



Treatment of Krukenberg Tumor with Hyperthermic Intraperitoneal Chemotherapy: A Report of Three Cases

Li-Yung Chen¹, Chun-Yu Fu¹, Huai-En Lu¹, De-Chuan Chan²

¹Department of Surgery, Song Shan Branch, Tri Service General Hospital, National Defense Medical Center, Taipei 105,

²Department of Surgery, Division of General Surgery, Tri Service General Hospital, National Defense Medical Center, Taipei 114, Taiwan, Republic of China

We report three cases of Krukenberg tumor (KT): two were synchronous and one metachronous. At presentation, the first synchronous KT patient had a palpable umbilical mass, the second had a perforated peptic ulcer, and the metachronous KT patient had an ovarian lesion, detected postoperatively. As we know, KT has a quite poor prognosis. According to some papers, surgery with chemotherapy increases survival more than 12 months. Consequently, our two synchronous KT patients received cytoreductive surgery with hyperthermic intra-abdominal chemotherapy and our metachronous KT patient received laparoscopic bilateral oophorectomy. No recurrences have so far been detected in any patient. Our patient with metachronous KT will undergo laparoscopy and hyperthermic intraperitoneal chemotherapy and our patients with synchronous KT will continue to be followed up to determine their final outcomes.

Key words: Krukenberg tumor, hyperthermic intraperitoneal chemotherapy, gastric cancer, carcinomatosis

INTRODUCTION

Krukenberg tumor (KT) is a rare malignant ovarian tumor that arises secondarily from gastric, breast or other alimentary cancer metastases. Even after extirpation of gastric cancer by surgery and chemotherapy, metastatic lesions can still occur in the ovary. Until now, there has been no standard treatment for KT. However, some papers have advocated hyperthermic intraperitoneal chemotherapy (HIPEC) for gastric cancer with carcinomatosis management.¹ We report on three rare cases of KT and discuss the feasibility of HIPEC as a treatment for these cases.

CASE REPORTS

Case 1

A 54-year-old female with gastric adenocarcinoma (pT4aN3bM0, Stage IIIC) underwent laparoscopic total

gastrectomy in October 2013, followed by eight cycles of adjuvant chemotherapy with an oxaliplatin-containing regimen from November 2013 to June 2014. Following surgery and chemotherapy, abdominal computed tomography (CT) was performed and serum carcinoembryonic antigen (CEA) levels were evaluated to prepare for therapy. Abdominal CT revealed two heterogeneous ovarian masses, which were suspected to be malignant [Figure 1]. In addition, we noted the gradual elevation of serum CEA/CA199 levels. Accordingly, KT due to gastric cancer was considered the likely diagnosis. She underwent a laparoscopic bilateral oophorectomy with partial peritonectomy due to one lesion on the bladder peritoneum [Figure 2]; however, intraoperative peritoneal washing cytology was negative for malignancy. Definitive pathology confirmed the presence of signet-ring cell carcinoma. Subsequently, intraperitoneal chemotherapy with paclitaxel was administered followed by salvage chemotherapy with paclitaxel every 21 days. In November

Received: March 13, 2016; Revised: June 20, 2016;
Accepted: August 29, 2016

Corresponding Author: Dr. De-Chuan Chan,
Department of Surgery, Division of General
Surgery, Tri-Service General Hospital, National
Defense Medical Center, Taipei 114, Taiwan, ROC.
Tel: 886-2-2768-4526; Fax: 886-2-2768-4526.
E-mail: chrischan1168@yahoo.com.tw

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How to cite this article: Chen LY, Fu CY, Lu HE, Chan DC. Treatment of Krukenberg tumor with hyperthermic intraperitoneal chemotherapy: A report of three cases. J Med Sci 2016;36:197-201.

Krukenberg tumor treated with HIPEC

2015, no obvious lesion was seen over the pelvic region on abdominal CT and serum CA199 had decreased to 33.14 U/mL [Figure 3]. At present, laparoscopic restaging with HIPEC remains an option to manage her gastric cancer with carcinomatosis.

Case 2

A 28-year-old female presented with a palpable umbilical mass in February 2015. The tumor was excised and pathologically diagnosed as metastatic adenocarcinoma. Following surgery, further imaging revealed an ulcerative mass extending from the gastric body to the antrum. Biopsy confirmed the presence of adenocarcinoma. Other findings included an obstructive colonic polypoid mass and right ovarian cystic lesion [Figure 4]. Therefore, gastric adenocarcinoma metastasized to the colon and right ovary was diagnosed. Six cycles of neoadjuvant chemotherapy with trastuzumab, oxaliplatin, and fluorouracil were

administered from February 2015 to August 2015. She underwent laparoscopic staging in October 2015, which showed intra-abdominal carcinomatosis. Definitive pathology confirmed gastric adenocarcinoma with metastasis to the bilateral ovaries, peritoneum, omentum, terminal ileum, ascending colon, and umbilicus. Following staging surgery, intraperitoneal chemotherapy with paclitaxel (120 mg in 1000 mL normal saline) was administered. Subsequently, laparoscopic subtotal gastrectomy with oophorectomy, bilateral right hemicolectomy, and D2 lymph node dissection was performed, and HIPEC with mitomycin-C and cisplatin was administered on January 6, 2016. Serum CA199 was 25.36 U/mL on January 25, 2016, having decreased from 108 U/mL, and she is currently undergoing salvage chemotherapy with paclitaxel plus TS-1 every 28 days.

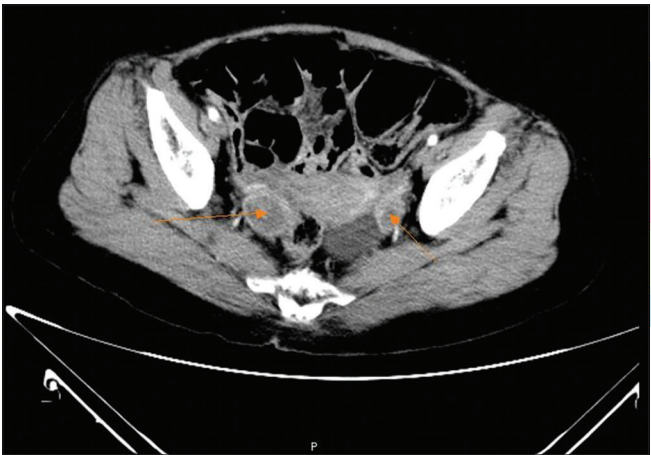


Figure 1: Case I: Abdominal computed tomography. Heterogeneous lesions (arrows) on both ovaries

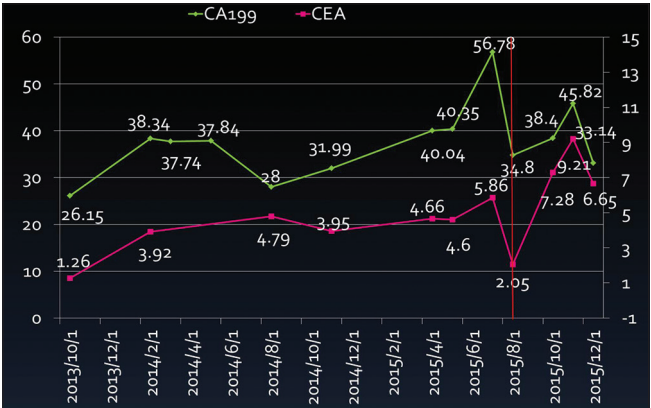


Figure 3: Case I: Time course of serum carcinoembryonic antigen/CA199 levels. The red line indicates the date of surgery



Figure 2: Case I: The ovarian tumors and bladder peritoneal lesions after resection

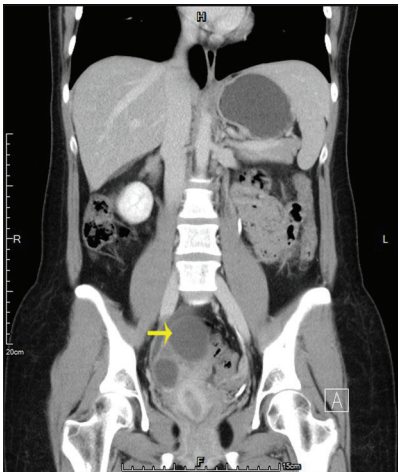


Figure 4: Case II: Abdominal computed tomography. Heterogeneous cystic lesions (arrows) on the right ovary

Case 3

A 33-year-old female presented with a perforated peptic ulcer. Exploratory laparotomy with the excision of the gastric ulcer was performed on July 2, 2015. Gastric adenocarcinoma with intra-abdominal carcinomatosis was surgically diagnosed. Following surgery, salvage chemotherapy with capecitabine plus oxaliplatin was administered biweekly (six cycles). Abdominal CT revealed left ovarian cystic lesions. She underwent exploratory laparotomy with total gastrectomy, left oophorectomy, partial peritonectomy, and D2 lymph node dissection, and on December 17, 2015, HIPEC with mitomycin-C and cisplatin. Definitive pathology confirmed the presence of gastric adenocarcinoma with metastasis to the left ovary, peritoneum, omentum, and gallbladder. Serum CA199 on February 2016 had decreased to 23.7 U/mL from 95.32 U/mL. Currently, she is undergoing salvage chemotherapy with paclitaxel plus oxaliplatin every 14 days.

DISCUSSION

In 70%–80% of cases, the source of KT is gastric tumors.² Other sources include tumors of the breast, esophagus, colorectal tissue, gallbladder, pancreas, small intestine, and appendix.^{3,4} KTs are usually bilateral and present in the ovarian stroma.⁵ Overall survival (OS) in patients with KTs is very poor, and median survival is about 14 months.² Patients often die within 2 years after they start palliative treatment.² Cho *et al.* have suggested that surgical intervention with metastasectomy plus chemotherapy in advanced gastric cancer patients with KT can improve their OS.⁶ While no definite or evidence-based strategy has been reported for KT, Sugarbaker has advocated HIPEC for peritoneal carcinomatosis management.⁷ HIPEC destroys cancer cells through thermal injury and facilitates cytotoxicity of chemotherapeutic regimens. Thermal injury (target temperature over 41°C) can induce heat-shock protein release from tumor cells to levels high enough to attract natural killer cells that trigger tumor cell apoptosis and inhibit tumor angiogenesis. Intra-abdominal peritoneal lavage with cytotoxic agents (when compared to intravenous therapy) elevates the peritoneal concentrations of these agents to higher levels, increases the depth of their tumor penetration (probably to 1–3 mm), and is associated with less systemic toxicity.⁸ Moreover, Bull noticed that certain regimens of cytotoxic drugs (when used with hyperthermia) had lower systemic toxicity.⁹ Hence, HIPEC is now considered a treatment option for gastric cancer, colorectal cancer with carcinomatosis or pseudomyxoma peritonei in the selected cases.¹⁰

There are currently few reports in the literature about the use of HIPEC for KT. Therefore, no standardized regimen is available. Sugarbaker reported the indications for HIPEC and postoperative intraperitoneal chemotherapy.⁷ Glehen *et al.* suggested the use of a mitomycin-C-based or oxaliplatin-based regimen with HIPEC for peritoneal carcinomatosis in gastric cancer.¹¹ Three randomized controlled studies reported the beneficial effects of HIPEC with a fluorouracil regimen.^{12–14} Sun *et al.* found no obvious statistical heterogeneity between subgroups receiving mitomycin-C versus fluorouracil.¹⁵ Hence, not enough evidence is currently available to aid the selection of the best regimen. Some studies preferred oxaliplatin over mitomycin-C due to its higher intratumoral penetration with similar hematologic toxicity.¹⁶ However, hemophagocytic syndrome was reported as an unusual complication of HIPEC with oxaliplatin in five patients¹⁷ and Prada-Villaverde *et al.* reported better OS in those treated with mitomycin-C than those treated with oxaliplatin.¹⁸ Hence, we decided to use a mitomycin-based regimen with HIPEC in our cases.

HIPEC has some disadvantages. Kakushima *et al.* indicated that retrograde lymphatic metastasis is the most likely pathway of KT due to gastric cancer and may lead to HIPEC failure.⁵ Piso *et al.* attributed HIPEC failure to chemotherapy toxicity, gastrointestinal symptoms, renal or hepatic toxicity and/or malfunction, anastomosis leakage, intestinal obstruction, and intra-abdominal abscess.¹⁹ In Cases II and III, no obvious complications of cytoreductive surgery with HIPEC occurred within postoperative 30 days. We currently continue to monitor CA199 level and follow the clinical course of these cases with imaging studies.

In Case I, laparoscopic surgery was followed by postoperative intraperitoneal chemotherapy and IV chemotherapy. Although no recurrence was apparent on imaging, serum CA199 level spiked to 45.82 U/mL postoperatively. Wu *et al.* had suggested that cytoreductive surgery with HIPEC could increase the survival of patients with ovarian metastasis.³ Consequently, we will choose HIPEC to treat the potential recurrence of tiny lesions in Case I. In addition; she had a postoperative history of gastric cancer combined with metachronous KT. A study by Rosa *et al.* reported better median survival time in 12 metachronous versus 15 synchronous cases (36 months vs. 17 months, $P < 0.0001$).²⁰ Although not providing enough clinical support for the hypothesis of increased OS, the data led us to conclude that further therapy could still extend the OS in this patient. In the future, she will undergo repeat laparoscopic examination (to detect occult disease in the intraperitoneal cavity) and HIPEC (if carcinomatosis is observed).

CONCLUSION

Although the prognosis of KT is quite poor with OS <12 months, current studies have revealed the benefit of cytoreductive surgery with HIPEC. Based on the results of our treatment in Cases II and III, we plan to conduct second-look laparoscopy in conjunction with HIPEC and mitomycin-C-based chemotherapy, continue to follow the outcomes of our cases, and conduct further studies.

Financial support and sponsorship

Nil.

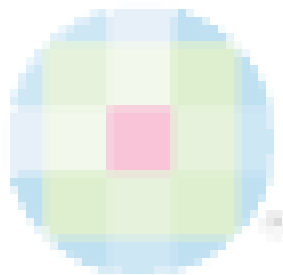
Conflicts of interest

There are no conflicts of interest.

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