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Case report

A case of glassy cell carcinoma of the uterine cervix effectively responding to chemotherapy with paclitaxel and carboplatin

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Glassy cell carcinoma (GCC) of the uterine cervix is a highly malignant tumor and has a poor prognosis. As yet, no effective systemic chemotherapy to this tumor has been reported. Here we describe a case of recurrent GCC that responded to paclitaxel and carboplatin combination treatment. The patient, a 32-year-old woman, with clinical staging FIGO IB1 disease had a radical hysterectomy and postoperative radiotherapy. Three months after initial treatment, she had a relapse as peritoneal dissemination, which was confirmed in the second surgery (adnectomy) and which did not respond to platinum-based conventional chemotherapy (cisplatin, adriamycin, cyclophosphamide and carboplatin, etoposide). The recurrent peritoneal tumors responded well to paclitaxel and carboplatin combination treatment. An elevated serum concentration of carcinoembryonic antigen (672 ng/ml) was reduced to 14.4 ng/ml by six such courses. Peritoneal histopathology confirmed a complete response in the third surgery (ileostomy) for adhesive ileus by the radiotherapy. This is the first report of effective systemic chemotherapy with paclitaxel and carboplatin to recurrent GCC of the uterine cervix. [© 2001 Lippincott Williams & Wilkins.]

Key words: Carcinoembryonic antigen, cervical cancer, chemotherapy, glassy cell carcinoma, paclitaxel.

Introduction

Glassy cell carcinoma (GCC) of the uterine cervix is a rare tumor and classified as a subtype of adenosquamous carcinoma.[1] The clinical behavior of this tumor is characterized by aggressiveness and poor prognosis, because of its resistance to conventional radiotherapy and surgery.[1–4] No effective systemic chemotherapy to GCC has been reported, although Mikami *et al.*[5] recently reported preoperative intra-arterial chemotherapy was effective. We present a case of GCC that was resistant to radiotherapy and platinum-based conventional chemotherapy, but effectively responded to treatment with paclitaxel (PTX) and carboplatin.

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Case report

The patient, a 32-year-old woman, gravida 1, para 1, presented to her physician for evaluation of a 6-month history of contact bleeding in November 1998. A Papanicolau's smear test showed class V and a subsequent biopsy specimen was interpreted as squamous cell carcinoma, non-keratinizing type. The patient was referred to Hamamatsu University Hospital.

Results of a general physical examination were unremarkable. Pelvic examination revealed a 3-cm tumor in the cervix that bled easily. There was no evidence of vaginal and parametrial extension. Results of blood examination were within the normal range except for a marked elevation of serum carcinoembryonic antigen (CEA) level, 267 ng/ml (Figure 1). Chest X-ray, an i.v. pyelogram, cystoscopy and proctosigmoid scopy showed no invasion and metastasis. Clinical staging confirmed a FIGO stage IB1 region. The screenings of other malignancies were all negative.

The patient underwent a radical hysterectomy on 3 March 1998. Her right ovary was transported lateral to the kidney under the liver. An exophytic tumor mass measuring $3 \times 3 \times 4$ cm was seen in macroscopic examination of the cervix. Microscopically, the tumor consisted of invasive nests of malignant epithelial cells lying in a scant stroma, and showed no peal formations and glandular elements. The tumor was composed of

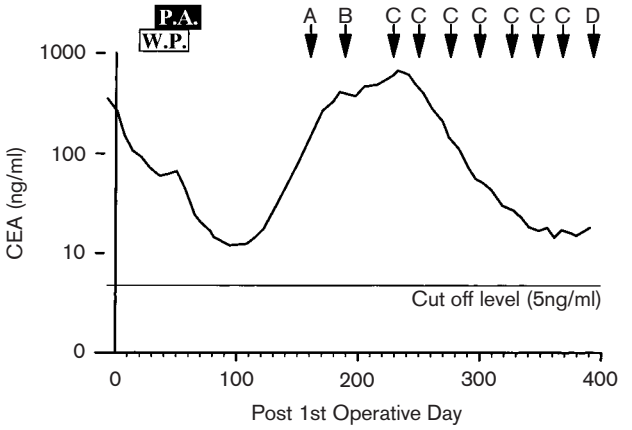

Figure 1. Clinical course and serum CEA concentration. W.P., 50.4 Gy irradiation on the whole pelvis; P.A., 45 Gy irradiation on the paraaortic region; arrow A, combination chemotherapy with cisplatin, adriamycin and cyclophosphamide; arrow B, second operation and i.p. chemotherapy with carboplatin and etoposide; arrow C, combination chemotherapy with PTX and carboplatin; arrow D, third operation.

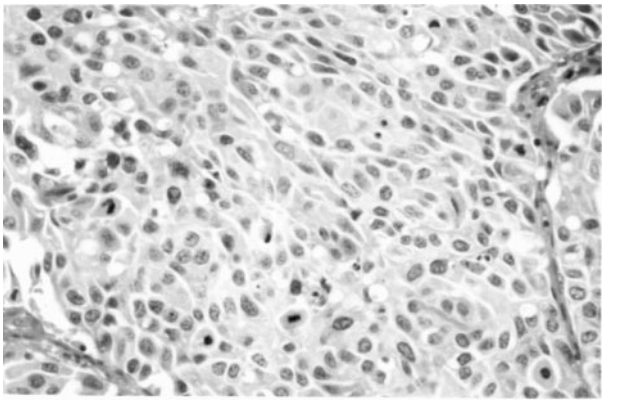

Figure 2. High-power view of the tumor showing GCC of the uterine cervix. Tumor cells have medium to large nuclei and rather plump fine granular or pale eosinophilic cytoplasm showing ground glass appearance. The cell borders are distinct and frequent mitosis is seen. Some tumor cells have large vacuoles in the cytoplasm.

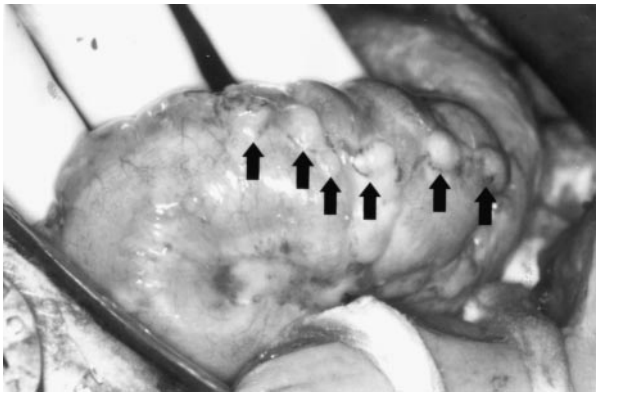

Figure 3. Peritoneal dissemination on the surface of the colon at the second operation. Numerous dissemination foci (arrows) were observed on the surface of the colon.

medium to large cells with fine granular or pale eosinophilic cytoplasm, which showed characteristic ground glass appearance. Most of the tumor cell borders were distinct and intercellular bridges were absent. Mitotic figures were very numerous (Figure 2). The stroma of the tumor was often infiltrated with acute inflammatory cells. Numerous lymphatic invasions, and internal iliac and cardinal ligament lymph node metastases were observed. Pathological diagnosis was GCC of the uterine cervix, pT1b1, pN1, pM0. Immunohistochemical staining exhibited diffuse cytoplasmic staining for CEA in the primary and metastatic tumor cells.

Post-operatively, the patient received 50.4 Gy irradiation on the whole pelvis and 45 Gy irradiation on the para-aortic region. The serum concentration of CEA went down gradually, but did not reach under the cut-off level (5 ng/ml) after the initial treatment (Figure 1). Computer tomographic scan, magnetic resonance imaging, bone scintigram and positron emission tomography were negative for residual disease. However, 3 months after the initial treatment, the serum CEA level increased gradually, but close clinical examinations also revealed no cancer foci. She received combination chemotherapy with 700 mg cyclophosphamide, 50 mg adriamycin and 70 mg cisplatin (CAP) for one cycle, but the serum CEA level was still increasing. Then she underwent the second operation on 9 September 1998. Numerous dissemination foci up to 5 mm diameter were observed in the pelvic peritoneum, on the surface of the colon (Figure 3) and the right ovary. Right adnectomy and biopsy were performed. Histopathologic studies again showed metastatic GCC with all viable tumor cells. So we judged this tumor was resistant to CAP therapy. Subsequently, she received i.p. chemotherapy with 450 mg carboplatin and 200 mg etoposide for one cycle, but the serum CEA level still increased up to 672 ng/ml (Figure 1). Then the regimen of chemotherapy was changed to PTX (a 3-h infusion of 175 mg/m^2) and carboplatin every 3 or 4 weeks for seven cycles. The carboplatin dose was calculated by the Calvert formula as a target area under the curve (AUC) of 5 mg·min/ml. After six cycles of PTX and carboplatin combination chemotherapy, the serum CEA level was reduced to 14.4 ng/ml (Figure 1). As side effects, grade 3 leukocytopenia and grade 2 neuropathy were observed. Subsequently she received the third laparotomy on 1 April 1999 because she had occulusive

ileus. The cause of ileus was considered to be due to the hard fibrous adhesion of ileum and colon due to the initial radiotherapy, and ileostomy was performed. The peritoneal dissemination observed at the second operation disappeared completely, which was confirmed by histopathological study of the biopsy specimens. Fibrous peritoneal nodules with no viable tumor cells represented a complete response to PTX and carboplatin combination chemotherapy. The patient is now receiving only symptomatolytic therapy because she refused any more chemotherapy.

Discussion

In 1956, Glücksmann and Cherry described a subtype of mixed adenosquamous carcinoma of the cervix composed of tumor cells with a moderate amount of cytoplasm of ground-glass appearance, a distinct cell wall that stains with eosin and PAS, and enlarged nuclei with prominent nucleoli, which these authors designated as GCC.[1] The main differential diagnosis of GCC is the squamous cell carcinoma, non-keratinizing type. It is important to distinguish between the two because of their difference in radiosensitivity.[4] The frequency of GCC was estimated at only 1–2% of cervical carcinoma.[1–3] GCC of the uterine cervix occurs in young women with a mean age 10 years younger than that of patients with squamous cell carcinoma.[1–4] This is in accordance with our case (32 years old).

It has been reported that GCC is highly malignant, and that this type of tumor is refractory to both radiation and surgical therapy.[1–4] There were no 5-year survivors in their series.[1] Littman *et al.*[2] mentioned that two major factors contributed to the poor survival with this tumor. The first was the difficulty of controlling the primary tumor with radiotherapy. The second factor was the high rate of metastasis outside of the pelvis. They reported that only four out of 13 patients survived 5 years. Tukahara *et al.*[3] reported that 13 out of 14 patients with GCC were in stage II–IV and died within 25 month. In our case, numerous lymphatic invasion and lymph node metastasis as well as dissemination of recurrent GCC in the radiation field were observed.

Why GCC is resistant to radiotherapy is unclear. Oki *et al.*[6] recently reported that the cell line established from GCC showed a slow doubling time, suggesting that this might be one of the reasons for the radiation resistance.

We suppose multimodal aggressive therapy should be used for GCC due to its aggressive behavior. In addition to our case there are two documented cases of ovarian metastasis with stage 1B GCC.[7,8] Atlas *et al.*[9] reported the absence of estrogen and progesterone receptors in this tumor. Thus we consider ovarian conservation may not be advisable even in young patients with GCC, since these patients can be treated with hormone replacement therapy after operation including bilateral salpingo oophorectomy.

Recently, Mikami *et al.*[5] reported that preoperative intra-arterial chemotherapy with cisplatin, epirubicin and mitomycin C was effective against GCC. To our knowledge, however, no effective systemic chemotherapy to the recurrent disease has been reported. Because GCC has a tendency to metastasize even in its early stage, we suppose an effective systemic chemotherapy regimen must be established to improve the prognosis of GCC. PTX and carboplatin therapy is becoming the first-line chemotherapy to epithelial ovarian cancer,[10] but this is the first report of treatment with this regimen to recurrent GCC. Our case of GCC was resistant to radiotherapy and also to platinum-based conventional chemotherapy. After six courses of PTX (175 mg/m^2) and carboplatin (AUC=5 mg·min/ml) therapy, the serum CEA concentration dropped from 672 to 14.4 ng/ml. This level was maintained until the third operation which was performed 7 weeks after the sixth course of this therapy. Disappearance of the recurrent cancer dissemination was confirmed macroscopically and pathologically at the third operation. Therefore, the effect of this regimen on GCC was pathological complete response in this case.

In our case, the tumor was resistant to the second-line chemotherapy including carboplatin. However, carboplatin was used together with PTX in the third-line chemotherapy, because we considered the platinum agent was the key drug. So the complete response acquired by PTX and carboplatin may be the effect of PTX alone. We speculate that the systemic chemotherapy with PTX and carboplatin, or PTX alone might be effective against primary and recurrent GCC. Further experience is needed to ensure that these regimens can afford a good prognosis for GCC.

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