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Case Report

Primary signet ring cell carcinoma of the cervix: A case report with review of the literature

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ABSTRACT

Objective: Primary cervical signet ring cell carcinoma (PCSRCC) is extremely rare. In this paper, we describe a case presenting with PCSRCC.
Case report: The 48-year-old woman visited the gynecological department because of postmenopausal bleeding. A cervical mass was discovered through pelvic examination, and the biopsy results indicated a poorly differentiated adenocarcinoma with a signet ring cell pattern. Colonoscopy revealed external compression of the rectum without intraluminal mucosal lesions. Abdominal computed tomography revealed a suspicious malignant lesion at the cervicorectal junction and multiple metastases. Debulking surgery was performed and the final pathology report documented a FIGO stage IVb PCSRCC involving multiple sites.
Conclusion: Complete tumor survey and staging are critical to differentiate primary from metastatic signet cell carcinoma of the cervix. Immunohistochemical studies cannot provide precise information. Because cases are rare, it is difficult to determine the proper treatment guidelines and prognosis.

Introduction

Cancer of the uterine cervix is the third most common gynecological cancer in the United States, and it is one of the top ten causes of cancer death in women in Taiwan (2017). The most common histological types of uterine cervical cancer are squamous cell carcinoma (69%) and adenocarcinoma (25%), and an increasing incidence of cervical adenocarcinoma has been observed among younger women in Western countries in recent decades. The histological types of uterine cervical adenocarcinomas are mucinous, endometrioid, papillary, and clear cell. Mucinous adenocarcinoma of the cervix has the subtypes of endocervical, intestinal, and signet ring cell [1]. Most cervical adenomcarcinomas are of the endocervical type, and the other subtypes are less common. Primary cervical signet ring cell carcinoma (PCSRCC) is extremely rare, and it is mostly a metastasis of cancers originating in other organs such as the stomach, breast, colon/rectum, or ovaries [2]. To date, fewer than 24 cases of PCSRCC have been reported [3–5]. In this paper, we review the relevant literature and describe a patient who had PCSRCC diagnosed through immunohistochemical (IHC) testing.

Case report

The patient was a 48-year-old woman who had the underlying disease of schizophrenia, which was under medicinal control. She had not menstruated since the age of 33 years because of prescribed psychiatric medication. After experiencing postmenopausal vaginal bleeding for one week, she visited our gynecological clinic for evaluation. She explained that she had also suffered from severe tenesmus, lower abdominal pain, and constipation for more than 6 months. Pelvic examination revealed a huge cervical mass. A biopsy of the cervical mass was performed, and pathology revealed a poorly differentiated adenocarcinoma with a signet ring cell pattern (Fig. 1a). An IHC test was conducted to differentiate the primary origin. The final results indicated negative CK7 and MUC6 (Fig. 1b and d) and positive CK20 (Fig. 1c), which suggested the colorectal origin of the mass. The patient was then transferred to our colorectal surgery department for further evaluation.

Upon examination of her medical history, it appeared the Papanicolaou smear yielded normal results 4 months before her hospitalization, and mammogram and breast ultrasonography had

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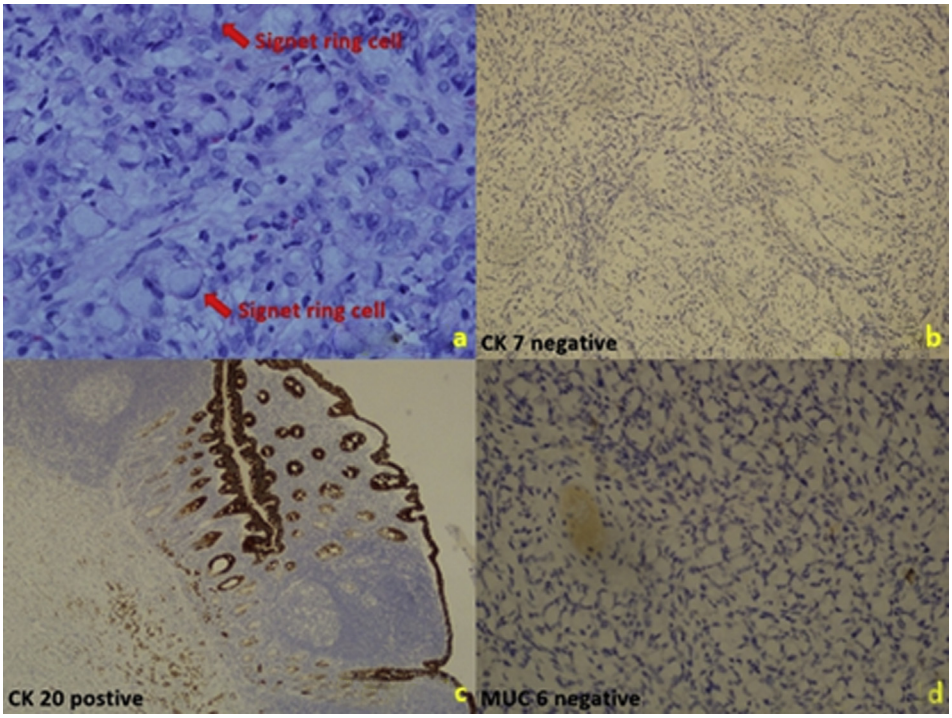

Fig. 1. Cervical mass biopsy was performed, and pathology revealed poorly differentiated adenocarcinoma with a signet ring cell pattern (a). The IHC study was conducted to differentiate the primary origin. The final result was CK7-negative (b), MUC-negative (d) and CK20-positive (c).

not revealed any abnormalities. Panendoscopy was performed, but no gastric primary site tumor was found. Colonoscopy revealed external compression of the rectum from 3 to 10 cm over the anal verge, but no obvious intraluminal mucosal lesions were found. Abdominal computed tomography revealed a suspicious malignant lesion at the cervicorectal junction (Fig. 2a) and multiple metastases in the bilateral lower lung (Fig. 3), para-aortic lymph nodes (Fig. 2b), bilateral external iliac lymph nodes (Fig. 2c), and peritoneal seeding (Fig. 2d). The tumor marker test results for carcinoma antigen 125 (CA-125), carcinoma antigen 199 (CA 19-9),

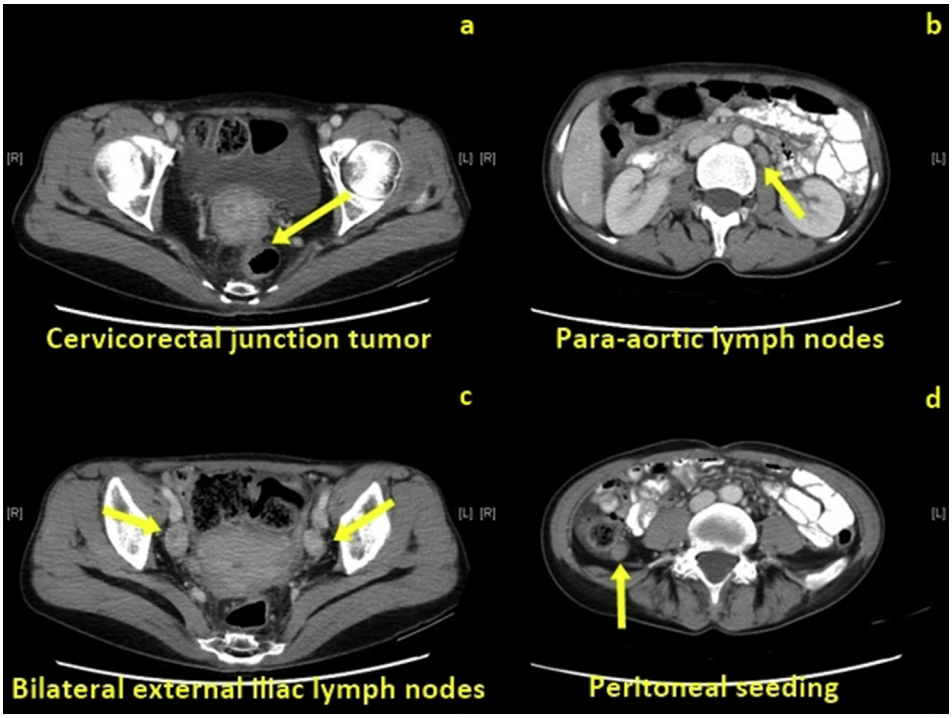

Fig. 2. Abdominal computed tomography revealed a suspicious malignant lesion at the cervicorectal junction (a), para-aortic lymph nodes (b), bilateral external iliac lymph nodes (c), and peritoneal seeding (d).

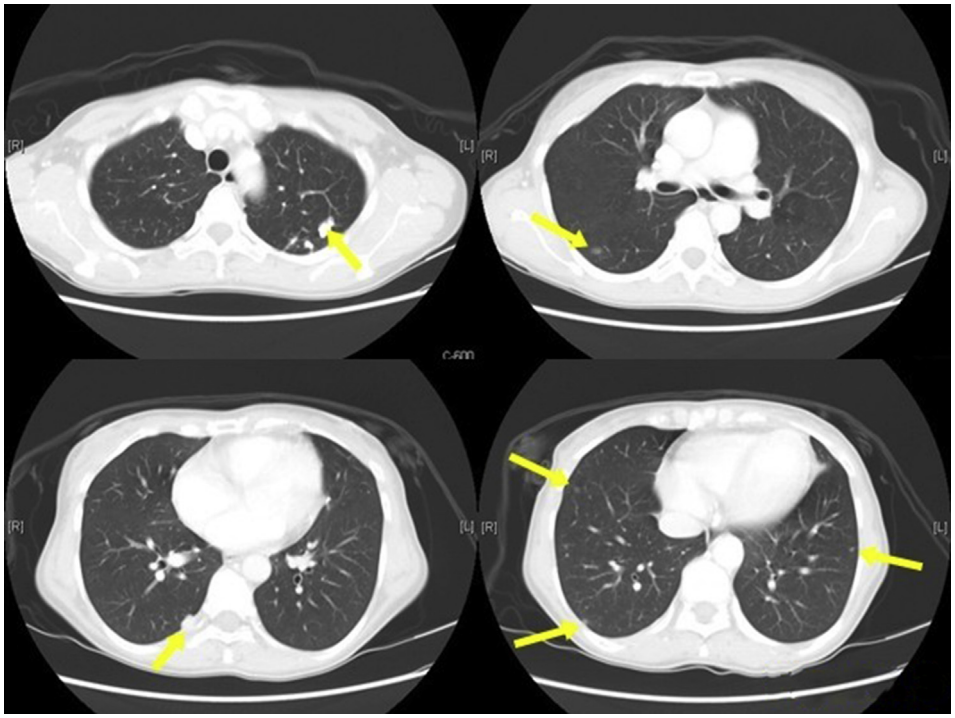

Fig. 3. Abdominal computed tomography revealed multiple metastases in the bilateral lower lungs.

and Alpha-Fetoprotein (AFP) were within normal limits, but an elevated level of carcinoembryonic antigen (CEA; 18.8 ng/mL) was found.

Because of severe gastrointestinal symptoms, the patient elected to receive debulking surgery. During the operation, low anterior resection with transverse loop colostomy, total hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection, para-aortic lymph node dissection, partial cystectomy, omentectomy, and bilateral peritonectomy was performed (Fig. 4). In the pathological gross examination process, the pathologist demonstrated that the primary tumor had infiltrated the entire cervix, part of the uterine myometrium, the right ovary, perirectal fat, and multiple lymph nodes, but the colorectal mucosa was completely uninvolved (Fig. 5). Microscopic examination revealed that the signet ring cells exhibited specific patterns of hyperchromasia, eccentric location, and pleomorphic nuclei (Fig. 6). The final IHC test results were positive for p16 (Fig. 7a) and negative for CD56 (Fig. 7b), chromogranin A (Fig. 7c), and synaptophysin (Fig. 7d). An appendix origin was excluded, and a cervical origin was indicated. The final pathology report detailed that the patients showed PCSRCC with involvement of the myometrium, ovary, omentum, appendix, peritoneum, and pericolic fat. According to the American Joint Committee on Cancer (AJCC) Eight Edition, the pathology stage was pT2aN1M1, FIGO stage IVb. The patient was transferred to our oncology department for postoperative palliative chemotherapy. At the time of writing this paper, she has received 10 cycles of chemotherapy with cisplatin and paclitaxel and 3 cycles of bevacizumab, and the condition of this patient is stable, as revealed by regular follow-up. The patient

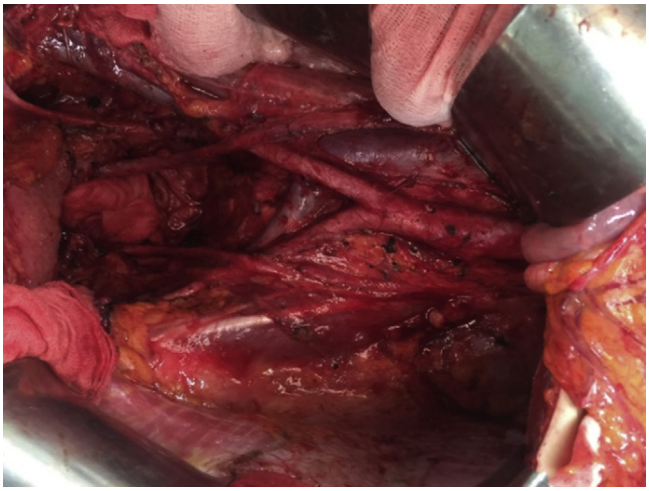

Fig. 4. Patient underwent debulking surgery, and this picture indicates a clear postoperative area.

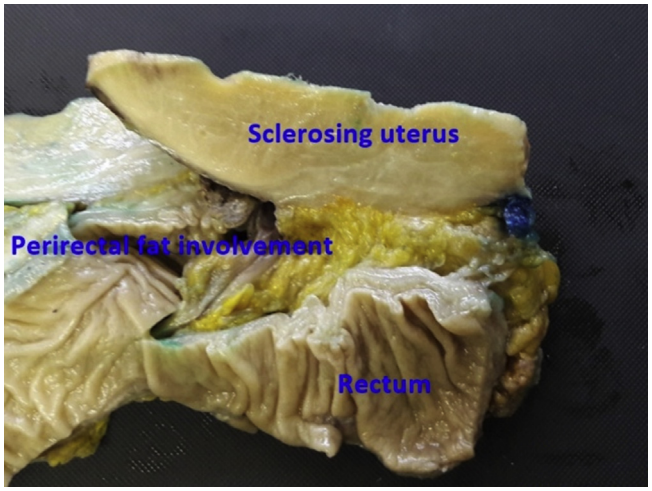

Fig. 5. The primary tumor infiltrated the entire cervix, part of the uterine myometrium, the right ovary, perirectal fat, and multiple lymph nodes, but the colorectal mucosa was not involved.

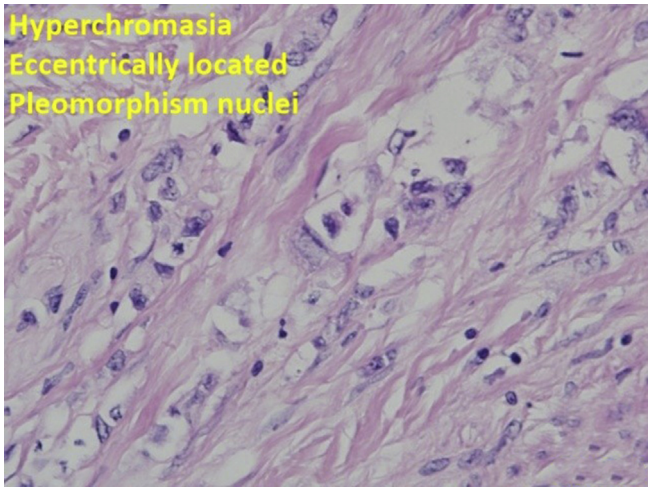

Fig. 6. Signet ring cells were noted with specific patterns of hyperchromasia, eccentric location, and pleomorphism nuclei.

received postoperative abdominal computed tomography follow-up at 8 months after surgery, and the results revealed stationary lymph node size without progression or new lesions. The tumor markers were all within normal limits.

Discussion

PCSRCC is extremely rare. To the best of our knowledge, our patient is the twenty-fourth case reported in the literature [3,4]. Diagnosing PCSRCC is a major challenge. Signet ring cell carcinoma of the cervix is typically a metastasis, originating most often from the stomach. It can also originate from the colon, breast, lungs, appendix, gallbladder, bladder, or ovaries, but cancers of these origins have been less frequently reported [2]. In addition, it must be differentiated from endocervical involvement in signet ring cell carcinoma of the endometrium, and other malignant neoplasms that may have signet-ring-like cells such as squamous cell carcinoma, malignant lymphoma, and myeloma [6].

The incidence of cervical cancer has decreased over the past several decades, which is largely attributable to screening with the Papanicolaou smear [7]. To the best of our knowledge, only one study in 2011 reported the discovery of PCSRCC through the Papanicolaou smear test. Tarak et al. identified some scattered signet ring cells with pleomorphic hyperchromatic eccentric nuclei and abundant vacuolated cytoplasm upon smear reexamination [8]. Haswani et al. mentioned that abnormal glandular cells may occasionally be evident in the Papanicolaou test [9]. The appearance of signet ring cells in the Papanicolaou test has still typically indicated metastatic carcinoma of the cervix in most cases [10]. Differentiating primary from metastatic tumors by using cytopathology is difficult.

The final diagnosis is generally based on the pathology report. Additional IHC and molecular studies can often provide critical information on the origin of the tumor. However, debatable results have been reported in the literature. Nine cases were tested for IHC expression of the estrogen receptor (ER) and progesterone receptor (PR), but only one case was positive for ER and PR. Negative results for ER and PR do not exclude primary cervical neoplasms [11]. Only one case was reported in which p16 was negative in IHC staining [2]. Expression of p16 may indicate the presence of human papillomavirus (HPV) infection. Four cases with HPV infection, especially HPV 18—which is strongly associated with cervical cancer, were positive for p16 expression. Paquette et al. reported that a positive cervical cytokeratin 7 (CK7) result is associated with high-grade cervical lesions [12]. To date, nearly one-third of cases were positive for CK7. Therefore, CK7 may be a significant indicator. However, cytokeratin 20 (CK20), which is immunoreactive to colorectal antigens, was positive in two cases [13], including ours, which were negative for CK7. Cervical adenocarcinomas can present markers common to gastric, intestinal, and pancreatobiliary epithelial cells.

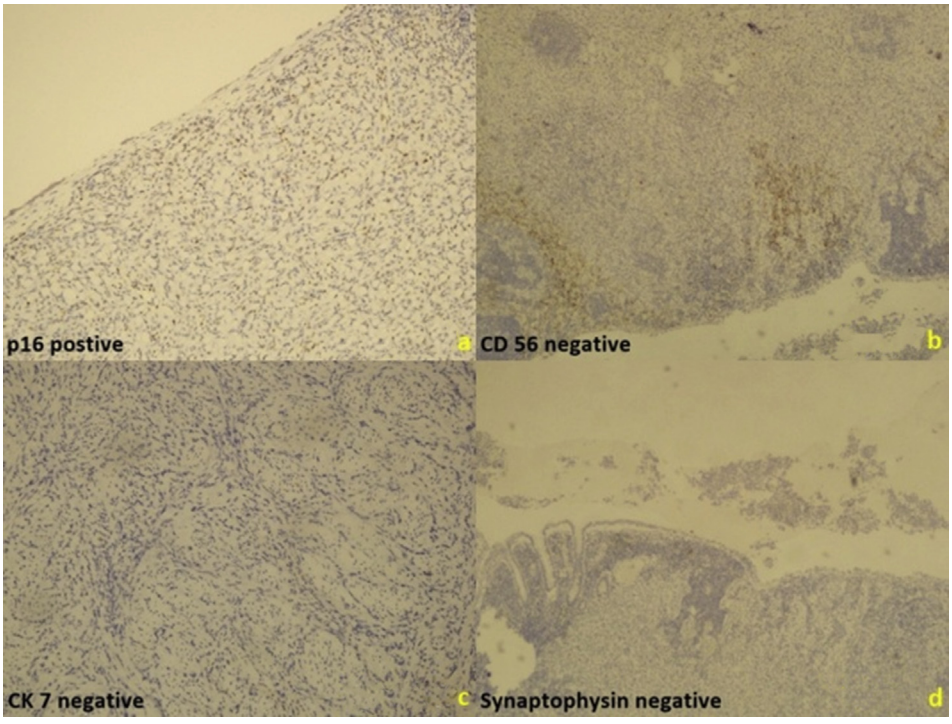

Fig. 7. The final IHC study revealed positive p16 expression (a) and negative CD56 (b), chromogranin A (c), and synaptophysin (d) staining.

Thus, primary cervical neoplasm cannot be excluded where a patient tests positive for CK20 and other colorectal antigens such as CEA or caudal-related homeobox gene 2 (CDX-2) [14]. In our case, although the preoperative biopsy was negative for CK7 and positive for CK20, indicating a colorectal origin, no colorectal intralumen lesions were discovered in the final specimen. Conflicting results have been reported for other IHC staining. Therefore, we assume that IHC studies alone are not precise enough to support or exclude the diagnosis of PCSRCC.

A complete tumor survey should be performed to exclude the possibility of metastasis from another organ. Combining patient history, clinical presentation, physical examination, imaging, endoscopic findings, and pathology is necessary to distinguish PCSRCC from other primary sites. In our case, panendoscopy, colonoscopy, and mammogram were performed and no specific focus was found. Based on the description of the features of primary cervical tumor reported in 1998 [9], PCSRCC may be diagnosed.

Treatment for PCSRCC is not well defined because of its rarity. In the early stage of the disease, surgery has been the primary choice. Combining surgery with chemotherapy or radiotherapy has been optional. Palliative chemotherapy alone is prescribed mostly at the advanced stage of the disease. The prognosis of the disease is also unclear because of the extremely rare incidence. Signet ring cell carcinoma in certain other tissues generally has a poor prognosis [14]. Nearly all—8 of 9—patients with cases of stage Ib1 disease achieved disease-free status. Patients with stage IV disease died within 1.6 months on average. Only one patient with advanced stage disease survived [15]. In our case report, a patient with stage IVb disease has had the longest overall survival of reported cases. No progression has occurred during the last year, and with regular treatment and followup, her general condition has remained relatively stable.

Conclusion

Complete tumor survey and staging are crucial. Differentiate primary from metastatic signet cell carcinoma of the cervix is necessary, and IHC studies cannot provide precise information. Thus, diagnosis must sometimes be made by exclusion. No consensus has been reached on treatment and prognosis because of the small number of cases.

Conflicts of interest

The authors declare there are no conflict of interest.

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