Anti-Cancer Drugs 2000, **11,** pp. 279–283

Case report

Colon carcinoma with synchronous ovarian metastasis—report and discussion of five cases

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Ovarian metastasis may present at the time of initial diagnosis of colon carcinoma or as a later recurrence. Little meaningful information is available regarding the treatment and outcome of synchronous ovarian metastasis of colon carcinoma. This report describes the clinical course of five patients with synchronous ovarian metastasis of colon carcinoma who were treated with aggressive surgery and chemotherapy. The treatment consisted of maximal surgical debulking followed by systemic chemotherapy with weekly 24 h infusion of high-dose 5-fluorouracil and leucovorin. All of the five patients had subsequent disease-free periods ranging from 6 to 43+ months following operation. Two of the patients who had no or minimal peritoneal involvement were still alive without disease at 33 and 43 months. The data from these cases suggest that aggressive surgery and systemic chemotherapy may be highly efficacious in the treatment of colon carcinoma with synchronous ovarian metastasis. Maximal debulking followed by chemotherapy may be particularly effective in those patients with minimal peritoneal involvement. [© 2000 Lippincott Williams & Wilkins.]

Key words: Colon carcinoma, debulking surgery, postoperative chemotherapy, synchronous ovarian metastasis.

Introduction

The ovary may become involved in patients with colon carcinoma by either direct invasion or metastatic spread. The reported incidence of ovary metastasis from colorectal carcinoma has ranged from 1.4 to 13.6%.[1–6] Ovarian metastasis at the time of initial surgery for colon carcinoma is uncommon. Little meaningful information is available regarding the incidence, characteristics and prognosis of synchronous ovarian metastasis of colon carcinoma. In a combined series, synchronous ovarian involvement by direct extension or metastasis occurred in 33 of 584 women (5.7%) selected to undergo oophorectomy at the time of colorectal surgery.[4–7] Many of these patients had only microscopically detectable disease.

Surgical therapy for primary ovarian carcinoma is well defined and surgical debulking has been shown to offer a clear survival benefit. However, in the presence of metastatic spread of colon carcinoma to the ovary, aggressive surgical therapy may be less beneficial.[8–10] Ovarian involvement of colon carcinoma is often part of diffuse intra-abdominal disease and implies a poor prognosis. Nevertheless, the efficacy of aggressive surgery combined with chemotherapy has not been well described.

Since there have been only limited descriptions of the clinical behavior and the implications of aggressive surgical therapy in cases of ovarian metastatic spread of colon carcinoma, the present study assessed the clinical course of five consecutive patients with a diagnosis of colon carcinoma with synchronous ovarian metastasis. All of the five cases received uniform treatment including aggressive surgery and postoperative chemotherapy with weekly 24 h infusion of high-dose 5-fluorouracil (5-FU) and leucovorin.

Patients and methods

From October 1995 to April 1997, we conducted a phase II trial of weekly 24 h infusion of high-dose 5-fluorouracil (5-FU) 2600 mg/m^2 and leucovorin 100 mg/m^2 (HDFL regimen) in patients with advanced colorectal carcinoma. A 47.2% response rate was achieved. The details of this clinical trial have been described previously.[11] In the meanwhile, five patients

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with colon carcinoma with synchronous ovarian metastasis treated with maximal surgical debulking followed by systemic chemotherapy with the same HDFL regimen formed the basis of the present study.

Results

The clinical characteristics and outcome of the five patients are described in the following case reports and summarized in Table 1.

Case 1

A 37-year-old previously healthy female patient visited a local physician in April 1996 complaining of a 6 months history of left lower abdominal discomfort associated with frequent urination and anemia. A 15×20 cm low abdominal mass was palpable. She was referred to the Gynecological Oncology Department of Chang Gung Memorial Hospital (CGMH) for further evaluation.

Radiographic examination revealed bilateral pelvic mass. Carcinoembryonic antigen (CEA) level was 22.2 ng/ml (normal <5 ng/ml) and CA-125 was 67.5 U/ml (normal <35 U/ml). Exploratory laparotomy revealed bilateral solid pelvic mass measuring 15×20 cm which adhered to the rectum and pelvic wall. Frozen section analysis showed metastatic adenocarcinoma in the ovary. A 4×4 cm tumor in the transverse colon (T-colon) and omental seeding were also found during the laparotomy. Transverse colectomy, abdominal total hysterectomy (ATH), bilateral salpigoophrectomy (BSO) and maximal debulking of omental tumor were done. Pathologic study revealed a well-differentiated adenocarcinoma in both colon, ovary and omentum. Four weeks later, abdominal CT scan found no gross evidence of tumor. Chemotherapy using an HDFL regimen was administered for 21 weekly cycles thereafter. However, intestinal obstruction and ascites developed in November 1996 during chemotherapy treatment. Additional chemotherapy was given without benefit. She died in March 1997.

Case 2

A 76-year-old female with no previous history of illness until April 1996, when she visited a local hospital with complaints of bowel habit change, body weight loss and abdominal distension for 3 weeks. Abdominal CT revealed a huge pelvic mass and coloscopy showed a descending colon (D-colon) tumor. She was referred to the Colorectal Surgery Department of CGMH. She underwent exploratory laparotomy in May 1996 and a right ovary tumor (18×16 cm) with dense adhesion to the pelvic side wall and cul-de-sac tumor seeding was found during the operation. Lower anterior resection, BSO and extended ATH was performed. Pathologic study revealed a well-differentiated adenocarcinoma in the D-colon, ovary, uterine serosa and omentum. Preoperative CEA was 8.6 ng/ml and CA-125 was 921 U/ml, and both levels returned to normal after operation. Chemotherapy with an HDFL regimen was administered post-operatively for 30 weekly cycles. She was noted to be without evidence of disease on clinical and radiological evaluation after completion of 30 cycles of HDFL therapy. However, evidence of disease progression was found in August 1997, with peritoneal carcinomatosis and bilateral hydronephrosis. She died of urinary tract infection with sepsis in September 1997.

Case 3

A 39-year-old female visited our clinic with the complaint of bowel habit change for 6 months in May 1996. Coloscopy revealed an annular narrowing in the D-colon. Abdominal CT scan was normal. She underwent exploratory laparotomy which revealed a schirrhous-type tumor in the D-colon. An ovary mass (3×7 cm) was identified by direct extension from the colon cancer. No gross peritoneal seeding was found and the right ovary was normal in appearance. Left

Table 1. Case summaries

Case	Age	Symptoms	Primary	Bilateral ovary	Peritoneum involvement	Outcome
1	37	low abdominal pain	T-colon	(+)	diffuse	DOD 11 months
2	76	bowel habit change	D-colon	(−)	diffuse	DOD 16 months
3	39	bowel habit change	Sigmoid	(+)	no	NED 43 months
4	57	low abdominal pain	T-colon	(+)	diffuse	DOD 16 months
5	24	low abdominal pain	T-colon	(−)	pelvic	NED 33 months

DOD, died of disease; NED, no evidence of disease.

hemicolectomy and left oophorectomy was done. Pathology revealed a signet-ring cell carcinoma in the D-colon, pericolic lymph nodes and left ovary. CEA level was 5.8 ng/ml before operation and returned to 2.25 ng/ml after operation. Post-operation adjuvant chemotherapy with HDFL for 30 cycles was administered from June 1996 to February 1997. However, a right pelvic mass was found in October 1997. Second laparotomy was performed which revealed a right ovary tumor 15×12 cm, no gross evidence of tumor was found in the peritoneal cavity. Pathology showed metastatic signet-ring cell carcinoma in the right ovary. Omental biopsy found no evidence of cancer. Chemotherapy with weekly 5-FU bolus plus high-dose leucovorin was delivered for 20 weekly cycles again. The patient was alive without evidence of disease on last follow-up in December 1999.

Case 4

A 57-year-old female visited our gynecological clinic with a 1 month history of lower abdominal pain, vaginal spotting, frequency and tenesmus in August 1996. Abdominal CT scan revealed bilateral adnexal mass with a large volume of ascites. Barium enema showed a large segmental stenosis with mucosal spiculation in the distal T-colon. Tumor markers levels were CEA 7.87 ng/ml and CA-125 265 U/ml. She underwent exploratory laparotomy under the impression of primary ovarian cancer. Bilateral ovary masses (12×12 and 15×15 cm) with dense adhesion to the cul-de-sac and a T-colon tumor (3×3 cm) were found during operation. ATH, BSO, omentectomy and segmental colectomy were performed. Pathology showed metastatic adenocarcinoma of the ovary. CEA and CA-125 levels returned to normal, and abdominal CT scan showed no evidence of tumor after operation. Chemotherapy with an HDFL regimen was given for 30 weekly cycles thereafter. Unfortunately, liver metastasis and peritoneal carcinomatosis developed in August 1997. Additional chemotherapy was administered, but in vain. She died in December 1997.

Case 5

A 24-year-old female was in good health until February 1997, when she visited a physician at a local hospital with a 2 week history of lower abdominal mass. She underwent exploratory laparotomy at the local hospital and left oophorectomy was performed. Pathology revealed metastatic adenocarcinoma of the ovary. She was then referred to the Gynecological Oncology Department of CGMH for further evaluation in March 1997. An abdominal CT tumor survey revealed no abnormalities while barium enema showed a T-colon tumor. The tumor markers were CEA 215 ng/ml, CA-19.9 88.4 U/ml (normal <37 U/ml) and CA-125 23.4 μg/ml. Exploratory laparotomy was performed again, and an ulcerative tumor at the proximal T-colon and small nodules in the pelvic peritoneum were found. ATH, right salpigoophorectomy and segmental colectomy were done. Pathology revealed a moderately differentiated adenocarcinoma in the T-colon, and metastatic adenocarcinoma in the peritoneum and inferior mesentery artery lymph nodes. The right ovary was negative for metastasis. CEA had decreased to 11.1 ng/ml 1 month later. Chemotherapy with an HDFL regimen was delivered from April 1997 to December 1997. CEA levels became normal after the completion of chemotherapy. She remained alive and disease-free on the last follow-up in December 1999.

Discussion

In this series of patients, the presenting symptoms of colon carcinoma with synchronous ovary metastasis, including pelvic mass, ascites and uterine bleeding, pointed more to a primary ovarian cancer than a colon cancer. Often, the correct diagnosis can only be made at the time of laparotomy. Thus, a thorough gastrointestinal examination should be undertaken in any patients presenting with a pelvic mass. Patients with advanced primary ovary carcinoma should undergo cytoreductive surgery to remove as much of the tumor and its metastasis as possible in order to facilitate the effectiveness of subsequent treatment. In cases of metastatic disease to the ovary, however, different guidelines may apply and an aggressive surgical approach may be less beneficial.[8–10] The differences between these two treatment strategies stem from the finding that most primary ovarian cancer responds better to chemotherapy than colon cancer.

The diagnosis of colon carcinoma with synchronous ovarian metastasis has been reported to be associated with a poor outcome.[12] The median survival time described in previous reports has ranged from 6 to 18 months.[12–14] Only a few 5 year survivors have been reported despite the surgeon's impression that patients were free of disease after the operation. Death generally occurs within a few months after the documentation of ovarian metastasis, usually as a consequence of multiple organ metastasis, suggesting that a subclinical metastasis was already present at the time of oophorectomy. However, with improvements in the effectiveness of chemotherapy, it is possible that such patients may be cured by maximal debulking and

aggressive chemotherapy. In an attempt to enhance 5-FU activity, researchers have administered it in combination with biochemical modulators and changed its dosage schedules to increase dose intensity.[11,15,16] The weekly 24 h infusion of high-dose 5-FU and leucovorin may be an optimal schedule because it allows administration of the highest dose intensity of 5-FU as well as biochemical modulation without requiring 5-FU dose reduction. In previous phase II studies, this regimen achieved 42–58% response rates in cases of advanced colorectal cancer.[11,16–18] This result was similar to results obtained with chemotherapy in primary ovarian cancer. In this series of cases, maximal debulking surgery and aggressive chemotherapy resulted in disease-free periods ranging from 6 to 43+ months following operation, with two patients achieving long-term disease-free survival. Several previous reports[13,19–21] as well as our results support that increased surgical efforts are justified in patients with colon cancer metastatic to the ovary.

When metastatic spread to the ovary occurs, it is usually bilateral.[14,22,23] In the presence of metastasis to the unilateral ovary, the preservation of any ovarian tissue is not indicated since the risk of contralateral ovary involvement is high. Ovaries which are grossly normal in appearance may contain microscopic metastases. In addition, the ovary, like the testis, may be a sanctuary site for systemic chemotherapy. Taylor *et al*. reported that patients with primary colorectal carcinoma had a 40% response rate at extraovarian sites compared to a 5% response rate in ovarian metastasis.[21] In Case 3 of the present series, the left ovary had been directly invaded by sigmoid colon cancer and the colon cancer relapsed in the contralateral ovary 2 years later despite aggressive systemic chemotherapy. This case supports the previous finding that the ovary may be a sanctuary site for systemic chemotherapy with 5-FU and suggests that bilateral oophorectomy is indicated for all patients with colon carcinoma with synchronous ovarian metastasis. Furthermore, the poor response of ovarian metastasis to chemotherapy suggests that surgical removal of ovarian metastasis may be the best palliative treatment for both synchronous and metachronous ovarian metastasis.

Patients with no gross residual disease after oophorectomy were reported to survive significantly longer than those with residual disease.[14,19,20] This finding is supported by the results of the present study. Indeed, in our patients who had disease which was confined to the ovaries or the pelvis (Case 3 and 5), there was a dramatic increase in survival compared to those patients with diffuse intra-abdominal disease. However, the ability to remove all gross disease at the time of oophorectomy may be the major determinant of survival, even if this involves resection of multiple anatomic sites.[14] Because of the small number of patients in this study, the effectiveness of postoperative chemotherapy could not be assessed. Further study is necessary to determine whether postoperative chemotherapy can improve survival in patients with colon carcinoma with synchronous ovarian metastasis. However, the finding that two of the five patients in our study had long-term disease-free survival seems to support the effectiveness of postoperative chemotherapy in cases where extra-ovarian disease appears to be resectable.

Conclusion

Aggressive surgery and chemotherapy may be highly effective therapy for colon carcinoma with synchronous ovarian metastasis. Maximal surgical debulking and postoperative chemotherapy provided excellent results in this series of patients, especially in those with minimal peritoneal involvement.

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(Received 18 January 2000; accepted 16 February 2000)