Underdiagnosis of early cervical cancer with an invisible cervical transformation zone in an elderly patient: A case report

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Abstract. The treatment of cervical intraepithelial neoplasia (CIN) can result in under- or overtreatment. The current report describes a case of undertreatment of a cervical tumor. A 72-year-old woman was preoperatively diagnosed with CIN3. Following surgery, the final diagnosis of the excised specimen was keratinizing squamous cell carcinoma that measured 2.5 cm in size. The exocervical margin and deep margin were negative. The patient received adjuvant therapy with concurrent chemoradiotherapy and never had disease recurrence. In elderly patients, making an accurate preoperative diagnosis based on specimens from cervical biopsies with or without colposcopy is difficult. MRI may be an accurate preoperative indicator of early cervical tumor, although some studies have demonstrated that MRI has a limitation with respect to its diagnostic ability. Other studies have reported that it is necessary to perform conization prior to hysterectomy. Physicians must reconsider the determined preoperative diagnosis of an early cervical tumor and establish standard guidelines for deciding when to use surgical treatment in elderly patients.

Introduction

Cervical cancer is the second most common cancer globally exceeding 275,000 deaths and 530,200 new cases in 2010 (1).

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Approximately 13,000 new cases of cervical cancer were diagnosed in Japan, and an estimated 3,500 women were died from this disease (2). To our knowledge, high-grade squamous intra epithelial lesions (HSILs) are able to progress to become invasive cervical cancer, the detection of HSIL plays a crucial role in preventing cervical cancer (3). Cervical carcinoma in young women is considered a social problem and is difficult to diagnose in elderly women (4-9).

In the previous report, Müller *et al* (5) described the accuracy of diagnosis between histological assessment of biopsy findings and the final histological result after conization. In their reports, complete agreement in between 45 and 89.6% of cases. Agreement within one histological grade was present in between 74 and 89.9% of cases (5-15). Other reports referred to the accuracy of histological diagnosis from the specimen taken by biopsy or cervical conization. There were different conclusions, one concluded about the good correlation between the histological results on colposcopically directed biopsy (CDB) and cone specimens, the other concluded that it was questioned (4). Fan *et al* (6) described the overall agreement between the histological results on biopsy and the corresponding cone specimens was 74.1%; underestimation occurred in 6.4% of cases and concluded that their data suggest that old age (≥50), postmenopausal status, and transformation zone type 3 might be positively associated with the under-diagnosis of CDB.

As discussed already, it had been difficult to diagnose early cervical disease, and treatments of cervical intraepithelial neoplasia (CIN) sometimes results in under- or overtreatment. However, accurately diagnosing patients with a small tumor in the cervix based on both biopsy results and imaging findings of modalities, such as magnetic resonance imaging (MRI), may be possible. Cervical conization is also a suitable option for diagnosing difficult cases. Herein, we describe a case of undertreatment of a cervical tumor and discuss difficulties associated with managing these small tumors.

Case report

A 72-year-old woman, gravida 4, para 3, was referred to our hospital because of treatment for CIN. She had abdominal

pain and abnormal vaginal bleeding. In a previous clinic, she was determined to have abnormal cervical cytology with atypical squamous cells of undetermined significance (ASC-US); therefore, she underwent colposcopy-guided biopsy (Figs. 1A, B and 2).

She was diagnosed with severe dysplasia 2 weeks before presenting to our hospital. In the physical examination, performing speculum examination was difficult owing to atrophic vaginitis. Colposcopy findings shew dense acetowhite epithelium (W2) with an irregular, geographic border in the 4-7-o'clock direction. Coarse mosaic (M2) was also observed in the 6-o'clock direction. In current case, because of the patient's pain complaint, it was difficult to perform punch biopsy; thus, the sample volume was small. Cytological examination revealed three-fold enlarged nuclei and mild aggregation of chromatin, but no koilocytosis, indicating the absence of low-grade squamous intraepithelial lesions (LSIL). Histological examinations showed atypical cells in all layers; however, the basal membrane was preserved. Furthermore, no invasive region was observed. Ultrasonography (US) findings also showed a normal-shaped uterine cervix. There was no doubt regarding tumor formation and the normal shape of the uterine cervix. Findings also showed there was no region doubt regarding the normal shape of the uterine cervix (Fig. 3). Finally, the patient was diagnosed with CIN3.

It was decided to perform total laparoscopic hysterectomy and bilateral salpingo-oophorectomy for CIN3. When the operative procedures were completed, we assessed the cervical canal of the uterus and detected a mass in her cervix measuring approximately 2 cm. Ultimately, the pathological diagnosis was keratinizing squamous cell carcinoma measuring 2.5 cm in size that was staged pT1b2pNxM0 according to the TNM classification. The clinical stages of the case were identified according to the definition of the International Federation of Gynecology and Obstetrics (FIGO) as stage IB2. The exocervical margin and deep margin were negative; however, lymphovascular invasion was noted (Fig. 4A and B). The time period from punch biopsy to laparoscopic surgery was 4 months.

On the grounds of these findings, we determined that she was preoperatively underdiagnosed. Therefore, it was recommended to undergo concurrent chemoradiotherapy (CCRT) that was necessary to prevent disease recurrence because the previous operation could not have been sufficient for stage IB2 cervical carcinoma. The patient and her family agreed with our recommendation, and she received CCRT (50 Gy of whole pelvic radiotherapy with 6 cycles of weekly 40 mg/m^2 cisplatin) (Fig. 5). No other treatment was administered, and over a 3-year follow-up, she did not demonstrate any recurrence. We describe the details of the current case in Table I.

Discussion

We experienced a difficult case in which cytological findings indicated ASC-US, histological findings of the biopsy specimen indicated severe dysplasia, and histological findings of the postoperative specimen indicated invasive carcinoma. Finally, the patient was diagnosed with stage IB2 cervical carcinoma. We analyzed cases from our

Table I. Clinicopathological characteristics of the current case.

Characteristic	Current case
Age, years	72
Histology	Keratinizing squamous cell carcinoma
FIGO stage	Not applicable
UICC stage	pT1b1pNxpMx
Tumor size, cm	2.5
LVSI	Positive
Metastases paraaortic LN (CT)	Negative
Metastases pelvic LN (CT)	Negative
Metastases distance (CT)	Negative
Treatment	Operation+adjuvant (CCRT)
Recurrence within 3 years	None
Death within 3 years	None

FIGO, Federation of Gynecology and Obstetrics; UICC, Union for International Cancer Control; LVSI, lymphovascular invasion; LN, lymph node; CCRT, concurrent chemoradiotherapy; CT, computed tomography.

institute in which the cytological and histological results did not match. In the past 3 years, 123 of 4780 patients (2.6%) have been diagnosed as having ASC-US, of whom 20 patients (1.6%) were diagnosed accurately, 17 were diagnosed with LSIL/CIN1, and 3 were diagnosed with HSIL/CIN3. Among HSIL cases, one patient was diagnosed with ASC-US during pregnancy, followed by a diagnosis of HSIL during the puerperal period. Our elderly patient was diagnosed with CIN3 and had an invisible type 3 cervical transformation zone (TZ).

After we analyzed these cases, we found that ASC-US tended to be underdiagnosed. In elderly women, obtaining a sample of the diseased lesion may be difficult, possibly leading to underdiagnosis. Furthermore, it was already known that in women aged >50 years, the findings of colposcopy cannot be adequately assessed (16). If a TZ is not visible or only partially visible on colposcopy, the examination may miss areas where changes have occurred, and these changes will not be biopsied. If performed correctly, endocervical cytology should be able to capture existing cellular changes (17). Furthermore, regarding histological examinations by punch biopsy, Stuebs *et al* (18) reported that the rate of underdiagnosis was worse in women with type 3 TZ. Müller *et al* (5) also demonstrated that the agreement between biopsy findings and results after conization was significantly affected by patient age and that the agreement between preoperative findings and final histological results was only 49.1% for early cervical cancer. Women aged >50 years are more likely to be postmenopausal and have a type 3 TZ, which results in a higher rate of colposcopies, which are difficult to assess, and a lower rate of agreement between the diagnosis based on colposcopy and histological results (19,20). However, sometimes, it could be diagnosed similarly between findings of cervical biopsy and those of cervical conization specimen (5),
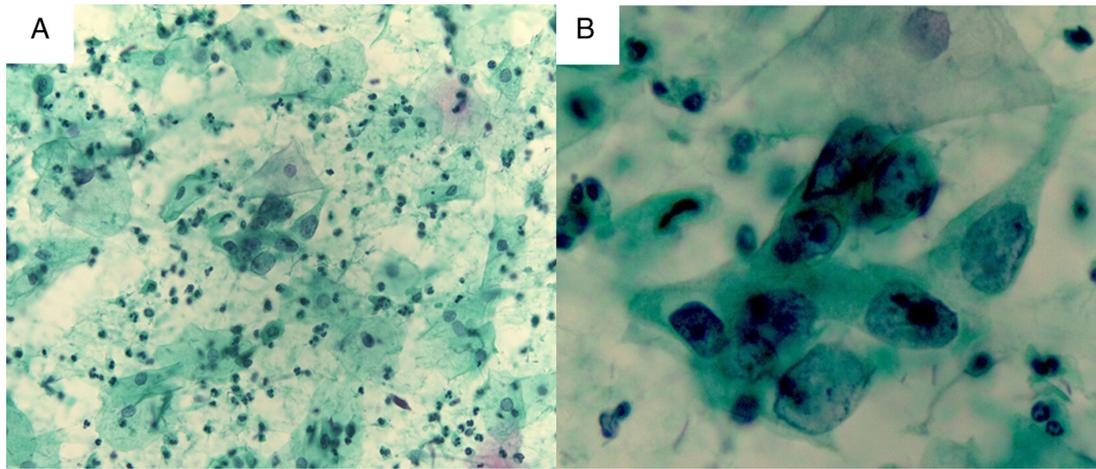
Figure 1. (A) Cytological findings of atypical squamous cells of undetermined significance; there are three-fold enlarged nuclei and mild aggregation of chromatin (low-power field; magnification, x40). (B) Cytological findings of ASC-US and cervical intraepithelial neoplasia 3. There is mild aggregation of chromatin but no koilocytosis, indicating the absence of low-grade squamous intraepithelial lesions. The patient's diagnosis is ASC-US (high-power field; magnification, x100). ASC-US, atypical squamous cells of undetermined significance.
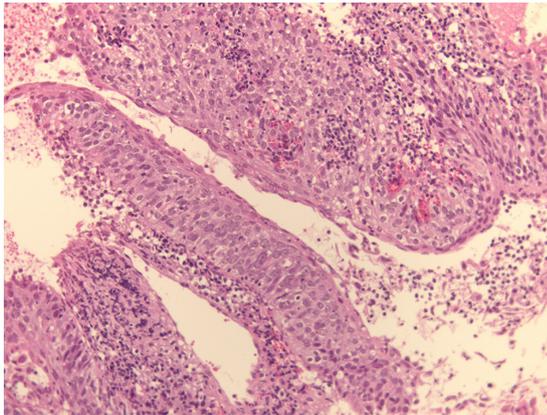

Figure 2. Histological findings of punch biopsy. Atypical cells are observed in all layers, but the baseline membrane is preserved. The patient's diagnosis is cervical intraepithelial neoplasia 3. No invasive regions are observed (low-power field; magnification, x40).

Figure 3. Ultrasound findings showing normal shape of the uterine cervix.

it is difficult for physicians to locate the diseased lesion on the deep in cervical canal in elderly women. Therefore, the biopsy results are not acceptable for making the final diagnosis. In elderly women, lesions of the squamocolumnar junction move up to the endocervical canal; therefore, it is sometimes very challenging to detect the diseased lesion of CIN and obtain the correct specimen for diagnostic purposes (6). According to current case, we established a procedure in which patients who were diagnosed with CIN3 based on punch biopsy results must undergo MRI. If the tumor mass comprises no diseased lesion, laparoscopic simple hysterectomy can be considered an operative procedure. MRI is a useful approach for detecting abnormal lesions in the cervix (21). Some studies reported that diffusion-weighed MRI can detect diseased lesions better than conventional MRI (22,23), whereas other studies demonstrated that MRI has a limitation in its diagnostic ability (24). Hence, we reported that it is necessary to perform conization before hysterectomy (5,6). We started preoperatively performing MRI for patients diagnosed with HSIL/CIN3, and

since this protocol has been established, no cases similar to the current case have been observed. The idea of performing conization before hysterectomy has been discussed; however, the gold standard guideline remains unknown. US may also help diagnose early cervical cancer, and although MRI is very useful for diagnosis, it is not commonly performed in developing countries. Therefore, contrast-enhanced computed tomography (CT) should be considered. In Japan, CT is commonly used for diagnosing early cervical cancer owing to the detection of lymph node metastasis. However, CT is not commonly used for CIN disease. In the current case, US was performed; however, the disease lesion was not detected. US may be a useful procedure for detecting disease lesions not only with B-mode image but also with color Doppler, although sometimes disease lesions cannot be clearly detected.

Microinvasive surgery (MIS) is common and most suitable procedure for early cervical lesions of carcinoma and CIN. The necessity for MIS has increased over the last several years; therefore, physicians must reconsider the determined preoperative diagnosis in cases similar to our case. Furthermore, in our country, although laparoscopic
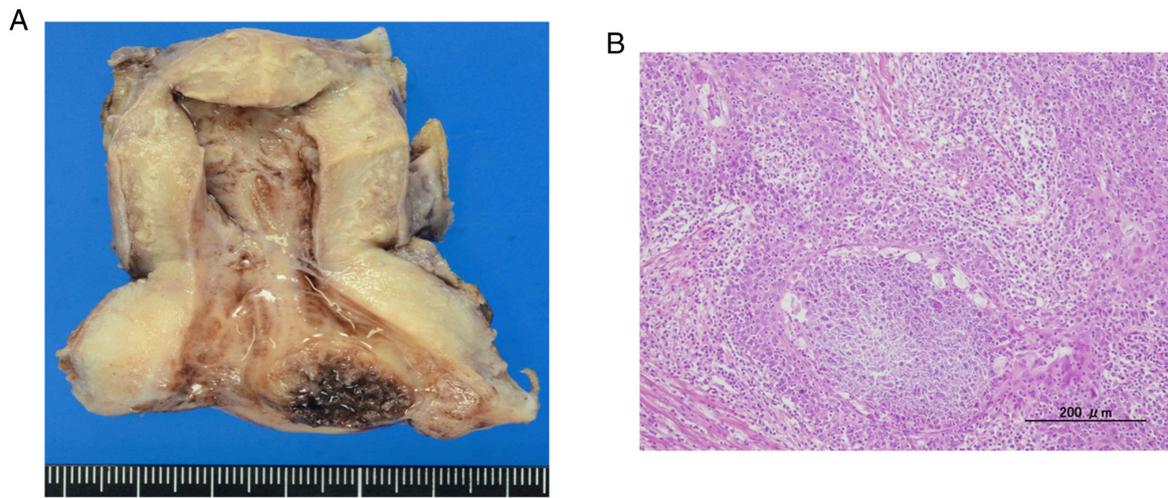
A

B

Figure 4. (A) Photograph of the resected portion of the uterus. A 2.5 cm-sized tumor is located in the cervical canal and was determined to be keratinizing squamous cell carcinoma. The pathological diagnosis is pT1b1pNxM0, stage 1B1 cervical carcinoma. (B) Isolated uterus for operation; Hematoxylin and eosin staining of the keratinizing squamous cell carcinoma. There were lymphovascular invasion (high-power field).

Figure 5. Radiotherapy field of the whole pelvis.

surgery is currently approved and covered by insurance for early cervical tumors such as HSIL/CIN3 and early cervical cancer, the recommended operative procedure is extremely different. Thus, it is imperative to improve preoperative diagnosis by utilizing useful tools so that the diagnosis is more accurate.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KN made the diagnosis and advised on manuscript preparation. MI made the diagnosis and drafted the manuscript. SR made substantial contributions to conception and design, and drafted the manuscript. HY contributed to analysis and interpretation of data. TI helped to collect the patient's data and corrected the manuscript. SS helped to collect the patient's data and was involved in critically revising the manuscript for important

intellectual content. NI carried out the pathological diagnosis. KS and SKu treated the patient and helped to collect the patient's data. HS helped to collect the patient's data and helped with statistical analysis. SR and HY confirmed the authenticity of all the raw data. SKy made substantial contributions to the analysis and interpretation of data, advised on manuscript preparation and made revisions to the final manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The case report protocol was approved by the institutional ethics and research review boards at Shimane University (IRB nos. 20070305-1 and 20070305-2). In the application forms given to patients, for the patients who could not come to hospital, it was clearly stated that the opportunity to opt out was always available to patients. Information on opting out was stated on our website, or arrangements were made for patients to opt out.

Patient consent for publication

Patient consent for publication was obtained using an online opt-out approach.

Competing interests

The authors declare that they have no competing interests.

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