Journal of Translational Gastroenterology **2023** vol. 1(2) | 94–98
DOI: 10.14218/JTG.2023.00019

Case Report

Goblet Cell Adenocarcinoma in the Background of a Ruptured Appendiceal Diverticulum Mimicking Low-grade Appendiceal Mucinous Neoplasm: A Case Report and Literature Review

Mitchell Zhao, Alfredo Molinolo, Vera Vavinskaya, Charmi Patel, Richard Wong and Jingjing Hu*

Department of Pathology, University of California, San Diego, CA, USA

Received: May 17, 2023 | **Revised:** August 30, 2023 | **Accepted:** September 26, 2023 | **Published online:** December 25, 2023

Abstract

The appendix, while a small portion of the gastrointestinal tract, can give rise to a variety of tumors. Goblet cell adenocarcinoma is an amphicrine tumor with both glandular and neuroendocrine features, and a molecular profile different from that of neuroendocrine tumors and conventional appendiceal adenocarcinomas. Low-grade appendiceal mucinous neoplasm is a tumor with low-grade cytology and histological findings that can mimic other benign entities. Here, we present a case of goblet cell adenocarcinoma that was associated with a ruptured diverticulum mimicking low-grade appendiceal neoplasm, and we review the available literature on these tumors.

Introduction

The appendix has been a topic of intense study, particularly because of the various neoplasms that arise from it, some of which are essentially unique to this organ. While abdominal pain is the reason why some of these tumors come into clinical suspicion, many others are caught incidentally upon appendectomy for appendicitis. The Word Health Organization currently classifies appendiceal tumors into the following categories: serrated lesions and polyps, mucinous neoplasms, adenocarcinomas, goblet cell adenocarcinoma and neuroendocrine neoplasms.[1,2] This classification is based on an improved understanding of the different types of appendiceal neoplasms, including knowledge gained from molecular studies. As an example of the diversity among appendiceal tumors, low-grade appendiceal mucinous neoplasm (LAMN) is categorized as a mucinous adenomatous tumor, while goblet cell adenocarcinoma (GCA) is distinct from both traditional adenocarcinomas and neuroendocrine neoplasms, as it blends morphologic features of both. In addition, GCA shows a molecular profile distinct from the other appendiceal neoplasms.[3] Herein, we discuss a case of GCA in which the difficulty in diagnosis arose from the classification of a synchronous mucinous lesion that falls between the descriptions of diverticular rupture and LAMN.

Keywords: Goblet cell adenocarcinoma; Low-grade appendiceal mucinous neoplasm; Ruptured diverticulum.

Abbreviations: GCA, goblet cell adenocarcinoma; LAMN, low-grade appendiceal mucinous neoplasm.

***Correspondence to:** Jingjing Hu, Department of Pathology, University of California, 9300 Campus Point Drive, San Diego, CA 92037, USA. ORCID: https://orcid.org/0000-0003-1957-2706. Tel: +1-858-657-5188, E-mail: jih001@health.ucsd.edu

How to cite this article: Zhao M, Molinolo A, Vavinskaya V, Patel C, Wong R, Hu J. Goblet Cell Adenocarcinoma in the Background of a Ruptured Appendiceal Diverticulum Mimicking Low-grade Appendiceal Mucinous Neoplasm: A Case Report and Literature Review. *J Transl Gastroenterol* 2023;1(2):94–98. doi: 10.14218/JTG.2023.00019.

Case report

A 70-year-old woman presented with a chief complaint of abdominal pain, prompting further evaluation by colonoscopy. Endoscopic examination of the colon was notable for its detection of a bulging appendix with mucus extruding from the appendiceal orifice into the colonic lumen. Otherwise, the colonoscopy findings were unremarkable. Given these observations, surgery was consulted and the patient was scheduled for an elective appendectomy. Intraoperatively, the appendix was noted to be dilated with a firm, mass-like lesion. There was an adhesion connecting the appendix to the anterior abdominal wall. The base of the appendix appeared uninvolved, and there was no evidence of perforation. The appendix was resected without complications.

On gross examination, the appendix measured 5.0 cm in length and 0.5–1.5 cm in diameter, with a distorted appearance and luminal dilation. Perforation was not grossly identified. Serial sectioning revealed the absence of fecalith but demonstrated the presence of mucus in the mesoappendix. The entire appendix was submitted for histologic evaluation.

Microscopic examination revealed an infiltrative, neoplastic

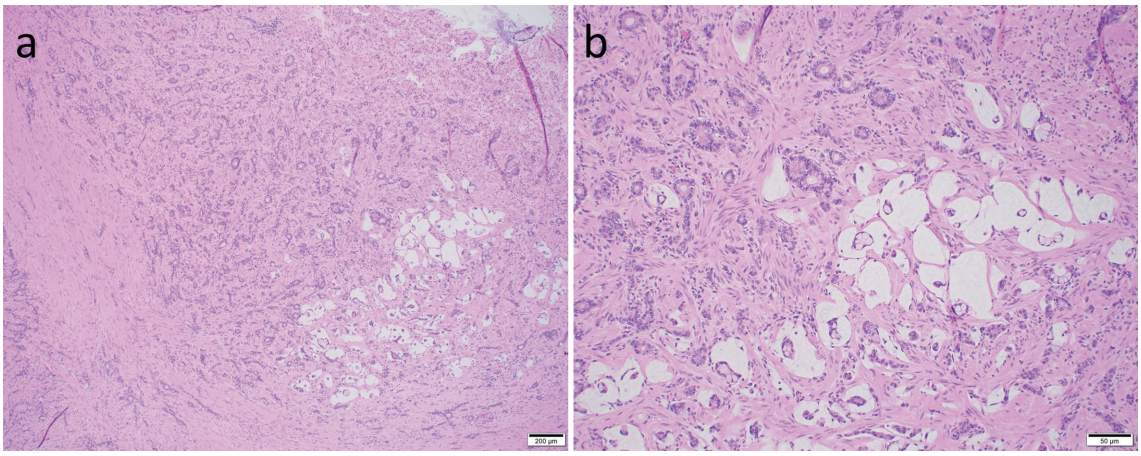

Fig. 1. Goblet cell adenocarcinoma. Sections show an amphicrine neoplasm with goblet cells in the mucin pool intermixed with mucinous cells arranged in glandular structures and cords. (a) 4× magnification. (b) 10× magnification.

process in the appendiceal wall. This neoplasm consisted of an amphicrine population of cells invading the muscularis propria without significant desmoplasia (Fig. 1). The epithelial cells were arranged in well-formed tubules and cords, architectural findings consistent with neuroendocrine differentiation. The cells were diffusely positive for CK20, CDX2, and synaptophysin, and negative for CK7. Immunohistochemical studies for chromogranin showed patchy, variable positive staining with the strongest staining in areas with more classic neuroendocrine architecture (Fig. 2). Taken together, the findings were most consistent with a diagnosis of GCA.

Sections of the appendix also demonstrated an appendiceal diverticulum with acellular mucin in the adjacent appendiceal wall. However, regions of the diverticulum demonstrated mild cytologic atypia and epithelial flattening alternating with regions of hyperplasic change. The lamina propria was also attenuated in some areas but not fully obliterated (Fig. 3). Given these additional findings, a diagnosis of LAMN or benign diverticulum was on our differential list. Overall, we favor a benign diverticulum with perforation.

Two lymph nodes were also identified in the attached soft tissue, and the results were negative for tumor cells.

The patient was diagnosed with GCA of the appendix in the background of a perforated diverticulum and extra-appendiceal mucin. GCAs are currently staged similarly to traditional adenocarcinomas of the appendix and gastrointestinal tract, and as such, this tumor was staged as pT2N0 by the depth of invasion.[1] While unlikely, the possibility of LAMN was raised in the pathology report, and close clinical follow-up was recommended.

Findings were discussed with the patient, who opted for conservative follow-up. Computerized tomography imaging performed at 1 month, 4 months, and 19 months, and magnetic resonance imaging performed at 7 months post-op showed no evidence of metastatic disease. A follow-up colonoscopy was performed approximately 14 months after the appendectomy, demonstrating a normal-appearing appendiceal orifice. Biopsies taken from the orifice showed an unremarkable colonic mucosa with no evidence of malignancy. Testing for carcinoembryonic antigen was performed post-op, with the initial value elevated at 12.6 ng/mL (normal: <3.8 ng/mL). Repeat testing has shown persistently elevated but stable carcinoembryonic antigen measurements. The patient remains asymptomatic at 19 months of follow-up.

Discussion

Out of the many neoplasms that arise from the appendix, GCA is a fairly unique entity that does not occur frequently outside of the appendix, if at all. In our case, what had complicated the final diagnosis was the presence of a separate mucinous epithelial lesion for which histological findings raised the possibility of a synchronous LAMN that was ultimately not diagnosed.

Multiple names have been used for GCA and its subtypes, including goblet cell carcinoid, adenocarcinoma ex goblet cell carcinoid, crypt cell carcinoma, microglandular carcinoma, and adenocarcinoid.[1,4] In general, this tumor consists of a combination of neuroendocrine cells, Paneth cells, and goblet cells, and it is suspected that these tumors originate from a pluripotent crypt stem cell able to differentiate into these different cell types.[3,5] It tends to involve the appendiceal wall circumferentially, and because of its growth patterns, it is often difficult, if not impossible, to estimate tumor size.[4] More recently, multiple groups have performed molecular studies on these tumors to better understand their relationship to other adenocarcinomas and neuroendocrine tumors. GCAs have been shown to carry mutations in chromatin remodeling genes such as *ARID1A*, *SOX9*, and *RHOA*.[5,6]

Typically, GCAs do not form a mass lesion, limiting their ability to be detected on gross evaluation aside from possible wall thickening.[4] Notably, they are not known to be associated with any *in situ* epithelial lesions.[5,7] In low-grade tumors, cells are typically arranged in tubules with mild atypia and rare mitoses. However, clusters of goblet cells are common throughout the tumor, and this finding is extremely useful in establishing a diagnosis. On the other hand, high-grade tumors demonstrate high-grade cytology and more infiltrative growth patterns, including complex anastomosing tubules and discohesive cells with streaming architecture. While not typically present in low-grade GCA, desmoplasia can occur in higher-grade tumors.[1,2,4,7,8] This tumor does have the potential for metastasis, and there have been cases documented where GCA had metastasized to the ovary, raising concern for a primary ovarian tumor in the differential diagnosis.[4,5] Neuroendocrine markers such as synaptophysin and chromogranin can be useful in suggesting the diagnosis of GCA, as GCAs typically display at least focal expression of these markers. However, they are not necessary for diagnosis. CK20 could potentially be useful in differentiating GCA from neuroendocrine tumors, as most well-differentiated neuroendocrine tumors are negative for this protein.[9]

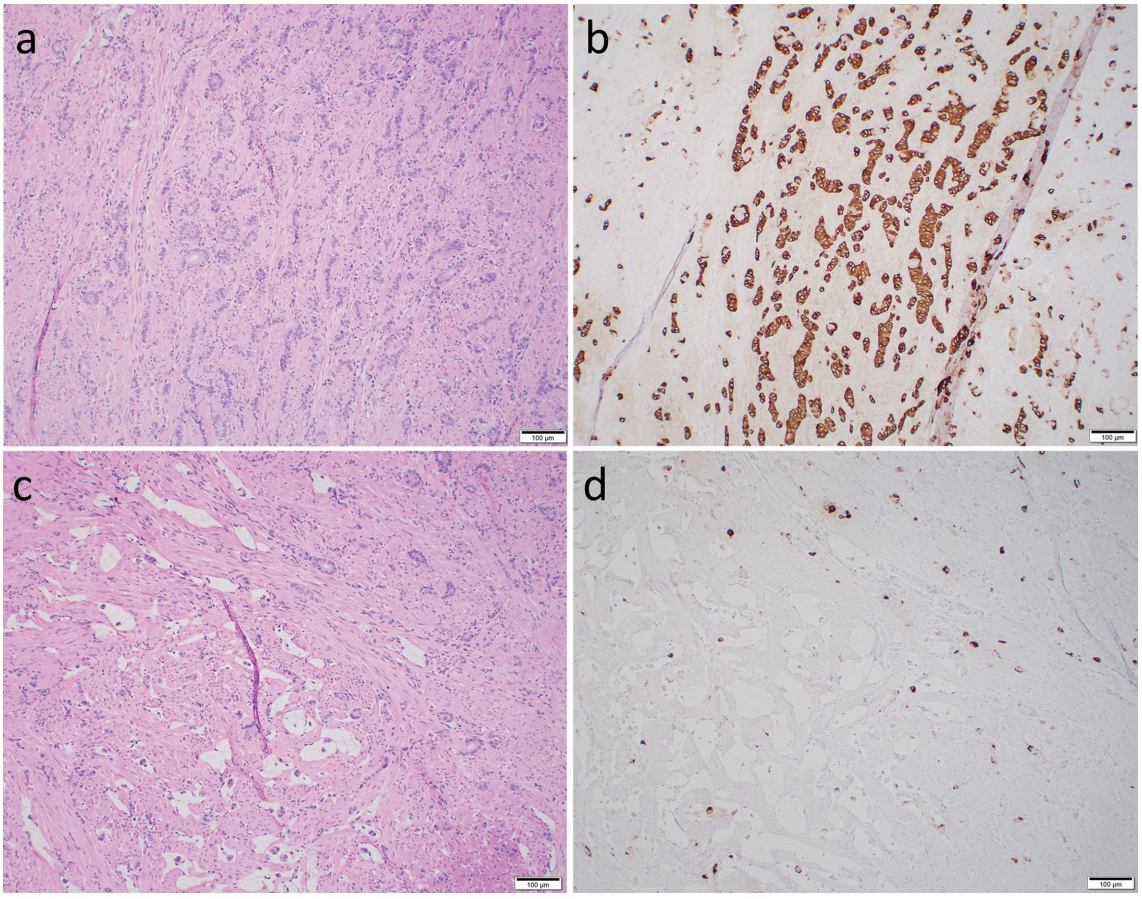

Fig. 2. Chromogranin staining in goblet cell adenocarcinoma. (a, b) Photomicrographs were taken in two adjacent areas, one showing a more neuroendocrine architecture (a) and the other with more mucinous differentiation (b). (c-d) Chromogranin is strongly positive in the neuroendocrine areas (c), while it is weaker with more patchy positivity in the mucinous areas (d).

Multiple attempts have been made to establish a standardized, tiered histologic grading system for GCA, as systematic studies are currently complicated by the profusion of different systems.[4,7,10–12] Currently, the Word Health Organization recommends the system proposed by Yozu *et al*.,[12] whereby the grade is determined by the percentage of low- and high-grade patterns in the tumor.[1] In our case, around 50–75% of the tumor had low-grade morphology, demonstrating a tubular or clustered growth pattern. Thus, it would be designated as low grade.

Studies have shown that GCAs clinically behave more similarly

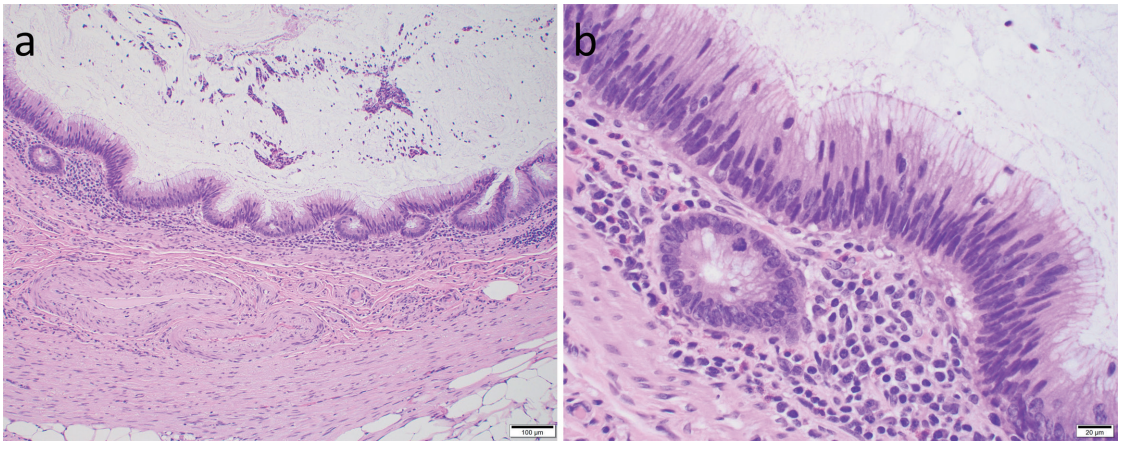

Fig. 3. Appendiceal diverticulum closely mimics LAMN. Sections show atypical appendiceal mucosa with serrated architecture and attenuation of the lamina propria. Note the preserved lamina propria underneath the mucinous epithelium. (a) 20× magnification. (b) 40× magnification.

to conventional appendiceal adenocarcinomas rather than neuroendocrine tumors. Consequently, they are staged similarly to conventional adenocarcinomas of the gastrointestinal tract.[1] This is also why it is no longer recommended to include "carcinoid" in the vocabulary of such tumors, a term that suggests the more benign clinical course characteristic of most neuroendocrine tumors.[4,5,7,9] The difference in behavior further highlights the importance of distinguishing GCA from neuroendocrine tumors, and care should be taken so that goblet cells are not missed when reviewing an incidentally discovered neuroendocrine tumor on appendectomy.

The prognosis of GCA varies depending on the tumor's grade and clinical stage at the time of diagnosis. Further management is similarly guided by these factors. Whereas some patients with low-grade tumors have been managed conservatively or with observation without issues, there are patients with high-grade stage IV disease where aggressive management, including cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, did not significantly improve survival.[1,8] In our case, the patient decided to proceed with a more conservative strategy with routine surveillance by imaging and laboratory tests.

The current diagnostic criteria for LAMN endorsed by the World Health Organization are taken from the Modified Delphi Process 2013 by the Peritoneal Surface Oncology Group International. Low-grade appendiceal neoplasm is defined as a mucinous neoplasm with low-grade cytologic atypia and at least one of the following features: loss of muscularis mucosae, submucosal fibrosis, expansile invasion, dissection of acellular mucin into the appendiceal wall, undulating or flattened epithelium, appendiceal rupture, or the presence of mucin or neoplastic cells outside of the appendix.[1,13] Extra-appendiceal mucin is a feature best associated with both LAMN and mucinous adenocarcinoma.[14] However, infiltrative invasion favors a diagnosis of mucinous adenocarcinoma.[13] The syndrome of low-grade mucinous carcinoma peritonei/disseminated peritoneal adenomucinosis (previously termed pseudomyxoma peritonei) and its higher-grade counterparts are well associated with the diagnosis of LAMN and similar neoplasms of the appendix, which are believed to be by far the most common precipitating tumors.[8,13] In molecular studies, these tumors tend to be associated with mutations in *GNAS*, and *KRAS* (Wnt/β-catenin pathway).[8,9,15]

Most diverticula of the lower gastrointestinal tract, including those of the appendix, are acquired protrusions of the mucosa and submucosa through a defect in the muscular propria, to be contrasted with true, congenital diverticula. The diverticular lumen may be seen by imaging such as CT, ultrasound, and barium studies but does not always depend on the specific characteristics of the outpouching. Appendiceal diverticula are typically identified incidentally, while appendiceal diverticulitis shares clinical and radiographic features with traditional appendicitis that cannot always be teased apart. Histologically, one would see portions of the appendiceal mucosa unassociated with muscularis propria extending to the external wall in diverticular disease. Notably, while appendiceal diverticula are not precursors to LAMN and mucinous carcinoma peritonei, a ruptured diverticulum can show findings suspicious for this neoplasm.[16]

In our case, the differential diagnosis for the mucinous lesion was LAMN vs. ruptured appendiceal diverticulum. A diverticulum was clearly identified on histological evaluation. However, several findings raised the possibility of a neoplastic lesion such as LAMN, including the presence of mild cytologic atypia, flattened epithelium, and the presence of acellular mucin in the appendiceal wall. There were areas of epithelial flattening alternated with areas showing hyperplasic changes. Additionally, while the lamina propria was attenuated, it was never fully obliterated in any of the sections examined. Taken together, all the suspicious findings in this case can be explained by microscopic perforation of an appendiceal diverticulum. However, LAMN cannot be completely excluded from the differential diagnosis based on histology alone. Further clinical and/or molecular follow-up could help clarify this differential. Our patient has had no evidence of recurrent disease or mucinous carcinoma peritonei after 19 months with continued surveillance.

There have been case reports documenting appendiceal perforation in the context of GCA. However, the clinical data and follow-up in these studies are limited, preventing more systematic attempts at establishing a relationship between perforation and prognosis regarding patient survival, peritoneal metastasis, and recurrence.[17] Further studies are needed to evaluate the perforation as a prognostic factor in GCA.

Conclusions

GCA is an appendiceal neoplasm with distinct histological and molecular findings compared to other primary appendiceal neoplasms, and this tumor should always be in the initial differential diagnosis when evaluating appendiceal tumors with neuroendocrine morphology because of its adverse prognosis relative to pure neuroendocrine tumors. This case represented a diagnostic challenge in differentiating diverticular rupture from low-grade appendiceal neoplasm, given the overlapping histologic features of the two entities. While diverticular rupture is the favored diagnosis, LAMN cannot be fully excluded from the differential diagnosis. While appendiceal perforation has been known to occur in cases of goblet cell carcinoma, its precise influence on prognosis has not been well established. Further studies are necessary to better characterize GCA's behavior and prognosis and investigate its prevalence in the context of all appendiceal neoplasms.

Acknowledgments

None.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Contributed to study conception and design (MZ, JH), acquisition of the data (MZ, RW, JH), drafting of the manuscript (MZ), critical revision of the manuscript (MZ, VV, CP, RW, AM), and supervision (RW, JH).

Ethical statement

The study was performed in accordance with the ethical standards of the institutions to which the authors are affiliated and with the Declaration of Helsinki (as revised in 2013). Written informed

consent was obtained from the patient for the anonymized publication of this case report and the accompanying images.

References

[1] Lokuhetty D, White V, Watanabe R, Cree I. WHO Classification of Tumours of the Digestive System. 5th ed. Lyon: International Agency for Research on Cancer; 2018.

[2] Assarzadegan N, Montgomery E. What is New in the 2019 World Health Organization (WHO) Classification of Tumors of the Digestive System: Review of Selected Updates on Neuroendocrine Neoplasms, Appendiceal Tumors, and Molecular Testing. Arch Pathol Lab Med 2021;145(6):664–677. doi:10.5858/ARPA.2019-0665-RA, PMID:32233993.

[3] Arai H, Baca Y, Battaglin F, Kawanishi N, Wang J, Soni S, *et al*. Molecular Characterization of Appendiceal Goblet Cell Carcinoid. Mol Cancer Ther 2020;19(12):2634–2640. doi:10.1158/1535-7163.MCT-20-0318, PMID:33037134.

[4] Hosseini M, Ronquillo N. Goblet cell adenocarcinoma: concepts and updates. Diagnostic Histopathology 2021;27(2):69–74. doi:10.1016/j.mpdhp.2020.11.003.

[5] Sinno SAJ, Jurdi NMH. Goblet cell tumors of the appendix: A review. Ann Diagn Pathol 2019;43:151401. doi:10.1016/J.ANNDIAGPATH.2019.151401, PMID:31675676.

[6] Wen KW, Grenert JP, Joseph NM, Shafizadeh N, Huang A, Hosseini M, *et al*. Genomic profile of appendiceal goblet cell carcinoid is distinct compared to appendiceal neuroendocrine tumor and conventional adenocarcinoma. Hum Pathol 2018;77:166–174. doi:10.1016/J.HUMPATH.2018.03.026, PMID:29634977.

[7] Tang LH, Shia J, Soslow RA, Dhall D, Wong WD, O'Reilly E, *et al*. Pathologic classification and clinical behavior of the spectrum of goblet cell carcinoid tumors of the appendix. Am J Surg Pathol 2008;32(10):1429–1443. doi:10.1097/PAS.0b013e31817f1816, PMID:18685490.

[8] Orr CE, Yantiss RK. Controversies in appendiceal pathology: mucinous and goblet cell neoplasms. Pathology 2022;54(2):167–176. doi:10.1016/J.PATHOL.2021.09.003, PMID:34836648.

[9] Mikaeel RR, Young JP, Tapia Rico G, Hewett PJ, Hardingham JE, Uylaki W, *et al*. Immunohistochemistry features and molecular pathology of appendiceal neoplasms. Crit Rev Clin Lab Sci 2021;58(6):369–384. doi:10.1080/10408363.2021.1881756/SUPPL_FILE/ILAB_A_1881756_SM2746.DOCX, PMID:33569997.

[10] Lee LH, McConnell YJ, Tsang E, Zerhouni S, Speers C, Kennecke H, *et al*. Simplified 2-tier histologic grading system accurately predicts outcomes in goblet cell carcinoid of the appendix. Hum Pathol 2015;46(12):1881–1889. doi:10.1016/J.HUMPATH.2015.08.005, PMID:26433702.

[11] Taggart MW, Abraham SC, Overman MJ, Mansfield PF, Rashid A. Goblet cell carcinoid tumor, mixed goblet cell carcinoid-adenocarcinoma, and adenocarcinoma of the appendix: comparison of clinicopathologic features and prognosis. Arch Pathol Lab Med 2015;139(6):782–790. doi:10.5858/arpa.2013-0047-OA, PMID:26030247.

[12] Yozu M, Johncilla ME, Srivastava A, Ryan DP, Cusack JC, Doyle L, *et al*. Histologic and Outcome Study Supports Reclassifying Appendiceal Goblet Cell Carcinoids as Goblet Cell Adenocarcinomas, and Grading and Staging Similarly to Colonic Adenocarcinomas. Am J Surg Pathol 2018;42(7):898–910. doi:10.1097/PAS.0000000000001056, PMID:29579011.

[13] Carr NJ, Cecil TD, Mohamed F, Sobin LH, Sugarbaker PH, González-Moreno S, *et al*. 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(1):14–26. doi:10.1097/PAS.0000000000000535, PMID:26492181.

[14] Tirumani SH, Fraser-Hill M, Auer R, Shabana W, Walsh C, Lee F, *et al*. Mucinous neoplasms of the appendix: a current comprehensive clinicopathologic and imaging review. Cancer Imaging 2013;13(1):14–25. doi:10.1102/1470-7330.2013.0003, PMID:23439060.

[15] Tsai JH, Yang CY, Yuan RH, Jeng YM. Correlation of molecular and morphological features of appendiceal epithelial neoplasms. Histopathology 2019;75(4):468–477. doi:10.1111/HIS.13924, PMID:31111538.

[16] Käser SA, Willi N, Maurer CA. Prevalence and clinical implications of diverticulosis of the vermiform appendix. J Int Med Res 2013;41(4):1350–1356. doi:10.1177/0300060513487651, PMID:23771712.

[17] Madani A, van der Bilt JD, Consten EC, Vriens MR, Borel Rinkes IH. Perforation in appendiceal well-differentiated carcinoid and goblet cell tumors: impact on prognosis? A systematic review. Ann Surg Oncol 2015;22(3):959–965. doi:10.1245/S10434-014-4023-9/TABLES/2, PMID:25190118.