

High Grade Mucinous Adenocarcinoma of the Appendix with Signet Features with Omental Metastasis

¹Department of Internal Medicine, Ascension Genesys Hospital, Grand Blanc, MI ³Division of Gastroenterology, Department of Internal Medicine, Ascension Genesys Hospital, Grand Blanc, MI

Abstract

Primary adenocarcinoma of the appendix is an uncommon malignancy of the gastrointestinal tract. Appendiceal neoplasms make up only 0.5 to 1% of all intestinal cancers, with signet cell pathology even fewer cases. The most common symptom is right lower abdominal pain, which could be indistinguishable from acute appendicitis. However, the clinical presentation is usually non-specific. In this present report, we describe a rare case of primary signet ring cell carcinoma of the appendix with omental metastases in an 81-year-old male patient. He underwent appendectomy with a laparoscopic procedure. He then received palliative systemic chemotherapy using a combination of Capecitabine and Bevacizumab.

Introduction

Primary adenocarcinoma of the appendix is an uncommon malignancy of the gastrointestinal tract. It was first described in 1882 and constitutes around 0.12 to 2.6 cases per one million people per year.¹ In addition, signet-ring cell carcinoma of the appendix is extremely rare, it constitutes approximately 4% of all primary appendiceal neoplasms.²

The most common symptom is right lower abdominal pain, which could be indistinguishable from acute appendicitis. However, the clinical presentation is usually non-specific.³ The diagnosis of signet cell adenocarcinoma is confirmed after surgical excision of the inflamed appendix and pathology analysis. The current treatment options for metastatic disease include systemic chemotherapy alone, cytoreductive surgery with a peritonectomy, hyperthermic intraoperative intraperitoneal chemotherapy.

There are few reported cases of primary signet cell appendiceal carcinoma. In this present report, we describe a rare case of primary signet ring cell carcinoma of the appendix with omental metastases in an 81-year-old male patient. He underwent appendectomy with a laparoscopic procedure. He then received palliative systemic chemotherapy using a combination of Capecitabine and Bevacizumab.

Contact

Kyle T. Knight, DO, PGY-II Ascension Genesys Hospital Email: kyle.knight@ascension.org Phone: (810) 730-1270

Fady Banno MD, MSc¹, Brandon Wiggins DO, MPH¹, Kanksha Peddi MD¹, Kyle Knight DO¹, Ali Alrammahi MD², Nathan Landesman DO²

Case Presentation

We present a case of an 81-year-old male with a past medical history of hypertension, hyperlipidemia, degenerative joint disease, depression, pulmonary fibrosis, and benign prostatic hypertrophy, prior negative esophagogastroduodenoscopy (EGD) and colonoscopy in 2017 who presented to an urgent care in January of 2021 with abdominal pain. Lab work was unremarkable and the patient was sent home with instructions to visit the emergency department if he experienced fever, increased abdominal pain, or blood in the stool. Patient presented to the emergency department (ED) with increased abdominal pain in April of 2021, and Computed Tomography (CT) scan of abdomen and pelvis with Intravenous (IV) contrast showed a cystic appendiceal lesion with right peritoneal nodularity suspicious for peritoneal carcinomatosis. Therefore, the patient underwent appendectomy the following day which revealed poorly differentiated, high-grade appendiceal adenocarcinoma with signet ring features, pT4a disease (Figure 1).

Follow-up CT scan of chest, abdomen, and pelvis a month later showed enlarged carinal lymph node measuring 2.4x 1.6 cm with diffuse mental infiltration suggestive of peritoneal carcinomatosis. In addition, tumor markers were checked and Carcinoembryonic Antigen (CEA) was elevated to 42.6. Patient had a diagnostic laparoscopy in June of 2021 and was found to have diffuse peritoneal carcinomatosis. Multiple biopsies were obtained and came back positive with high-grade mucinous adenocarcinoma with signet ring features. Patient agreed to pursue systemic chemotherapy. He was initiated on Capecitabine (Xeloda) 2000 mg tab PO, twice daily for 14 days and off for 7 days. Bevacizumab (Avastin) 7.5 mg IV infusion every 3 weeks.

In September of 2021, he presented to the ED again complaining of dull and diffuse abdominal pain, 4 out of 10 in severity. Lab work was significant for elevated lactic acid at 3.7, and hypokalemia at 3.3; however, all other lab work, including Clostridium difficile were unremarkable. CT abdomen/pelvis showed diffuse nodularity throughout the omentum consistent with omental metastasis unchanged from previous imaging in May, 2021. His abdominal pain was attributed to Xeloda and his metastatic cancer. Patient deteriorated during his admission and further labs were significant for increased lactic acid to 5.9, hypocalcemia at 7.1 (ionized calcium was 0.86) and very mild hyponatremia at 134. His respiratory function worsened, likely secondary to his underlying pulmonary fibrosis. Patient was Do Not Resuscitate/Do Not Intubate (DNR/DNI) and he unfortunately passed away during his lengthy admission after the family decided to focus on comfort measures only.

Discussion

Appendiceal malignancies are very rare, and incidence has been rising ever since the turn of the 21st century, likely related to improved access to healthcare, imaging, surveillance, and awareness of the disease process.^{4,5} Appendiceal neoplasms make up only 0.5 to 1% of all intestinal cancers, with signet cell pathology even fewer cases.⁶ Of the 1% of appendiceal intestinal malignancies, 66% are carcinoid in nature and adenocarcinoma making up the remaining portion.⁷

Appendiceal malignancies and specifically signet ring adenocarcinoma typically secrete mucin, leading to usual metastasis throughout the peritoneum and eventual obstruction.⁸ This has been termed pseudomyxoma peritonei ("Jelly Belly"), which histologically spans between high grade, poorly differentiated signet cell tumors to low grade, well differentiated neoplasms.⁹ They are classified pathologically as either mucinous/intestinal type or non-mucinous/colonic type depending on the amount of mucin seen in tumor samples, with over 50% mucin samples being designated as mucinous.¹⁰ Mucinous adenocarcinoma of the appendix is usually characterized by large quantities of invasive tumors cells with associated desmoplastic stromal reactivity.¹¹

Immunochemistry is especially helpful when classifying colorectal tumors, including appendiceal malignancies. Appendiceal malignancies can sometimes be mistaken for ovarian cancer and are differentiated by their genetic markers via CK20, CK7, and CDX2.¹²

Patients with appendiceal neoplasms are usually asymptomatic, with diagnosis made incidentally on imaging or appendectomy or have vague lower abdominal pain.¹³ Other possible presentations include GI bleed due to local invasion into the lumen of the GI tract and/or obstruction due to the aforementioned mucinous nature of the tumors.¹⁴ Labs can possibly be significant for anemia, leukocytosis, or have elevated tumor markers, typically CEA.¹⁵

Diagnosis can be assisted with computerized tomography, magnetic resonance imaging, barium enema, ultrasound or direct endoscopy. Certain diagnosis can be made on biopsy of the tumor, metastatic lesion or appendectomy if the lesion is isolated to the appendix.¹⁶ Due to the high risk of peritoneal spread, biopsy of the primary tumor should be avoided if possible, with appendectomy or peritoneal metastasis biopsy preferred.¹⁷

Treatment is dictated by extent of disease, including metastasis, as well as tumor integrity. Localized malignancy should be treated with appendectomy, especially for diagnostic purposes, as biopsy may cause seeding.¹⁸ If there is concern of spread from the primary location, more distant resection may be required. If rupture is suspected or confirmed, right hemicolectomy, whole bowel irrigation, and cytoreductive surgery maybe required.¹⁹ For patients with nodal metastasis, adjuvant FOLFOX or CAPOX regimens are recommended.²⁰ Radiation therapy is controversial and has not been thoroughly studied enough for recommendation. Further gene targeted therapies are presently being researched, and recently EGFR positive cancers have been treated with bevacizumab, a vascular endothelial growth factor inhibitor.²¹

Prognosis for mucinous adenocarcinomas of the appendix is poor, with higher morbidity/mortality in those with signet cell pathology. Five year survival for mucinous adenocarcinomas is 53.6% with five year mortality increasing to 90% for stage IV poorly differentiated adenocarcinoma, typically the signet cell type.²²

3.0'Donnell ME, Badger SA, Beattie GC, Carson J, Garstin WI, Malignant neoplasms of the appendix, Int J Colorectal Dis. 2007 Oct:22(10):1239-48. doi: 10.1007/s00384-007-0304-0. Epub 2007 Apr 20. PMID: 17447078.

5. Marmor S, Portschy PR, Tuttle TM, Virnig BA. The rise in appendiceal cancer incidence: 2000-2009. J Gastrointest Surg. 2015 Apr;19(4):743-50. doi: 10.1007/s11605-014-2726-7. Epub 2015 Jan 6. PMID: 25560182

14.Landen S, Bertrand C, Maddern GJ, Herman D, Pourbaix A, de Neve A, Schmitz A. Appendiceal mucoceles and pseudomyxoma peritonei. Surg Gynecol Obstet. 1992 Nov;175(5):401-4. PMID: 1440166.

17.Zuzarte JC, Liu YC, Cohen AM. Fine needle aspiration cytology of appendiceal mucinous cystadenoma: a case report. Acta Cytol. 1996 Mar-Apr;40(2):327-30. doi: 10.1159/000333762. PMID: 8629421.

19.Soweid AM, Clarkston WK, Andrus CH, Janney CG. Diagnosis and management of appendiceal mucoceles. Dig Dis. 1998 May-Jun;16(3):183-6. doi: 10.1159/000016863. PMID: 9618138.

6.HESKETH KT. The management of primary adenocarcinoma of the vermiform appendix. Gut. 1963 Jun:4(2):158-68. doi: 10.1136/gut.4.2.158. PMID: 13954206: PMCID: PMC1413434.

13 Hamilton DL, Stormont JM. The volcano sign of appendiceal mucocele. Gastrointest Endosc, 1989 Sep-Oct;35(5):453-6. doi: 10.1016/s0016-5107(89)72860-1. PMID: 2792684

8. Overman MJ, Asare EA, Compton CC, et al. Appendix-Carcinoma, In: AJCC Cancer Staging Manual, 8th ed, Amin MB, (Ed), AJCC, Chicago 2017, p.237

4.Connor SJ, Hanna GB, Frizelle FA. Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. Dis Colon Rectum. 1998 Jan;41(1):75-80. doi: 10.1007/BF02236899. PMID: 9510314

10.MIsdraii J. Carr NJ. Pai RK. Appendiceal adenocarcinoma. In: WHO Classification of Tumours: Digestive System Tumours, 5th ed. WHO Classification of Tumours Editorial Board (Ed). International Agency for Research on Cancer, 2019, p.147.

18.Nitecki SS. Wolff BG. Schlinkert R. Sarr MG. The natural history of surgically treated primary adenocarcinoma of the appendix. Ann Surg. 1994 Jan:219(1):51-7. doi: 10.1097/00000658-199401000-00009. PMID: 8297177: PMCID: PMC1243090.

2. Fusari M, Sorrentino N, Bottazzi EC, Del Vecchio W, Cozzolino I, Maurea S, Salvatore M, Imbriaco M. Primary signet ring cell carcinoma of the appendicitis. Acta Radiol Short Rep. 2012 Oct 5;1(9):arsr.2012.120017. doi: 10.1258/arsr.2012.120017. PMID: 23986852; PMCID: PMC3738361.

9. Sugarbaker PH, Ronnett BM, Archer A, Averbach AM, Bland R, Chang D, Dalton RR, Ettinghausen SE, Jacquet P, Jelinek J, Koslowe P, Kurman RJ, Steves MA, Stuart OA, White S, Zahn CM, Zoetmulder FA. Pseudomyxoma peritonei syndrome. Adv Surg. 1996;30:233-80. PMID: 8960339.

12.Werling RW, Yaziji H, Bacchi CE, Gown AM. CDX2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin: an immunohistochemical survey of 476 primary and metastatic carcinomas. Am J Surg Pathol. 2003 Mar;27(3):303-10. doi: 10.1097/00000478-200303000-00003. PMID: 12604886.

22.Asare EA, Compton CC, Hanna NN, Kosinski LA, Washington MK, Kakar S, Weiser MR, Overman MJ. The impact of stage, grade, and mucinous histology on the efficacy of systemic chemotherapy in adenocarcinomas of the appendix: Analysis of the National Cancer Data Base. Cancer. 2016 Jan 15;122(2):213-21. doi: 10.1002/cncr.29744. Epub 2015 Oct 27. PMID: 26506400; PMCID: PMC4860278.

15.Carmignani CP, Hampton R, Sugarbaker CE, Chang D, Sugarbaker PH. Utility of CEA and CA 19-9 tumor markers in diagnosis and prognostic assessment of mucinous epithelial cancers of the appendix. J Surg Oncol. 2004 Sep 15;87(4):162-6. doi: 10.1002/jso.20107. PMID: 15334630.

16.Wang H, Chen YQ, Wei R, Wang QB, Song B, Wang CY, Zhang B. Appendiceal mucocele: A diagnostic dilemma in differentiating malignant from benign lesions with CT. AJR Am J Roentgenol. 2013 Oct;201(4):W590-5. doi: 10.2214/AJR.12.9260. PMID: 24059397.

Appendiceal malignancies are very rare. Signet ring adenocarcinoma of the appendix typically secretes mucin leading to metastasis throughout the peritoneum and eventual obstruction. Treatment is based on stage and histology. Surgical resection and peritoneal debulking is possible. High-grade tumors require further prospective trials to evaluate treatment, but treatment options include surgical management as well systemic chemotherapy.



Conclusions

Figure 1.



Figure 1: Histologic examination showing a signet cell carcinoma of the appendix infiltrating the peritoneum and diaphragm. (A) right lower quadrant peritoneum biopsy, (H&E stain 100x): High grade mucinous carcinoma peritonei with signet ring cells. Pool of mucin with a cluster of epithelium that shows signs of metastatic carcinoma (enlarged nuclei, atypia, pleomorphic changes). (B, C, and D) Right diaphragm peritoneum biopsy. High grade mucinous carcinoma peritonei with signet ring cells. Image B at 100x, C at 200x, and D at 400x. (E & F) immunohistochemical cytokeratin stain (AE1/AE3) shows strong positivity of high grade carcinoma. E at 100x, and F at 400x.

7.Ronnett BM, Kurman RJ, Shmookler BM, Sugarbaker PH, Young RH. The morphologic spectrum of ovarian metastases of appendiceal adenocarcinomas: a clinicopathol. 1997 Oct;21(10):1144-55. doi: 10.1097/00000478-199710000-00004. PMID: 9331286.

11.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 histopathology. 2017 Dec;71(6):847-858. doi: 10.1111/his.13324. Epub 2017 Sep 19. PMID: 28746986.

20.André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A; Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004 Jun 3;350(23):2343-51. doi: 10.1056/NEJMoa032709. PMID: 15175436 21.Choe JH, Overman MJ, Fournier KF, Royal RE, Ohinata A, Rafeeq S, Beaty K, Phillips JK, Wolff RA, Mansfield PF, Eng C. Improved Survival with Anti-VEGF Therapy in the Treatment of Unresectable Appendiceal Epithelial Neoplasms. Ann Surg Oncol. 2015 Aug;22(8):2578-84. doi: 10.1245/s10434-014-4335-9. Epub 2015 Jan 13. PMID: 25582740.