

Appendiceal Adenocarcinoma Arising after Bone Marrow Transplantation for Non-Hodgkin Lymphoma: An Unusual Treatment Dilemma

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Citation

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Abstract

INTRODUCTION

Appendiceal tumors are rare neoplasms occurring in approximately 0.1% of appendectomy specimens¹. The majority present as acute appendicitis and are treated by simple appendectomy. Although controversial, in the setting of peritoneal carcinomatosis discovered at the time of appendectomy, cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) may represent potential therapeutic options. However, debate exists with regard to patient selection, quality of life and procedure-associated morbidity, what constitutes effective cytoreduction, and whether cytoreduction alone offers a survival benefit in the absence of intraperitoneal chemotherapy. This report describes a rare case of a perforated appendiceal adenocarcinoma arising after bone marrow transplantation for non-Hodgkin lymphoma. The occurrence of peritoneal carcinomatosis in this setting has not previously been reported, but exemplifies the importance of an individualized approach to therapy based on a patient's presentation.

CASE REPORT

A 48-year-old female with a past medical history significant for high-grade immunoblastic large cell non-Hodgkin lymphoma (NHL) presented to an outside emergency department of another institution with the chief complaint of generalized abdominal pain. She described the pain as dull, gradual in onset, of a single day's duration, and associated with nausea and subjective fever. Having undergone four cycles of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone) and bone marrow transplantation, with a 3 month cyclosporine taper, ten years earlier, her NHL was felt to be in remission,

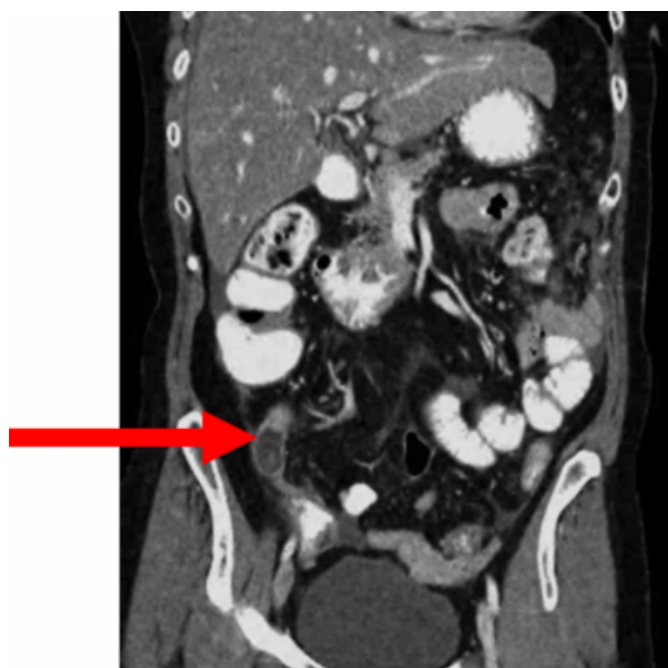
despite an episode of graft-versus-host disease (GVHD) 5 years ago.

At the other institution, physical examination revealed diffuse discomfort to palpation, but no overt peritoneal signs. Laboratory studies demonstrated a white blood cell count of 11,000 with a left shift and a lactic acid level of 4 mmol / L . A non-contrast computed tomography (CT) scan at the outside facility was performed, demonstrating the presence of a fecalith, but also diffuse mesenteric edema, omental thickening, free fluid in the pelvis, and around the spleen. With these findings, the patient was transferred to our institution for further evaluation.

Upon arrival at our facility, the patient was tachycardic, febrile at 39.1 C, and complained of steadily worsening abdominal pain. Upon review of the CT scan (Figure 1) and after a repeat physical examination, there was concern that the patient's symptoms were not consistent with acute appendicitis, but a more diffuse intraabdominal process. She was counseled regarding the differential diagnosis and was offered diagnostic laparoscopy to better determine the cause of her abdominal pain.

Figure 1

Figure 1: CT of the abdomen (coronal) demonstrating abnormal appendix

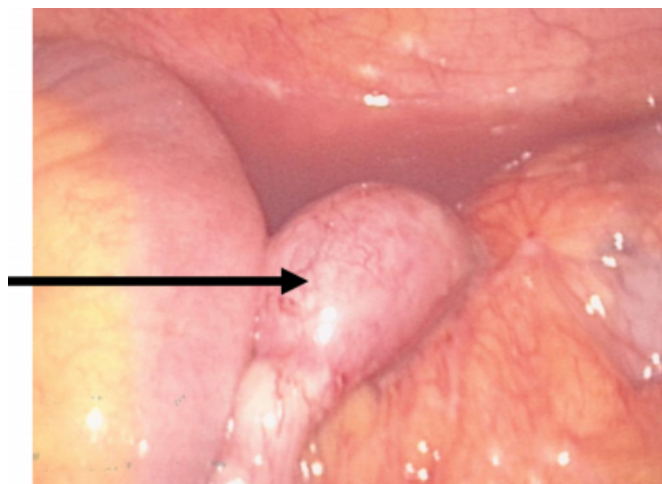


At surgery, there was a significant amount of purulent material in the pelvis, above the liver, and around the spleen. In addition, there was peritoneal studding along the anterior abdominal wall. The distal tip of the appendix was dilated and surrounded by purulent material which did not appear to be overtly mucinous. These findings were discussed with the patient's family and the decision was made to convert to a formal celiotomy to further evaluate the peritoneal cavity.

Upon converting to an open procedure, the small bowel was inspected and innumerable tumor deposits were encountered, most less than 5 mm in diameter, primarily at the junction of the mesentery and the small bowel, but also firmly adherent to the root of the mesentery. The large intestine was also diffusely involved. Additional findings included a markedly thickened omentum and a significant amount of peritoneal plaque on bilateral diaphragmatic surfaces, with the right side having more disease than the left. Representative samples were sent for frozen section and the pathology was consistent with adenocarcinoma. Further inspection demonstrated an appendiceal mass with evidence of appendiceal perforation (Figure 2) and bilateral ovarian involvement. The stomach appeared free of tumor.

Figure 2

Figure 2: Appendiceal mass (intraoperative photo)

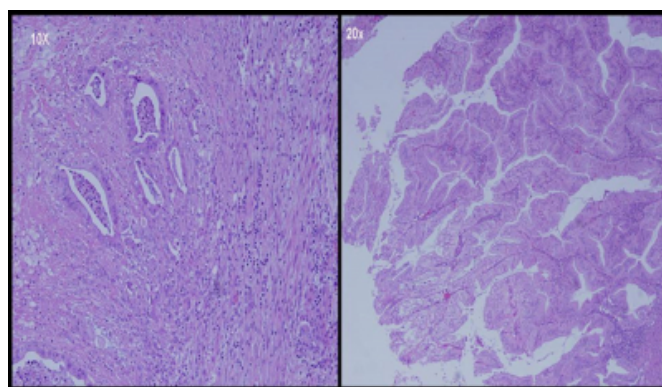


A right hemicolectomy, omentectomy, and bilateral oophorectomies were performed given the intraperitoneal spread of tumor from a perforated appendiceal cancer. Additional cytoreductive surgery of remaining intraperitoneal carcinomatosis greater than 5 mm was performed with a combination of electrocautery and with the use of the cavitron ultrasonic surgical aspirator (CUSA).

Histological examination of the specimens revealed moderately to poorly differentiated adenocarcinoma of the appendix metastatic to the diaphragm, omentum, ovaries, and fallopian tubes. Sections of the markedly dilated appendix demonstrated the bulk of the tumor to be arising from the proximal appendix and measuring approximately 1.0 cm in diameter. The tumor extended into the distal appendix as well as into the peri-appendiceal fat (Figure 3).

Figure 3

Figure 3: Left. Adenocarcinoma infiltrating muscularis propria of appendix (Routine H&E 20X) Left. Adenoma of proximal appendix with serrated architecture and dysplastic epithelium (Routine H&E, 10X)



The mucosa overlying the invasive component of the tumor exhibited a villiform architecture with dysplastic epithelium, thereby supporting the origin of the tumor to be within the appendix. Thirty-eight regional nodes were identified; twenty were positive for metastatic adenocarcinoma. Given the morphologic similarities of the adnexal tumors and the appendiceal tumor, as well as the in situ component identified within the appendix, the adnexal tumors were favored to represent bilateral metastases from an appendiceal primary.

The patient did well immediately post-operatively and was discharged on post-operative day six, tolerating a normal diet.

DISCUSSION

Data does not exist regarding the development of appendiceal cancer in association with bone marrow transplantation due to the rarity of this neoplasm, but the question remains as to whether this unusual presentation of appendiceal adenocarcinoma was influenced by having a previous bone marrow transplantation, prior chemotherapy, or the combination of both. Evidence in the literature suggests that patients undergoing bone marrow transplantation are at significantly higher risk for developing new solid cancers later in life². Although appendiceal cancer may have arisen de novo in this patient, it is reasonable to assume that the patient's status as a bone marrow recipient may have contributed. Kolb et al. reported that the rate of developing a secondary malignancy within ten years of initial bone marrow transplant was 3.8 times higher than the general population³. Moreover, through multivariate analysis, risk factors identified for contracting a secondary malignancy included cyclosporine, increased age, and graft versus host disease³, two of which (cyclosporine and GVHD) were present in this particular patient. Looking specifically at the incidence of solid cancers, Curtis et al. reported that 13 of the 690 transplanted patients followed over a ten year period had developed a solid tumor within ten years, supporting an increased risk of 8.3².

This patient's presentation posed unique management challenges. Historically, with the use of 5-FU and leucovorin-based treatment regimens, survival against a backdrop of peritoneal carcinomatosis averaged only 5-6 months^{4,5,6}, allowing most oncologists and surgeons to contend that peritoneal carcinomatosis is a terminal event. In up to 25% of patients, however, peritoneal spread represents

the only site of disease^{4,7}. In these patients, it is argued, the peritoneum may represent the first site in a metastatic continuum, prior to systemic spread of disease⁸. As such, total peritoneal resection combined with hyperthermic intraperitoneal chemotherapy (HIPEC) was introduced in the 1980's⁹ as a means to sterilize small deposits of residual disease, achieve high local concentrations of tumoricidal agents, and exploit the synergy between heat and anti-neoplastic agents.

The lack of evidence supporting a survival advantage in patients receiving systemic chemotherapy for carcinomatosis has been the impetus for more than 20 studies examining the morbidity, mortality, and efficacy of HIPEC¹⁰. All have differed with respect to design, patient selection, and treatment protocols¹⁰. Results have varied and conclusions have been difficult to render. Median survival has ranged from 12-32 months and the 1, 2, 3, and 5-yr survival rates have been between 65-90%, 25-60%, 18-47%, and 17-30%, respectively¹⁰. Grade III to IV toxicity has ranged from 14-55% and mortality from 0-19%¹⁰. Prolonged ileus, anastomotic dehiscence, fistulization, abdominal sepsis, pancreatitis, and hematologic toxicities have all been reported with a high degree of frequency¹⁰.

With numerous phase II trials in the past 5-6 years demonstrating an improved survival over historical controls with the use of HIPEC and cytoreductive surgery¹¹, there are some who would argue for the acceptance of this approach as standard of care for peritoneal carcinomatosis¹². However, as Koppe points out, of the three controlled studies which compare cytoreductive surgery / HIPEC to systemic chemotherapy¹⁰, only two are randomized. However, all have concluded that the completeness of cytoreduction is the most influential factor affecting outcome¹⁰, possibly suggesting that the addition of HIPEC may be superfluous. What's more, trials invoking the use of cytoreductive surgery in the context of HIPEC have applied surgical interventions to both treatment arms¹³, and have been slow to utilize contemporary agents such as irinotecan and oxaliplatin, making it difficult to draw conclusions over the effectiveness of cytoreductive surgery and leaving open the possibility that perceived differences in outcome may be minimized with the use of more modern agents¹⁰.

With a prior history of systemic chemotherapy and bone marrow transplantation for non-Hodgkin lymphoma and subsequent development of graft versus host disease, it was

unclear whether this patient could tolerate additional myelotoxic systemic chemotherapy. The use of such therapy for secondary malignancies following bone marrow transplantation is poorly-documented in the literature, although there have been no studies showing that patients with successful bone marrow grafts are at significant risk of morbidity or mortality after receiving additional systemic chemotherapy. Because of the relative paucity of data regarding its use in this setting, systemic chemotherapy was relegated to a secondary role in favor of HIPEC and the patient sought additional treatment at a center with expertise in this field.

DISCLAIMERS

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