A case of glassy cell carcinoma of the uterine cervix that responded to neoadjuvant chemotherapy with paclitaxel and carboplatin

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Glassy cell carcinoma of the uterine cervix is a rare tumor, and has a poor prognosis because of its aggressive clinical behavior and resistance to radiotherapy and chemotherapy. We report a case of bulky glassy cell carcinoma of the uterine cervix that effectively responded to paclitaxel and carboplatin in a neoadjuvant setting. The patient was a 30-year-old woman who became aware of vaginal bleeding and was referred to our hospital because of a cancerous tumor of the uterine cervix. Physical examination showed the cervical tumor to be approximately 8 cm in diameter with no involvement of the parametrium or vagina. The biopsy results suggested a diagnosis of glassy cell carcinoma. The final diagnosis was glassy cell carcinoma of the uterine cervix, stage 1b2. Neoadjuvant chemotherapy with paclitaxel and carboplatin was administered for downstaging. The response rate was 67.9% (partial response) under magnetic resonance imaging, and elevated serum cancer-related antigen 125 (119 U/ml) and squamous cancer cell antigen (34 ng/ml) were reduced to 34 U/ml and 3.3 ng/ml, respectively. Following neoadjuvant chemotherapy, she underwent radical hysterectomy and adjuvant chemotherapy with the same regimen. The clinical course was very good. We speculate that glassy cell carcinoma is a sensitive tumor to paclitaxel and carboplatin. Further evaluation concerning diagnosis and treatment, however, is needed to improve the prognosis of patients with glassy cell carcinoma. ***Anti-Cancer Drugs*** **17:715–718 © 2006 Lippincott Williams & Wilkins.**

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Introduction

Glassy cell carcinoma (GCC) of the uterine cervix is a rare tumor, accounting for only 1–5% of all cervical cancers [1–4]. This carcinoma tends to occur more frequently in younger women than does squamous cell carcinoma, and shows a poor prognosis because of its aggressive clinical behavior and resistance to radiotherapy or chemotherapy. In 1976, Littman *et al.* [5] published the first series of 13 patients with GCC, reporting an overall survival rate of 31%.

We report a case of bulky GCC of the uterine cervix. The patient underwent neoadjuvant chemotherapy (NAC) with paclitaxel (PTX) and carboplatin (CBDCA), and a partial response was obtained. Therefore, she could be treated by radical hysterectomy.

Case report

The patient was a 30-year-old woman, gravida 4, para 4, who presented to her local hospital for evaluation of vaginal bleeding in May 2005 and was referred to Shizuoka Cancer Center Hospital because of a bulky mass detected on her uterine cervix. Pelvic examination showed an approximately 8-cm exophytic tumor in the cervix with no involvement of the parametrium and vagina. On speculum examination, her cervix appeared macroscopically cancerous. A cervical scraping cytology revealed malignant cells and, subsequently, a cervical biopsy was performed. Microscopically, the tumor cells were poorly differentiated, and had a moderate amount of cytoplasm, distinct cytoplasmic membrane, a large nucleus with prominent single or multiple nucleoli and numerous mitoses, suggesting a diagnosis of GCC (Fig. 1). On laboratory data, the serum CA125 and squamous cancer cell (SCC) levels were markedly elevated at 119 U/ml and 34 ng/ml, respectively, but other data were within normal limits. Cystoscopy, proctosigmoidoscopy and chest X-ray revealed no invasion and metastasis. Magnetic resonance imaging (MRI) revealed an 8.1-cm mass of the uterine cervix and bilateral iliac lymph node swelling, which indicated

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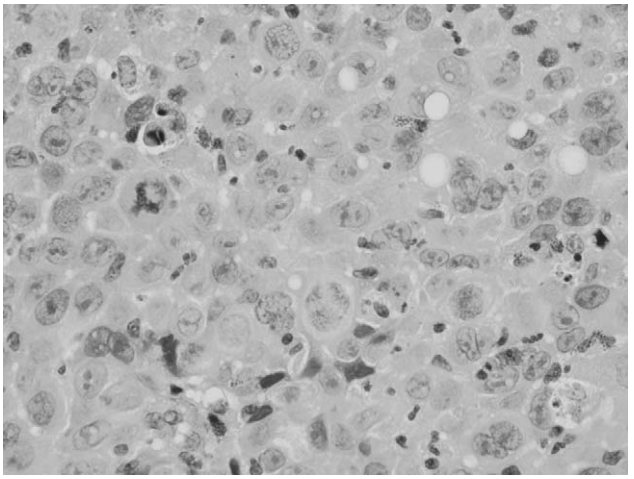
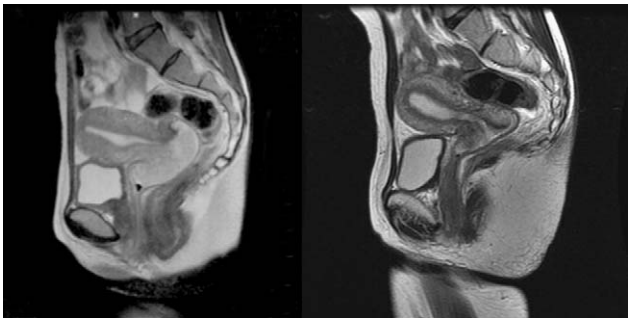
Fig. 1



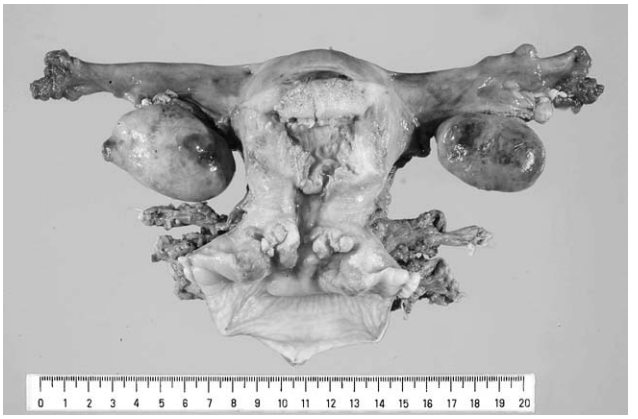
The cervical biopsy specimen on her first visit to our hospital. Microscopically, the tumor cells were poorly differentiated, and had a moderate amount of cytoplasm, a distinct cytoplasm membrane, a large nucleus with prominent single or multiple nucleoli and numerous mitoses, suggesting a diagnosis of glassy cell carcinoma (hematoxylin and eosin, $\times 400$).

Fig. 2



Magnetic resonance imaging (T2-weighed sagittal image) before (left) and after (right) neoadjuvant chemotherapy. The tumor size was remarkably reduced.

Fig. 3



The extracted specimen. Macroscopically, an endophytic tumor mass measuring 2.6 cm was seen at the cervix, but vaginal and parametrial invasion was not observed.

metastasis. The final clinical diagnosis was GCC of the uterine cervix, the International Federation of Gynecology and Obstetrics stage 1b2.

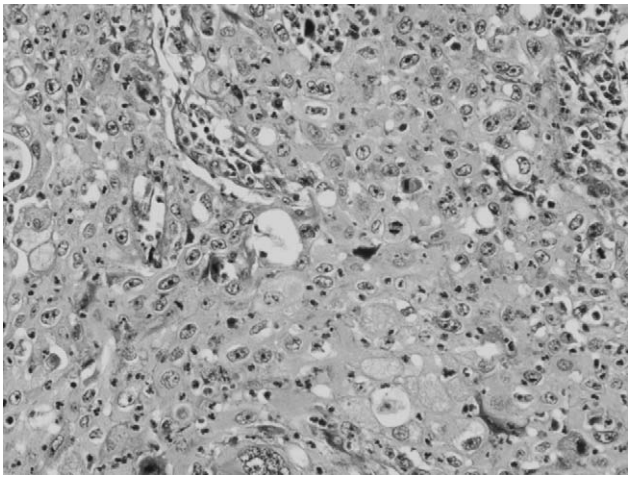
She was treated with NAC for downstaging. The regimen was, on day 1, 180 mg/m^2 of PTX and CBDCA for two courses every 3 weeks (TJ therapy). The dose of CBDCA was calculated by the Calvert formula as a target area under the curve of 6 mg min/ml. Two courses of TJ therapy were administered, and completed without severe toxicity and treatment delay. Then, the serum CA125 and SCC levels were reduced to 34 U/ml and 3.3 ng/ml, respectively. As a side-effect, grade 3 leukocytopenia was observed, but the patient quickly recovered. Tumor size was markedly reduced on MRI after NAC (Fig. 2) and the reduction rate was 67.9% (response evaluation criteria in solid tumors; PR). Subsequently, she underwent radical hysterectomy and pelvic lymph node dissection in August 2005 (operation time: 5 h 46 min; total blood loss: 775 ml). Although she was young, both her ovaries were dissected. Examination at the time of surgery revealed that the bilateral obturator lymph nodes were swollen, as shown on MRI, but the uterus was well mobilized and the cervix was not swollen, so the surgery was performed completely and safely.

Macroscopically, an endophytic tumor mass measuring 2.6 cm was seen at the cervix, but vaginal and parametrial invasion were not observed. Bilateral ovaries were swollen (right: 5.2×3.2 cm^2, left: 4.5×3.3 cm^2), but they seemed to be functional (Fig. 3). Pathological examination revealed large cells with ground-glass cytoplasms, as in the preoperative pathologic findings. Some parts, however, seemed to show squamous cell carcinoma (Fig. 4). We considered that the NAC had changed the pathologic findings. Finally, we diagnosed the tumor as GCC.

We also evaluated the estrogen and progesterone receptor statuses by immunohistochemistry, and these receptors were not found in our case. Although preoperative MRI showed bilateral lymph node swelling, there were no lymph node and ovarian metastases, and no invasion into the parametrium.

Lymphvascular infiltration, which is one of the pathological risk factors for the recurrence of uterine cervical cancer, was noted. She was therefore treated with

Fig. 4



The pathological examination of the extracted specimen revealed large cells with ground-glass cytoplasms, the same as in the preoperative pathologic findings (hematoxylin and eosin, × 200).

chemotherapy with TJ, because NAC with the same regimen was effective.

Discussion

GCC was first described in 1956 by Glucksman and Cherry [1], and has been traditionally classified as a poorly differentiated subtype of adenosquamous carcinoma. This neoplasia is pathologically characterized by a moderate amount of granular pale cytoplasm, centrally located nuclei with prominent nucleoli, distinct cell membranes and prominent eosinophil infiltration of the stroma. The clinical features of GCC are as follows: (a) a rare occurrence (frequency of about 1–5% of cervical carcinomas), (b) an aggressive behavior, (c) poor sensitivity to radiotherapy or chemotherapy and (d) a poor prognosis. Therefore, the differential diagnosis from squamous cell carcinoma, non-keratinizing type, which has a good sensitivity to both radiotherapy and chemotherapy, is very important. Even though there is some debate about whether GCC is a distinct clinicopathologic entity and a separate histologic subtype, it is necessary to know the cytologic features of GCC because this tumor has not only unique cytologic findings, but also diagnostic pitfalls, leading to occasional underdiagnosis. Chung *et al.* [6] reported that, in their series, only one case (11%) was correctly diagnosed on cervico-vaginal smear.

In agreement with previous reports, the age of our patient was younger than patients with usual squamous cell carcinoma. Although the reason, why patients with GCC are younger is unknown, the occurrence of GCC may be affected by steroid hormones. Estrogen receptors, however, are present in more than 50% of cervical squamous cell carcinomas and appear to be more prevalent in adenocarcinomas [7,8], while Atlas *et al.* reported that no estrogen and progesterone receptors were identified by immunohistochemistry in any of their 13 patients with GCC [9]. In our case, these receptors were not found. On surgery to young patients with cervical carcinoma, generally, their ovaries are spared if they wish and if the stage is early. The poor prognosis of GCC is caused by metastases occurring in an early stage and a high recurrence rate after conventional surgical or radiation therapy. Reisinger *et al.* reported that a patient with GCC whose treatment consisted of a radical hysterectomy, bilateral ovarian transposition and postoperative pelvic radiation therapy had a relapse in one of the transposed ovaries [10]. We considered ovarian conservation not advisable for our patient, because she could be treated with hormone replacement therapy (HRT) after surgery. So we dissected bilateral her ovaries. No estrogen and progesterone receptors were identified by immunohistochemistry in our case, and she underwent HRT safely.

The prognosis of GCC is poor owing to its rapid growth, frequent metastasis, and resistance to radiotherapy and chemotherapy [1–5]. Matsuura *et al.* [11] reported that rapid local recurrence had been shown even though the tumor was limited to the cervix and no pathological risk factors such as lymphvascular infiltration were identified. We considered that a combination therapy of surgery and radiotherapy and/or chemotherapy was necessary for our patient.

It is unknown which of the two, radiotherapy or chemotherapy, is effective for GCC. Lotocki *et al.* [3] reported that the survival of patients with stage 1b GCC improved by radical hysterectomy and radiotherapy, but there are some reports that surgery and/or radiotherapy is less effective than in squamous cell carcinoma [5,12,13]. Littman *et al.* [5] reported poor results with either surgery and/or radiotherapy. Only four of 13 patients with GCC survived to 5 years. Deshpande *et al.* [12] reported that patients with GCC treated with a combination of surgery, radiotherapy and chemotherapy showed a poor response. Oki *et al.* [14] reported that a cell line established from GCC showed a slow growth and doubling time, which might be one of the reasons for the radiation resistance.

Few reports exist on chemotherapy for GCC. Matsuura *et al.* [11] reported that combination chemotherapy with TJ was administered for recurrent GCC, and the reduction rate was 56%. Hirashima *et al.* [15] reported that they treated a recurrent GCC case with TJ therapy and histopathologically a complete response was confirmed. In the preoperative setting, Mikami *et al.* [16] reported intra-arterial cisplatin epirubicin and mitomycin C therapy for primary GCC, and the tumor was almost completely eliminated. In our patient, because the tumor was very bulky, we

considered it very risky for her to undergo a radical hysterectomy, so we selected NAC for downstaging. TJ therapy was selected as the regimen of NAC because Matsuura *et al.* [11] and Hirashima *et al.* [15] showed the usefulness of these agents against recurrent GCC. The reduction rate was 67.9%, and the subsequent radical hysterectomy was performed completely and safely. We speculate that GCC is sensitive to TJ therapy.

NAC in cervical cancer can be applied using two methods, i.e. a monthly or weekly schedule. We selected the monthly schedule because the TJ therapy efficacy for GCC was reported with a monthly schedule [11,15] and there are some reports in which an NAC monthly schedule for cervical cancer was useful [17–19]. If radiotherapy is administered after NAC, dose-dense delivery should be used as NAC at longer intervals may reduce the efficacy of radiotherapy [20]. We did not consider the use of radiotherapy because there are no reports that radiotherapy is effective for GCC, and if NAC was not effective we intended to perform surgery because our patient was at stage 1b2 and operability had been achieved before NAC.

GCC is a rare tumor and so we have little information about it. Further evaluation concerning diagnosis and treatment is needed to improve the prognosis of patients with GCC, and we consider that PTX and CBDCA might be key drugs for GCC. We hope that the efficacy of TJ therapy for GCC is confirmed in a prospective study.

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