

Is T3 appendiceal goblet cell adenocarcinoma still an oncological riddle for acute care surgeons? A case report

Alessandro Bergna,^{1,2,3} Francesco Salvetti,¹ Simona Carando,^{1,2} Marco Monti,² Edoardo Segalini²

¹Department of Clinical, Surgical, Diagnostic and Paediatric Sciences, University of Pavia, Italy; ²Department of General Surgery, ASST Crema, Ospedale Maggiore di Crema, Italy; ³Department of General Surgery, Humanitas San Pio X, Milan, Italy

Abstract

Appendectomy for acute appendicitis is one of the most commonly performed surgical procedures nowadays. Here we present

Correspondence: Alessandro Bergna, ASST Crema - Ospedale Maggiore di Crema, via Largo Ugo Dossena 2, 26013 Crema (CR), Italy.
Tel.: +39.0373.280323.
E-mail: alessandro.bergna01@universitadipavia.it

Key words: goblet cell adenocarcinoma; acute appendicitis; laparoscopic appendectomy; CRS-HIPEC; case report.

Contributions: AB conceived, designed, wrote, and submitted the case report. FS wrote the paper and made contributions to a critical review of the case report before final drafting. SC made contributions to data collection and wrote the paper. MM managed the case, wrote the paper, and was involved in the revision of the paper before final drafting. ES managed the case, wrote and critically revised the paper before final drafting. All authors read and approved the final version of the paper and agreed to be accountable for all aspects of the work.

Ethical approval: this case report does not include any interaction or intervention with human subjects and does not include any access to identifiable private information. For this reason, no ethical approval was needed.

Availability of data and material: data that support the findings of this study are available on request from the corresponding author.

Competing interests: all authors declare that they have no competing interests.

Funding: the authors did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Received: 29 May 2023.
Accepted: 19 September 2023.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

©Copyright: the Author(s), 2023
Licensee PAGEPress, Italy
Case Reports in Emergency Surgery and Trauma 2023; 1:16
doi:10.4081/crest.2023.16

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).

the case of a 48-year-old man who was admitted to our emergency department with abdominal pain suggestive of acute appendicitis. Then, the patient underwent a laparoscopic appendectomy, and the histological examination of the surgical specimen revealed an unexpected occult neoplasm: goblet cell adenocarcinoma (GCA). After a multidisciplinary evaluation, a right colectomy was performed with good oncological and clinical outcomes at the 1-year follow-up evaluation. To date, either non-operative strategies or surgical radicalization treatment have been proposed for this condition. Therefore, the choice of the proper therapeutic algorithm is still a challenge for surgeons. This case report is an addition to the existing literature to hold surgeons' attention when managing such cases: multidisciplinary evaluation and patient-targeted therapies are the key steps to achieving good oncological and surgical outcomes.

Introduction

Acute appendicitis is one of the most common causes of acute abdominal pain and appendectomy is one of the most performed surgical procedures in the world every year.¹ Histological examination of surgical specimens could find an unexpected occult tumoral disease such as GCA.²⁻⁴ GCA is a rare neoplasm with specific histological and clinical features characterized by both exocrine and neuroendocrine differentiation.^{2,3} Due to this dual nature, GCA is more aggressive than other carcinomas of the gut and has a greater risk of loco-regional and peritoneal spreading that significantly affects patient survival.⁴ Histological features of this tumor allow many management strategies according to different interpretations of the risk of tumoral spreading. To date, no standard of care for this condition has been established. Appendectomy alone, right colectomy or cytoreductive surgery, and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) are feasible treatment options according to the grade and stage of the disease.⁵ Here, we present the case of a T3, stage II GCA to underline the need for multidisciplinary management to overcome the current concerns in the management of locally advanced appendiceal GCA.

Case report

A 48-year-old man was admitted in March 2022 to our emergency department complaining of pain in the right lower abdomen that had started two days before in the mesogastrium and fever (39°C). Past medical history was unremarkable. Physical examination showed abdominal tenderness in the right iliac fossa and both positive Rovsing's and Blumberg's signs. Blood examination showed a CRP of 12.85 mg/dL and a white blood cell count of

15.9×10⁹/L (53% polymorphonuclear neutrophils). An Appendicitis Inflammatory Response (AIR) score of 8 was calculated according to WSES guidelines.^{6,7} An abdominal POCUS showed a thickened appendix wall (5 mm) without abdominal free fluid. A CT scan was then performed showing an appendix with a thickened wall (8 mm) and a luminal diameter of 8 mm. Other CT findings were the presence of coprolites inside the appendix, fat stranding of the mesentery, and loco-regional lymph node enlargement (Figure 1).

An exploratory laparoscopy made the diagnosis of gangrenous appendicitis with minimal local exudate and regional pelvic peritonitis according to Gomes *et al.*⁸ The intraoperative evaluation confirmed the absence of an appendicular abscess and perforation. An appendectomy was performed. The specimen was handled safely to avoid any rupture and then removed with the use of a sample bag. The recovery was uneventful, and the patient was discharged on postoperative day 2. Histological examination of the appendix showed an unexpected G2, pT3, KRAS-, BRAF- Goblet Cell Adenocarcinoma with perineural invasion and clear resection margins. A colonoscopy and a thoracoabdominal CT scan were performed without any suspicious finding of synchronous primitive or metastatic disease. According to AJCC, the patient was diagnosed with a stage II neoplasm.⁹ A multidisciplinary team with the presence of a surgeon, an oncologist, and a pathologist decided to perform a right colectomy. The decision was shared with the patient who agreed with the treatment plan. A laparoscopic right colectomy was then performed about a month after the appendectomy. The recovery was uneventful, and the patient was discharged on postoperative day 5 with a fast return to daily activities. Histological examination of the specimen showed the absence of any residual neoplastic tissue in the right colon; no metastases were found in the 16 regional lymph nodes removed. According to the histological findings, the multidisciplinary team decided to avoid adjuvant chemotherapy and to proceed with a periodic clinical and radiological follow-up. After 1 year, the CT scan did not find any recurrence. The patient reported his satisfaction with the therapeutic pathway.

Discussion

GCA is a rare primary appendiceal neoplasm that is usually incidentally discovered following an appendectomy performed for acute appendicitis.³ This condition set up a double challenge for surgeons: the choice of proper treatment for appendicitis in the acute care setting and the even trickier management of a tumoral disease. We managed the case of a patient complaining of abdominal pain with an intermediate risk for acute appendicitis according to the result of the AIR score. A CT scan showed the presence of an appendicolith. This is a recognized independent risk factor for non-operative management (NOM) failure.^{7,10} Thus, even if in this clinical scenario and the result of the AIR score could leave the choice between NOM versus operative management to the surgeon, the presence of a CT-detected appendicolith made it necessary to perform an appendectomy. In the absence of any appendicolith, the patient would have been admitted for starting a conservative treatment, thereby delaying a surgical intervention, and leaving the diagnosis of a tumoral disease unrecognized. Acute appendicitis is often the only early clinical manifestation of appendiceal tumors, as happened in our experience.⁵ With the benefit of insight, the choice to proceed to a laparoscopic appendectomy turned out to be beneficial for the patient. As rarely happens, the histological examination of the specimen indeed uncovered an occult GCA. This diagnosis is often unexpected because the diagnostic investigation required to detect an appendiceal neoplasm is both not feasible in the emergency setting and unnecessary due to their rarity. GCA is a neoplasm with specific

histological features that can exhibit both mucinous and neuroendocrine differentiation.^{2,3} Due to this dual nature, GCA is characterized by a wide range of possible clinical evolutions with a greater risk of loco-regional diffusion and peritoneal spreading mostly in the case of high-grade and locally advanced tumors. Although surgery plays a key role in the treatment of early-stage and organ-confined tumors, long-term survival and local recurrence are primarily determined by GCA grade and stage.⁵ The patient had a G2, T3, stage II GCA. A right colectomy seems to be mandatory according to guidelines to treat a T3 GCA but, to date, there is no consensus about the standard of care for a tumor at this stage.^{5,11} Real benefits from radicalization surgery and other procedures (*i.e.* CRS- HIPEC) still stand unexplored due to the rarity of GCA and the lack of prospective studies. According to the literature, negative surgical margins and harvesting more than 12 lymph nodes are related to improved survival.^{12,13} However, a recent systematic review found that T3 GCAs were N0 in 81-87% of cases.¹⁴ In 2021, a retrospective analysis confirmed a survival benefit for patients with a T3 GCA after a hemicolectomy with a 5-year survival rate of 85,4% in the hemicolectomy group vs 82,0% in the non-hemicolectomy group ($p=0.028$).⁵ According to the literature, recurrences can also occur in patients after a radical resection: two retrospective cohort studies in 2015 found a recurrence rate of 20%-29% for patients who underwent a hemicolectomy, and a multicenter study in 2018 found a recurrence rate of 16%.¹⁵⁻¹⁷ In our experience, a multidisciplinary team selected the treatment strategy, and a right colectomy was then performed. The age of the patient and the tumor grade indeed leaned toward the need for a radicalization procedure. Beyond grading and staging, other risk factors have been identified for disease recurrence and peritoneal spreading such as the perforated appendix, perpendicolar abscess, and resection margin <1mm. Madsen *et al.* investigated the use of CRS-HIPEC in eight patients with localized disease presenting these criteria of high risk for peritoneal metastases: in their experience, the 5-year overall survival was 100% with a median follow-up time of 3.5 years.¹⁸ However, in this case, none of these criteria was present. To date, it is still unclear whether a hemicolectomy alone is enough to treat T3 GCA or whether CRS-HIPEC is a therapeutic option in patients without metastatic disease at onset since many of these patients may experience a disease relapse even after a hemicolectomy. In this case, a laparoscopic right colectomy was performed safely with a fast recovery and an uneventful postop-



Figure 1. CT scan performed at the onset of symptoms showed a thickened appendix wall with coprolites and edema of the mesentery.

erative period. Moreover, hemicolectomy alone was effective in treating the patient's disease without any recurrence at 1-year follow-up. CRS-HIPEC seems to improve survival, but the procedure-related complications are a major concern: a recent systematic review by Wajekar *et al.* reported morbidity rates between 12%-60% and a mortality rate of 0.9%-5.8%.¹⁹ For this reason, the use of CRS-HIPEC is currently reserved for selected patients within clinical trials at referral high-volume centers. Our experience, although a case report, demonstrates how difficult it is to define a proper therapeutic strategy in patients affected by a locally advanced appendiceal GCA without clinical and histological high-risk recurrence features. When managing such cases, a multidisciplinary evaluation can properly assess the safety and effectiveness of the different management strategies to improve patient survival.^{5,11}

Conclusions

Appendectomy is one of the most commonly performed procedures in the emergency setting. Although rare, the sudden finding of a rare and potentially wide-spreading neoplasm could represent a challenge for acute care surgeons. The presence of an underlying GCA does not change the surgical strategy in the emergency setting but a further proper assessment of the condition is mandatory to improve patients' survival. To date, different approaches have been proposed for the treatment of this condition when it presents as a T3, advanced, but organ-confined neoplasm. In our experience, right colectomy was found to be safe and effective without any recurrence at 1-year follow-up. Real benefits occurring from more invasive treatments (*i.e.* CRS-HIPEC) are still to be cleared. Thus, the choice of the proper treatment algorithm still represents a riddle for surgeons because a variety of treatments is affordable. In our experience, multidisciplinary management was a crucial step to properly define a tailored treatment strategy, however, further prospective studies and disease-specific consensus guidelines are required to achieve high-quality statements in the completion treatment of appendiceal GCA.

References

1. Cervellin G, Mora R, Ticinesi A, et al. Epidemiology and outcomes of acute abdominal pain in a large urban Emergency Department: retrospective analysis of 5,340 cases. *Ann Transl Med* 2016;4:362–362.
2. Tang LH, Shia J, Soslow RA, et al. Pathologic classification and clinical behavior of the spectrum of goblet cell carcinoid tumors of the appendix. *Am J Surg Pathol* 2008;32:1429–43.
3. Taggart MW, Abraham SC, Overman MJ, et al. 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;139:782–90.
4. McCusker ME, Coté 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;94:3307–12.
5. Kowalsky SJ, Nassour I, AlMasri S, et al. Omission of right hemicolectomy may be safe for some appendiceal goblet cell adenocarcinomas: A survival analysis of the national cancer database. *Ann Surg Oncol* 2021;28:8916–25.
6. Andersson M, Andersson RE. The appendicitis inflammatory response score: a tool for the diagnosis of acute appendicitis that outperforms the Alvarado score. *World J Surg.* 2008;32:1843–9.
7. Di Saverio S, Podda M, De Simone B, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. *World J Emerg Surg* 2020;15:27.
8. Gomes CA, Sartelli M, Di Saverio S, et al. Acute appendicitis: proposal of a new comprehensive grading system based on clinical, imaging and laparoscopic findings. *World J Emerg Surg* 2015;10:60.
9. Amin MB, Edge S, Greene F, et al. *AJCC Cancer Staging Manual.* Springer International Publishing; 2017.
10. Vons C, Barry C, Maitre S, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *Lancet* 2011;377:1573–9.
11. Pape U-F, Perren A, Niederle B, et al. ENETS consensus guidelines for the management of patients with neuroendocrine neoplasms from the jejunum-ileum and the appendix including goblet cell carcinomas. *Neuroendocrinology* 2012;95:135–56.
12. Fields AC, Lu P, Enzinger A, et al. Treatment patterns and outcomes in goblet cell carcinoid tumors of the appendix. *J Surg Oncol* 2019;120:1096–101.
13. Wang G, Li Q, Chen W. Chemotherapy in the treatment of different histological types of appendiceal cancers: a SEER based study. *BMC Cancer* 2021;21:778.
14. Palmer K, Weerasuriya S, Chandrakumaran K, et al. Goblet cell adenocarcinoma of the appendix: A systematic review and incidence and survival of 1,225 cases from an English cancer registry. *Front Oncol* 2022;12:915028.
15. Rossi RE, Luong T-V, Caplin ME, et al. Goblet Cell Appendiceal Tumors - Management Dilemmas and Long-Term Outcomes. *Surg Oncol* 2015;24:47–53.
16. Olsen IH, Holt N, Langer SW, et al. Goblet cell carcinoids: characteristics of a Danish cohort of 83 patients. *PLoS One* 2015;10:e0117627.
17. Tsang ES, McConnell YJ, Schaeffer DF, et al. Outcomes of surgical and chemotherapeutic treatments of goblet cell carcinoid tumors of the appendix. *Ann Surg Oncol* 2018;25:2391–9.
18. Madsen AH, Ladekarl M, Villadsen GE, et al. Effects of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of goblet cell carcinoma: A prospective cohort study. *Ann Surg Oncol* 2018;25:422–30.
19. Wajekar AS, Solanki SL, Patil VP. Postoperative complications and critical care management after cytoreduction surgery and hyperthermic intraperitoneal chemotherapy: A systematic review of the literature. *World J Crit Care Med* 2022;11:375–86.