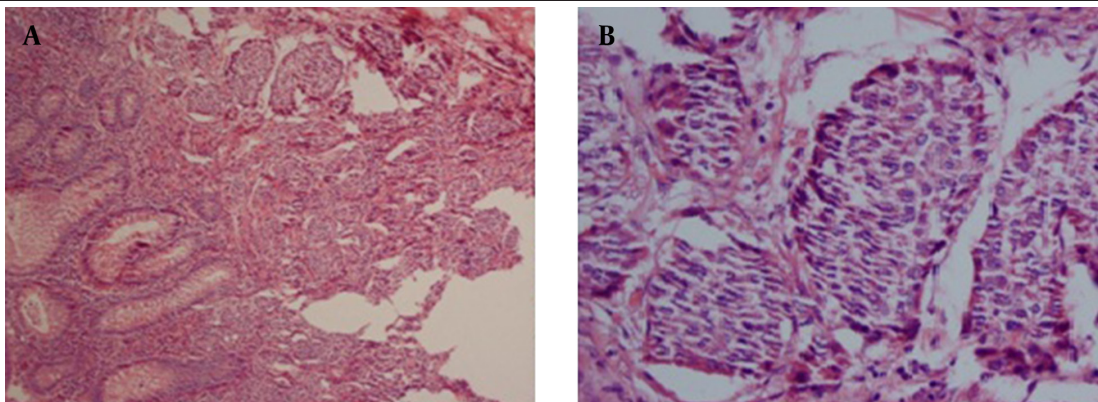


Figure 1. Nests of Endocrine Cells With Uniform Benign Looking Nuclei, HandE staining, magnification × 400

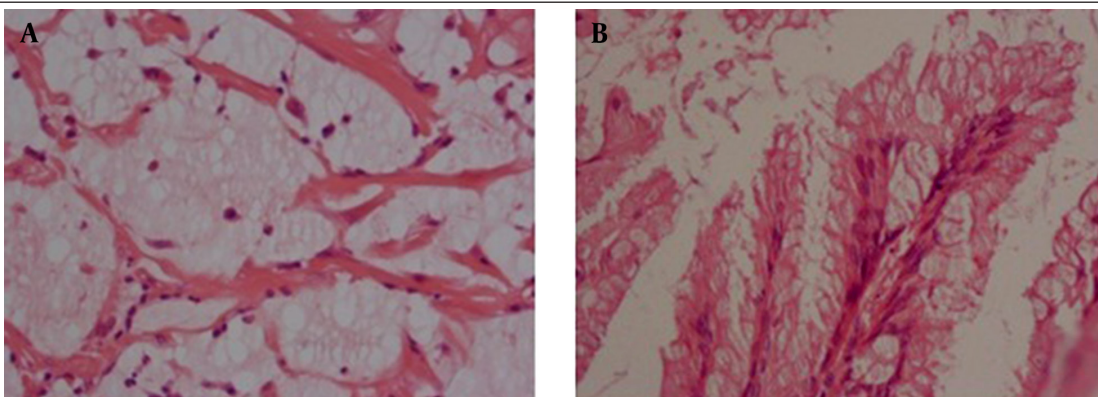


Figure 2. Benign Mucinous Tumors Showing Acellular Mucin Lakes or Presented as Mucinous Cyst adenomas (a, b)

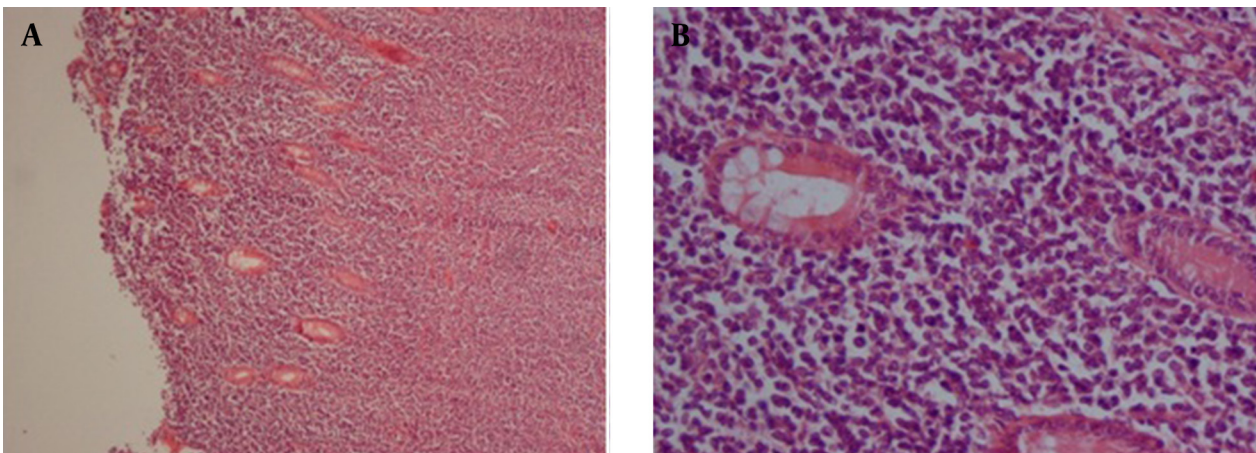


Figure 3. Burkett's Lymphoma was the Most Common Type of Lymphomatous Involvement of Appendix (a, b)



Figure 4. The Appendiceal Adenocarcinoma Presented as Invasion of Neoplastic Glands through the Wall of Appendix into the Muscularis Propria

4. Results

All consecutive appendectomy specimens between January 2010 and July 2014 were studied. The total appendectomies were 4800 of which 86 patients had appendiceal tumor (1.8%). The mean age at presentation was 32 + 8.64 years with a male to female ratio of 3:1. The most common appendiceal tumor was classic carcinoid, detected in 37 specimens (43%), following by benign mucinous tumors in 30 (34.8%) and adenocarcinoma in 12 specimens (14%). There were six cases of leukemia lymphoma (7%) and one metastasis from bladder transitional cell carcinoma (1.2%). The most common clinical presentation was acute abdomen followed by nonspecific abdominal pain and incidental finding during radiologic investigation for other reasons. The primary and metastatic malignant tumors presented at older age than benign tumor did ($P > 0.05$). Most of patients with appendiceal adenocarcinoma were male. Acute surgical abdomen was more frequently seen with benign tumors than with malig-

nant ones. The latter presented with nonspecific clinical presentation or showed tumor-related symptoms such as weight loss or anemia. The histopathologic findings in various types of appendix tumors were studied and recorded. The most common neoplasms of appendix in this study were classic carcinoid tumors, which showed neoplastic endocrine cells with nesting or trabecular pattern. They were composed of uniform cells with fine chromatin without necrosis or mitosis (Figure 1). Benign mucinous tumors showed both mucinous cyst adenoma and in some cases only acellular mucin lakes (Figure 2). Burkitt's lymphoma was been the most common type of lymphomatous involvement of appendix (Figure 3). The Figure 4 shows a case of adenocarcinoma of appendix.

5. Discussion

Tumors of appendix are uncommon and most often diagnosed unexpectedly in emergency conditions. The most common tumor is classic carcinoid tumor. They are found in one of every 300 appendectomies (8-10). Moertel et al. studied 144 cases of classic carcinoid tumors and showed that 70% were located at the tip of appendix, 23% in the body, and 7% at the base. The size of tumor were less than 1cm in 70% of the cases (11). The appendiceal carcinoid is most often benign and in contrast to gastric endocrine tumors, metastasis is rare. The tumor size is proportional to the risk for metastatic disease (12, 13). The calculated risk of metastasis from tumors < 1 cm is zero, while a definite increase occurs with a tumor size is > 2 cm, with a metastasis rate of 20% (14, 15). Most of the mucinous tumors of appendix are benign. The classification of these tumors has been revised recently by two proposals suggested by Misdraji et al. and Pai et al. (16, 17). The term mucocele stands for a wastebasket and should not be used anymore because there are wide varieties of benign and malignant lesions that can produce mucocele. Primary adenocarcinoma of appendix is a rare entity. It can be located in any part of the appendix. The microscopic appearance often resembles colon adenocarci-

noma and refers to as colonic type. Some of adenocarcinomas are mixed with carcinoid tumor (carcinoma with neuroendocrine differentiation) (18). Malignant lymphoma leukemia, especially Burkett's lymphoma, usually involves the appendix. In the present study, we studied all appendectomy specimens from two large centers for appendiceal tumors. The interesting finding was the high incidence of lymphomatous involvement of appendix. Overall, these neoplasms composed 5% of appendiceal tumors. The Burkett's lymphoma, which is a high-grade B-cell tumor, was the most common appendiceal lymphomatous involvement. They usually presented with nonspecific symptoms or might present at emergency department with acute abdomen. Most of the cases were children under age of 15 years and the tumors were accompanied by mesentric and para-aortic lymphadenopathy. Most of the carcinoid tumors had small size of <2cm in diameter and none of them showed metastasis. Carcinoid syndrome was not seen in the present study and the detected tumors were non-secretory. Adenocarcinomas were colonic type and treated with right hemicolectomy. The mucocele and benign mucinous tumors were classified according to Pai et al. (17) proposal. They were benign tumors treated with appendectomy. The most important limitation of this study was lack of long-term follow-up of the patient to determine their survival. Table 1 shows the characteristics and clinical findings of various subtypes of appendiceal neoplasms. The most common appendix neoplasm was been carcinoid followed by benign mucinous tumors. The interesting finding was appendiceal lymphomatous involvement which most commonly seen among children

Table 1. Characteristics and Clinical Presentation of Histopathologic Subgroups ^a

	Carci- noids	BMT	AC	LL	MET
No. (%)	37 (43)	30 (34.8)	12 (14)	6 (7)	1 (1.2)
Age, y	25	35	51	12	60
Gender					
Male toFemale Ratio	2:1	2:1	2:1	1:1	-
Clinical Presentation, %					
Acute Abdomen	62	50	32	20	-
Nonspecific	22	15	10	45	-
Incidentaloma	10	25	35	12	-
Tumor-Related	6	10	23	23	100

^a Abbreviations: BMT, benign mucinous tumor; AC, adenocarcinoma; LL, lymphoma leukemia; and MET, metastasis

Authors' Contributions

Massood Hosseinzadeh: data collecting, writing and final editing; Mohammad Hossein Anbardar: Data collecting; Mahammad. Mohammadianpanah: primary idea and consulting; and Behrooz Ilkhani: corresponding author.

Funding/Support

The study was financially supported by Shiraz University of Medical Sciences.

References

- Machado NO, Chopra P, Pande G. Appendiceal tumour-retrospective clinicopathological analysis. *Trop Gastroenterol.* 2004;**25**(1):36-9.
- McCusker ME, Cote TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. *Cancer.* 2002;**94**(12):3307-12.
- Iwuagwu OC, Jameel JK, Drew PJ, Hartley JE, Monson JR. Primary carcinoma of the appendix - Hull series. *Dig Surg.* 2005;**22**(3):163-7.
- O'Donnell ME, Badger SA, Beattie GC, Carson J, Garstin WI. Malignant neoplasms of the appendix. *Int J Colorectal Dis.* 2007;**22**(10):1239-48.
- Misdraji J, Yantiss RK, Graeme-Cook FM, Balis UJ, Young RH. Appendiceal mucinous neoplasms: a clinicopathologic analysis of 107 cases. *Am J Surg Pathol.* 2003;**27**(8):1089-103.
- Miettinen M, Sobin LH. Gastrointestinal stromal tumors in the appendix: a clinicopathologic and immunohistochemical study of four cases. *Am J Surg Pathol.* 2001;**25**(11):1433-7.
- Misdraji J, Graeme-Cook FM. Miscellaneous conditions of the appendix. *Semin Diagn Pathol.* 2004;**21**(2):151-63.
- Tchana-Sato V, Detry O, Polus M, Thiry A, Detroz B, Mawaja S, et al. Carcinoid tumor of the appendix: a consecutive series from 1237 appendectomies. *World J Gastroenterol.* 2006;**12**(41):6699-701.
- Goede AC, Caplin ME, Winslet MC. Carcinoid tumour of the appendix. *Br J Surg.* 2003;**90**(11):1317-22.
- Connor SJ, Hanna GB, Frizelle FA. Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. *Dis Colon Rectum.* 1998;**41**(1):75-80.
- Moertel CG, Weiland LH, Nagorney DM, Dockerty MB. Carcinoid tumor of the appendix: treatment and prognosis. *N Engl J Med.* 1987;**317**(27):1699-701.
- McGory ML, Maggard MA, Kang H, O'Connell JB, Ko CY. Malignancies of the appendix: beyond case series reports. *Dis Colon Rectum.* 2005;**48**(12):2264-71.
- Whitfield CG, Amin SN, Garner JP. Surgical management of primary appendiceal malignancy. *Colorectal Dis.* 2012;**14**(12):1507-11.
- Bucher P, Mathe Z, Demirag A, Morel P. Appendix tumors in the era of laparoscopic appendectomy. *Surg Endosc.* 2004;**18**(7):1063-6.
- Benedix F, Reimer A, Gastinger I, Mroczkowski P, Lippert H, Kube R, et al. Primary appendiceal carcinoma-epidemiology, surgery and survival: results of a German multi-center study. *Eur J Surg Oncol.* 2010;**36**(8):763-71.
- Misdraji J, Young RH. Primary epithelial neoplasms and other epithelial lesions of the appendix (excluding carcinoid tumors). *Semin Diagn Pathol.* 2004;**21**(2):120-33.
- Pai RK, Beck AH, Norton JA, Longacre TA. Appendiceal mucinous neoplasms: clinicopathologic study of 116 cases with analysis of factors predicting recurrence. *Am J Surg Pathol.* 2009;**33**(10):1425-39.
- Carr NJ, McCarthy WF, Sobin LH. Epithelial noncarcinoid tumors and tumor-like lesions of the appendix. A clinicopathologic study of 184 patients with a multivariate analysis of prognostic factors. *Cancer.* 1995;**75**(3):757-68.