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CASE REPORT

Tomonori Nagai · Takashi Okubo · Riko Sakaguchi
Hiroyuki Seki · Satoru Takeda

Glassy cell carcinoma of the uterine cervix responsive to neoadjuvant intraarterial chemotherapy

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Abstract Described as a poorly differentiated adenosquamous cancer, glassy cell carcinoma of the uterine cervix is a rare disease considered to have an extremely poor prognosis. Saitama Medical Center has been offering neoadjuvant intraarterial chemotherapy (NAC) to cervical cancer patients as a means of avoiding postoperative radiation therapy, achieving downstaging, and improving prognosis. We report a patient with glassy cell carcinoma of the uterine cervix who responded to NAC, and we discuss this case with reference to reports in the literature. A 28-year-old gravida 1, para 0 patient was referred to the Department of Obstetrics and Gynecology at Saitama Medical Center for concurrent cervical cancer at 23.5 gestational weeks. The patient was admitted to our center following the diagnosis of stage IIb cervical cancer (glassy cell carcinoma), to await fetal development, and an elective cesarean section was performed at slightly more than 29 gestational weeks. Three cycles of NAC with carboplatin (CBDCA)/etoposide/epirubicin, started 3 days after the operation, shrank the tumor remarkably. An extended radical hysterectomy was subsequently performed. It has been 6 years, to date, since the initial treatment, and our patient is alive and disease/recurrence free.

Key words Glassy cell carcinoma · Cervical cancer · Neoadjuvant chemotherapy

Introduction

Glassy cell carcinoma of the uterine cervix is described as a poorly differentiated adenosquamous cancer. It is a rare tumor, accounting for only 1.6% of all cervical cancers; however, the prognosis is said to be extremely poor due to rapid progression and high resistance to radiation therapy.[1]

Saitama Medical Center has been offering neoadjuvant intraarterial chemotherapy (NAC) to cervical cancer patients with the aims of avoiding postoperative radiation therapy, achieving downstaging, and improving the prognosis. We report a patient with glassy cell carcinoma of the uterine cervix who responded to NAC, and we discuss this case with reference to reports in the literature.

Case report

A 28-year-old gravida 1, para 0 patient with no remarkable family history or past disorders became pregnant without fertility treatments. Her last menstruation was on March 20, 2000. Cervical cytology performed during pregnancy follow-up at the patient's previous clinic as part of the initial screening revealed class V cervical cancer. In September 2000 (at 23.5 gestational weeks), she was referred to the Department of Obstetrics and Gynecology at Saitama Medical Center with suspected cervical cancer complicating pregnancy. Colposcopic findings identified a cauliflower-shaped friable tumor about 3 cm in diameter (Fig. 1a). Cervical biopsy confirmed glassy cell carcinoma. Pathological findings included well-defined nuclear envelopes in the tumor cells, distinct nucleoli, abundant cytoplasm, and a characteristic ground-glass appearance. Stromal eosinophilic, lymphocytic, and plasmacytic infiltrations were seen (Fig. 2). Stage IIb cervical cancer was diagnosed, based on the resistance felt in the left parametrial area, which did not reach the pelvic wall. The initial diagnostic tumor marker levels were squamous cell carcinoma related antigen (SCC), at 2.8 ng/ml and carbohydrate antigen (CA) 125, at 28 U/ml. The patient was admitted to Saitama Medical Center with stage IIb cervical cancer (glassy cell carcinoma) complicating pregnancy for inpatient management. Post-admission course.

We waited for the optimal timing to achieve survival of the child, and then performed a cesarean section. A radical

T. Nagai (✉) · H. Seki · S. Takeda
Department of Obstetrics and Gynecology, Saitama Medical Center, Saitama Medical School, 1981 Tsujido-cho, Kamoda, Kawagoe-shi, Saitama 350-8550, Japan
Tel. +81-49-228-3681; Fax +81-49-226-1495
e-mail: tomono@saitama-med.ac.jp

T. Okubo · R. Sakaguchi
Department of Obstetrics and Gynecology, Sekishindo Hospital, Saitama, Japan

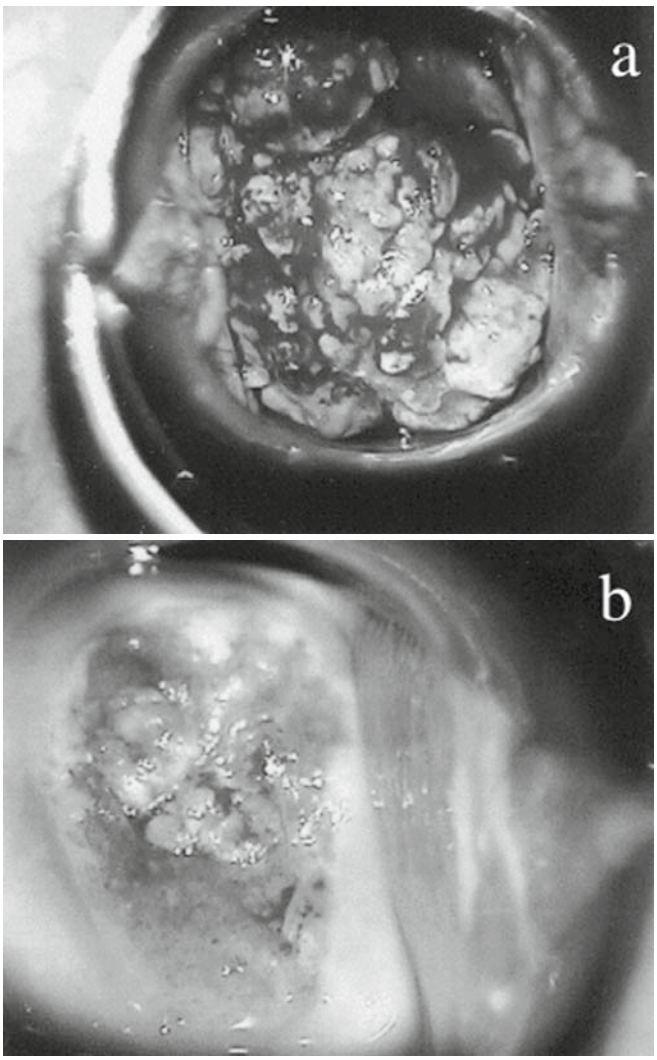

Fig. 1a,b. Colposcopic findings. **a** Initial diagnosis; a cauliflower-shaped friable tumor about 3 cm in diameter can be seen. **b** After three cycles of neoadjuvant intraarterial chemotherapy (NAC), the tumor shows remarkable shrinkage as compared to its size at the initial diagnosis

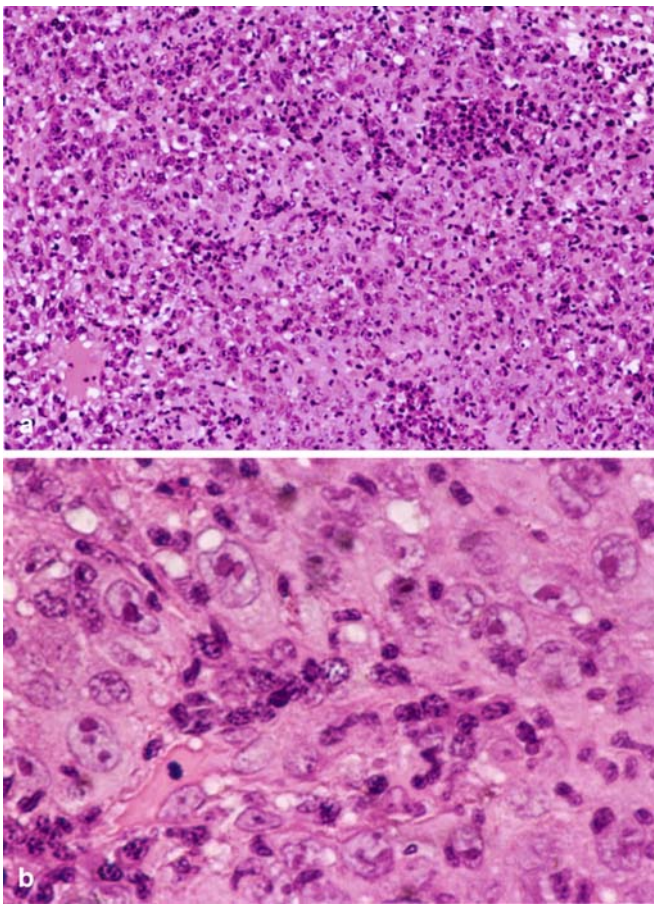

Fig. 2a,b. Pathological findings, showing well-defined nuclear envelopes in tumor cells, distinct nucleoli, abundant cytoplasm, and characteristic ground-glass appearance. **a** H&E, ×100; **b** H&E, ×400

hysterectomy was scheduled following NAC. In general, those who are 20 weeks' pregnant or less should be treated at the time of diagnosis, whereas those who are over 20 weeks may be allowed to await fetal lung maturity and delivery before treatment. A delay of 6–12 weeks in the second trimester is generally considered to be safe to attain fetal maturity. However, the patient and her family play an important decision-making role when it comes to the timing of delivery.[2,3]

Other than a hemoglobin of 9.1 g/dl and a C-reactive protein (CRP) of 2.3 mg/dl, post-admission blood, biochemical, and hemostasis tests revealed no abnormalities. No fetal abnormalities were seen on abdominal echography. Fetal heart rate monitoring detected no abnormalities. Post-admission magnetic resonance imaging (MRI) showed a tumor in the cervix, measuring approximately 3 cm in diameter (Fig. 3).

A 1048-g baby girl was delivered by elective cesarean section at just over 29 gestational weeks.

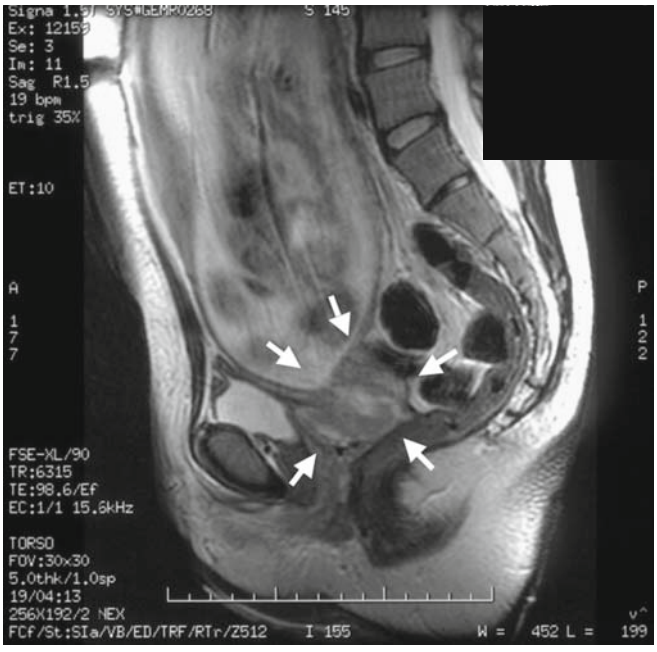

Fig. 3. Post-admission magnetic resonance imaging (MRI) findings. There is a tumor of approximately 3 cm in diameter in the cervix (*arrows*)

Systemic computed tomography (CT) was performed and no metastatic lesions were detected. NAC, with carboplatin (CBDCA) 500 mg/body (AUC 4.5), etoposide 350 mg/m^2, and epirubicin 40 mg/m^2 was started 3 days after the operation. The drugs were given in single injections into the bilateral internal iliac arteries at doses equally using the Seldinger method.

After three 21-day NAC cycles, the tumor showed marked shrinkage. Post-NAC colposcopic findings are shown in Fig. 1b. Decreases in tumor markers were seen post-treatment: SCC dropped to 0.8 ng/ml and CA125 to 12 U/ml. No adverse events, such as hematotoxicity, occurred in association with this chemotherapeutic regimen.

A radical hysterectomy (left adnexectomy) and pelvic node dissection were performed in January 2001 (83 days post-cesarean section).

No tumor tissue was macroscopically detected in the isolated sample. A few tumor cells were identified at about 6 mm below the cervical surface on pathological examination. The surgical margin was negative, showing neither vascular infiltration nor nodal metastasis. Post-surgical TNM staging was pT1b1N0M0.

Postoperatively, the patient has been followed on an outpatient basis without further treatment. It has been 6 years, to date, since the initial treatment, and the patient is alive and disease/recurrence free.

Discussion

First described as a poorly differentiated adenosquamous cancer by Glucksmann and Cherry in 1956,[1] glassy cell carcinoma of the uterine cervix is a rare tumor, accounting for only 1.6% of all cervical cancers. According to the present WHO histological classification, glassy cell carcinoma is included among "other epithelial tumors" not belonging to either the "squamous cell carcinoma" or the "adenocarcinoma" group. Glassy cell carcinoma tends to develop in relatively young patients, the mean age being 37.3 years, about 10 years younger than that in patients affected by the more common uterine squamous cell carcinoma or adenocarcinoma.[4] The prognosis of patients with glassy cell carcinoma is considered to be poor because of its rapid progression, resistance to radiation therapy and chemotherapy, and metastatic/recurrent nature.[5] Histologically characterized by solid alveolar growth of tumor cells with abundant glassy cytoplasm, glassy cell carcinoma is a poorly differentiated cancer lacking glandular structures, plasmodesma, or keratinocytes. Intercellular boundaries are clear, and distinct nucleoli are present. The clear cytoplasm contains little glycogen. Scant stroma and numerous small round cells, as well as substantial eosinophilic infiltration, have been described.[1,4,5,6] The differential diagnosis of glassy cell carcinoma from large-cell, nonkeratinizing squamous cell carcinoma or other poorly differentiated carcinoma is often difficult.[4] Histologic features that are often seen in nonkeratinizing squamous cell carcinoma, but very rarely seen in glassy cell carcinoma, include intercellular bridges, abundant intracellular glycogen, and squamous differentiation in the form of dyskeratotic cells. In addition, this variety of squamous cell carcinoma usually lacks the prominent cell walls and large nucleoli that are characteristic of glassy cell carcinoma. Other poorly differentiated and possibly closely related cervical carcinomas have some but not all the characteristics of glassy cell carcinoma, and still other cervical carcinomas contain minor components of glassy cell carcinoma; tumors in both these groups should be excluded from the category of glassy cell carcinoma as originally defined.[5]

Glassy cell carcinoma was found in the present patient by cervical cyto-screening performed during pregnancy. Glassy cell carcinoma generally affects younger women, as described above, and its association with pregnancy has been indicated.[1,6] The present patient was no exception; the cancer was found during pregnancy.

Glassy cell carcinoma is generally associated with a poor prognosis due to its rapid progression and low radiosensitivity. However, the prognosis of patients with glassy cell carcinoma is equivalent to that of patients with the more common cervical adenocarcinoma, if complete removal of the lesion is confirmed.[7] The present patient had cervical cancer at International Federation of Obstetricians and Gynecologists (FIGO) stage IIb, an advanced stage but one at which the tumor is still completely resectable. However, we attempted cytoreduction using NAC before radical hysterectomy to improve the chance of a complete cure. As yet, there is no consensus as to the efficacy of NAC for cervical cancer. However, NAC is useful in patients with normally operable cancer at stage IIb or lower but for whom surgery is not indicated because of tumor bulkiness, in terms of local control of the tumor and successful completion of subsequent radical surgery.[8] Patients need to be thoroughly monitored for exacerbation during NAC. Furthermore, the drugs used for NAC must be carefully selected to achieve an optimal response. In addition, the lesion should be evaluated frequently during NAC, and surgery must be performed immediately should the effectiveness of NAC be insufficient. Saitama Medical Center has been offering NAC to patients with cervical cancer at FIGO stage Ib2 or higher who provide adequate, fully informed consent. The response rate for patients with cervical squamous cell carcinoma treated at Saitama Medical Center has been 84.3%. In the present patient, NAC was performed in accordance with the treatment regimen (CBDCA, etoposide, and epirubicin) generally used for adenocarcinoma and adenosquamous carcinoma at Saitama Medical Center. Platinum-based combination chemotherapy has been tested extensively as salvage therapy in advanced and recurrent carcinoma of the cervix. Etoposide or epirubicin has demonstrated antitumor activity in gynecological malignancies, including cervical carcinoma, endometrial carcinoma, and uterine sarcoma. Mikami et al.[9] reported that NAC with the cisplatin, etoposide, and mitomycin-C (PEM) regimen was effective for the treatment of stage IIIb glassy cell carcinoma of the uterine cervix. According to recent reports on NAC for cervical cancer, two-drug or three-drug regimens

that included cisplatin have been used in most patients. Several treatment regimens including taxanes have also been reported. However, no consensus has been established as to the treatment regimens to be used for NAC, even for cervical squamous cell carcinoma.[10–12]

An extended radical hysterectomy and pelvic lymphadenectomy were performed in the present patient following NAC (which achieved remarkable shrinkage of the tumor). The bulky tumor initially seen in the cervix had mostly regressed in the isolated lesion, indicating partial remission. Postoperative adjuvant therapy is usually recommended for patients considered to be at high risk of recurrence, based on recurrence risk factors such as tumor diameter, interstitial infiltration in the cervix, vascular invasion, pelvic lymph node metastasis, and parametrial infiltration. However, no adjuvant therapy was performed in the present patient, because she was not considered to be at high risk of recurrence, based on the postoperative examination of the isolated lesion. Although concrete evidence of the indications for post-NAC adjuvant therapy is lacking, postoperative radiation therapy may be avoided in patients whose recurrence risk is reduced by NAC.

The clinical presentation of glassy cell carcinoma of the uterine cervix is clearly different from that of cervical squamous cell carcinoma. The prognosis is poor due to resistance to conventional treatments, including radiation therapy. Therefore, tailor-made treatment regimens are required for individual patients. However, randomized controlled studies of glassy cell carcinoma are not feasible because of the small patient population. NAC was extremely effective in the present patient. The use of NAC in more patients is desired to establish an effective treatment regimen for glassy cell carcinoma of the uterine cervix.

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