Case report

Extraregional lymph node recurrence of stage IA1 squamous cell carcinoma of the uterine cervix after initial surgery: two case studies

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Abstract

Objective: Lymph node recurrence is extremely rare in cases of stage IA1 squamous cell carcinoma (SCC) of the uterine cervix without lymphovascular space invasion (LVSI). We present two cases of extraregional lymph node recurrence after initial surgery for stage IA1 SCC of the uterine cervix without LVSI.

Patients: Both patients initially underwent hysterectomy and developed recurrent extraregional lymph nodes within a few years postoperatively.

Case 1: The patient showed no symptoms of recurrence, and follow-up computed tomography (CT) for evaluation of gallstones revealed a para-aortic lymph node (9 mm). The patient subsequently underwent serum SCC antigen testing and CT and was diagnosed with recurrence.

Case 2: The patient noticed a right inguinal node swelling, which was evaluated using CT.

Both patients survived without relapse for 8 and 4 years, respectively.

Conclusion: Although stage IA1 SCC of the uterine cervix without LVSI is associated with a low risk of lymph node recurrence, oncologists should consider the possibility of recurrence in such cases. Evaluation for recurrence is difficult in asymptomatic patients. Serum SCC antigen testing may be a useful biochemical marker before imaging for early detection of recurrence, even in asymptomatic patients.

Key words: cervical cancer, lymph node recurrence, stage IA1, serum squamous cell carcinoma (SCC) antigen, in situ hybridization

Introduction

Recurrent lymph node metastasis is rare in cases of stage IA1 cervical cancer (The International Federation of Gynecology and Obstetrics classification 2018). Both the depth of invasion and lymphovascular space invasion (LVSI) are important predictors of nodal disease. The risk of lymphatic metastasis is only <1% in cases of stage IA1 squamous cell carcinoma (SCC) of the uterine cervix without LVSI; however, LVSI may increase the risk up to 8.2%. Lymph node metastasis is the most consistent and strongest predictor of survival in patients with early invasive cervical cancer.

Imaging is not always required for follow-up of recurrent lesions. Evaluation of lymph node recurrence is difficult in asymptomatic patients; currently, evaluation in such cases depends upon the attending physician’s discretion.

In this report, we present two cases of lymph node recurrence after initial surgery performed for stage IA1 SCC of the uterine cervix.
Case Presentation

Case 1

A 63-year-old woman underwent uterine leiomyoma evaluation at our hospital. Cytodiagnostic examination of the cervix revealed SCC, and biopsy evaluation confirmed cervical microinvasive SCC. All tests for serum tumor markers yielded normal results (the serum cancer antigen 125 [CA125] level was 12.9 U/mL, the serum cancer antigen 19-9 [CA19-9] level was 2.7 U/mL, and the serum SCC antigen [serum SCC] level was 0.9 ng/mL). Conization using the loop electrosurgical excision procedure was performed, and the patient was diagnosed with stage IA1 SCC of the uterine cervix (Figure 1). The depth of invasion and tumor length were 3 mm and 6 mm, respectively. However, LVSI was not detected.

Therefore, we performed total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO). Histopathological examination revealed only carcinoma in situ without any residual microinvasive carcinoma. Postoperatively, the patient was monitored using vaginal smears, transvaginal ultrasonography, and serum tumor marker measurements.

Follow-up computed tomography (CT) performed for gallstones after 13 months revealed para-aortic lymph node enlargement (9 mm) with a serum SCC level of 0.7 mg/mL, which increased to 1.8 ng/mL from the previous standard value of <1.5 ng/mL, 5 months later, and the lymph node showed further enlargement to 2 cm. Additionally, 18-fluorodeoxyglucose positron emission tomography (FDG-PET) showed abnormal uptake. Owing to a high index of clinical suspicion for recurrence, a second operation was performed 1 year and 10 months after the initial surgery. A lymph node palpated under the inferior vena cava was excised, and intraoperative rapid histopathological examination confirmed diagnosis of SCC. We performed immediate pelvic lymphadenectomy and para-aortic lymphadenectomy (90 nodes were resected); only the palpated lymph node showed evidence of recurrence. Histopathologically, the lymph node was structurally replaced by tumor cells. Six courses of normal interstitial fluid chemotherapy (nedaplatin 80 mg/m², ifosfamide 1,500 mg/kg body weight, and 5-fluorouracil 250 mg/kg body weight) were administered postoperatively. The patient has survived without relapse for 8 years and 11 months.

Case 2

A 74-year-old woman visited a neighborhood clinic for evaluation of abdominal fullness and pain. Magnetic resonance imaging revealed hydrometra (10 cm) (Figure 2). The lower end of the cyst bulged into the vagina, and the external aspect of the uterus was undetectable. The patient underwent uterine puncture with aspiration of 1 L of yellow serous fluid. However, fluid accumulation worsened, and she presented to our hospital for consultation. Blood tests showed normal results as follows: white blood cell count 7,534/μL, serum C-reactive protein 0.19 mg/dL, CA125 was 14.2 U/mL, and CA19-9 was 2.0 U/mL; however, the serum SCC level was high (5.8 ng/mL). Cytological findings of the uterine cervix revealed no intraepithelial lesions or malignancy.

The patient’s abdominal pain worsened; therefore, we performed TAH and BSO. Bacterial cultures of intrauterine fluid yielded negative results. However, histopathologi-
cal examination revealed stage IA1 SCC at two sites in the cervix. The depth of invasion and tumor length were <1 mm and 2 mm, respectively, without LVSI (Figure 3). We observed that cervical intraepithelial neoplasia (grade 3) with atypical squamous epithelium had metastasized to the uterus, and we detected swelling of the right inguinal node, 14 months after the initial surgery. CT revealed enlargement of the right suprainguinal and deepinguinal nodes. The serum SCC level was maintained at 0.7 mg/mL; however, FDG-PET revealed abnormal uptake in both lymph nodes; therefore, we performed a biopsy of the suprainguinal node. The histopathological diagnosis confirmed recurrent cervical SCC; therefore, the patient received chemoradiation therapy (chemotherapy: six courses of nedaplatin 30 mg/m²/week, radiation: 50.4 Gy delivered as 28 fractions to the pelvis and both groins). The patient has survived without relapse for 4 years and 7 months.

For diagnostic confirmation, the cervical specimen was fixed in 10% formalin and divided into 12 sections. Immunohistochemical analysis using D2-40, WT1, CD31 and CD34 antibodies and Factor VIII was performed to reconfirm LVSI.

We performed p16 immunostaining and in situ hybridization (ISH) to confirm high-risk human papilloma virus (HPV) infection in SCC of the uterine cervix and lymph node recurrence.

### Discussion

Table 1 summarizes the clinical features of patients with lymph node recurrence reported by previous studies. We performed a search of the PubMed database for SCC, stage IA1, and lymph node metastasis, excluding adenocarcinoma. Furthermore, we selected studies that have described LVSI and excluded cases with suspected recurrence from other organs.

Lee et al. investigated 202 patients with microinvasive SCC. Lymph node recurrence was observed in one patient (1.5%) with depth of invasion ≤1 mm and no LVSI, in two patients (4.2%) with depth of invasion of 1–3 mm, and in one patient with LVSI. The LVSI showed no definite correlation with lymph node recurrence. Bohm et al. investigated lymph node recurrence in 69 patients with SCC of the uterine cervix with depth of invasion ≤3 mm. Only two patients had LVSI, and although these patients did not show LVSI, lymph node recurrence was observed after the initial surgery. In the current cases, we performed immunostaining using hematoxylin and eosin, D2-40, WT1, CD31, and CD34 antibodies, and Factor VIII and did not detect LVSI. Both patients developed recurrence in the extraregional lymph nodes. Additionally, p16 immunostaining and ISH revealed strong positivity and dot-like positivity, which

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**Table 1**  Clinical features of patients with lymph node recurrence of squamous cell carcinoma reported by previous studies

| Author | Surgery type | Positive nodes | DOI (mm) | LVSI | Lymph node recurrence | Prognosis |
|--------|--------------|----------------|----------|------|------------------------|-----------|
| 1 Bohm | NM           | Pelvic node    | <3       | −    | NM                     | NM        |
| 2      | NM           | Pelvic node    | <3       | +    | NM                     | NM        |
| 3      | NM           | Pelvic node    | <3       | −    | NM                     | NM        |
| 4      | NM           | Pelvic node    | <3       | +    | NM                     | NM        |
| 5 Hasumi | NM         | Pelvic node    | ≤1       | −    | NM                     | NM        |
| 6 Argenta | MRH, BLS   | Pelvic node    | 1        | −    | NM                     | NED       |
| 7 Lee  | RH, PLND    | unknown part   | 1–3      | +    | −                      | NED       |
| 8      | RH, PLND    | unknown part   | 1–3      | −    | −                      | NED       |
| 9      | LEEP (trachelectomy, RT) | −          | <1       | −    | Left supraclavicular    | DOD       |
| 10 Yeasmin | RH, PLND, PAN | Pelvic and parametrical nodes | 3        | +    | −                      | NED       |

DOI: depth of invasion; LVSI: lymphovascular space invasion; BLS: bilateral salpingectomy; DOD: died of disease; LEEP: loop electrosurgical excision procedure; MRH: modified radical hysterectomy; NED: no evidence of disease; NM: not mentioned; PAN: para-aortic lymphadenectomy; PLND: pelvic lymphadenectomy; RH: radical hysterectomy; RT: radiation therapy.
confirmed high-risk HPV in SCC of the uterine cervix and lymph node recurrence, respectively. We did not detect recurrence in the regional lymph nodes of the uterine cervix; however, additional staining procedures confirmed cervical cancer recurrence. Katrine et al. reported that HPV DNA was detected in the primary tumors in 18 patients (72%) who showed recurrence. HPV infection in pelvic lymph nodes is associated with an increased risk of recurrence. Both patients in this study showed positive results on ISH testing of the uterine cervix, together with lymph node recurrence. Patients who show positive results on HPV DNA testing require more rigorous monitoring primarily focused on detection of recurrence.

Relapse observed in the patient described in Case 2 may be attributable to uterine puncture performed before the initial surgery. A previous study has reported that diagnostic puncture promotes tumor cell dissemination through the puncture site. Our patient showed disseminated cervical intraepithelial neoplasia grade 3 lesions, therefore, it is reasonable to conclude that the lesion was most likely punctured. However, the association between recurrence and uterine puncture remains unclear.

The National Comprehensive Cancer Network guidelines recommend imaging (whole-body PET or chest/abdomen/pelvic CT) for stage 1 cervical cancer if comprehensive physical evaluation reveals abnormal findings and patients present with new onset of symptoms in the pelvis, abdomen, lungs, or other locations. Evaluation of lymph node recurrence is difficult in asymptomatic cases; currently, such evaluation is performed at the discretion of the attending physician. The patient described in Case 2 observed swelling of a right inguinal node and underwent CT. However, the patient described in Case 1 was asymptomatic, and the cancer was incidentally detected on CT. Detection of recurrence in the preclinical phase is difficult. The patient’s serum SCC level was not high at the time that CT revealed the lymph node measuring 0.9 mm; however, the serum SCC level was elevated to 1.8 ng/mL following enlargement of the lymph node to 2 cm. Dodd et al. observed that serum SCC levels >2.0 ng/mL predicted tumor recurrence preclinically in 50% of patients investigated in the study. Dodd et al. observed that serum SCC levels >2.0 mg/mL predicted tumor recurrence preclinically in 50% of patients investigated in the study. Therefore, serum SCC is a useful biochemical marker for progressive SCC of the cervix. Measurement of serum SCC levels is inexpensive and minimally invasive and can easily be followed by imaging evaluation. Therefore, this method is useful for early detection of recurrence, even in asymptomatic patients, as observed in Case 1 in this report.

Conclusion

Oncologists should consider the possibility of lymph node recurrence in patients with stage IA1 SCC of the uterine cervix without LVI/S, despite a low risk of recurrence in such cases. The serum SCC level is a useful biochemical marker for imaging evaluation and may enable early detection of recurrence even in asymptomatic patients.

Informed consent and ethical considerations: Written informed consent was obtained from the patient and the patient’s family for the publication of this case report.

Conflict of interest: The authors declare no conflicts of interest associated with this manuscript.

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