Pathologic complete response in poorly differentiated adenocarcinomas of the appendix: A case series

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To the Editor,

Appendiceal tumors are rare neoplasms and the most common histological subtype is adenocarcinoma, sub-grouped as: mucinous, non-mucinous, and signet-ring cell [1,2]. Poorly differentiated adenocarcinomas of the appendix are known to have an unfavorable prognosis and the optimal treatment approach for this subtype of appendiceal adenocarcinoma is not known [3].

This article describes a series of four patients who presented with poorly differentiated adenocarcinoma of the appendix and were treated with neoadjuvant systemic chemotherapy (SC) followed by cytoreductive surgery (CRS). In all cases a pathologic complete response to chemotherapy (pCR) was found at the time of cytoreductive surgery.

Case 1

A 38-year-old female developed right lower quadrant pain in February 2010. Computed tomography (CT) scans demonstrated a 6.9 cm pelvic mass. Exploratory laparotomy revealed a large mass that appeared to arise from the appendix involving the cecum, terminal ileum, right pelvic side wall, and right ovary with no evidence of peritoneal disease. A right hemicolectomy was performed. Pathology demonstrated a microsatellite-stable poorly differentiated adenocarcinoma arising from the appendix with 0/21 lymph nodes and a positive pelvic sidewall margin (Supplementary Figure 1A to be found online at http//informahealthcare.com/doi/abs/10.3109/0284186X.2012.724772).

In April 2010, a restaging CT scan showed a recurrent 5 cm pelvic mass (Supplementary Figure 2A to be found online at http//informahealthcare.com/doi/abs/10.3109/0284186X.2012.724772). Pathology from a CT guided biopsy revealed poorly differentiated adenocarcinoma that had a CDX2+, cytokeratin 7-, and cytokeratin 20+ immunohistochemical profile. KRAS and BRAF were wild-type. She underwent 12 cycles of FOLFOX/cetuximab with radiographic response (Supplementary Figure 2B to be found online at http//informahealthcare.com/doi/abs/10.3109/0284186X.2012.724772)

In November 2010, she underwent exploratory laparotomy with en bloc resection of the right pelvic mass involving the small intestine, right ureter and right ovary. Pathology revealed foci of acellular mucin pools without evidence of viable tumor, consistent with pCR (Supplementary Figure 1B to be found online at http//informahealthcare.com/doi/abs/10.3109/0284186X.2012.724772). She underwent an additional three months of adjuvant infusional 5-FU and currently 16 months from surgery has no evidence of disease.

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Case 2

A 62-year-old male underwent a screening colonoscopy that showed a mass at the appendiceal orifice. At the time of right hemicolectomy in December 2008, a large mass in the cecum by the appendiceal orifice was seen and numerous peritoneal implants involving the small bowel mesentery and anterior abdominal wall were biopsied but not removed. Pathology demonstrated KRAS wild-type poorly differentiated adenocarcinoma with signet ring cell features and a smaller component of goblet cell carcinoid with 5/38 lymph nodes (Supplementary Figure 1C to be found online at http//informahealthcare.com/doi/abs/10.3109/0284186X.2012.724772). Both peritoneal biopsies were positive for adenocarcinoma. He underwent 11 cycles of FOLFOX and bevacizumab.

In September 2009, he underwent exploratory laparotomy with omentectomy, excision of multiple peritoneal nodules and HIPEC with mitomycin-C. The pathology revealed no evidence of viable tumor, consistent with pCR (Supplementary Figure 1D to be found online at http//informahealthcare.com/doi/abs/10.3109/0284186X.2012.724772).

He remained without any evidence of recurrent disease until 20 months from surgery, when the patient noticed red papules surrounding his umbilicus. CT scans were negative but a skin biopsy showed adenocarcinoma with signet-ring features. He underwent eight cycles of FOLFIRI/cetuximab with improvement in his cutaneous disease. A second CRS and HIPEC with mitomycin-C was performed and involved an abdominal wall resection and resection of a second 3.5 cm area of disease involving the small bowel. Pathology revealed poorly differentiated adenocarcinoma with signet ring cell features. He recovered well after surgery but developed recurrent disease five months later.

Case 3

A 57-year-old female developed right lower quadrant discomfort and abdominal bloating in January 2011. CT scans demonstrated a large complex solid and cystic pelvic mass (7×8 cm) and ascites. Exploratory laparotomy revealed a large mass in the pelvis with extensive involvement of the appendix and the right ovary with implants on the anterior abdominal wall, sigmoid colon and a large amount of serous ascites. Subsequent cecectomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, resection of sigmoid colon and anterior abdominal wall implants were done. All involved organs and palpable-visible tumors were removed. The pathology was consistent with CDX2+, cytokeratin 7-, and cytokeratin 20+ poorly differentiated adenocarcinoma with mucinous and signet ring cell features arising from a goblet cell carcinoid of the appendix (Supplementary Figure 1E to be found online at http//informahealthcare.com/doi/abs/10.3109/0284186X.2012.724772). Metastatic adenocarcinoma was present in the right ovary, peritoneum, uterus, adnexa, and sigmoid colon but no regional lymph nodes were evaluated. She underwent 12 cycles of FOLFOX chemotherapy and presented to our institution for definitive cytoreductive surgery.

In October 2011 she underwent CRS that included a right hemicolectomy, omentectomy, resection of peritoneum from Morrison's pouch and HIPEC with mitomycin-C. Pathology revealed no viable tumor in the specimen, including nine lymph nodes. In three of the lymph nodes from the hemicolectomy specimen, acellular mucin was present, consistent with a pCR (Supplementary Figure 1F to be found online at http//informahealthcare.com/doi/abs/10.3109/0284186X.2012.724772). She recovered well after surgery and currently seven months from surgery has no evidence of disease.

Case 4

A 38-year-old female developed abnormal vaginal bleeding in November 2005 and pelvic ultrasound showed a 10 cm complex pelvic mass. Exploratory laparotomy revealed a large pelvic mass involving the appendix, bilateral ovaries and distal sigmoid colon with pelvic implants and omental seeding. Colon resection, resection of peritoneal implants, partial omentectomy, total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. Multiple small nodules over the mesentery of small bowel and the peritoneum were seen, but not removed completely resulting in a near-total debulking. The pathology was consistent with poorly differentiated adenocarcinoma with a focal signet-ring cell component from the appendix, involving bilateral ovaries (Supplementary Figure 1G to be found online at http//informahealthcare.com/doi/abs/10.3109/0284186X.2012.724772), rectosigmoid, omentum and multiple other peritoneal sites.

She was treated with 12 cycles of FOLFOX/bevacizumab and then underwent exploratory laparotomy including multiple peritoneal biopsies, ileocecectomy and HIPEC with mitomycin C. Pathology revealed no evidence of viable tumor, consistent with a pCR (Supplementary Figure 1H to be found online at http//informahealthcare.com/doi/abs/10.3109/0284186X.2012.724772). She recovered well after surgery, but 20 months from surgery she recurred and died 16 months following this recurrence.

Discussion

Appendiceal neoplasms compose a rare group of tumors with an incidence of 0.12 cases per 1 million

people per year [2]. The majority of metastatic appendiceal adenocarcinomas are well differentiated mucinous adenocarcinomas that present with the syndrome of pseudomyxoma peritonei (PMP). The treatment of choice for this subset of appendiceal neoplasms is CRS followed by HIPEC [4–7].

However, a not insignificant subset of appendiceal adenocarcinomas have poor histological differentiation and demonstrate a far more aggressive biology with a markedly worse prognosis [3,8]. In a retrospective study of 106 patients with stage IV poorly differentiated or signet-ring cell adenocarcinoma of the appendix the median overall survival for patients was 1.8 years [9]. Given this more aggressive natural history, the role and benefit from CRS and HIPEC is uncertain. Though, the role of systemic chemotherapy is controversial in patients with well differentiated mucinous adenocarcinoma (PMP) [10,11], a recent study has suggested a benefit from systemic chemotherapy in patients with poorly differentiated and signet ring cell appendiceal adenocarcinomas [9,12]. Lieu et al. showed that front-line systemic chemotherapy resulted in a radiographic response rate of 44% and a median PFS of 6.9 months [9]. Powell et al. reported a case involving a patient with metastatic poorly differentiated appendiceal adenocarcinoma who responded to FOLFOX with bevacizumab [12]. In another case, a patient with signet-ring cell adenocarcinoma of the appendix who underwent an incomplete CRS, demonstrated no progression following six months of FOLFOX [13].

Given the more aggressive behavior for this subset of appendiceal adenocarcinomas we have adopted a neoadjuvant chemotherapy approach followed by CRS plus HIPEC for patients who have a response, or in some cases, stable disease after several months of chemotherapy. We present four cases in which this approach was applied and demonstrates the potential activity from systemic chemotherapy, as these select cases showed pathological complete response at the time of surgery. At present, two patients have developed recurrence at 20 months following surgery, while the other two patients have not recurred at seven and 15 months. As a total of 66 stage IV poorly differentiated appendiceal adenocarcinomas were seen at our institution over this same time period, the four cases reported here represent a highly selected subset.

However, we believe the importance of these selected cases is to highlight the potential activity of systemic chemotherapy in this subset of appendiceal adenocarcinomas. Additionally we believe that any investigation into the role of CRS and HIPEC in poorly differentiated appendiceal adenocarcinomas should incorporate the use of neoadjuvant chemotherapy.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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References

[1] Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225–49.
[2] McCusker ME, Cote 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] 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.
[4] Sugarbaker PH. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome? Lancet Oncol 2006;7:69–76.
[5] Smeenk RM, Verwaal VJ, Antonini N, Zoetmulder FA. Survival analysis of pseudomyxoma peritonei patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg 2007;245:104–9.
[6] Sugarbaker P, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. Ann Surg Oncol 1999;6:727–31.
[7] Stewart JH 4th, Shen P, Russell GB, Bradley RF, Hundley JC, Loggie BL, et al. Appendiceal neoplasms with peritoneal dissemination: Outcomes after cytoreductive surgery and intraperitoneal hyperthermic chemotherapy. Ann Surg Oncol 2006;13:624–34.
[8] Shapiro JF, Chase JL, Wolff RA, Lambert LA, Mansfield PF, Overman MJ, et al. Modern systemic chemotherapy in surgically unresectable neoplasms of appendiceal origin: A single-institution experience. Cancer 2010;116:316–22.
[9] Lieu CH, Lambert LA, Wolff RA, Eng C, Zhang N, Wen S, et al. Systemic chemotherapy and surgical cytoreduction for poorly differentiated and signet ring cell adenocarcinomas of the appendix. Ann Oncol 2012;23:652–8.
[10] Smith J, Kemeny N, Caldwell C, Banner P, Sigurdson E, Huvos A. Pseudomyxoma peritonei of appendiceal origin. The Memorial Sloan-Kettering Cancer Center experience. Cancer 1992;70:396–401.
[11] Farquharson AL, Pranesh N, Witham G, Swindell R, Taylor MB, Renehan AG, et al. A phase II study evaluating the use of concurrent mitomycin C and capecitabine in patients with advanced unresectable pseudomyxoma peritonei. Br J Cancer 2008;99:591–6.
[12] Powell ED, Macdonald DB, Elkeilani AM, Asmis TR. A case of appendiceal adenocarcinoma with clinical benefit from FOLFOX and bevacizumab. Case Rep Oncol 2009;2:111–5.
[13] Ko YH, Jung CK, Oh SN, 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.

Supplementary material available online

Supplementary Figures 1 and 2.