Clinical Case Report

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# Short tandem repeat analysis for confirmation of uterine non-gestational choriocarcinoma in a postmenopausal Taiwanese woman

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**Abstract**

**Rationale:** Rare uterine choriocarcinoma can be differentiated gestational from nongestational choriocarcinoma by using short tandem repeats (STRs).

**Patient concerns:** A 56-year-old Taiwanese woman underwent staging surgery because of suspicion of high-grade endometrial cancer. The pathology-confirmed uterine tumor with syncytiotrophoblasts and decidual change of the endometrium was harvested.

**Diagnosis:** Uterine nongestational choriocarcinoma.

**Interventions:** The tumor specimen, the patient's blood, and her husband's blood were drawn for STRs analysis using polymerase chain reaction amplification kit. The genotype of the tumor cells was solely maternal and made the diagnosis of uterine nongestational choriocarcinoma.

**Outcome:** Adjuvant chemotherapy with etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine regimen achieved good response in the patient. The patient is now recurrence-free for 12 months.

**Lessons:** STRs aid precise classification of rare choriocarcinoma. We encourage using the method to analyze suspicious choriocarcinoma.

**Abbreviations:** EMA-CO = etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine, hCG = human chorionic gonadotropin, HSD3B1 = hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1, PCR = polymerase chain reaction, STR = short tandem repeat.

**Keywords:** menopause, non-gestational choriocarcinoma, short tandem repeats, Taiwanese

## 1. Introduction

Choriocarcinoma is a trophoblastic neoplasm that is usually arising from the gestational tissue, but can also be nongestational. Nongestational choriocarcinoma has been described in the ovaries in <1% of germ cell ovarian tumors. However, it is much rarer in uterus.[1–3] Compared with uterine gestational choriocarcinoma, nongestational uterine choriocarcinoma is particularly unusual, especially in postmenopausal period. In addition, the pathogenesis is still uncertain.[4] The genetic analysis with short tandem repeats (STRs) can differentiate nongestational origin. Accurate differentiation of gestational and nongestational choriocarcinoma is clinically important because the prognosis and treatment differ.[5] Here we present our case using STRs to detect uterine nongestational choriocarcinoma in a postmenopausal woman.

## 2. Case report

A 56-year-old Taiwanese woman (gravida 5, para 4, induced abortion 1) visited our clinic with the chief complaint of vaginal bleeding for 6 months. She had 4 full-term pregnancies, and all were followed by normal vaginal deliveries. She experienced menopause at the age of 52 years. She did not undergo hormone replacement therapy. A pelvic examination at our clinic revealed a slightly enlarged uterus. Transvaginal ultrasonography showed significantly thickened endometrium, measuring up to 49 mm in thickness, with a blurry border between the myometrium and endometrium. Color Doppler sonography demonstrated hyperechoic focal lesions with prominent blood flow. The resistance index was 0.7. Endometrial biopsy revealed a high-grade carcinoma. Magnetic resonance imaging illustrated a 7-cm hypointense tumor with peripheral enhancement in the uterine cavity, which had invaded more than half the uterine wall as shown on T2-weighted images (Fig. 1A and B). There were no enlarged lymph nodes visible on the magnetic resonance images.

The patient underwent staging surgery owing to suspicion of high-grade endometrial cancer. The surgery included total

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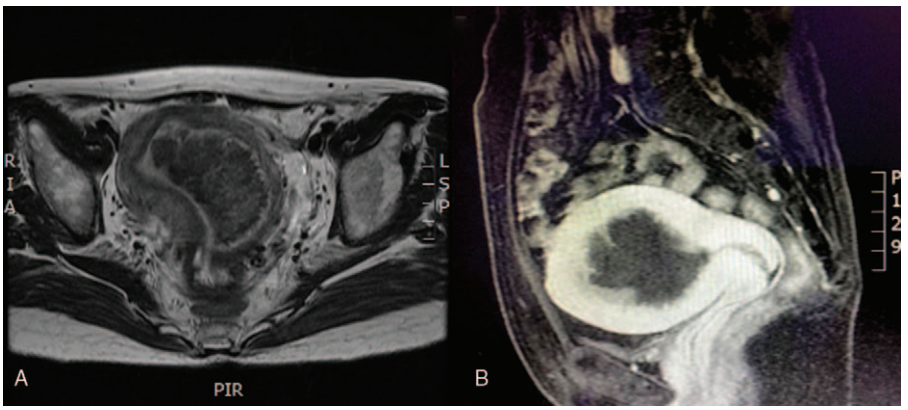


**Figure 1.** (A) Axial T2-weighted image of a hypointense irregular tumor in the uterine cavity with peripheral enhancement in the endometrial cavity. (B) Sagittal T1-weighted image.

hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection, and pelvic wash cytology. The uterus measured $9.5 \times 7.4 \times 6.5$ cm. A dark-red tumor with a hemorrhage at the edge was found inside the uterine body, without cervical involvement, and measured $8.5 \times 7.5 \times 3.5$ cm (Fig. 2A and B). There were no specific findings in the bilateral adnexa. A microscopic examination of the tumor showed marked nuclear pleomorphism, frequent mitoses with abundant syncytiotrophoblast-like tumor cells (Fig. 2C). The nearby endometrium revealed focal atypical endometrial hyperplasia with areas of pseudo-decidualization of endometrial stroma (Fig. 2D). The immunochemical staining of the tumor cells was positive for human chorionic gonadotropin (hCG) and hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1 (HSD3B1) (Fig. 2E and F).

Choriocarcinoma arising from a menopausal woman raised our attention. We sent preserved tumor tissue and a blood sample from the patient and her husband for genetic comparison to determine the origin of the tumor. Institutional review board approved informed consents were obtained from the patient and her husband for performing the pathologic and genetic profiles. DNA extraction from the tissues and blood samples were amplified using AmpF$\ell$ STR Identifiler polymerase chain reaction (PCR) Amplification Kit (Applied Biosystems, Foster City, CA). This kit consists of a STR, multiplex PCR assay that amplifies 1 amelogenin and 15 autosomal STR loci. Electrophoresis was performed using an ABI 3130XL Genetic Analyzer (Applied Biosystems). Fragment sizes were automatically determined using Genemapper ID software (Version 3.2.1; Applied Biosystems). The genotype we extracted from the paraffin-embedded tumor

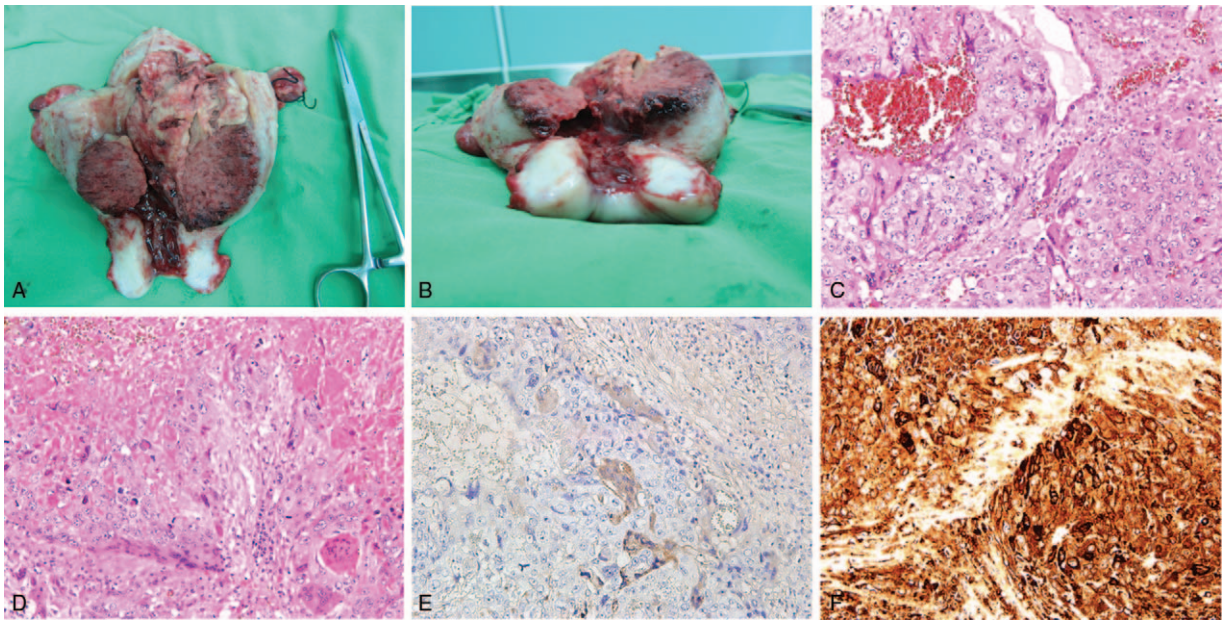


**Figure 2.** Clinical and pathologic pictures. (A) Resected uterus shows a dark-red tumor surrounding the endometrial cavity. (B) Absent cervical involvement. (C) *M*icroscopic findings show the choriocarcinoma tumor cells comprised of cytotrophoblasts and syncytiotrophoblasts, without other germ cell components. (D) Tumor necrosis and nearby syncytiotrophoblasts. (E) Positive immunohistochemical staining for HSD3B1 in the syncytiotrophoblasts. (F) Positive immunohistochemical staining for human chorionic gonadotropin in the syncytiotrophoblasts.

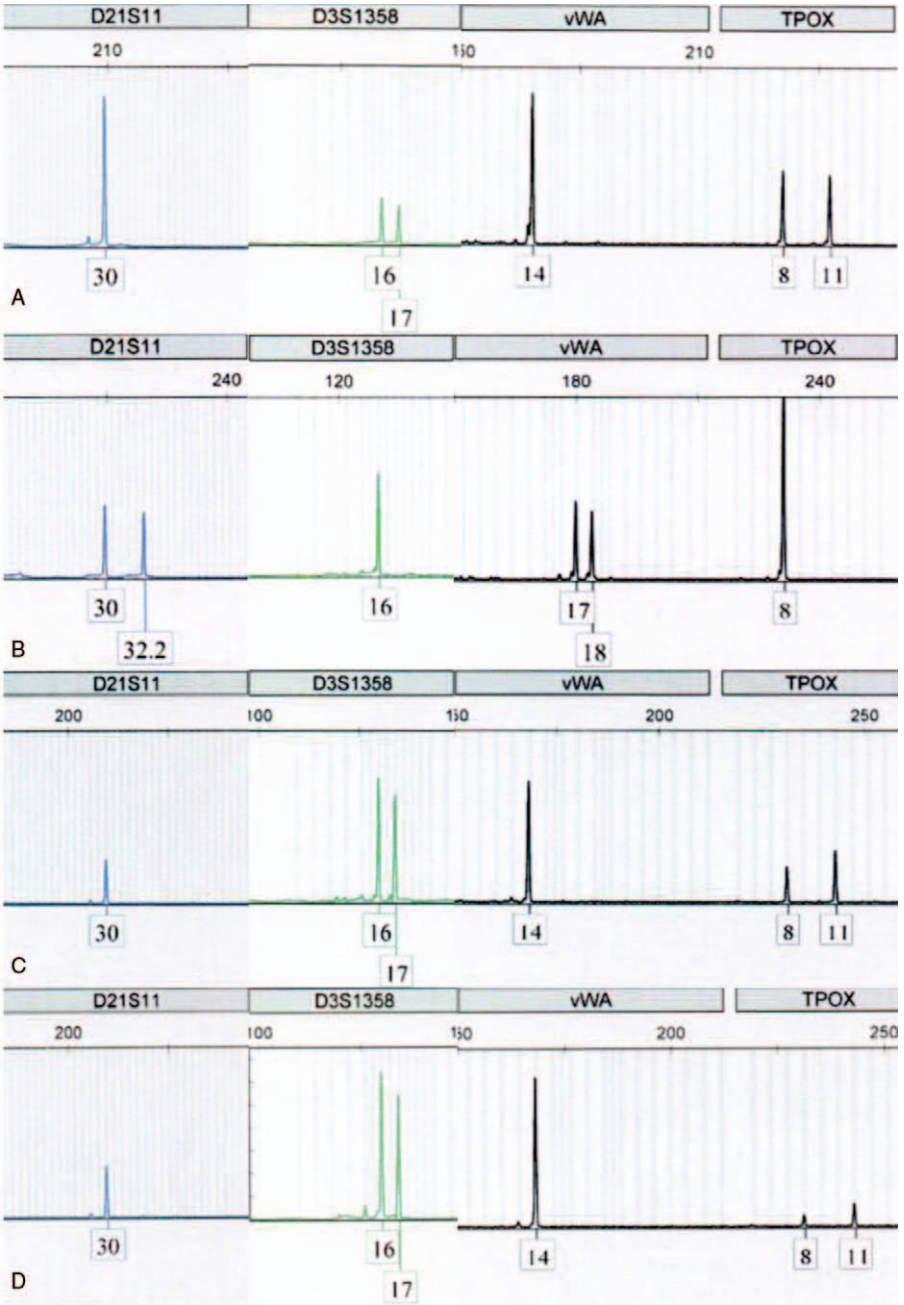


**Figure 3.** Four selected different short tandem repeats (D21S11, D3S1358, vWA, and TPOX) show the purely maternal origin of the tumor. The genotypes of A, C, and D are identical. (A) Patient's blood sample. (B) Husband's blood sample. (C) Patient's fresh tumor sample. (D) Patient's tumor paraffin-block tumor sample.

specimen, and the result was identical to that of the previous fresh tissue for multiple probes (Fig. 3C and D), showing a nongestational choriocarcinoma. The nongestational choriocarcinoma matched the patient's blood sample (Fig. 3A) and differed from her husband's sample (Fig. 3B) for multiple probes. The complete analysis result is shown in supplement, http://links.lww.com/MD/C123.

A postoperative study with computed tomography of the chest showed the absence of any metastatic lesion. According to World Health Organization prognostic scoring, she met age (1 point), antecedent abortion (1 point), >12 months since her previous pregnancy (4 points), tumor size (3 points), and unknown pretreatment hCG level risk factors. She was categorized as high risk, and she received 6 cycles of adjuvant chemotherapy with etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine (EMA-CO). The postoperative β-hCG level dropped from 89.8 to 4.0 mIU/mL after 6 cycles of chemotherapy (below the normal limit at the 4$^{th}$ cycle). She had regular follow-up at our clinic for 12 months without evidence of recurrence.

## 3. Comment

Genotype analyses have been used to differentiate gestational from non-gestational choriocarcinoma in cases of rare postmenopausal gestational choriocarcinoma.[3,5–7] There are only sporadic cases of nongestational choriocarcinoma in the

literature, and those arising from the uterus endometrium are extremely rare. The genotype of our patient's tumor cells was solely maternal, providing substantial evidence of nongestational choriocarcinoma. Most of the reported cases of choriocarcinoma in the literature were derived from nongestational ovarian tissue,[1,2,8] whereas only 1 reported case was derived from the uterus.[8] In our patient's case, the endometrium near the tumor revealed focal atypical endometrial hyperplasia, with areas of pseudo-decidualization of endometrial stroma. We suggest this pseudo-decidualization resulted in dedifferentiation of the endometrium, causing the occurrence of this rare type of uterus-derived nongestational choriocarcinoma.

The patient achieved a good response to the EMA-CO chemotherapy regimen, in contrast to that of previously reported cases of uterine nongestational choriocarcinoma.[8] She is following up at our clinic after treatment for 12 months without recurrence.

Currently, the pathogenesis of nongestational choriocarcinoma remains unknown. Three hypotheses attempt to explain the origin: the first hypothesis suggests a group of germ cells resting in the region of the urogenital ridge undergoes malignant transformation. The second assumes totipotent germ cells, left in ectopic sites outside of the urogenital ridge during early embryonal development, fail to undergo apoptosis, and then subsequently transform into choriocarcinoma. The third hypothesis suggests retrodifferentiation of adult tissue cells into cancer cells.[9] Tracing the development of the nongestational choriocarcinoma through pathologic staining has reached a bottleneck in the past few years.

An STR analysis is used to compare specific loci on DNA from ≥2 samples. An STR is a microsatellite, consisting of a unit of 2 to 13 nucleotides repeated hundreds of times in a row on the DNA strand. These repeated nucleotides are highly polymorphic DNA region during meiosis, which means unrelated people have different STR results. STRs are wildly used to perform paternity testing. Because unrelated people almost certainly have different numbers of repeat units, STRs can be used to differentiate doubtful choriocarcinoma, which allows us to categorize gestational trophoblastic neoplasms in a precise way. These techniques may also provide information about better therapeutic approaches for the treatment of these types of rare tumors in the future.

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