Molecular pathology and clinical treatment of primary serous carcinoma of the uterine cervix: A case report

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Abstract

A 69 years old Chinese female patient presented with independent HPV serous carcinoma uterine cervix. The genetic testing identified gene variants of PAX8 and TP53, microsatellite instability stable, TMB 7.33Muts/Mb. The patient had a good response to Docetaxel, carboplatin, and radiation with 18 months of free disease survival.

Molecular pathology and clinical treatment of primaryserous carcinoma of the uterine cervix: A case report Lina Niu1, Fangying Ruan2, Qisheng Yang2, Chaoran Xia2, Bifeng Zhang2, Tao Xu3, Fei Dong4, Lizhen Zhang1, Sheng Guo1, Weiqin Lv1, Junxia Wang1, Yun Shang1 1 Department of Gynecology, Yuncheng Central Hospital, Shanxi Province, Yuncheng 044000, China; 2 Zhejiang Shaoxing Topgen Biomedical Technology CO.,LTD., Shanghai 201321, China; 3 Department of Pathology, Yuncheng Central Hospital, Shanxi Province, Yuncheng 044000, China; 4 Department of medical imaging, Yuncheng Central Hospital, Shanxi Province, Yuncheng 044000, China. *Corresponding author Name: Yun Shang Postal address: Department of Gynecology, Yuncheng Central Hospital, Shanxi Province, No. 3690 Hedong East Street, Salt Lake District , Yuncheng 044000, China Tel: 13513599158 Fax: 0359-6396222 Email Address: 8634050@qq.com**Abstract** A 69 years old Chinese female patient presented with independent HPV serous carcinoma uterine cervix. The genetic testing identified gene variants of PAX8 and TP53, microsatellite instability stable, TMB 7.33Muts/Mb. The patient had a good response to Docetaxel, carboplatin, and radiation with 18 months of free disease survival.**Keywords:** cancer of cervix, neoadjuvant chemotherapy, molecular diagnostics.**Running head:** A case report of rare cervical carcinoma**Introduction**Serous carcinoma of the uterine cervix (USCC) is classified as a rare subtype of cervical adenocarcinoma, which has the same morphological features as serous carcinoma of the ovary, the fallopian tubes, the endometrium, and the peritoneum[1]. It is a challenge to diagnose primary USCC due to the limited number of published reports. USCC was classified by World Health Organization (WHO) Classification of Tumors-Female Genital Tumors in 2014 and morphologically featured as complex papillary and/or micropapillary structures[2], whereas the 2020 WHO classification regrouped this category[3]. The most recent WHO classification (2020) focused on the association between HPV infection and cervical carcinoma[4]. Accordingly, USCC was subdivided into HPV-associated and HPV-independent tumors. The treatment guidelines of HPV-independent cervical adenocarcinoma have yet to be established, possible due to lack of knowledge of its pathology[5]. In this report, we provided the pathological diagnosis and detailed treatment of USCC (or HPV-independent invasive adenocarcinomas uterine cervix) of a Chinese female with 20 months free of disease progression.**Case statement**A 69 years old Chinese female patient was admitted to Yuncheng Hospital on October 23,2020 with five months of history of postmenopausal bleeding and lower abdominal pain. In May 2020, she complained of occasional vaginal bleeding which ceased spontaneously 4 to 5 days later. Blood was occasionally spotted in stool, but

not in urine. Her last menstrual period occurred more than 14 years before. The gynecological examination showed vulvar hypopigmentation, atrophy, and smooth vagina. A small amount of dark red blood, and cauliflower-like mass about 5 cm in diameter were observed in the front lip of the uterine cervix. The uterine cervix is mobile with crispy texture, atrophy shallow vaginal fornix. There was not palpable abnormality in bilateral adnexal areas. The color Doppler ultrasound of the pelvis showed that the cervix was enlarged, the echo was unevenly reduced, and the size of tumor measured as 5.7*4.0 cm. The first differential was cervical cancer. On October 19th, 2020, cervical cone biopsy was performed and pathology showed high grade endometrioid glands lined by columnar cells with eosinophilic cytoplasm and pseudostratified nuclei. Typical papillary and micropapillary architectures and highly atypical nuclei were found (Figure 1A,B). The immunohistochemistry results focally positive for PR and ER, and positive for p16, p53, EMA and WT-1, withKi67 index of 70% in the tumor tissue (Figure 2). However, the immunohistochemistry result was negative for Vimentin, Napsin A, HNF1β and CEA. The HPV test was also negative. On October,2020, pelvic MRI showed an anteverted uterus, left deviation, abnormalities of anterior and posterior lips, and an irregular mass with a size of 3.0 × 5.0 × 4.1 cm (Figure 3A). The diffusion-weighted MRI was mildly heterogenous increased. The fundus of the uterus was unevenly thickened and the internal signal was heterogenous. The shape and signal of bilateral appendages showed no obvious abnormality, and scattered small lymph nodes were seen adjacent to the right iliac vessels. There were scattered small lymph nodes adjacent to the right iliac vessels and glandular glands at the bottom of the uterus (Figure 3A). Pathology suggested the cervical tumor with FigoII A stage. Thus, our diagnosis favored USCC (according to the 2014 WHO-the Female Genital Tumors classification) or other adenocaricinoma of the uterine cervix, which is HPV-independent and the diagnosis is made after exclusion of other differentials (according to 2020 WHO-the Female Genital Tumors classification). In order to further study the molecular pathology and effective treatment strategy, the patient was tested with NGS-based 603 panel gene detection, and two variant PAX8 c.1230C>G (p.Tyr 410 Ter) and TP53 c.740A>T (p.Asn247Ile) were discovered. The microsatellite status of tumor was stable, the Tumor Mutation Burden score was 7.33Muts/Mb, and the tumor neoantigen load was high.**Treatment**The patient was treated with 3 cycles of neoadjuvant chemotherapy with docetaxel (100mg/3h/intravenous), carboplatin(450mg/1h/intravenous) and thiopefilgrastim (6 mg /injection). On December 25, 2020, pelvic MRI scan showed that the tumor size was significantly reduced to about 2.5 × 1.9 × 3.0 cm (Figure 3B). On January 20, 2021, radical hysterectomy was performed including bilateral adenoxetomy, pelvic paraaortic lymph node dissection and omentectomy. The pathological examination showed serous carcinoma of the uterine cervix (Supplementary Figure 1D), the tumor has invaded into the muscle layer of the vaginal fornix and the lower uterine segment. Moreover, the H&E staining showed that the histology of bilateral parametrium, endometrium, bilateral fallopian tubes and ovaries were normal (Supplementary Figure 1 A,B,C). Adenomyosis or endometriosis was not found, and lymph nodes were negative for malignancy. Postoperative immunohistochemical results showed CDX-2(-), p53 (mutant), PAX-8(+), SATB-2(-). After the operation, patient remained on chemoradiation therapy for another3 cycles (docetaxel (100mg/3h, intravenous), carboplatin (500mg/1h, intravenous), and25 cycles of intensity modulated radiotherapy DT46Gy/2Gy/23f with concurrent cisplatin (450mg/1h). The patient developed Grade IV myelosuppression (Supplementary Table 1). After the treatment, the patient was followed up every three months. The CT on August 3, 2022did not show evidence of recurrence (Supplementary Figure 2).**Discussion** Primary cervical HPV-independent invasive adenocarcinomas with serous-like is characterized by the morphological features of complex papillary and/or micropapillary structures with high-grade nuclear atypia[6]. This report provides a case of primary HPV-independent invasive adenocarcinoma of the uterine cervix in a patient with the molecular analysis and the patient was effectively treated and free of disease recurrence for 18 months as of now. Immunohistochemistry (IHC) is very helpful in diagnosis and classification of uterine cervical carcinomas[7]. IHC of p53 and p16 were positive in serous carcinoma[1, 8]. WT-1 and estrogen receptor (ER) were positive in serous carcinoma of the ovary[9], whereas USCC showed weak or negative expression[10]. In fact, our case was positive for p16, p53, WT-1 (weakly) and ER (weakly). CEA and Vimentin were sometimes positive in USCC. Napsin A and HNF-1β arefrequently positive for clear carcinoma of the uterine cervix, ovary and endometrium[11]. The IHC were negative for Vimentin, Napsin A, HNF1 and CEA biomarkers. In previous reports, micro-satellite status and TMB status are rarely adopted in uterine serous carcinoma[12]. In fact, the patient in this report

had MSS and TMB of 7.33Muts/Mb, and high tumor neoantigen load. Furthermore, two variant PAX8 c.1230C>G (p.Tyr 410 Ter) and TP53 c.740A>T (p.Asn247Ile) were detected. To date, few studies have reported the genetic features of HPV-negative serous carcinoma of the cervix. Jenkins et al. recently reported that cervical serous carcinoma (n = 6, HPV-negative) harbors mutations in TP53 (50%), KRAS (33%), PIK3CA (17%), and PTEN (17%)[13]. Our case enriched the molecular features of cervical serous carcinoma and helped to understand the underlying molecular mechanisms. Neoadjuvant chemotherapy was first used to treat cervical cancer in 1988 with a response rate 75.7% and since then it has gradually become a treatment of this cancer in clinic[14]. In our study, the patient showed good response to neoadjuvant chemotherapy free of disease for 18 months as of now 2-3 cycles of neoadjuvant chemotherapy were recommended for patients with stage IB3 or IIA2 uterine cervical cancer, while in this study the clinician used 3 cycles of neoadjuvant chemotherapy and 3 cycles of adjuvant chemoradiation therapy to treat this rare type of carcinoma. Our treatment has showed longer disease-free time. As of now, the patient does not have recurrence. Cervical serous carcinoma is a very rare tumor with no reported pathological and molecular profile. In this report, we elaborated molecular features of a typical serous carcinoma and treatment strategy maybe help form the best management and diagnosis methods in the near future.**Conflict of interest** We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.**Acknowledgements** Not applicable.**Funding** No funding was received.**Authors' contributions** Fangying Ruan and Qisheng Yang was responsible for the conceptualization of the present study and writing the manuscript. Lina Niu, Sheng Guo, Junxia Wang, Tao Xu, Fei Dong and Weiqin Lv acquired the majority of the data, analyzed the data, performed literature research and prepared the original draft. Lina Niu and Lizhen Zhang guided the diagnosis and treatment of patients.Yun Shang, Chaoran Xia and Bifeng Zhang were responsible for editing and performing critical review of the manuscript. All authors read and approved the final manuscript for publication.**Ethics approval and consent to participate** The study involving a human participant was reviewed and approved by The Yuncheng Central Hospital, Shanxi, China. Written informed consent was obtained from the patient and all procedures were conducted in accordance with the Declaration of Helsinki.**Patient consent for publication** The patient provided consent for publication.**Competing interests** The authors declare that they have no competing interests.**References**

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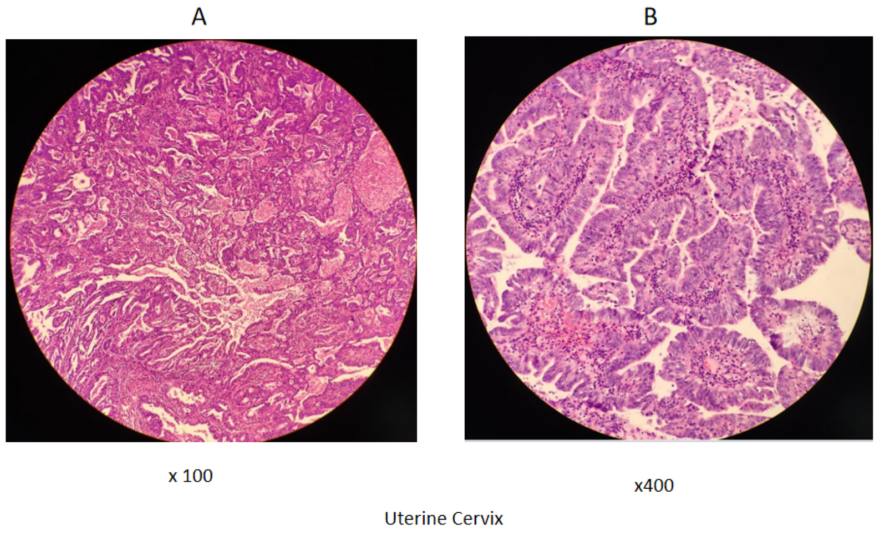
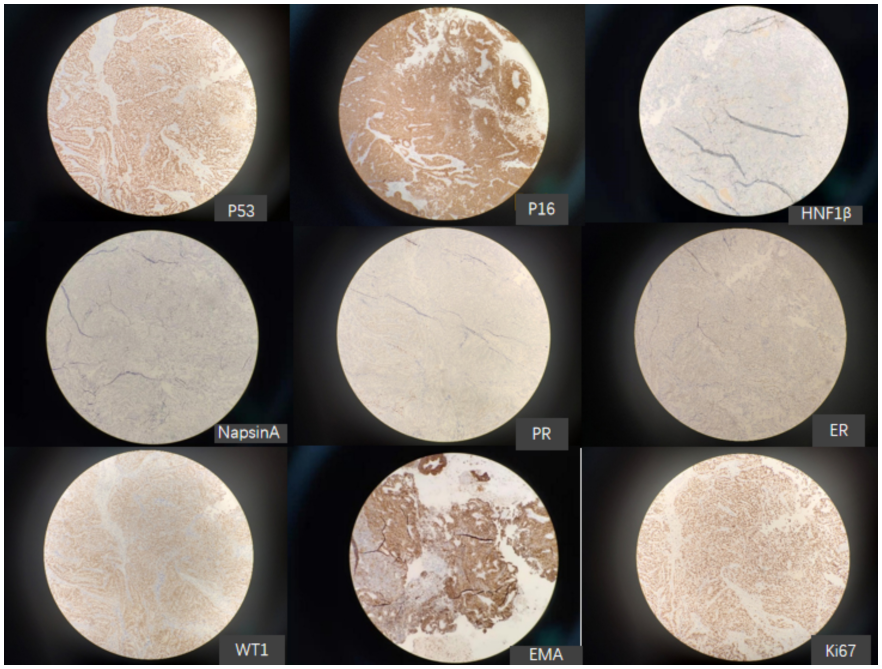
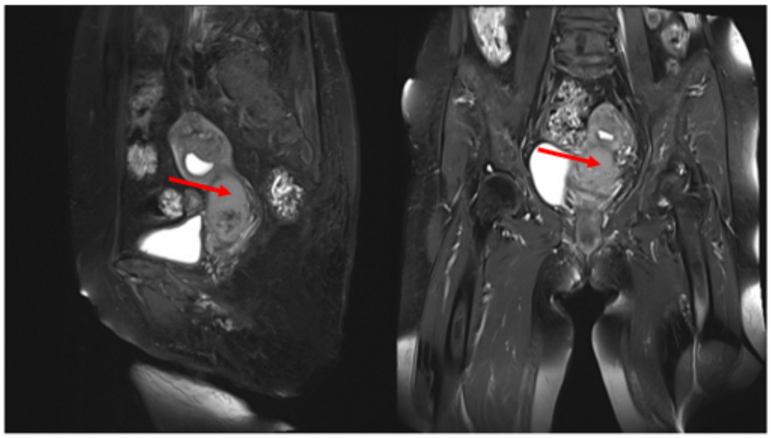
13. Jenkins D, Molijn A, Kazem S, et al. Molecular and pathological basis of HPV-negative cervical adenocarcinoma seen in a global study[J]. International Journal of Cancer, 2020, 147(9): 2526-2536. 14. Wang Y, Wang G, Wei LH, Huang LH, Wang JL, Wang SJ, et al. Neoadjuvant chemotherapy for locally advanced cervical cancer reduces surgical risks and lymph-vascular space involvement. Chinese journal of cancer. 2011;30(9):645-54.**Figure legends Figure 1.** Histology of serous carcinoma of the uterine cervix shows endometrioid gland lined by columnar cells with eosinophilic cytoplasm and pseudostratified nuclei, H&E staining, x100(A), X400(B).**Figure 2.** Immunohistochemistry was focally positive for PR, and ER and positive for p16, WT-1, p53, and EMA with a Ki67 index of 70% in the cervix carcinoma, (magnification: 100X).**Figure 3.** Responses to neoadjuvant chemotherapy treatment assessed by MRI before (A) and after (B) 3 cycles of chemotherapy show regression of the paracervical mass.**Supplementary Figure 1.** H&E stainingshows histology of endometrium (A), ovary (B), fallopian tube(C)(40X), uterine cervix (D) was abnormal tissue with serous carcinoma, (100x).**Supplementary Figure 2.** Computed tomography scan. CT scan,(A) lung window, demonstration, (B) mediastinal window, (C) abdomen, (D) abdomen, (E) pelvic cavity, (F) pelvic bone window, (G) chest lung window.**Table Supplementary Table 1. The blood parameter of patient during treatment**

Date	Leucocyte Count	Hemoglobin concent
2021.2.3(The third day after chemotherapy and the fourteenth day after surgery)	2.1×10ˆ9/L	109g/L
2021.2.7	0.92×10ˆ9/L	
2021.2.11	13.4×10ˆ9/L	124g/L
2021.2.22	1.9×10ˆ9/L	111g/L
2021.2.26	0.93×10ˆ9/L	
2021.3.2	8.5×10ˆ9/L	105g/L
2021.5.24	0.74*10ˆ6/L	
2021.5.30	5.5×10ˆ9/L	98g/L





A



B