CASE REPORT

Successful delivery after abdominal radical trachelectomy followed by adjuvant chemotherapy for advanced invasive uterine cervical cancer: a case report and literature review

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Abstract Uterine cervical cancer is increasingly prevalent among young Japanese women who are eager to preserve their fertility, and abdominal radical trachelectomy (ART) is often performed in patients with early-stage invasive lesions. Herein we present details of a 27-year-old woman with stage IB1 cervical cancer. Although the patient received ART, histopathological findings revealed a parametrial invasion. Hence, 3 courses of adjuvant chemotherapy with paclitaxel and carboplatin (TC) were administered, and the patient conceived spontaneously 44 months later. Rupture of the membrane occurred at 32 weeks and 4 days, and a 1822 g female baby was delivered by emergency cesarean section. The patient is alive without disease and her child is growing favorably. This case demonstrates the balance between preservation of fertility and curative adjuvant chemotherapy after ART.

Keywords Abdominal radical trachelectomy · Adjuvant chemotherapy · Fertility preservation · Pregnancy · Uterine cervical cancer

Introduction

Vaginal radical trachelectomy was first performed to retain fertility in 1987 by Daniel d'Argent et al. [1], and the use of this procedure has since become widespread globally. In Japan, uterine cervical cancer is increasingly prevalent

among young women and abdominal radical trachelectomy (ART) is performed in most cases (74.7 %, 201/269) because of the narrow vaginal anatomy in Japanese women [2], abundant experience of abdominal radical hysterectomy, and adjustments to the radicalness of parametrial resections. Although radical trachelectomy is indicated for relatively shallow invasive or small cancers, deep stromal invasions, lymphovascular space invasions, and large cervical tumors are occasionally identified as moderate risks, and pelvic lymph node metastases and parametrial invasions as high risks. Hence, adjuvant pelvic irradiation or concurrent chemoradiotherapy (CCRT) are required [3], potentially resulting in loss of ovarian function [4].

Herein, we describe the clinical course of a patient with an International Federation of Gynecology and Obstetrics (FIGO) stage IB1 uterine cervical squamous cell carcinoma who was treated with ART. Subsequent pathological diagnosis demonstrated the presence of a pT2b cancer, and adjuvant chemotherapy without radiotherapy was administered to preserve fertility. Subsequently, the patient became pregnant and delivered successfully. To our knowledge, this is the first case of spontaneous pregnancy and delivery following ART and adjuvant chemotherapy.

Case report

A 27-year-old gravida 1, para 0 Japanese woman visited a local clinic for cervical cancer screening while studying in the United States. She tested positive for a high-risk type of human papilloma virus (HPV) and her Pap smear indicated a cervical intraepithelial neoplasia grade III. After consultation at her hospital in Japan, a loop electrosurgical excision procedure (LEEP) was performed and a squamous cell carcinoma (SCC) in situ with a negative margin was

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excised. The patient returned to the United States and failed to observe strict follow-up. One year later, she visited Japan and a Pap smear and biopsy revealed a high-grade squamous intraepithelial lesion (HSIL) and a microinvasive SCC. A second LEEP was performed in the following month, and revealed an invasive cancer in deep sections and a positive margin. The patient was immediately diagnosed with stage IB1 SCC and radical hysterectomy was recommended. The patient desired preservation of fertility, and was referred to our hospital.

A papillary exophytic cervical tumor of 3 cm in diameter was detected (Fig. 1) and a pelvic examination revealed a normal sized uterus with a soft vaginal wall, non-palpable bilateral adnexa, and soft bilateral parametrium. The Pap smear and biopsy revealed a HSIL and an invasive non-keratinizing squamous cell carcinoma.

Analyses of tumor markers showed SCC antigen, carbohydrate antigen 19-9, cancer antigen 125, and carcinoembryonic antigen levels of 1.3 ng/mL, 7.9 U/mL, 24 U/mL, and 1.3 ng/mL, respectively, and the patient was positive for HPV type 18.

Pelvic magnetic resonance imaging (MRI) showed a uterine cervical tumor with exophytic growth that was 28 mm at the greatest dimension (Fig. 2). Compared with colposcopic examinations, MRI indicted tumor invasion into the inner muscle layer.

An ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) computed tomography (CT) showed accumulation of FDG in the uterine cervix, but no other lymph node or distant metastases were observed (Fig. 3).

The stage IB1 cervical carcinoma (SCC, non-keratinizing type) was diagnosed preoperatively, and fertility-preserving surgery was considered. ART was performed and bilateral uterine arteries and pelvic nerves were preserved.

Fig. 1 Colposcopic findings: a papillary exophytic cervical tumor of 3 cm in diameter was detected

No apparent swollen pelvic lymph nodes were observed during dissection, and frozen histological examinations confirmed a negative endocervical cut end. ART was successfully completed, and a cervical cerclage with nylon sutures was placed at the internal cervical os to prevent premature delivery in future pregnancies. The operation was completed in 5 h with total blood loss of 796 mL.

Final histopathological examinations revealed no lymph node metastasis, but observations of a left parametrial invasion (Fig. 4) indicated a pT2bN0M0 tumor. Additional therapy was recommended, although the patient refused radiation therapy to preserve fertility. After comprehensive

Fig. 2 Pelvic MRI: arrows indicate the tumor on a **a** T2-weighted sagittal image and on a **b** T2-weighted axial image

Fig. 3 FDG-PET CT showed FDG accumulation in the uterine cervix

counseling, the patient understood that adjuvant chemotherapy was not established as a standard of care, and provided written informed consent. Subsequently, institutional review board approval was obtained and 3 courses of adjuvant chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (area under the curve = 6) were performed. No severe adverse effects were observed, apart from cessation of menstrual cycles, which returned 3 months following the surgery. No subsequent recurrences were detected, and the patient became pregnant spontaneously 3 years and 5 months after ART.

At 18 weeks of gestation the patient was admitted to our hospital for bed rest, and frequent uterine contraction was observed from around 22 weeks of gestation. Accordingly, the patient had complete bed rest and was treated with continuous intravenous infusions of ritodrine hydrochloride for tocolysis. Premature rupture of the membrane occurred at 32 weeks and 4 days, and an emergency cesarean section was performed on the same day. An immature female baby of 1822 g was born with Apgar scores of 8 at 1 min and 9 at 5 min. The postoperative course was mostly uneventful and the patient remains disease free with a healthy child after childbirth.

Fig. 4 Histopathological images show invasion of non-keratinizing type squamous cell carcinoma (**a** hematoxylin and eosin; $\times 200$ magnification) and parametrial invasion (**b** $\times 40$ magnification)

Discussion

Our eligibility criteria for ART therapy included the desire to preserve fertility, common histopathological type, FIGO staging of IB1 (tumor size $<4 \text{ cm}$ by inspection and invasion of $<1 \text{ cm}$) and no lymph node metastasis on pre-operative pelvic MRI or FDG-PET CT. In the present case, the postoperative pathological stage was more advanced than the clinical stage.

Although the current standard of care for advanced cervical cancer is a combination of surgery, radiotherapy, and chemotherapy, the efficacy of adjuvant chemotherapy alone remains controversial. Lee et al. revealed that cisplatin-based combined adjuvant chemotherapy for intermediate-risk tumors is promising after radical hysterectomy, with significant improvements in overall survival. Moreover, overall survival rates for all intermediate-risk tumors was 92 % (92/100), and was 81.8 % (18/22) and 94.9 % (74/78) for surgery-only and adjuvant chemotherapy groups, respectively [5].

Concurrent chemoradiotherapy is generally recommended for high-risk cervical cancer [3]. Hence, radical hysterectomy or/and CCRT would have been administered if the present patient had clinical stage IIB tumors or pelvic lymph node metastases, regardless of damage to ovarian tissues. Hosaka et al. [6] improved survival after radical hysterectomy by administering paclitaxel/cisplatin (TP) for three to six cycles rather than radiation therapy. Ovaries are sensitive to cytotoxic treatments, and are particularly sensitive to alkylating agents such as doxorubicin, and to alkylating-like agents, which produce high risks of gonadal dysfunction. In contrast, cisplatin and carboplatin are classified as medium risk [7–10], and Tarumi et al. [11] suggested that paclitaxel-mediated ovarian toxicity is mild and transient. Hence, to limit the impact on fertility, the present patient was administered adjuvant chemotherapy with TC for three cycles.

In a review of abdominal trachelectomy in 485 cases, Pareja et al. [12] regarded 413 patients as fertile after the procedure, but among 113 (38 %) who attempted pregnancy, only 67 achieved live births (59.3 %). Nishio et al. [13] also reviewed 31 pregnancies in 25 patients (6 patients had 2 pregnancies each) after ART. Although 9 of these pregnancies followed natural conception, 18 of 25 patients (72.0 %) had fertility problems, 21 patients had cesarean section deliveries, 4 had preterm births in the second trimester, and 17 patients delivered in the third trimester. Of the 17 pregnancies that reached the third trimester, 2 (11.8 %) were preterm births at 29 and 32 weeks, 11 (64.7 %) were delivered between 32 and 37 weeks, and 4 (23.5 %) were delivered at >37 weeks of gestation.

More than 5 years have passed since ART was performed, no evidence of tumor recurrence was observed,

and the spontaneous pregnancy following adjuvant chemotherapy without radiotherapy was unprecedented. This case indicates the potential of chemotherapy alone as adjuvant therapy for advanced cervical cancer patients who are treated with ART and are eager to preserve their fertility.

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Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ramirez PT, Schmeler KM, Soliman PT et al (2008) Fertility preservation in patients with early cervical cancer: radical trachelectomy. *Gynecol Oncol* 110:S25–S28
2. Sato S, Aoki D, Kobayashi H, Saito T et al (2011) Questionnaire survey of the current status of radical trachelectomy in Japan. *Int J Clin Oncol* 16:141–144
3. National Comprehensive Cancer Network Clinical Practice Guidelines for treatment of cancer (NCCN Clinical Practice Guidelines in Oncology™), Cervical Cancer. http://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf
4. Baker TG (1971) Radiosensitivity of mammalian oocytes with particular reference to the human female. *Am J Obstet Gynecol* 110:746–761
5. Lee TY, Jeung YJ, Lee CJ et al (2013) Promising treatment results of adjuvant chemotherapy following radical hysterectomy for intermediate risk stage IB cervical cancer. *Obstet Gynecol Sci* 56:15–21
6. Hosaka M, Watari H, Kato T et al (2012) Clinical efficacy of paclitaxel/cisplatin as an adjuvant chemotherapy for patients with cervical cancer who underwent radical hysterectomy and systematic lymphadenectomy. *J Surg Oncol* 105:612–616
7. Hortobagyi GN, Buzdar AU, Marcus CE et al (1986) Immediate and long-term toxicity of adjuvant chemotherapy regimens containing doxorubicin in trials at M.D. Anderson Hospital and Tumor Institute. *NCI Monogr* 1986:105–109
8. Wallace WH, Shalet SM, Crowne EC et al (1989) Gonadal dysfunction due to cis-platinum. *Med Pediatr Oncol* 17:409–413
9. Maneschi F, Benedetti-Panici P, Scambia G et al (1994) Menstrual and hormone patterns in women treated with high-dose cisplatin and bleomycin. *Gynecol Oncol* 54:345–348
10. Tangir J, Zelterman D, Ma W et al (2003) Reproductive function after conservative surgery and chemotherapy for malignant germ cell tumors of the ovary. *Obstet Gynecol* 101:251–257
11. Tarumi W, Suzuki N, Takahashi N et al (2009) Ovarian toxicity of paclitaxel and effect on fertility in the rat. *J Obstet Gynaecol Res* 35:414–420
12. Pareja R, Rendón GJ, Sanz-Lomana CM et al (2013) Surgical, oncological, and obstetrical outcomes after abdominal radical trachelectomy—a systematic literature review. *Gynecol Oncol* 131:77–82
13. Nishio H, Fujii T, Sugiyama J et al (2013) Reproductive and obstetric outcomes after radical abdominal trachelectomy for early-stage cervical cancer in a series of 31 pregnancies. *Hum Reprod* 28:1793–1798