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Primary mucinous adenocarcinoma of appendix treated with chemotherapy and radiotherapy: a case report

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ABSTRACT

A rare case of primary appendiceal mucinous adenocarcinoma is reported. The presenting signs and symptoms were suggestive of acute appendicitis. An appendectomy was performed resulting in a histological diagnosis of grade 2 mucinous adenocarcinoma of the appendix. The patient was referred to our clinic where he underwent a complementary right hemicolectomy with lymph node dissection. Two of the 17 resected lymph nodes were tumor positive but there was no residual tumor in the hemicolectomy specimen. The patient was staged as $T_4N_1M_0$ and adjuvant multimodality treatment was planned because he was considered at high risk for local-regional recurrence and distant metastasis. Three cycles of capecitabine 1250 mg/m^2 on days 1-14 and oxaliplatin 130 mg/m^2 on day 1, every 21 days (CAPOX) were administered, then a total dose of 50.4 Gy external-beam radiation therapy was delivered to the primary tumor region and 45 Gy to the lymphatics, and finally 3 further cycles of the CAPOX regimen were administered. Multimodality treatment was well tolerated by the patient, who is still alive 25 months after the hemicolectomy procedure with no evidence of disease progression.

Introduction

Primary appendiceal adenocarcinomas (PAAs) are rare tumors accounting for 0.05-0.2% of all appendectomies and only 6% of all malignant tumors of the appendix[1,2]. Recently, PAAs have been classified into 4 groups: mucinous adenocarcinoma, colonic-type adenocarcinoma, goblet-cell carcinoma, and signet-ring cell carcinoma[3]. Mucinous adenocarcinoma is a very rarely reported mucin secreting variant of this rare tumor type. PAAs commonly present with signs and symptoms of acute appendicitis from luminal obstruction or as a palpable abdominal mass. Except for occasional cases, PAAs are not diagnosed preoperatively because of the lack of specific symptoms indicating the presence of a tumor. The vast majority are detected during histopathological examination of the surgical specimen or as an incidental finding during exploration for another disease[2,3].

There is no consensus regarding adjuvant treatment for PAAs following right hemicolectomy in locally advanced cases[4,5]. Here, we present a rare case of locally advanced mucinous-type PAA and discuss its clinical course. The patient was treated with initial appendectomy followed by secondary right hemicolectomy, adjuvant chemotherapy and radiotherapy.

Case report

In January 2005 a 64-year-old man with mucinous-type PAA was referred to our clinic. He had first been admitted to another center with abdominal pain located in

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the lower right quadrant and loss of appetite persisting for about 12 days. His food intake had been considerably decreased because of nausea and vomiting, and he had had no bowel movements for the past 4 days. Physical examination had been reported as follows: heart rate 76 bpm, body temperature 38.7 °C, blood pressure 140/90 mmHg, generalized abdominal distention, no bowel sounds, tenderness and muscle rigidity located in the right lower quadrant suggesting a bowel obstruction. Laboratory parameters had been reported as Hb 11.7 g/dL, WBC 18,100/mm³, platelets 296,000/mm³, SGOT 41 U/L, and SGPT 29 U/L. A mass of 6×5 cm with cystic and solid components suggesting an infected intestinal invagination or acute appendicitis, and proximal diffuse thickening of the intestinal wall had been reported by ultrasound examination under emergency conditions. Intraoperative gross examination had revealed a retrocecal appendix with a grossly infected periappendicular, 8×8 cm mass. The appendix and cecum had been found to adhere to the lateral abdominal wall. Appendectomy had been performed and an intraoperative diagnosis had been made of acute appendicitis and a periappendicular infected mass. Pathological examination had revealed a grade 2 mucinous-type PAA of 9.5×8.3×7.8 cm with extension behind the bowel wall but negative surgical margins (Figure 1).

The patient was referred to our clinic and his case was discussed by our abdominal surgeons. A secondary right hemicolectomy procedure with regional lymph node dissection was performed in February 2005. Two of the 17 resected lymph nodes were tumor positive but no residual cancer cells were detected in the hemicolectomy specimen. The tumor was staged as $T_4N_1M_0$ (Modified Astler-Coller C_3). Because the patient was classified as having a high risk of locoregional recurrence and distant metastasis development, 6 cycles of adjuvant combination chemotherapy consisting of capecitabine 1250 mg/m² on days 1-14 and oxaliplatin 130 mg/m² on day 1, every 21 days (CAPOX) were administered and radiotherapy was planned. Following administration of the first 3 cycles of chemotherapy, the patient was referred to a center with adequate radiotherapy facilities. A 45-Gy (1.8 Gy per fraction) dose of external-beam radiotherapy was delivered to the cecoappendicular region and related lymphatics along with a local tumor boost of 5.4 Gy (1.8 Gy per fraction) to the involved field. Following radiotherapy the remaining 3 cycles of CAPOX were administered. The multimodality treatment was well tolerated except for mild diarrhea during radiotherapy, which was managed with loperamide and antibiotics. Follow-up was uneventful and the patient was still alive 25 months since the right hemicolectomy procedure with no signs of progressive disease.

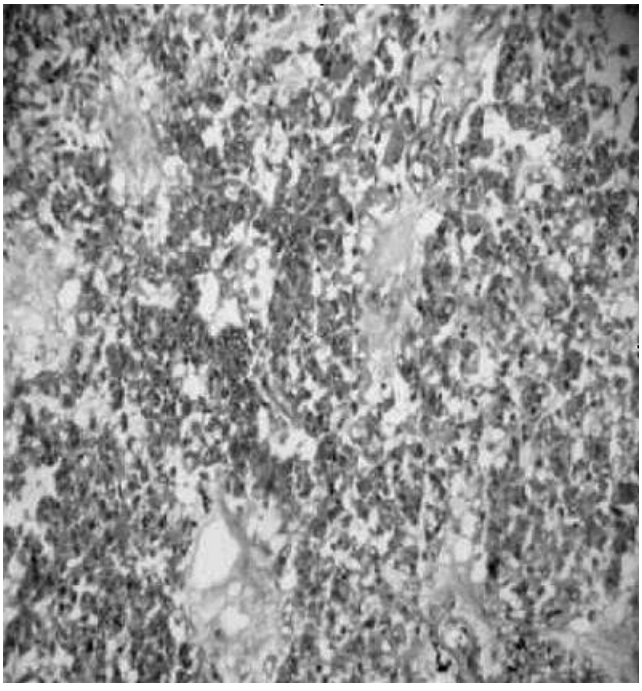

Figure 1 - Photomicrograph showing mucinous adenocarcinoma of appendix with evident extracellular mucin deposits.

Discussion

PAAs are rare tumors of the gastrointestinal system with an age-adjusted incidence of 0.12 per 1,000,000[3]. In the series reported by Collins[2], carcinoids, mucoceles, and primary adenocarcinomas accounted for 51%, 32%, and 6% of all primary malignant tumors of the appendix, respectively. Most PAAs are colorectal-type tumors that develop from pre-existing adenomas[6]. Mucinous-type PAA is a very rarely reported mucin secreting variant with a prevalence of 0.05-0.2% of all appendectomies[1,2]. The mean age at presentation is around 50 years with a male predominance of 4:1[7]. Most mucinous-type PAAs are well-differentiated, slowly growing tumors with pushing rather than infiltrating margins; they have a tendency to rupture and spread through the abdominal cavity, with resultant pseudomyxoma peritonei. Variants of higher histological grade and with an infiltrative pattern like the one presented here are very rare[8].

PAA usually presents, like in our patient, as a lower right quadrant mass or with typical clinical features of acute appendicitis. A preoperative diagnosis of PAA is therefore rarely made; furthermore, an incidental diagnosis during abdominal surgery for an unrelated medical condition is as common as 20.2% of cases as reported by Nitecki *et al.*[4].

Tumor stage, histology, grade, size, and the type of surgery are the most important prognostic factors for primary noncarcinoid tumors of the appendix and other colonic sites. Mucinous histology was reported to have a better prognosis than colonic histology[5]. Nitecki *et al.* reported that patients with mucinous adenocarci-

nomas fared significantly better than those with the colonic type, with 5-year survival rates of 71% and 48%, respectively (P <0.01)[4]. Tumor size was shown to be an important prognostic factor and the 5-year survival rate was significantly higher in patients with tumor size ≤1 cm than those with tumors >2 cm (78% *vs* 43%, respectively). The local-regional and distant metastasis rates for mucinous-type PAAs are 21% and 51%, respectively[5]. The reported risk of the development of distant metastases varies between 30% and 70% for well and poorly differentiated tumors, respectively[6,7]. The most common site of metastatic involvement is the peritoneal cavity with either simple metastases or pseudomyxoma peritonei, followed by regional lymphatics, liver, ovaries, abdominal wall and lungs[4]. The recently reported 5-year overall survival in mucinous PAA patients with localized disease, regional lymphatic involvement, and distant organ metastasis were 64%, 54%, and 32%, respectively[5]. Our case shared some unfavorable characteristics with those reported in the literature including its grade (grade 2), size (9.5 cm in largest diameter), and stage T_4N_1 (with 2 metastatic lymph nodes).

According to the current guidelines, a right hemicolectomy should be performed for all histological variants of noncarcinoid invasive tumors and also for carcinoid tumors of >2 cm[9]. The series of McGory *et al.*[5] shows the significant underutilization of appropriate surgical intervention for PAAs. Right hemicolectomy or en bloc excision was performed as the first surgical intervention in 63% of cases whereas 30% of cases were treated solely with appendectomy. In our case, appendectomy and subsequent right hemicolectomy were performed by 2 different surgical groups. Similarly, in the series of Nitecki *et al.*[4], 59 of 94 patients (63%) were initially appendectomized; furthermore, 27 patients (29%) underwent appendectomy as the only surgery without a secondary right hemicolectomy procedure, as a total of only 62 patients (66%) were treated with right hemicolectomy. These results indicate inappropriate oncological resection of mucinous PAAs in a significant number of cases. This may be related to the reliance of the current treatment algorithm on a tissue diagnosis of carcinoid *versus* noncarcinoid histology, which requires frozen section in the operating room or a final pathology report. We believe, however, that the prognostic superiority of right hemicolectomy over appendectomy should not be underestimated because of practical difficulties.

It is possible to obtain better results with aggressive surgery than with appendectomy. In the series of Nitecki *et al.*[4], patients treated with a right hemicolectomy, either as initial or secondary procedure, had a better 5-year survival than patients who underwent appendectomy alone, 68% *vs* 20%, respectively. These results were supported by more recent series reported by McGory *et al.*[5], Lo *et al.*[10], and Ito *et al.*[11]. Not only do they emphasize the importance of more aggressive surgery in the management of patients with PAAs, but they imply that a significant number of patients still die because of uncontrolled primaries or metastatic progression.

The role of adjuvant therapy for PAAs of the appendix is controversial. Indications for adjuvant therapy, including intraperitoneal and/or systemic chemotherapy, radiotherapy, and radioimmunotherapy have not been incorporated into the current algorithm for PAAs. Chemotherapy is a well proven effective modality in treatment of colorectal cancers whereas radiotherapy has rarely been considered in the management of tumors of the colon including PAAs. In the recently published phase III Intergroup Protocol 0130, Martenson *et al.*[12] reported that there was no difference between the chemotherapy alone and chemoradiotherapy arms of locally advanced colon carcinoma patients in terms of 5-year overall and disease-free survival. However, although very important results were presented, there were significant limitations to this study, as stated by Tepper *et al.*[13] in an editorial: small sample size, low power to detect a moderate but clinically important impact of radiotherapy because of lower accrual than planned, and broader criteria for eligibility. It appears logical to consider local irradiation to improve treatment results for certain subsets of patients with high-risk features in the treatment of PAAs and adenocarcinomas of other colonic sites because of their biological similarities to rectal carcinoma. In a Mayo Clinic series, patients with locally advanced and recurrent colon cancers were treated with chemotherapy and radiotherapy, and the 5-year survival was 49%[14]. In another study, Willet *et al.*[15] stated that certain subsets of patients with colon carcinomas including modified Astler-Coller B_3 and C_3 groups would benefit from postoperative chemoradiotherapy.

No controlled data specifically oriented towards the efficacy of adjuvant chemotherapy and radiotherapy for locally advanced PAAs are available. In a small study by Proulx *et al.*[16], 3 of 5 patients (60%) treated with chemoirradiation were disease free at 5 years of follow-up. In the case presented here, we preferred to treat our patient with chemoradiotherapy (although not a standard approach) because of the presence of factors considered to entail a high risk for local-regional recurrence and distant metastases including T_4 (tumor adherence to abdominal wall), N_1 (2 metastatic lymph nodes), a diameter of 9.5 cm (>2 cm), and histological grade 2 (not grade 1). We administered 6 courses of CAPOX chemotherapy, a commonly used regimen in the management of colorectal carcinomas, and external beam radiotherapy with the well-known "sandwich technique", and the patient was still alive after 25 months with no evidence of disease progression. Although these are only case experiences, we believe that they may serve as touchstones in the evaluation of the available adjuvant treatment modalities in patients with PAAs having unfavorable prognostic factors.

The case presented here is interesting for several reasons: first, it illustrates the clinical course of a rarely reported mucinous-type PAA with high-risk features after multimodality treatment; second, given that appendectomy was the initial surgical approach, it emphasizes the continuing use of inappropriate surgical intervention for noncarcinoid PAAs; third, it shows the efficacy and tolerability of adjuvant chemotherapy and radiotherapy; and lastly, it suggests the potential of such treatment, although not standard, as an alternative option in the management of patients with high-risk features.

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