A Case of Primary Gastric Choriocarcinoma Presenting with Amenorrhea

Seung-Hyun Nam, M.D.¹, Seock-Ah Im, M.D.¹, Ki-Sun Bae, M.D.¹, In-Sook Kang, M.D.¹, Jung-Mi Kwon, M.D.¹, Kyung-Eun Lee, M.D.¹, Hye-Sung Moon, M.D.², Sun-Hee Sung, M.D.³, Woon-Sup Han, M.D.³, Chu-Myong Seong, M.D.¹ and Soon Nam Lee, M.D.¹

Departments of ¹Internal Medicine, ²Gynecology and ³Pathology, College of Medicine, Ewha Womans University, Seoul, Korea

Primary gastric choriocarcinomas are very rare, and their prognosis is extremely poor. A 37-year-old woman presented with amenorrhea, vaginal spotting and severe nausea, which mimicked a pregnancy and gestational trophoblastic disease. The serum level of the beta-subunit of human chorionic gonadotrophin (β-hCG) was significantly increased. An endoscopic biopsy of the stomach mass showed the features of a choriocarcinoma, with marked anaplasia and necrosis. Immunohistochemical staining for β-hCG showed positive results in the choriocarcinoma. Chemotherapy for the choriocarcinoma was administered, but she died 8 months following diagnosis. (Cancer Research and Treatment 2002;34:457-460)

Key Words: Choriocarcinoma, Stomach, Human chorionic gonadotrophin, Chemotherapy

INTRODUCTION

Primary choriocarcinomas are a highly malignant neoplasm, producing human chorionic gonadotrophin (hCG), which is almost always of the ovary or testes. Non-gestational, extragonadal choriocarcinomas are very rare, but have been reported to occur within the lungs, breasts, mediastinum, bladder, kidneys and gastrointestinal tract (1,2). Primary gastric choriocarcinomas are very rare, and result in high levels of β-hCG in urine and serum. We report a case of a chemotherapy refractory primary gastric choriocarcinoma, with carcinomatosis peritonei in a 37-year-old woman presenting with amenorrhea.

CASE REPORT

A 37-year-old, G2, P2, woman visited our emergency room in May, 2001. She had experienced amenorrhea, vaginal bleeding and nausea for about 7 weeks, and lower abdominal pain for 1 week. A physical examination revealed acutely ill-looking in appearance, pale conjunctive. Her pulse was 100/min, and her blood pressure was 100/60 mmHg. Her abdomen was flat with no palpable abnormal mass. A pelvic examination revealed a normal-sized uterus, and no adnexal mass. The laboratory tests found the levels of hemoglobin, hematocrit, serum β-hCG and CEA to be 7.7 g/dl, 22.6%, 5,581 mIU/ml and 0.0 ng/ml, respectively. The Chest x-ray was unremarkable. She received a laparoscopic bilateral salpingectomy, due to the initial diagnosis of an ectopic pregnancy, in the Department of Obstetrics and Gynecology. At surgery, the adnexa were unremarkable, and a biopsy revealed no fetal tissue.

The follow up serum β-hCG level had increased to 10,263 mIU/ml, and under the impression of a hydatidiform mole; she was treated weekly with intramuscular methotrexate injections. A month later, the follow-up serum β-hCG level had increased to 19,569 mIU/ml. She underwent an exploratory laparotomy and total abdominal hysterectomy, with a left oophorectomy, due to the impression of gestational trophoblastic disease.

A stomach mass, with carcinomatosis peritonei, was found incidentally during the operation. The pathology of the tissue from the ovary revealed a hemorrhagic corpus luteum without malignancy, but the tissue from the peritoneum and omentum revealed a metastatic choriocarcinoma (Fig. 1A), with a positive reaction for β-hCG by immunohistochemical staining (IHS) (Fig. 1B). Three days after the operation, a gastric endoscopy revealed a huge ulceroinfiltrative mucosal lesion on the greater curvature side of the body (Fig. 2). Abdomen and pelvis CT scans revealed diffuse gastric wall thickening, with metastatic lymphadenopathies, suggestive of an advanced gastric cancer (Fig. 3). Endoscopic biopsies of the stomach showed features of a choriocarcinoma, with marked anaplasia and necrosis (Fig. 4A), and IHS for β-hCG showed a positive reaction (Fig. 4B). Combination chemotherapy, consisting of etoposide, Adriamycin and cisplatin (EAP), was administered in June, 2001. After the
Fig. 1. (A) The peritoneal biopsied specimen shows proliferation of anaplastic tumor cells. Some of them show multinucleated giant cells (arrows), consistent with syncytiotrophoblast. Multifocal necrosis is noted between the tumor cells (H&E, ×400). (B) Immunohistochemical staining for β-HCG of peritoneal tissue shows focal strong positive reaction (peroxidase-HRP, ×400).

Fig. 2. Gastric endoscopic feature shows a huge ulceroinfiltrative mucosal lesion on greater curvature of the body.

Fig. 3. Abdominal CT shows diffuse gastric wall thickening with metastatic lymphadenopathies.

first cycle of EAP chemotherapy she felt comfortable, without complaint of nausea or vomiting, and a marked drop in the serum β-hCG level (Fig. 5). The chemotherapy regimen was changed to a combination chemotherapy of EMA/CO (etoposide, methotrexate, dactinomycin, cyclophosphamide and vincristine) after the second cycle of EAP chemotherapy due to the progressive disease, with an increased level of serum β-hCG. She developed ascites after the third cycle of chemotherapy, and an abdomen CT revealed a progressive disease. Therefore, she was treated with a new regimen (taxol 175 mg/m² and carboplatin [AUC 6]). However, she did not respond to the chemotherapy. Although the sixth cycle of chemotherapy was administered, the patient died 8 months after diagnosis.

**DISCUSSION**

A choriocarcinoma is an invasive, widely metastatic epithelial neoplasm, derived from either trophoblastic or totipotential germ cells of gonadal origin. Choriocarcinomas also occur, rarely, as nongestational neoplasms, including those of extragonadal origin, such as the stomach, lungs, liver, breasts and mediastinum (1, 2), with the stomach being the most common site. Since the first reported Korean case of a primary gastric choriocarcinoma in 1975 (3), seven further cases have been reported (Table 1) (4–6). The median age of the reported cases was 54 years, ranging from 52 to 74. Gastric choriocarcinomas have a 2.5:1 male-to-female ratio. The presenting symptoms of the reported cases were mainly abdominal pains and palpable masses. Of seven cases, 5 received a gastrectomy. However, the clinical
Fig. 4. (A) Endoscopic biopsied specimen of the stomach reveals choriocarcinoma (arrows) showing marked anaplastic tumor cells with necrosis in gastric mucosa. Noneoplastic stomach mucosa with intestinal metaplasia is focused in the left side (H&E, ×100). (B) Immunohistochemical staining for β-HCG shows focal strong positive reaction in the tumor of the stomach (peroxidase-HRP, ×200).

Table 1. Clinical characteristics of primary gastric choriocarcinoma from eight case reports in Korea

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age</th>
<th>Presenting symptom</th>
<th>Operation</th>
<th>Chemotherapy regimen</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim OK (1975)</td>
<td>F/52</td>
<td>Melena</td>
<td>Gastrectomy</td>
<td>None</td>
<td>Expired due to postoperative infection</td>
</tr>
<tr>
<td>Kim EK et al (1992)</td>
<td>M/74</td>
<td>Abdominal pain</td>
<td>Gastrectomy</td>
<td>Unknown regimen</td>
<td>Expired after first chemotherapy</td>
</tr>
<tr>
<td>Jung KC et al (1994)</td>
<td>M/50</td>
<td>palpable mass</td>
<td>Gastrectomy</td>
<td>Unknown regimen</td>
<td>Expired after first chemotherapy</td>
</tr>
<tr>
<td>Kwon KH et al (1994)</td>
<td>M/54</td>
<td>Abdominal pain</td>
<td>Gastrectomy</td>
<td>Unknown regimen</td>
<td>Expired after first chemotherapy</td>
</tr>
<tr>
<td>Kim MK et al (1995)</td>
<td>M/53</td>
<td>Abdominal pain</td>
<td>None</td>
<td>None</td>
<td>Expired due to hepatic failure during admission</td>
</tr>
<tr>
<td>Kim H et al (1999)</td>
<td>M/60</td>
<td>Abdominal pain</td>
<td>None</td>
<td>EAP, EMA/CO</td>
<td>Expired after discharge</td>
</tr>
<tr>
<td>Present case (2002)</td>
<td>F/37</td>
<td>Amenorrhea</td>
<td>None</td>
<td>paclitaxel+carboplatin</td>
<td>Expired 8 months after 6th chemotherapy</td>
</tr>
</tbody>
</table>

Fig. 5. The change of serum β-hCG after chemotherapy. ↓ EAP: etoposide 100 mg/m² D1-3, Adriamycin 40 mg/m² D1, cisplatin 80 mg/m² D2, every 3 weeks. VEMA/CO: etoposide 100 mg/m³ D1, 2, methotrexate 300 mg/m² D1, dactinomycin 0.5 mg D1, 2, cyclophosphamide 600 mg/m³ D8, vincristin 2 mg D8. ↓ Taxol 175 mg/m³ D1, carboplatin (AUC=6) D2, every 3 weeks. courses, following chemotherapy, were not described for these cases due to the case reports focusing on their unique pathological features, and the diagnosis itself.

The diagnosis of a primary non-gestational, extragonadal choriocarcinoma is based on the clinical presentation and characteristic histological findings. The clinical features of these tumors may include some hormonal effects, such as amenorrhea, vomiting mimicking pregnancy in adult females, and gynecomastia in adult males. The patient in this report was of childbearing age woman experienced severe nausea and amenorrhea, reminiscent of pregnancy, which led to the misdiagnosis of gestational trophoblastic disease. If the β-hCG level was elevated, with no evidence of pelvic organ abnormality, we should consider a diagnosis of a primary nongonadal extragonadal choriocarcinoma. A primary gastric choriocarcinoma is accompanied by a markedly elevation in the level of β-hCG, and its diagnosis is further supported by a rapid decline in the β-hCG levels following either, resection of the tumor, or chemotherapy.

A primary gastric choriocarcinoma is frequently accompanied by an adenocarcinoma or other elements, and occasionally take
a transitional form between an adenocarcinoma and a choriocarcinoma. In our case, endoscopic biopsies of the stomach showed multinucleated cells, with the features of syncytiotrophoblasts and marked anaplasia and necrosis, accompanied by a poorly differentiated adenocarcinoma. The coexistence of an adenocarcinoma and a choriocarcinoma has been found histologically in 68.4% of reported cases (7).

There are several theories regarding the pathogenesis of gastric choriocarcinomas. The tumor may arise from displaced gonadal anlage within the abdomen, or as a result of delayed metastasis of a primary intrauterine lesion (7). Others have postulated that these neoplasms are derived from metastases of primary gonadal tumors undergoing spontaneous regression (8), or arise from the retro-differentiation of gastric carcinoma cells to the embryonal ectoderm, and subsequently as a metastasis to trophoblastic precursor cells (9,10). Some researchers believe they represent some focal emboli from a previous normal or molar gestations, even after a long latency periods (11). The retro differentiation theory appears to be the most likely explanation, since 70% of primary gastric choriocarcinoma patients had other adenocarcinoma components.

A primary gastric choriocarcinoma is usually unresponsive to single, or multi-agent combination chemotherapy, which are very effective in gestational choriocarcinomas (12). In our case, the patient was unresponsive to the combination chemotherapy usually used in gastric choriocarcinomas and adenocarcinomas. Paclitaxel has been reported to inhibit the proliferation, and to promote differentiation, of choriocarcinoma cells (13). Some reports have shown that paclitaxel is an effective salvage antineoplastic agent when EMA/CO has failed in choriocarcinoma patients (14). Paclitaxel is also active against stomach adenocarcinomas. Therefore, we used paclitaxel with carboplatin.

Reports of cases similar to ours suggest that a primary gastric choriocarcinoma constitutes a clinical entity of a tumor in the digestive tract, rather than a germ cell tumor. These neoplasms readily metastasize via the lymphatic and hematogenous routes, and are often complicated by necrosis and massive bleeding. Gastric choriocarcinomas may metastasize to other sites, such as the liver, lymph nodes, lungs and peritoneum. The prognosis is extremely poor, with a reported average survival of only 2.5 months (7,15). In this case, the symptoms including severe nausea and vomiting relieved during the initial two months of chemotherapy. Despite the transient improvement of symptoms, the disease progressed, and she died 8 months after diagnosis.

CONCLUSIONS

Choriocarcinomas are highly malignant neoplasms, which are almost intrauterine and gestational in origin, but also occur, rarely, as nongestational neoplasms. Primary gastric choriocarcinomas are very rare and resistant to chemotherapy, with an extremely poor prognosis. We report a case of a chemotherapy refractory primary gastric choriocarcinoma, presenting with amenorrhea, vaginal bleeding and severe nausea, in a 37-year-old woman.

REFERENCES