J Gastrointest Canc (2019) 50:331–333
DOI 10.1007/s12029-017-0018-7

CASE REPORT

An Unusual Progression of Signet-Ring Cell Carcinoma of the Appendix in a Caucasian Woman

Katelynn Davis[1,2] · **Andrew M. Bellizzi**[2] · **Carlos H. F. Chan**[1,3]

Published online: 18 October 2017
© Springer Science+Business Media, LLC 2017

Introduction

Malignant neoplasms of the appendix are rare. The least common of this group is signet-ring cell carcinoma (SRCC), making up about 4% of primary appendiceal malignant neoplasms [1]. According to a SEER (Surveillance, Epidemiology, and End Results) database study analyzing data between 1973 and 2001, SRCC of the appendix has an incidence of 0.15 per million people per year [1]. This tumor carries a worse prognosis than other primary appendiceal neoplasms with patients more likely to have locally advanced (T4) disease (56%), node-positive disease (61%), and metastases (56%) [2, 3]. Median disease-specific survival is 25 months, and 5-year disease-specific survival is 27% [3].

Case Report

A 38-year-old woman with past medical history significant for hypothyroidism presented for a laparoscopic tubal ligation in May of 2004. An enlarged appendix was noted intraoperatively and removed. Histological analysis revealed a SRCC of the appendix with transmural involvement. She then underwent a right hemicolectomy with positive peritoneal lavage. She received 5 months of adjuvant chemotherapy with FOLFOX (leucovorin, 5-fluorouracil, and oxaliplatin) and was then followed with serial CT scans and colonoscopies. Despite having a disseminated high-grade cancer, she was recurrence free for 11 years until a screening CT scan, which showed mesenteric masses near the ileocolic anastomosis suspicious for cancer recurrence (Fig. 1). Exploratory laparotomy was done with segmental resection of the previous ileocolic anastomosis and bilateral salpingo-oophorectomy. Pathology showed poorly differentiated SRCC involving the ileocolic anastomosis site transmurally (Fig. 2) and metastatic deposits in the right ovary, serosal surface of the ileum, and one lymph node. Molecular analysis of recurrent tumor was negative for mutations in BRAF (exons 11 and 15), KRAS (exons 2, 3, and 4), NRAS (exons 2, 3, and 4), and HRAS (exons 2 and 3). Additionally, no microsatellite instability was detected: BAT25, BAT26, D2s123, D5s346, and D17s250 were all stable. The patient was then referred to the University of Iowa Hospital and Clinics for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC). A new gastric primary SRCC was excluded with upper endoscopy and random biopsies. She then underwent CRS-HIPEC in February of 2016 where surgical exploration revealed a peritoneal carcinomatosis index of 21 out of 39. Omentectomy, cholecystectomy, total pelvic peritonectomy, right upper quadrant peritonectomy, and ablation of multiple small bowel nodules were performed achieving a complete cytoreduction prior to the HIPEC treatment. Pathology showed widespread fibrosis and granulation tissue with areas suspicious for metastatic adenocarcinoma in the omentum and pelvic peritoneum. A surveillance CT scan was performed in June of 2016 revealing increased septal thickening of the right and left lung parenchyma with scattered nodular thickening of the lingular segment of the left lung, findings consistent with lymphangitic spread of her cancer (Fig. 3). Transbronchial biopsies revealed

✉ Carlos H. F. Chan
carloshfchan@gmail.com

[1] Department of Surgery, Carver College of Medicine, University of Iowa, Iowa City, IA, USA

[2] Department of Pathology, Carver College of Medicine, University of Iowa, Iowa City, IA, USA

[3] Division of Surgical Oncology and Endocrine Surgery, University of Iowa Hospital and Clinics, 200 Hawkins Drive, Iowa City, IA 52242, USA

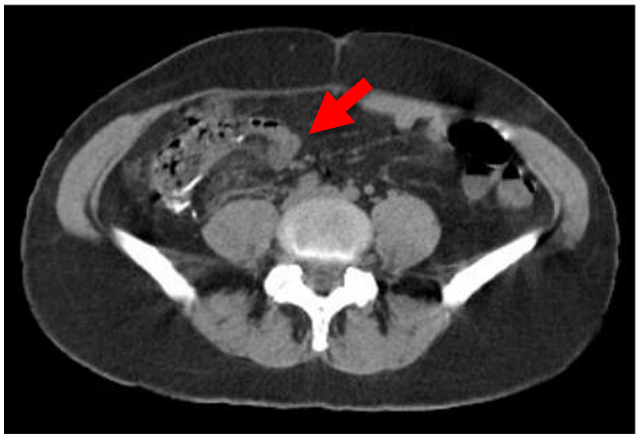

Fig. 1 CT image showing the recurrence of signet-ring cell carcinoma at the ileocolic anastomosis (red arrow)

metastatic adenocarcinoma with signet-ring features in the left lung (Fig. 4). Palliative chemotherapy treatment with panitumumab and irinotecan was initiated. In January of 2017, she died without evidence of peritoneal recurrence.

Discussion

This case reports an unusual course of primary appendiceal SRCC, following the patient from diagnosis to death. She lived with disseminated appendiceal SRCC over 12 years after diagnosis, far surpassing the median disease-specific survival of 25 months [3]. Many of the reported cases do not follow the patient for recurrence or death, and no prior case report has described a primary appendiceal SRCC with this length of survival or recurrence-free interval [4–12]. The underlying reason for her prolonged survival is unknown.

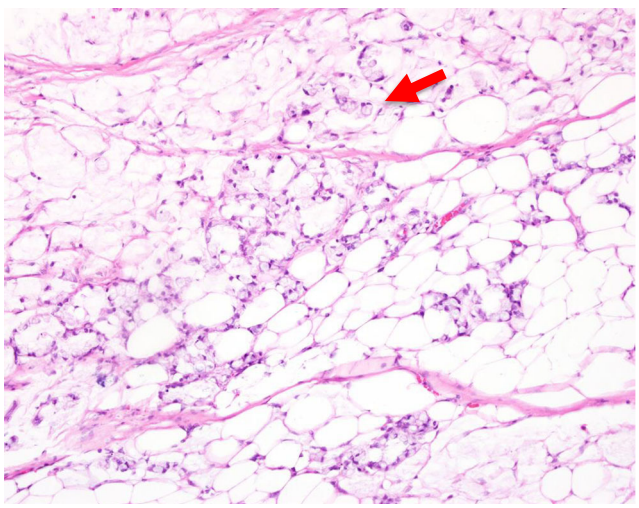

Fig. 2 Histological image showing infiltration of SRCC cells (red arrow) in the mesenteric fat at the ileocolic anastomosis

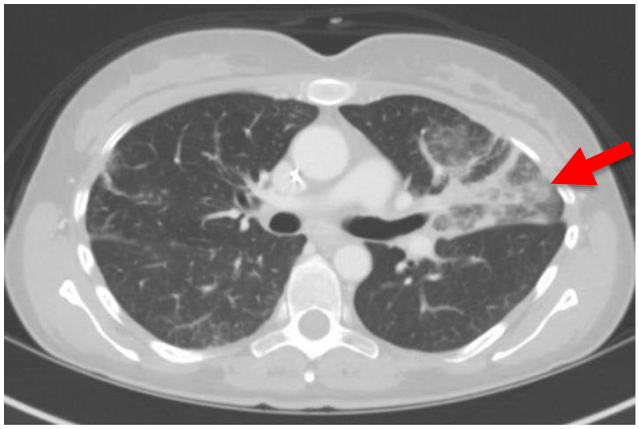

Fig. 3 CT image showing lymphangitic spread of SRCC in the lung (red arrow)

Patients with cancer of the appendix tend to present with advanced disease because they are often asymptomatic until later in the disease course when symptoms become apparent. Patients with fulminant peritoneal carcinomatosis often present with anorexia, abdominal bloating, generalized abdominal pain, fatigue, and unintentional weight loss. Unless incidentally found on imaging or during surgery as in the present case, the initial presenting symptoms could resemble acute appendicitis with a primary presenting complaint of right-lower-quadrant pain. Due to the non-specific findings on imaging studies, patients are often treated with appendectomy based on a presumed diagnosis of acute appendicitis. Correct diagnosis is commonly made with post-operative pathology report.

Ruptured appendiceal cancer with peritoneal spillage or seeding could lead to the development of peritoneal carcinomatosis. Although the presence of free-peritoneal cancer cells is a well-known risk factor for the development of peritoneal metastasis for colorectal cancers, only about 20–40% of patients with positive peritoneal cytology develop peritoneal

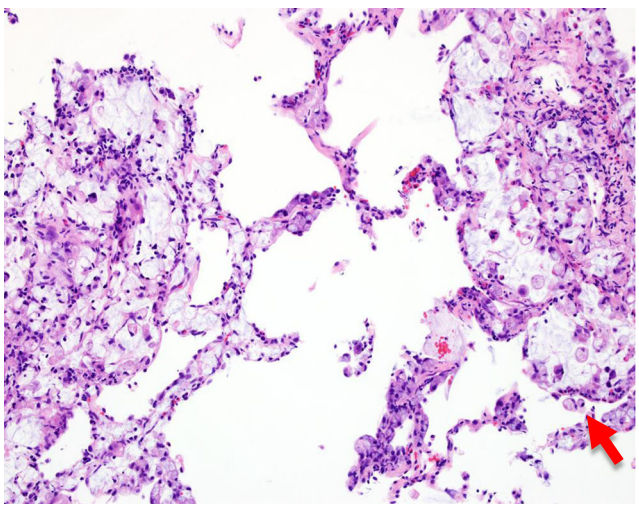

Fig. 4 Histological image showing SRCC cells in lung biopsy (red arrow)

recurrence [13–15]. This could be due to a good response of adjuvant chemotherapy or the natural inability for these cells to survive and grow in the peritoneal cavity. In the present case, the patient received 5 months of adjuvant chemotherapy that could have suppressed the growth of these free-peritoneal cancer cells. However, the mechanism of extremely late recurrence is currently unknown. Since those studies did not have very long-term follow-up [13–15], there could be a subset of patients with late peritoneal recurrence. Her cancer was microsatellite stable and did not have any known mutations in the KRAS, NRAS, HRAS, and BRAF genes. Although extended mutational profiling could uncover other mutations and shed light on the underling mechanism, it was not performed in her case.

This SRCC also displayed an unusual pattern of metastasis to the lungs. Prior case reports have shown metastases to the peritoneal cavity [8, 10–12], ovary [5, 10, 11], lymph nodes [8, 9, 12], colon [10], ileocecal valve [4], and epididymis [12]. No other cases of lung metastasis from primary appendiceal SRCC have been reported. Psathakis et al. compared primary colorectal adenocarcinoma and primary colorectal SRCC [16]. In evaluating the metastases in patients with primary colorectal SRCC, 64.3% (9/14) had peritoneal metastasis, 14.3% (2/14) had hepatic metastasis, and no patients had pulmonary metastasis. In the primary colorectal adenocarcinoma patients, 14.3% (8/56) had peritoneal metastasis, 42.9% (24/56) had hepatic metastasis, and 7.1% (4/56) had pulmonary metastasis. The difference in incidences of the peritoneal and hepatic metastases was statistically significant ($p < 0.05$). Pulmonary metastasis was rare in both groups, indicating how unusual this case of primary appendiceal SRCC with lung metastasis is. In addition, lymphangitic spread to the lungs is also a very rare phenomenon for gastrointestinal cancers. There are only a few reported cases [17–20].

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. McGory ML, Maggard MA, Kang H, O'Connell JB, Ko CY. Malignancies of the appendix: beyond case series reports. Dis Colon Rectum. 2005;48:2264–71.
2. 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.
3. Turaga KK, Pappas SG, Gamblin T. Importance of histologic subtype in the staging of appendiceal tumors. Ann Surg Oncol. 2012;19:1379–85.
4. Murdock T, Lim N, Zenali M. Lymphangitic spread from the appendiceal adenocarcinoma to the ileocecal valve, mimicking Crohn's disease. World J Gastroenterol. 2015;21:2206–9.
5. Kulkarni RV, Ingle SB, Siddiqui S. Primary signet ring cell carcinoma of the appendix: a rare case report. World J Clin Cases. 2015;3:538–41.
6. Ploenes T, Börner N, Kirkpatrick CJ, Heintz A. Neuroendocrine tumour, mucinous adenocarcinoma and signet-ring cell carcinoma of the appendix: three cases and review of literature. Indian J Surg. 2013;75:299–302.
7. Fusari M, Sorrentino N, Bottazzi EC, Del Vecchio W, Cozzolino I, Maurea S, et al. Primary signet ring cell carcinoma of the appendix mimicking acute appendicitis. Acta Radiol Short Rep. 2012;1. https://doi.org/10.1258/arsr.2012.120017.
8. Bertuzzo VR, Coccolini F, Pinna AD. Peritoneal seeding from appendiceal carcinoma: a case report and review of the literature. World J Gastrointest Surg. 2010;2:265–9.
9. Mastoraki A, Papanikolaou IS, Kanakis D, Safioleas P, Sakorafas G, Safioleas MA. Case of signet ring carcinoma of the appendix: dilemmas in differential diagnosis and management. J Gastrointest Cancer. 2010;41:141–4.
10. Suzuki J, Kazama S, Kitayama J, Uozaki H, Miyata T, Nagawa H. Signet ring cell carcinoma of the appendix manifesting as colonic obstruction and ovarian tumors: report of a case. Surg Today. 2009;39:235–40.
11. Ko YH, Jung CK, SN O, Kim TH, Won HS, Kang JH, et al. Primary signet ring cell carcinoma of the appendix: a rare case report and our 18-year experience. World J Gastroenterol. 2008;14:5763–8.
12. Niesel T, Böhm J, Paul R, Breul J, Hartung R. Rare metastases of signet ring cell carcinomas to the scrotum: report of two cases. Urology. 1996;47:769–71.
13. Homma Y, Hamano T, Akazawa Y, Otsuki Y, Shimizu S, Kobayashi H, et al. Positive peritoneal washing cytology is a potential risk factor for the recurrence of curatively resected colorectal cancer. Surg Today. 2014;44:1084–9.
14. Bosanquet DC, Harris DA, Evans MD, Beynon J. Systematic review and meta-analysis of intraoperative peritoneal lavage for colorectal cancer staging. Br J Surg. 2013;100:853–62.
15. Honoré C, Goéré D, Souadka A, Dumont F, Elias D. Definition of patients presenting a high risk of developing peritoneal carcinomatosis after curative surgery for colorectal cancer: a systematic review. Ann Surg Oncol. 2013;20:183–92.
16. Psathakis D, Schiedeck TH, Krug F, Oevermann E, Kujath P, Bruch HP. Ordinary colorectal adenocarcinoma vs. primary colorectal signet-ring cell carcinoma: study matched for age, gender, grade, and stage. Dis Colon Rectum. 1999;42:1618–25.
17. Cinar P, Calkins SM, Venook AP, Kelley RKA. Case series of patients with HER2-overexpressed primary metastatic gastroesophageal adenocarcinoma. Anticancer Res. 2014;34:7357–60.
18. Khachekian A, Shargh S, Arabian S. Pulmonary lymphangitic carcinomatosis from metastatic gastric adenocarcinoma: case report. J Am Osteopath Assoc. 2015;115:332–7.
19. Moubax K, Wuyts W, Vandecaveye V, Prenen H. Pulmonary lymphangitic carcinomatosis as a primary manifestation of gastric carcinoma in a young adult: a case report and review of the literature. BMC Res Notes. 2012;5:638.
20. Thomas A, Lenox R. Pulmonary lymphangitic carcinomatosis as a primary manifestation of colon cancer in a young adult. CMAJ. 2008;179:338–40.