A Case of Appendiceal Adenocarcinoma with Clinical Benefit from FOLFOX and Bevacizumab

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Key Words

Appendiceal adenocarcinoma · FOLFOX · Bevacizumab · Clinical benefit · Disease stability

Abstract

A 44-year-old woman presented with lower abdominal pain and bilateral ovarian masses on ultrasound. Exploratory laparotomy revealed extensive peritoneal and intra-abdominal disease and an abnormal appendix. Bilateral salpingo-oophorectomy, infracolic omentectomy, ileocolic resection and primary anastomosis were performed. Final pathology revealed a primary appendiceal adenocarcinoma, poorly differentiated, of signet ring cell type. CT scan postoperatively revealed gross residual disease. The patient was treated with FOLFOX chemotherapy combined with bevacizumab. Repeat CT scan showed a decrease in residual disease and the patient clinically improved. After her treatment has been continued for 13 months, she remains clinically well and her CT scan shows sustained disease stability. Disseminated appendiceal carcinoma is generally considered to be refractory to 5-FU-based chemotherapy and, to our knowledge, this is the first reported case of a patient with appendiceal adenocarcinoma demonstrating clinical benefit and sustained stability of disease with combination chemotherapy plus bevacizumab.

Case Report

A 44-year-old woman with a history of endometriosis, multiple Cesarean sections, depression and tubal ligation presented with lower abdominal pain. Ultrasound revealed bilateral ovarian masses. Laparoscopy was performed and biopsy of peritoneal disease revealed a mucin-producing adenocarcinoma. The patient was taken to the operating room in February 2008 for an exploratory laparotomy with the presumptive diagnosis of ovarian carcinoma. There was extensive peritoneal and intra-abdominal disease and the appendix was abnormal. Bilateral salpingo-oophorectomy, infracolic

omentectomy, ileocolic resection and primary anastomosis were performed. Final pathology revealed a primary appendiceal adenocarcinoma, poorly differentiated, of signet ring cell type ([fig. 1](#), [fig. 2](#)). There was involvement of both ovaries, the right fallopian tube, right peritubular soft tissue and omentum; none of the 14 resected lymph nodes were involved. The patient developed a partial small bowel obstruction postoperatively which resolved with conservative management.

A postoperative CT scan in March 2008 revealed gross residual disease over the serosal surfaces of the pelvic organs and small nodules in the upper abdomen possibly representing early carcinomatosis. Having recovered well from surgery, the patient was offered palliative FOLFOX chemotherapy. She was also offered bevacizumab based on data showing efficacy in metastatic colon cancer. She began these therapies in March 2008.

Repeat CT scan following 6 cycles of chemotherapy revealed a decrease in the size and number of foci of peritoneal carcinomatosis. The patient was tolerating therapy well and underwent another 6 cycles of chemotherapy before further CT scanning in August 2008, which showed stability of disease. After 14 cycles, she developed peripheral neuropathy necessitating discontinuation of the oxaliplatin. Repeat CT scanning in December 2008 and March 2009 confirmed stability of disease ([fig. 3](#)) and the patient continues to tolerate treatment well.

Discussion

Appendiceal tumors are rare neoplasms that often present with symptoms of acute appendicitis or are discovered incidentally during surgery for another indication [1, 2]. In a review of 7,970 patients with appendectomies, 74 were found to have appendiceal tumors (incidence of 0.9%) ranging from benign to malignant [1]. The reported age-adjusted incidence of cancer of the appendix is 0.12 cases per 1,000,000 people per year [3]. Adenocarcinomas of the appendix represent an unusual variant of colon cancer and fall into one of three histologic categories. The most common is the mucinous type, followed by the intestinal or colonic type, and the least common is signet ring cell adenocarcinoma, which is considered to be the most virulent and is associated with a poor prognosis [3]. Adenocarcinoma of the appendix is the most frequently spontaneously perforating carcinoma of the gastrointestinal tract [2, 4] and is commonly associated with synchronous or metachronous tumors, particularly of the gastrointestinal tract [2].

Standard treatment for a localized appendiceal adenocarcinoma is a right hemicolectomy [1, 2, 5]. The role for adjuvant chemotherapy is controversial and there are no controlled data regarding the efficacy of chemotherapy following resection of localized disease. The role of adjuvant radiotherapy is also unclear due to the lack of randomized data. In one study, the overall 5-year survival for patients with adenocarcinoma of the appendix was only 55% [2], leading some medical oncologists to extrapolate from the data on colorectal cancer and consider adjuvant treatment with 5-FU-based chemotherapy.

For patients with disseminated appendiceal adenocarcinoma, the optimal treatment is unclear. These tumors are generally considered to be refractory to 5-FU-based chemotherapy. However, there is at least one case report of a patient with metastatic adenocarcinoid (histological features of both adenocarcinoma and carcinoid) demonstrating a complete and persistent response to FOLFOX-4 [6]. There is also a case report of a patient with hybrid histology (features of both disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis) and pseudomyxoma peritonei, previously treated with cytoreduction and intraperitoneal hyperthermic chemotherapy, demonstrating an objective response to capecitabine [7].

Aggressive cytoreduction and intraperitoneal hyperthermic chemotherapy (IPHC) for secondary peritoneal carcinomatosis have been used in several centers, although there is only one published prospective randomized trial [8]. 105 patients with peritoneal carcinomatosis from appendiceal or colorectal cancer were randomly assigned to either standard treatment consisting of systemic chemotherapy (fluorouracil-leucovorin) with or without palliative surgery or experimental therapy consisting of aggressive cytoreduction with IPHC followed by the same systemic chemotherapy regime. The median survival at a median follow-up of 21.6 months was significantly longer in the IPHC group (22.3 vs. 12.6 months, $p = 0.032$); the treatment-related mortality in the IPHC arm was 8% [8]. Several other institutions have published their experience with this aggressive treatment, but appendiceal cancers have generally constituted the minority of cases, and these single institution series represent highly selected patient populations [9, 10].

To our knowledge, this is the first reported case of a patient with appendiceal adenocarcinoma demonstrating sustained stable disease and clinical benefit with combination chemotherapy plus bevacizumab.

Disclosure Statement

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Fig. 1. Low-power view of poorly differentiated mucinous adenocarcinoma in the wall of the appendix with lakes of mucin (hematoxylin and eosin, original magnification $\times 40$).

Fig. 2. High-power view of the signet ring cells (hematoxylin and eosin, original magnification $\times 400$).

Fig. 3. CT scan images from March 2008 (left) and December 2008 (right) with peritoneal disease on the surface of the uterus, in the midline and left upper quadrant omentum.

References

- 1 Connor S, Hanna G, Frizelle F: Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. *Dis Colon Rectum* 1998;41:75–80.
- 2 Nitecki S, Wolff B, Schlinkert R, Sarr M: The natural history of surgically treated primary adenocarcinoma of the appendix. *Ann Surg* 1994;219:51–57.
- 3 McCusker M, Coté T, Clegg L, Sobin L: Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973–1998. *Cancer* 2002;94:3307–3312.
- 4 Cerame M: A 25-year review of adenocarcinoma of the appendix: a frequently perforating carcinoma. *Dis Colon Rectum* 1988;31:145–150.
- 5 Ito H, Osteen R, Bleday R, Zinner M, Ashley S, Whang E: Appendiceal adenocarcinoma: long-term outcomes after surgical therapy. *Dis Colon Rectum* 2004;47:474–480.
- 6 Garin L, Corbinais S, Boucher E, Blanchot J, Le Guilcher P, Raoul J: Adenocarcinoid of the appendix vermiformis: complete and persistent remission after chemotherapy (folfox) of a metastatic case. *Dig Dis Sci* 2002;47:2760–2762.
- 7 Levitz J, Sugarbaker P, Lichtman S, Brun E: Unusual abdominal tumors, case 1. Pseudomyxoma peritonei: response to capecitabine. *J Clin Oncol* 2004;22:1518–1520.
- 8 Verwaal V, van Ruth S, de Bree E, van Slooten G, van Tinteren H, Boot H, Zoetmulder F: Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003;21:3737–3743.
- 9 Loggie B, Fleming R, McQuellon R, Russell G, Geisinger K: Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for disseminated peritoneal cancer of gastrointestinal origin. *Am Surg* 2000;66:561–568.
- 10 Culliford A, Brooks A, Sharma S, Saltz L, Schwartz G, O'Reilly E, Ilson D, Kemeny N, Kelsen D, Guillem J, Wong W, Cohen A, Paty P: Surgical debulking and intraperitoneal chemotherapy for established peritoneal metastases from colon and appendix cancer. *Ann Surg Oncol* 2001;8:787–795.