World Cancer Research Journal

WCRJ 2023; 10: e2664
DOI: 10.32113/wcrj_20239_2664

CHALLENGES IN DIAGNOSING MUCINOUS NEOPLASMS OF APPENDIX: A RETROSPECTIVE OBSERVATIONAL STUDY

P. NICHAT[1], V. RANA[1], M.K.S. PARIHAR[1], A. MISHRA[2], K.R. RAO[3]

• • •

[1]Department of Laboratory Sciences and Molecular Diagnostics, Command Hospital (Northern Command), Army Medical Corps (Indian Army), Udhampur, Jammu, Kashmir, India
[2]Department of Radiodiagnosis, Command Hospital (Northern Command), Army Medical Corps (Indian Army), Udhampur, Jammu, Kashmir, India
[3]Department of Surgery, Command Hospital (Northern Command), Army Medical Corps (Indian Army), Udhampur, Jammu, Kashmir, India

Corresponding Author
Prachi Bhaurao Nichat, MBBS, MD; e-mail: prachibnichat@gmail.com

ABSTRACT – *Objective:* Mucinous neoplasms of vermiform appendix are rare tumors that often result in mucocoele formation. The definite diagnosis is provided on histopathology examination and further management relies on appropriate classification. In this study, we explore the histopathological spectrum of appendicular mucinous neoplasms through a series of cases encountered in practice.

Patients and Methods: This is a retrospective observational study of all emergency/ interval appendectomies from Jan 2022 to Jan 2023. Cases with extracellular mucinous lesions were included and their clinical, radiological, gross, and microscopic findings were analyzed.

Results: There were 4 cases (11.4%) out of total 35 appendectomies. These included two cases of benign retention cysts, one case of Low grade appendicular mucinous neoplasm and one case of mucinous adenocarcinoma.

Conclusions: Appendicular mucinous neoplasms can evade detection by virtue of being rare tumors with bland cytomorphology. In all cases of appendicular mucocoele, an effort must be made to confirm or rule out mucinous neoplasms/ carcinoma. Radiological findings in conjunction with characteristic histological features like subepithelial fibrosis, dissecting mucin pools or tongues of dysplastic epithelium etc. assist in diagnosis. Classification of mucinous tumors of appendix is crucial in the management and must be applied carefully.

KEYWORDS: Mucinous neoplasms, Mucocoele, Vermiform appendix.

INTRODUCTION

Mucin over-secretion in the appendicular cul de sac results in mucocoele, an outdated term for mucin retention and cystic dilatation of the appendicular lumen. Mucocoeles develop as a result of obstruction[1-3] due to faecoliths, parasites, endometriotic foci, external compression by lymphadenopathy, infective and neoplastic caecal lesions, or appendicular neoplasms.

Appendectomies are the commonest specimens received for histopathological examination and should be carefully assessed for common appendicular tumors, notably neuroendocrine tumors (65%) and adenocarcinomas (20%) among others [4]. On the other hand, Appendicular Mucinous Neoplasms

(AMN) are rare neoplasms endowed with a characteristic morphology and an amusing biology due to which these may evade detection. AMNs can progress to pseudomyxoma peritonei, a much-dreaded complication. Of particular interest is the tumor previously termed as mucinous cystadenoma or mucinous tumor of uncertain malignant potential and now classified as low-grade appendicular mucinous neoplasm (LAMN). In light of the recently revised classification, there is a need to understand the histological patterns of mucinous tumors in the appendix. In this study, we explore the histopathological spectrum of AMNs through a series of cases encountered in practice.

PATIENTS AND METHODS

This is a retrospective observational study of a one-year duration, from Jan 2022 to Jan 2023. All the emergency/ interval appendectomies including those combined with right hemicolectomies received in the histopathology section were reviewed. Cases with extracellular mucinous lesions on histopathology were included and their clinical, radiological, gross, and microscopic findings were analyzed. The frequency of the cases was expressed in percentage. The histopathological findings were recorded according to the World Health Organisation (WHO) Classification of Digestive system tumors, 5th Edition, 2019 [4]. This study protocol was reviewed and approved by Institutional Ethics Committee, Command Hospital (NC), Udhampur, Project proposal No 03/2023, approved on 30 April 2023. For this type of study formal consent is not required as all personal identification data is anonymized. The research was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

RESULTS

A total of 35 appendectomies were received from Jan 2022 to Jan 2023. Of these, 4 (11.4%) cases of appendicular mucinous lesions were diagnosed. These included two cases of benign retention cysts, one case of low grade appendicular mucinous neoplasm and one case of mucinous adenocarcinoma. None of the cases was associated with peritoneal mucin dissemination. The details of cases are described in Table 1.

DISCUSSION

Primary tumors of vermiform appendix comprise 0.5% of all gastrointestinal tumors and these include epithelial, mesenchymal, and lymphoid malignancies. Among epithelial neoplasms, non-mucinous neuroendocrine tumors form the largest group (65%) followed by adenocarcinomas (20%) and mucinous tumors (8%) [5]. Appendicular mucinous neoplasms are often incidental findings constituting 0.2 to 0.3% of appendectomy specimens [6]. In our study, 11.4% cases (4 out of total 35 cases) were mucinous lesions. The quantum of cases is low due to the short duration of study in a region with difficult terrain that hampers the accessibility of healthcare to patients. However, the data is comparable to various South Asian studies. Geetha et al[7], in a retrospective study of five-year duration, recorded an incidence of 0.8% (10/1200) while Pradhan et al[8] have reported 21 cases in five years (total number of appendectomies has not been mentioned). Shreshtha et al[9] have reported a 1.2% incidence with nine cases in two years. It is a need of the hour to review the mucinous lesions retrospectively, in light of the new classification to get a realistic estimate of the actual incidence of this disease in the South Asian population.

Epidemiology: whom to suspect?

AMNs are rare tumors with 3500 cases diagnosed annually in the United States[10]. Indian statistics, in this regard, are found wanting. AMNs are tumors of the elderly age group with presentation in the sixth decade and studies have shown female predominance [11-13]. Pain in the lower abdomen, specifically the right iliac fossa, is the common presentation (35%) as in all of our cases, simulating the pain in acute appendicitis. They may be incidentally detected (15-20%) either on radiology or histopathology but may present as an abdominal mass or obstruction and bleeding due to volvulus or malignant ascites [14]. Rarely AMNs may present as an inguinal hernia with mucin deposits [15].

Table 1. Clinical, radiological, and pathological details of appendicular mucinous lesions.

SR NO	Case 1	Case 2	Case 3	Case 4
AGE IN YEARS/ GENDER	67/Female	27/Male	48/Male	57/Female
PRESENTATION	Pain in abdomen	Pain in right iliac fossa	Pain in abdomen	Pain in abdomen, recurrent
INDICATION OF APPENDECTOMY	Elective	Primary (Emergency)	Primary Elective	Primary Elective
TYPE OF SURGERY	Cholecystectomy and Appendicectomy	Appendicectomy	Appendicectomy (followed by Right Hemicolectomy after histopathology report)	Appendicectomy combined with Right hemicolectomy
RADIOLOGICAL FINDINGS	Not available	Not available	USG‡ – Tubular non-compressible structure with hypoechoic contents in RIF- possibility - mucocele of appendix CT† - well-defined tubular lesion measuring 24 x 26 x 90 mm is seen arising from the base of caecum. lateral and inferior to IC junction - suggestive of appendix. The contents are hypodense (HU 30) with no post-contrast enhancement. A thin enhancing wall is seen with no septations or enhancing mural nodules	USG‡ – Appendix could not be traced completely, a short tubular structure without any active colour flow seen in vicinity of caecum. CT† – a smoothly demarcated well defined tubular shaped asymmetrically bilobed hypodense mass with vertical – oblique orientation measuring 32x 40x 74 mm. Enhancing(HU 25) as well as nonenhancing internal contents seen. Appendix is not visualized separately. The mass appears contiguous with caecal base
GROSS FINDINGS				
Length	3.5 cm	5.5 cm	4 cm	5 cm
Diameter of lumen	0.6 cm	1 cm	2 cm	3.5 cm
Perforation	Not seen	Not seen	Not seen	Not seen
Lumen	Mild dilatation	dilated in the distal 3 cm with mucoid contents	dilated in the middle 2.5 cm segment	intraluminal polypoid mass of size 4.2x 3.5x 3 surrounded by mucin contents
HISTO-PATHOLOGY DIAGNOSIS	Mucocoele Benign retention cyst of appendix.	Mucocoele Benign retention cyst of appendix	Low-grade Appendicular mucinous neoplasm	Mucinous adenocarcinoma

Legend: ‡ Utrasonography; †Computed tomography scan.

Nomenclature: what shall I call it?

These tumors have been christened quite a few times[16] over the years owing to the deceptively bland cytomorphology, lack of frank invasion, and their ability to disseminate throughout the peritoneal cavity, despite the former. Analogous to colorectal adenomas, AMNs were termed appendicular adenomas. However, over time it became difficult to justify the peritoneal spread of mucin and the progressive behavior of adenomas. At the same time, not all AMNs culminate into PMP and so they were classified as mucinous tumors of uncertain malignant potential, a borderline entity with features inclusive of adenomas but with a risk of progression to mucinous adenocarcinoma [16,17]. The most recent WHO Classification of digestive system tumors, 5th Edition (2019)[4] has broadly classified neoplastic mucinous lesions of the vermiform appendix into serrated lesions (hyperplasia and polyps), mucinous neoplasms (low grade and high grade) and adenocarcinomas.

Histopathology: what do I need to see?

Despite the strenuous efforts at classifying them, AMNs keep mystifying our slide trays steering us towards underdiagnosis or overdiagnosis equally. The dilemma is huge, especially for a young histopathologist, to give a verdict that has profoundly different impacts in either case: is it just a benign retention cyst or is it part of a mucinous adenocarcinoma? Mucinous neoplasms, especially low-grade tumors (LAMN) form the sweet middle between both the extremes discussed above with features that can mimic both. They are characterized by a low-grade dysplastic epithelium overlying a markedly attenuated lamina and muscularis mucosae (Figure 1a), subepithelial fibrosis, broad pushing invasion, and/or dissecting acellular mucin. The

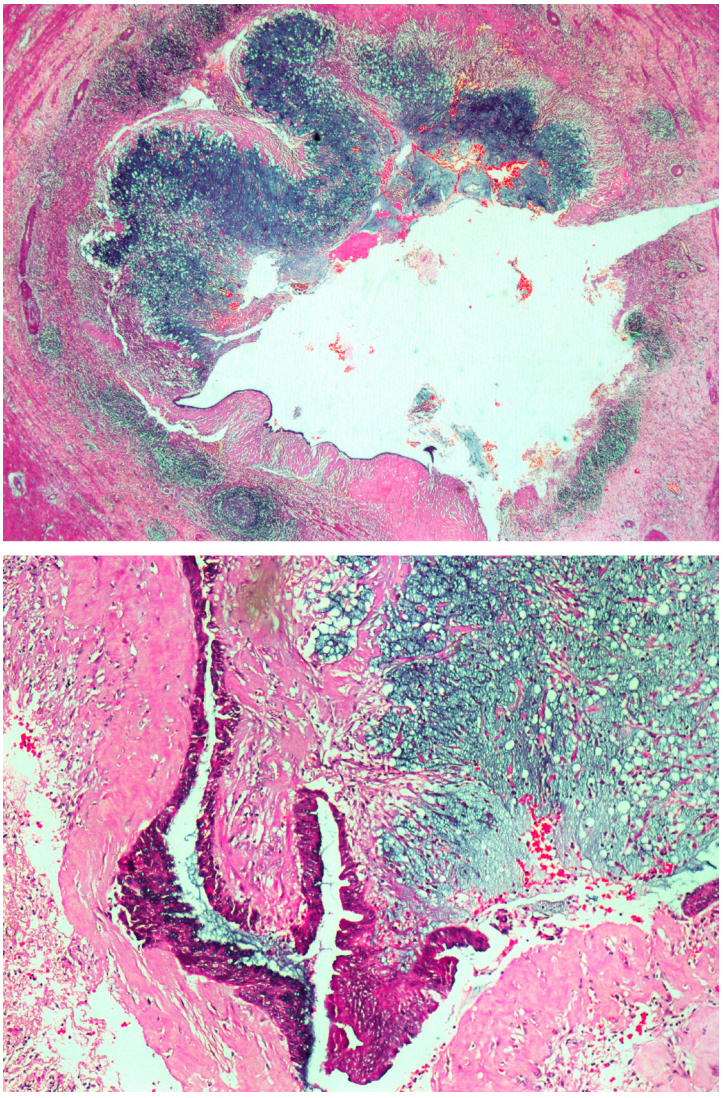
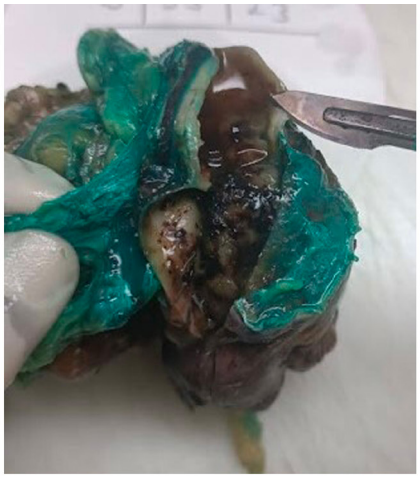


Figure 1. a. Low grade appendiceal neoplasm: Magnification 2x of HE stained section showing appendiceal lumen with mucin pools and flat dysplastic mucosal lining with underlying hyalinised stroma and loss of muscularis mucosae. **b**. Low grade appendiceal neoplasm: Magnification 40x of HE stained section showing a tongue of dysplastic epithelium dissecting into deeper layers.

diagnosis is easier if there is associated peritoneal mucin dissemination since it establishes the malignant behavior. The epithelium is frequently denuded [17] and gives the false impression of a mucus retention cyst until a strip of dysplastic epithelium pops out in a deeper section or an extra section as observed in Figure 1b. It is, therefore, necessary to completely gross an appendix with extracellular mucin contents along with mesoappendix, if submitted. The most confounding yet pathognomonic feature for AMN is the notorious pushing invasion, which is a challenge for eyes that are trained to recognize invasion only as infiltrating glands with desmoplasia. Pushing invasion entails a neoplastic epithelium overlying a fibrotic/hyalinized stroma with broad tongues, diverticulae, or dissections advancing towards the serosa, depicting the tumor's propensity to breach the wall and causing mucin extrusion onto the peritoneal surface. In our case, mucosal dysplasia was evident, but it took complete grossing of the appendix and deeper sectioning to acknowledge the markedly hyalinized stroma and tongues of neoplastic epithelium pushing towards muscularis propria. The diagnosis was supported by the acellular mucin pools with broad bases, also seen dissecting through the nonexistent muscularis mucosae into the submucosa. Unlike adenocarcinoma, the immunohistochemistry for pan cytokeratin did not highlight any epithelial cells in the mucin pools.

Mucinous adenocarcinomas of appendix form a lumen obstructing mass visible grossly as in our case (Figure 2a). The mucin constitutes > 50% of tumor and histologically resembles the counterpart in colon with infiltrating pools of mucin and neoplastic epithelial cells lining them, suspended in the mucin or forming complex glandular structures within (Figure 2b). Adenocarcinomas of appendix are classified



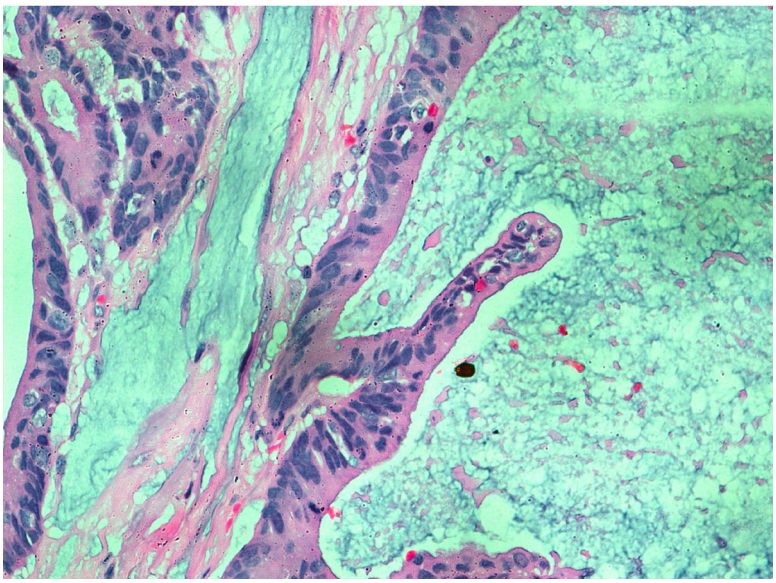


Figure 2. a. Gross specimen of mucocoele of appendix (appendectomy with right hemicolectomy) showing dilated distal segment due to an obstructive luminal mass. **b**. Mucinous adenocarcinoma: Magnification 20 x of HE stained section showing pools of mucin lined by strips of malignant epithelial cells with complex glandular architecture.

depending on the predominant component as mucinous adenocarcinoma (mucin > 50%), signet ring cell adenocarcinoma (> 50% signet ring cell morphology), or goblet cell adenocarcinoma (goblet cell-like mucinous cells with endocrine and Paneth like cells).

Imaging and serology: are there any supportive findings?

Mucocoele is a clinico-radiologic term. The diagnosis of appendicular mucinous neoplasms can be complemented by radiological findings. Appendicular cystic dilatation can be ascertained on ultrasound as well as computed tomography (CT) scanning but the latter is preferred and considered gold standard as it provides vital information regarding the extent of disease, the status of perforation, mucin deposits and presence of any other lesions in the colon/caecum. A well-demarcated mass with cystic dilatation of > 15 mm in relation to caecal base and nonenhancing contents with Hounsfield Units (HU) ranging from 15 to 29 are some features suggestive of mucinous appendicular lesions [18]. Mural calcification and onion skin sign on sonography are other characteristic findings [19]. In our cases, dilated tubular structure in relation to caecal base was observed with a low radiodensity between 25 to 30 HU and transverse diameter of 24 mm to 32 mm (as described in Table 1 and shown in Figure 3). Few studies have also advocated testing for tumor markers such as Carcinoembryonic Antigen (CEA) and Cancer Antigen 19.9 (CA 19.9) since elevated levels have been associated with progression to pseudomyxoma peritonei [20,21].

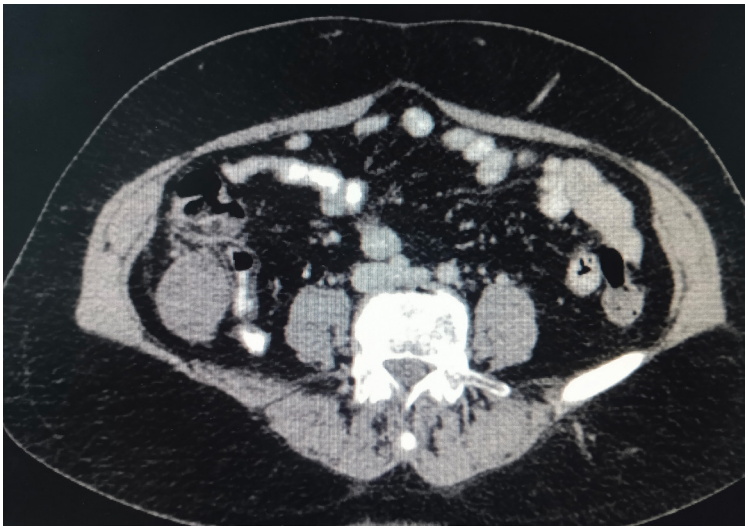


Figure 3. Contrast enhanced computed tomography of abdomen shows a well-defined, smoothly marginated, elongated tubular heterogeneously enhancing solid mass in right iliac fossa.

Staging and management: surgeon's perspective

Benign retention cyst is completely treated after appendectomy. In case of serrated lesions and mucinous neoplasms, the status of surgical margin will decide the course of further management [10]. If surgical margin is not involved, the appendectomy is sufficient. However, if margin is involved, a caecal resection or right hemicolectomy is needed. Also, if the primary surgery was performed for acute appendicitis and mucocoele is discovered on the operating table, it is imperative to carefully handle the lesion and inspect the viscera thoroughly for mucin dissemination. Aggressive peritonectomy with hyperthermic intraoperative chemotherapy followed by systemic chemotherapy are recommended in cases of pseudomyxoma peritonei [22,23].

CONCLUSIONS

Appendectomies are common surgical procedures for the management of acute appendicitis but in rare cases, may harbor mucinous neoplastic lesions. These tumors behave aggressively and given a chance, may invade the entire peritoneal cavity. It is of utmost importance to treat cystically dilated vermiform appendices with greater care and suspicion to observe the unique characteristics leading to diagnosis

and proper classification. The diagnosis of appendicular mucinous lesions requires due diligence and a comprehensive study of clinical, radiological, and histological findings. A multi-center study is needed to assess the actual incidence and characteristics of this unique entity in practice, considering the rarity and paucity of data in both respects.

Ethics approval:

This study protocol was reviewed and approved by Institutional Ethics Committee, Command Hospital (NC), Udhampur, Project proposal No 03/2023, approved on 30 April 2023.

Informed consent:

This is an observational retrospective study and does not involve any intervention or human participants. For this type of study formal consent is not required as all personal identification data is anonymized. We, the authors, have performed the research in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Data Availability Statement:

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Funding:

No funding was received for this study.

Acknowledgement:

Authors wish to acknowledge the support of our histotechnicians: Mr Chauhan Satyapal Ramsabad Singh, Mr Sarvesh Kumar Soni and Mr S Suresh Reddy.

Conflict of Interest :

The authors have no conflicts of interest to declare.

ORCID ID:

Prachi Nichat – https://orcid.org/0000-0002-3261-7545; Vandana Rana – https://orcid.org/0000-0003-2756-8088; A. Mishra – https://orcid.org/0000-0002-8434-426X; KR Rao – https://orcid.org/0009-0008-9507-1691.

Author Contributions:

P. Nichat – conception and design of study, primary reporting , analysis and interpretation of data on histopathology, drafting of intellectual content. V. Rana - conception of study, primary reporting, analysis and interpretation of cases on histopathology, critical revision of final draft. M.K.S. Parihar – analysis of surgical data, literature review in surgical management and revision of intellectual content. A. Mishra – radiological analysis of cases. K.R. Rao – surgical approach of cases. All the authors participated in Instititional Ethics Committee review and vouch for the integrity of published data.

REFERENCES

1. Wackym PA, Gray GF Jr. Tumors of the appendix: I. Neoplastic and nonneoplastic mucoceles. South Med J 1984; 77: 283-287.
2. Rymer B, Forsythe RO, Husada G. Mucocoele and mucinous tumours of the appendix: A review of the literature. Int J Surg 2015; 18: 132-135.
3. Tsuda M, Yamashita Y, Azuma S, Akamatsu T, Seta T, Urai S, Uenoyama Y, Deguchi Y, Ono K, Chiba T. Mucocele of the appendix due to endometriosis: a rare case report. World J Gastroenterol 2013; 19: 5021-5024.
4. Misdraji J, Carr N and Pai R. Appendiceal mucinous neoplasm. In: WHO Classification of Tumours Editorial Board. WHO Classification of Tumours: Digestive System Tumours. 5th ed. Lyon, France: International Agency for Research on Cancer 2019; pp. 144-146.
5. McCusker ME, Cote TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: A populationbased study from the surveillance, epidemiology and end-results program, 1973–1998. Cancer 2002; 94: 3307-3312.
6. Smeenk RM, van Velthuysen ML, Verwaal VJ, Zoetmulder FA. Appendiceal neoplasms and pseudomyxoma peritonei: A population based study. Eur J Surg Oncol 2008; 34: 196-201.
7. Geetha C, Farheen A, Deshpande AK. Histopathologic study of mucinous lesions of the appendix. IP Arch Cytol Histopathol Res 2020; 5: 41G-46G.
8. Pradhan R, Mondal S, Sikdar M, Bandyopadhyay A. Mucinous Neoplasms of the Appendix - A Clinicopathologic Study of 21 Cases With Special Insight into Current Classification & Controversies. Asian J Med Sci 2023; 14: 185-190.
9. Shrestha O, Baral R. Mucinous Lesions of the Appendix: A Histopathological Study. J Pathol Nep 2022; 12: 1893-1899
10. Shaib WL, Assi R, Shamseddine A, Alese OB, Staley C 3rd, Memis B, Adsay V, Bekaii-Saab T, El-Rayes BF. Appendiceal Mucinous Neoplasms: Diagnosis and Management. Oncologist 2017; 22: 1107-1116.

11. Choudry HA, Pai RK. Management of Mucinous Appendiceal Tumors. Ann Surg Oncol 2018; 25: 2135.
12. 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: 1089-1103.
13. Akay E, Arslan A, Eren SK, Özhan N, Karaman H. Mucinous appendiceal neoplasms and pseudomyxoma peritonei: Morphological and clinical findings, differential diagnosis, and prognosis. Indian J Pathol Microbiol 2022; 65: 565-571.
14. Carr NJ, Bibeau F, Bradley RF, Dartigues P, Feakins RM, Geisinger KR, Gui X, Isaac S, Milione M, Misdraji J, Pai RK, Rodriguez-Justo M, Sobin LH, van Velthuysen MF, Yantiss RK. The histopathological classification, diagnosis and differential diagnosis of mucinous appendiceal neoplasms, appendiceal adenocarcinomas and pseudomyxoma peritonei. Histopathology 2017; 71: 847-858.
15. Young RH, Rosenberg AE, Clement PB. Mucin deposits within inguinal hernia sacs: a presenting finding of low-grade mucinous cystic tumors of the appendix. A report of two cases and a review of the literature. Mod Pathol 1997; 10: 1228-1232.
16. Carr NJ, Cecil TD, Mohamed F, Sobin LH, Sugarbaker PH, González-Moreno S, Taflampas P, Chapman S, Moran BJ; Peritoneal Surface Oncology Group International. A Consensus for Classification and Pathologic Reporting of Pseudomyxoma Peritonei and Associated Appendiceal Neoplasia: The Results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process. Am J Surg Pathol 2016; 40: 14-26.
17. Misdraji J. Mucinous epithelial neoplasms of the appendix and pseudomyxoma peritonei. Mod Pathol 2015; 28: S67-S79.
18. Yu XR, Mao J, Tang W, Meng XY, Tian Y, Du ZL. Low-grade appendiceal mucinous neoplasms confined to the appendix: clinical manifestations and CT findings. J Investig Med 2020; 68: 75-81.
19. Gaetke-Udager K, Maturen KE, Hammer SG. Beyond acute appendicitis: imaging and pathologic spectrum of appendiceal pathology. Emerg Radiol 2014; 21: 535-542.
20. Matias-García B, Mendoza-Moreno F, Blasco-Martínez A, Busteros-Moraza JI, Diez-Alonso M, Garcia-Moreno Nisa F. A retrospective analysis and literature review of neoplastic appendiceal mucinous lesions. BMC Surg 2021; 21: 79.
21. Gündoğar Ö, Kımıloğlu E, Komut N, Cin M, Bektaş S, Gönüllü D, İlgün AS, Erdoğan N. Evaluation of appendiceal mucinous neoplasms with a new classification system and literature review. Turk J Gastroenterol 2018; 29: 533-542.
22. Overman MJ, Compton CC, Raghav K, Lambert LA. Appendiceal mucinous lesions. In: Weiser M, editor. UpToDate. Chen W: UpToDate Inc.; April 08, 2023. [cited 2023 Apr 8]. Available from: https://www.uptodate.com/contents/appendiceal-mucinous-lesions#H1755935805
23. Fournier K, Rafeeq S, Taggart M, Kanaby P, Ning J, Chen HC, Overman M, Raghav K, Eng C, Mansfield P, Royal R. Low-grade Appendiceal Mucinous Neoplasm of Uncertain Malignant Potential (LAMN-UMP): Prognostic Factors and Implications for Treatment and Follow-up. Ann Surg Oncol 2017; 24: 187-193.