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CASE REPORT PEER REVIEWED | OPEN ACCESS

Intramucosal goblet cell adenocarcinoma: The evil got nipped in the bud

John Yablonski, Christian D Tvetenstarnd, Jagmohan Sidhu

ABSTRACT

Introduction: Appendiceal goblet cell adenocarcinoma is a rare cancer that usually has histological features of both well-differentiated carcinoid tumors and adenocarcinomas (neuroendocrine cells are not required for the diagnosis). Appendiceal goblet cell adenocarcinoma can present as acute appendicitis, abdominal pain, a mass, or be discovered incidentally following appendectomy.

Case Report: A 67-year-old female presented with signs of acute appendicitis and underwent laparoscopic appendectomy. Pathological evaluation showed evidence of both acute appendicitis/periappendicitis and an incidental appendiceal intramucosal well-differentiated adenocarcinoma in the lamina propria of a 12 mm long segment in the middle of the proximal half of the appendix.

Conclusion: Appendiceal goblet cell adenocarcinoma can sometimes be an incidental finding. It can be difficult to identify it, especially when it is in the form of only a few cells and clusters of cells limited to lamina propria. This case is the first reported incidence of an intramucosal goblet cell adenocarcinoma that was present in a 12 mm long segment in the middle of the proximal half of the appendix. The location of this tumor provides justification for making submission of an appendix in its entirety for histologic examination as a standard-of-care.

Keywords: Acute appendicitis, Adenocarcinoma, Appendiceal goblet cell adenocarcinoma, Carcinoid tumor

John Yablonski[1], MLitt, Christian D Tvetenstarnd[2], MD, Jagmohan Sidhu[3], MD

Affiliations: [1]The Norton College of Medicine at SUNY Upstate Medical University, Syracuse, NY, USA; [2]MD, Attending General Surgeon, Department of Surgery, United Health Services, Binghamton, NY, USA; [3]Medical Director and Chairman, Department of Pathology and Laboratory Medicine, United Health Services, Binghamton, NY, USA.

Corresponding Author: John Yablonski, MLitt, The Norton College of Medicine at SUNY Upstate Medical University, 750 E Adams St, Syracuse, NY 13210, USA; Email: yablonsj@upstate.edu

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INTRODUCTION

Appendiceal goblet cell adenocarcinoma (formerly characterized as appendiceal goblet cell carcinoid [GCC]) is a rare diagnosis that has an approximate incidence of 0.01–0.05 per 100,000 per year [1]. The clinical presentation of appendiceal goblet cell adenocarcinoma can be similar to acute appendicitis; in fact, appendiceal tumors can in some cases cause acute appendicitis via a similar mechanism to a traditional appendicolith [2]. Appendiceal goblet cell adenocarcinoma can also present with abdominal pain in either the presence or absence of an abdominal mass [1]. Goblet cell adenocarcinomas demonstrate histological characteristics of both well-differentiated carcinoid tumors as well as adenocarcinomas [2]. However, the presence of neuroendocrine cells is not required for the diagnosis because goblet cell adenocarcinomas are known to behave more similarly to colonic adenocarcinomas and are now recognized to only contain a minor neuroendocrine component [2, 3]. The prognosis is determined by the grade and stage of the tumor as described by the tumor,

node, metastasis (TNM) system [2]. There is currently no consensus standard of care with respect to appendiceal goblet cell adenocarcinomas. The primary clinical concern is establishing if further surgical intervention is required for staging and further treatment considerations [2, 4]. In this report, a case of appendiceal intramucosal goblet cell adenocarcinoma discovered incidentally following an emergency appendectomy and not requiring further treatment is presented.

CASE REPORT

The patient was a 67-year-old female who developed abdominal pain in the periumbilical region 10 days prior to her presentation to the emergency department. She had a prior history of unspecified thyroid cancer. Family history was significant for renal neoplasm in her father (deceased). She was a former smoker with a 36 pack-year history. The patient's current medications were levothyroxine and fluoxetine.

The physical exam showed a well-developed and well-nourished female. Abdominal exam showed a soft abdomen with tenderness to palpation over the right lower quadrant with rebound tenderness. The patient's blood pressure was 149/78 mm, pulse 108/minute, temperature 36.8°C (98.2°F), respiratory rate 18 breaths/minute, and basal metabolic index (BMI) 21 kg/m^2. Laboratory results were notable for a mild leukocytosis of 11.7 × 10^9/L (4.5 × 10^9/L–11 × 10^9/L). The patient was subsequently sent for a computed tomography (CT) scan of the abdomen.

Computed tomography scan of the abdomen was performed with both intravenous (IV) and oral contrast. Results showed an inflammatory process in the right lower quadrant with edema/stranding adjacent to the cecum and appendix. The appendix also appeared diffusely thickened, measuring approximately 10 mm thick. These findings were consistent with acute appendicitis. There was a partially lobulated low-attenuation structure/collection measuring approximately 3.4 × 2.3 × 2.3 cm that was closely contiguous with the midportion of the appendix medially. This finding was consistent with the presence of an abscess. There was thickening of the inferior aspect of the cecum and terminal ileum, which was likely secondary to the adjacent inflammatory process. There was no significant free fluid within the pelvis. A few incidental colonic diverticula were noted, and there was no evidence of bowel obstruction. The patient was advised to undergo a laparoscopic appendectomy.

Intraoperatively, after smooth induction of general tracheal anesthesia, a small periumbilical incision was made, and an abdominal trocar was inserted without difficulty. After the insertion of the remaining trocars, the appendix was seen to be encased in a retrocecal position. The appendix was carefully mobilized, and abscesses were visualized in the midportion and medial aspect of the appendix. The abscesses were immediately evacuated with minimal spillage. The appendix was then transected with a white load stapler. The patient tolerated the procedure well and returned to stable condition within an appropriate timeframe. The patient was discharged two days following the procedure.

The appendix was sent to pathology for routine evaluation following the procedure. The resected appendix was received in formalin and measured 8.3 cm in length. There was an indurated ragged area at the junction of the proximal one-third with the rest of the appendix, but no perforation was noted. The specimen was serially sectioned at 4 mm intervals. The cut surfaces showed a 3–4 mm narrowed lumen in the proximal half of the appendix and a 0.5 cm lumen in the rest of the appendix. The entire specimen was sequentially submitted in 9 cassettes. Cassette 1 had one section from the margin of resection. Cassette 2 had the section from the appendix distal to the margin of resection. Cassettes 3–5 had sections from rest of proximal one-third of the appendix. Cassette 9 had the 1.3 cm bisected tip, and cassettes 6–8 had the grossly normal looking remainder of the appendix.

Histologic examination showed marked acute appendicitis and acute periappendicitis in the distal half of the appendix. In the sections from the middle portion of the proximal half of the appendix, a few single cells and several small clusters of goblet cells were seen in the lamina propria (Figures 1 and 2). On higher magnification, a few Paneth cells and occasional neuroendocrine cells were also seen admixed with goblet cell clusters (Figure 3). Goblet cell clusters were focally involving the inner portion of muscularis mucosae. Goblet cells showed a low nucleo-cytoplasmic ratio, mild cytologic atypia, no conspicuous nucleoli, and no mitoses. Based on these findings, a diagnosis of pTis low-well-differentiated intramucosal goblet cell adenocarcinoma mas made. There was no significant desmoplasia, and there were increased numbers of eosinophils noted in the lamina propria. Mucosal destruction and transmural acute and chronic inflammation with periappendiceal acute inflammation were seen only in the distal portion of the appendix.

Immunohistochemical analysis showed positivity of malignant epithelial cells for CDX2 (Figure 4), cytokeratin 20 (Figures 5 and 6), cytokeratin 7, chromogranin (Figures 7–9), synaptophysin, and pancytokeratin. Mucicarmine stain confirmed the presence of mucin in the malignant goblet cells (Figure 10). Immunohistochemical stain for lysozyme showed weak positivity in the goblet cells and strong positivity in the Paneth cells of adenocarcinoma (Figure 11). It was difficult to assess CD56 due to the diffuse staining of nerve fibers in the lamina propria of the appendix. The cells were limited to the lamina propria and muscularis mucosae with no involvement of the appendiceal submucosa, muscularis propria, subserosa, or external surface of the appendix. The intramucosal adenocarcinoma was present in three consecutive transverse sections, each with an approximate thickness

of 4 mm. The maximum dimension of the intramucosal adenocarcinoma was, therefore, approximately 12 mm. Upon review of multiple levels and deeper sections, the tumor did not increase in size and the margins were completely free of tumor. The final diagnosis was determined to be a low grade (G1), well-differentiated intramucosal goblet cell adenocarcinoma measuring 1.2 × 0.3 × 0.2 cm.

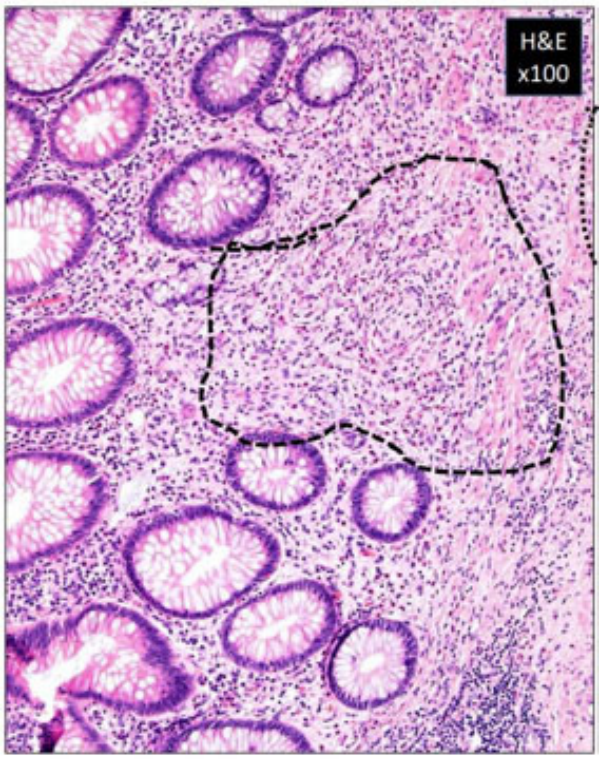

Figure 1: Single scattered and clustered goblet cells in the lamina propria (H&E stain; ×100).

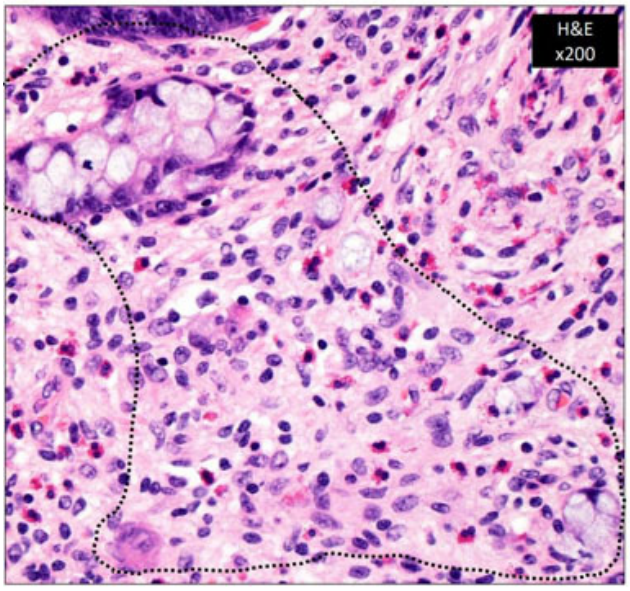

Figure 2: Single scattered and clustered goblet cells in the lamina propria (H&E stain; ×200).

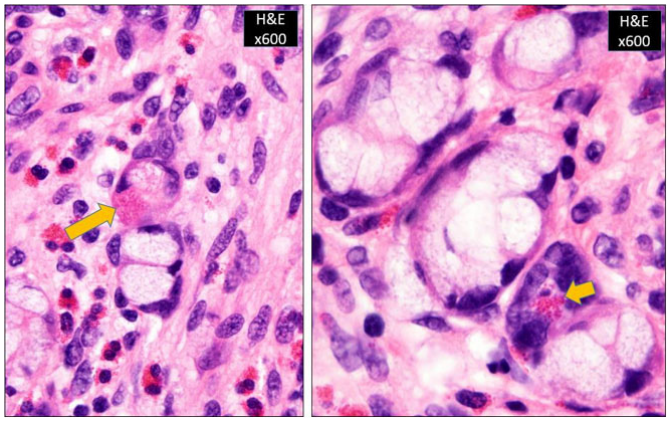

Figure 3: Paneth cell (long arrow) and a neuroendocrine cell (short arrow) (H&E Stain; ×600).

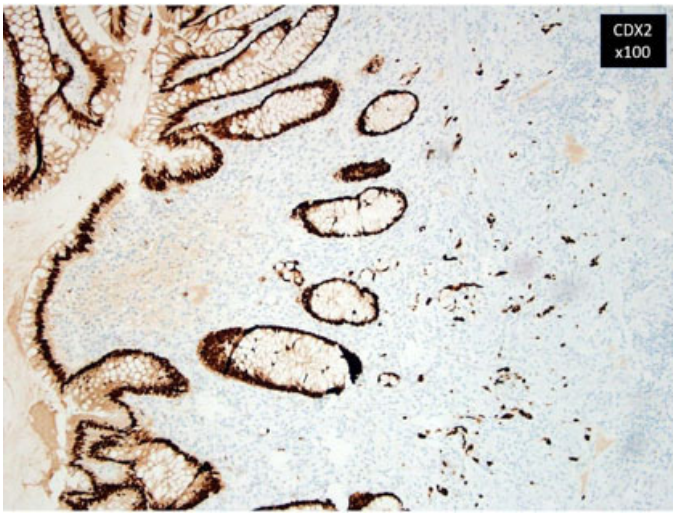

Figure 4: CDX2 positivity in single scattered and clustered goblet cells in the lamina propria (CDX2 immunohistochemical stain; ×100).

Figure 5: Cytokeratin 20 positivity in single scattered and clustered goblet cells in the lamina propria (CK20 immunohistochemical stain; ×100).

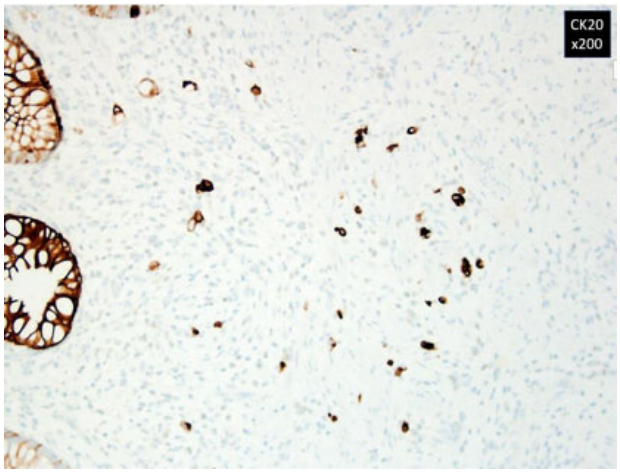

Figure 6: Cytokeratin 20 positivity in single scattered and clustered goblet cells in the lamina propria (CK20 immunohistochemical stain; ×200).

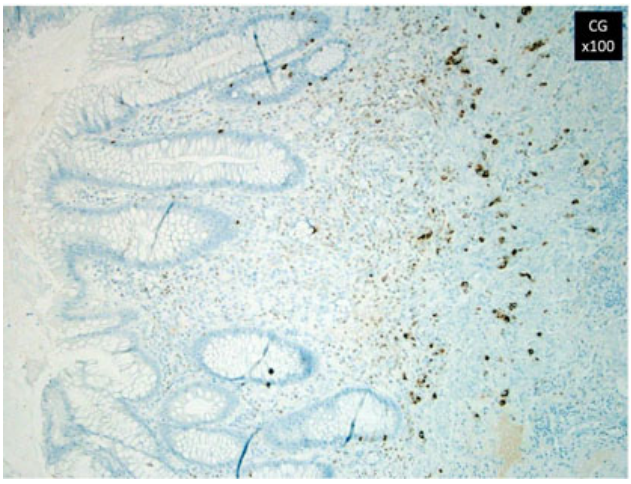

Figure 7: Chromogranin positivity in single scattered and clustered goblet cells in the lamina propria (chromogranin immunohistochemical stain; ×100).

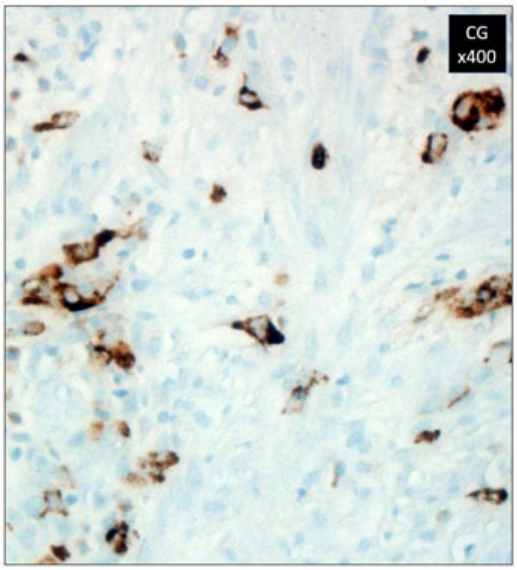

Figure 8: Chromogranin positivity in single scattered and clustered goblet cells in the lamina propria (chromogranin immunohistochemical stain; ×400).

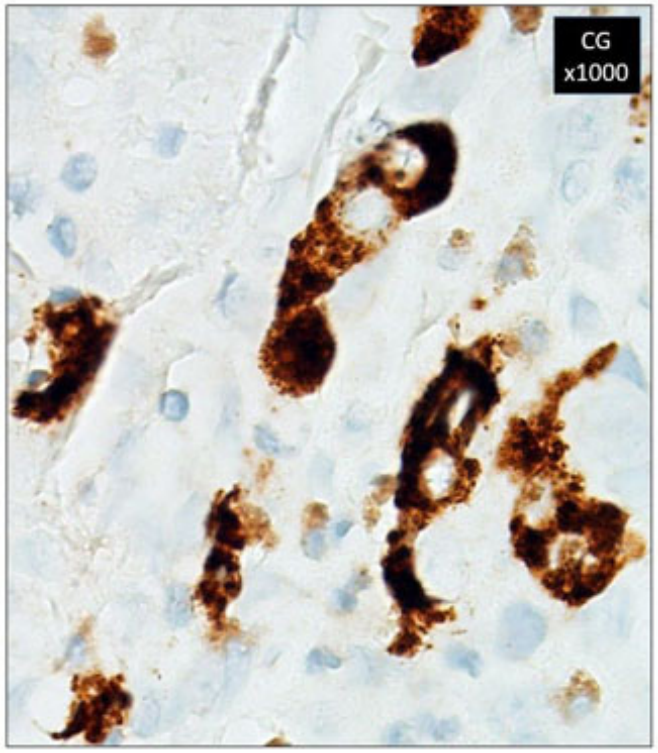

Figure 9: Chromogranin positivity in single scattered and clustered goblet cells in the lamina propria (chromogranin immunohistochemical stain; ×1000).

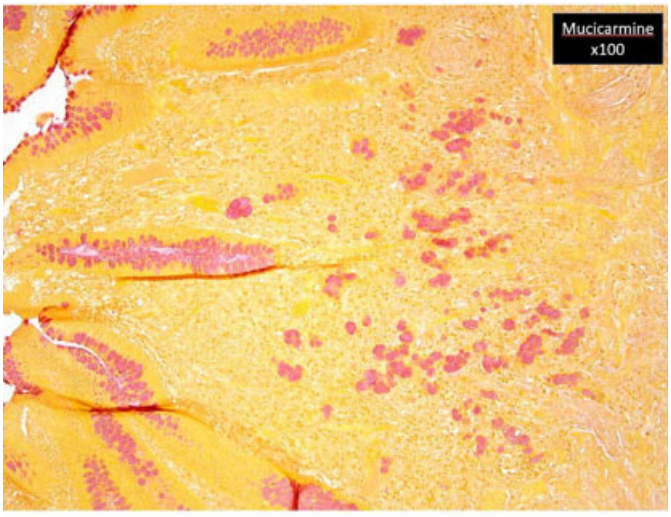

Figure 10: Mucicarmine positivity in single scattered and clustered goblet cells in the lamina propria (Mucicarmine stain; ×100).

DISCUSSION

Appendiceal goblet cell adenocarcinomas usually have features of both a neuroendocrine tumor as well as an adenocarcinoma. However, because these tumors are composed mainly of mucin-secreting cells (goblet cells) and have only a minor neuroendocrine component, they

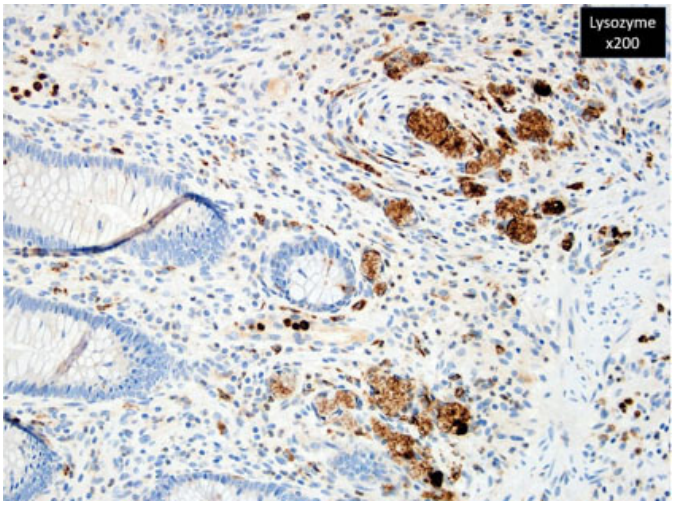

Figure 11: Weakly positive lysozyme in single scattered and clustered goblet cells and strong lysozyme positivity in the Paneth cells (arrows) in the lamina propria (lysozyme immunohistochemical stain; ×200).

were removed from the category of carcinoid tumors (i.e., neuroendocrine tumors) and were reclassified as goblet cell adenocarcinomas in the 2019 World Health Organization (WHO) classification of tumors of the digestive system. Appendiceal goblet cell adenocarcinomas are thus both staged and classified as adenocarcinomas [2]. The tumors are considered low grade if they have components of small tubular or goblet cell clusters in combination with cuboidal glandular cells and variable numbers of Paneth-like cells [3]. The tumor cells in the low-grade type have a low nucleocytoplasmic ratio, mild to moderate cytologic atypia, and infrequent mitoses [3]. They are graded as high grade if they grow as single files of tumor cells, large aggregates, and fused goblet cell clusters [3]. Immunohistochemically, the 2019 WHO classification does not require positivity for neuroendocrine marker(s) for the diagnosis, but goblet cell adenocarcinomas most often show strong positivity for chromogranin A in some of the tumor cells, and synaptophysin can be negative in some cases. CD56 can also be positive [1]. According to a recent study, appendiceal goblet cell adenocarcinoma should be diagnosed when it has low grade features and positivity for neuroendocrine marker(s) because the tumor is a unique morphological, immunohistochemical, transcriptomic, and immunological entity that is very different from both classic signet ring-cell adenocarcinomas with discohesive signet ring cells and intestinal adenocarcinoma with a cohesive ring cell component [5]. For this reason, the authors recommend differentiating goblet cell adenocarcinoma from these intestinal signet ring cell carcinoma types that can involve the appendix and have the potential to be histologically confused with appendiceal goblet cell adenocarcinoma [5].

The mean age of diagnosis for appendiceal goblet cell adenocarcinoma is 52 years, with both men and women being affected at roughly the same frequency [2]. While no risk factors have been successfully elucidated for developing this rare tumor, there have been some cases in China that were associated with schistosomiasis [6]. The overall 5-year survival for patients with stages I, II, III, IV has been described as 100%, 76%, 22%, and 14%, respectively [2]. Staging is accomplished using the TNM nomenclature [2, 7]. Our case represents a pTis pN0 pM0 tumor.

The treatment for appendiceal goblet cell adenocarcinoma centers around surgical intervention (i.e., appendectomy and right hemicolectomy) with adjuvant chemotherapy being appropriate in certain circumstances [8]. Intramucosal appendiceal goblet cell adenocarcinoma (pTis tumors) requires no further treatment. Therefore, the literature supports no further treatment for the patient presented in this paper. Tumors that are stage 1 can be safely and effectively treated with appendectomy exclusively [8]. For tumors that are a higher stage, a right hemicolectomy can be performed, with the goal being to adequately assess for nodal metastasis [8]. Similarly, the management becomes a right hemicolectomy if the margin of resection is positive, but this procedure has been mentioned in the literature as a common mode of treatment even in cases without involvement of the margin of resection [1]. Aggressive measures to assess for nodal metastasis in pT1 and higher stage is potentially justified due to the high propensity of goblet cell adenocarcinomas to metastasize to the lymph nodes [8, 9]. However, there is controversy in the literature regarding the efficacy of right hemicolectomy in patients with goblet cell adenocarcinoma. For example, an analysis done in 2006 of 53 patients showed no difference in the 5-year survival rate between those treated with right hemicolectomy and those treated with appendectomy alone [8, 10]. In addition, there is controversy surrounding the efficacy of adjuvant chemotherapy following surgery. For example, one study showed a statistically insignificant difference between chemotherapy with 5FU and leucovorin versus right hemicolectomy alone [8, 10]. All of this underscores the need for further research to establish a standard of care with regard to the management of appendiceal goblet cell adenocarcinomas.

Interestingly, the diagnosis of appendiceal goblet cell adenocarcinoma in this case was made following appendectomy, and neither the patient nor the various treatment teams were antecedently aware of the presence of the tumor. The evil as represented by the goblet cell adenocarcinoma was, so to speak, accidentally and fortunately nipped in the bud. This case represents a reason for considerable prudence among those responsible for routine evaluation of tissue following appendectomy. At many institutions, grossing guidelines recommend the submission of only three sections of the appendix: the base, the bisected tip, and the middle.

However, following this protocol would have caused this case of appendiceal goblet cell adenocarcinoma to be missed because the tumor in our case was located in the middle 12 mm of the proximal half of the appendix. At our institution, the practice of submitting representative sections (a bisected 1.5 cm tip, a section from the middle of the appendix or from the site of perforation and a section from the margin of resection) was changed in 2020 to submitting the entire appendix (a bisected 1.5 cm tip and sequential submission of the entire appendix with the last block containing the section from margin of resection) because of the incidental detection of carcinoid or goblet cell adenocarcinoma in some of the cases. After the practice was changed to submitting the whole appendix, more tumors such as that described in this case were discovered. Therefore, our case provides evidence that submission of the entire appendix for histological examination should be the standard of care. By submitting the entire appendix, rare cancers such as that presented in this case will be less likely to be overlooked.

There have been other calls for a more thorough examination of the appendix following routine appendectomy. For example, a recent retrospective cross-sectional study showed that a significant portion of rare appendiceal pathologies were not suspected either radiologically or clinically prior to microscopic analysis [11]. Moreover, given the dearth of research with respect to the treatment of patients with appendiceal goblet cell adenocarcinoma, it is important to identify cases of this rare tumor and add to the literature.

CONCLUSION

Appendiceal goblet cell adenocarcinoma is a rare tumor of the appendix that has histologic features of both a well-differentiated carcinoid tumor and adenocarcinoma, but the presence of neuroendocrine cells is not required for the diagnosis because they are more aggressive than well-differentiated neuroendocrine tumors of the appendix and are both staged and classified as adenocarcinomas. Clinically this tumor can present like more traditional cases of acute appendicitis; however, it can also be found incidentally following routine appendectomy. Intramucosal appendiceal goblet cell adenocarcinomas can be difficult to initially find, so considerable care is required to identify cases. In addition, this article provides evidence that the standard of care should include submission of the entire appendix for histological analysis. There is currently no consensus regarding treatment, and more research to this end is required.

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Author Contributions

John Yablonski – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Christian D Tvetenstarnd – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jagmohan Sidhu – Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission
The corresponding author is the guarantor of submission.

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.