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Case Report

Gestational choriocarcinoma with renal and pulmonary metastases lacking a primary uterine origin

Hao-Ming Li [a], Wen-Chien Hou [b], Yu-Ju Lai [b], Chien-Chang Kao [c], Tai-Kuang Chao [d], Mu-Hsien Yu [b], Her-Young Su [b,*]

[a] Department of General Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[b] Department of Obstetrics and Gynecology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[c] Section of Urology, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[d] Department of Pathology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

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ABSTRACT

Objective: We describe a case of gestational choriocarcinoma metastasized to the kidney and lung, which presented initially as refractory hematuria after a term pregnancy 5 years earlier.
Case Report: A 35-year-old woman, G2P1, with a previous history of full-term pregnancy in 2009, presented to the emergency department complaining of intermittent gross hematuria for 2 months. Abdominal computed tomography showed a suspicious arteriovenous malformation in the right kidney and a thrombus within the right renal vein. Transarterial embolization was performed twice to treat the refractory hematuria but was unsuccessful, and radical nephrectomy of the right kidney was performed. The diagnosis was gestational metastatic choriocarcinoma of the kidney based on morphological, immunohistochemical, and DNA studies. Lung metastases were found by computed tomography of the chest. Pelvic ultrasound was performed but showed no primary tumor in the uterine cavity. After surgical intervention, adjuvant chemotherapy involving first single-agent chemotherapy with methotrexate followed by multiagent chemotherapy (EMACO regimen) failed.
Conclusion: In women of reproductive age, unexplained hematuria should raise concerns about possible choriocarcinoma, either metastatic gestational or primary nongestational choriocarcinoma of the kidney.

Introduction

Choriocarcinoma is characterized as a highly invasive tumor of gestational trophoblastic neoplasia (GTN). It can rapidly progress and metastasize via the hematogenous pathway to distant organs. Metastases to the kidneys are rarely mentioned in the literature [1]. Choriocarcinoma can be either gestational or nongestational. Gestational choriocarcinoma commonly originates from the uterus and can occur in any type of pregnancy [2]. Nongestational choriocarcinoma derives from germ cells of the gonads or, rarely, from extragonadal germ cells. As these two types of tumor differ in their genetic origin, prognosis, and sensitivity to chemotherapy, determining whether the tumor has a gestational or nongestational origin is essential [3]. Choriocarcinoma is known to be sensitive to chemotherapy, and the cure rate is >90% even in cases involving widespread metastatic disease [4]. We describe a case of gestational choriocarcinoma metastasized to the kidney and lung, which presented initially as refractory hematuria after a term pregnancy 5 years earlier.

Case Report

A 35-year-old woman, G2P1, had a full-term pregnancy with delivery via cesarean section because of failure to progress 5 years earlier, in 2009. The patient presented to the emergency department complaining of intermittent gross hematuria with blood clots for 2 months. Abdominal computed tomography (CT) was suggested for evaluation, but magnetic resonance imaging (MRI) was used because of a positive urinary pregnancy test. Pelvic ultrasound revealed an intrauterine gestational sac, which confirmed the pregnancy. Recall of the patient's gynecological history indicated that she experienced regular menstruation with normal duration and interval, and that the last menstrual period was 4 weeks before

* Corresponding author. Department of Obstetrics and Gynecology, Tri-Service General Hospital, 325, Section 2, Chenggong Road, Neihu District, Taipei 11490, Taiwan.
E-mail address: su108868@gmail.com (H.-Y. Su).

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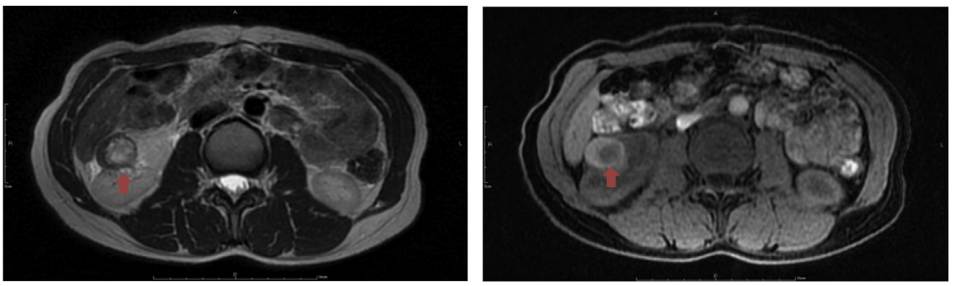

Figure 1. Magnetic resonance imaging of the abdomen showing a right renal tumor measuring approximately 3.4 cm × 3.7 cm (arrow).

presentation. MRI of the abdomen showed a right renal tumor (Figure 1). However, marked vaginal bleeding developed 2 days after this MRI, and a pelvic ultrasound revealed no gestational sac in the uterus, which indicated that a spontaneous abortion had occurred.

The patient visited our urology department for second opinion regarding the renal tumor. Abdominal CT showed a suspicious arteriovenous malformation in the right kidney and a thrombus within the right renal vein (Figure 2).

Repeated transarterial embolization was performed twice to treat the refractory hematuria but was unsuccessful. Radical nephrectomy of the right kidney was performed to control the refractory hematuria and bleeding, and the symptoms subsided after this surgical intervention (Figure 3).

Microscopic examination of the resected tumor revealed tumor cells infiltrating into the renal parenchyma, causing focal renal pelvis invasion, and had seeded and embolized into the large vessel wall. The tumor was immunopositive for beta-human chorionic gonadotropin (β-hCG), 3-β-hydroxy-δ(5)-steroid dehydrogenase (HSD3B1), Ki67, and cytokeratin 7 (Figure 4). The morphological and immunohistochemical findings suggested that the likely diagnosis was gestational choriocarcinoma or primary choriocarcinoma of the kidney. DNA studies were performed and revealed Y chromosomes in the tumor cells (Figure 5), which confirmed gestational choriocarcinoma with renal metastasis.

Prominence of the right hilar region of the lung was detected in a preoperative chest X-ray. CT of the chest was performed after surgery and revealed an irregular mixed soft-tissue, cystic lesion in the superior right lower lobe, and multiple cavitary lesions in both lungs, which were suspected as lung metastases (Figure 6). No respiratory manifestations, except for those noted in the imaging studies, were observed during the entire course of the disease.

According to the revised staging system for GTN approved by the International Federation of Gynecology and Obstetrics (FIGO) in 2002, the final diagnosis was choriocarcinoma, FIGO Stage IV. To evaluate the prognosis and treatment selection, the Prognostic Scoring Index modified by the World Health Organization (WHO) was applied. Although the prognostic score was considered high risk, single-agent chemotherapy with a regimen of methotrexate

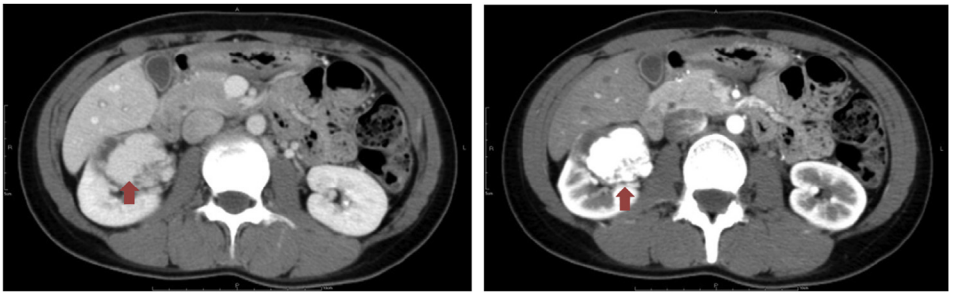

Figure 2. Computed tomography of the abdomen showing a tumor measuring approximately 5 cm × 4.5 cm (arrow), which raised suspicion of an arteriovenous malformation in the right kidney with a thrombus measuring approximately 1.3 cm within the right renal vein.

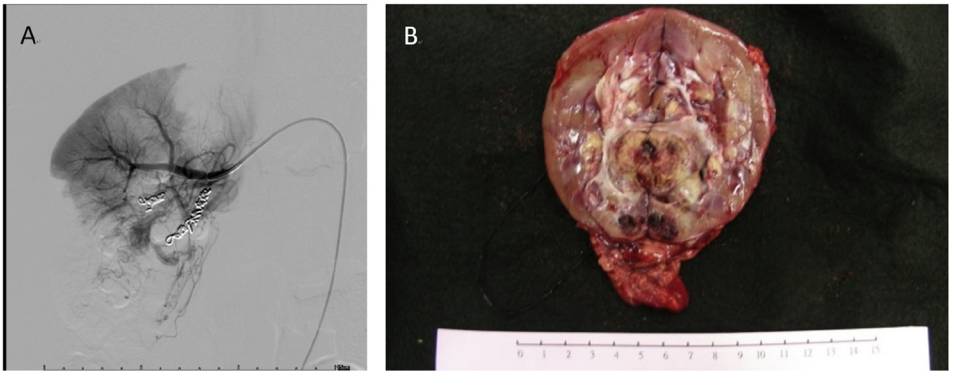

Figure 3. (A) Angiography of the right kidney when the transarterial embolization was performed to control the refractory hematuria; (B) gross photograph showing multiple heterogeneous, well-defined, and multicystic mass lesions in the middle and lower poles of the right kidney measuring 5 cm in diameter with some hematoma and necrosis.

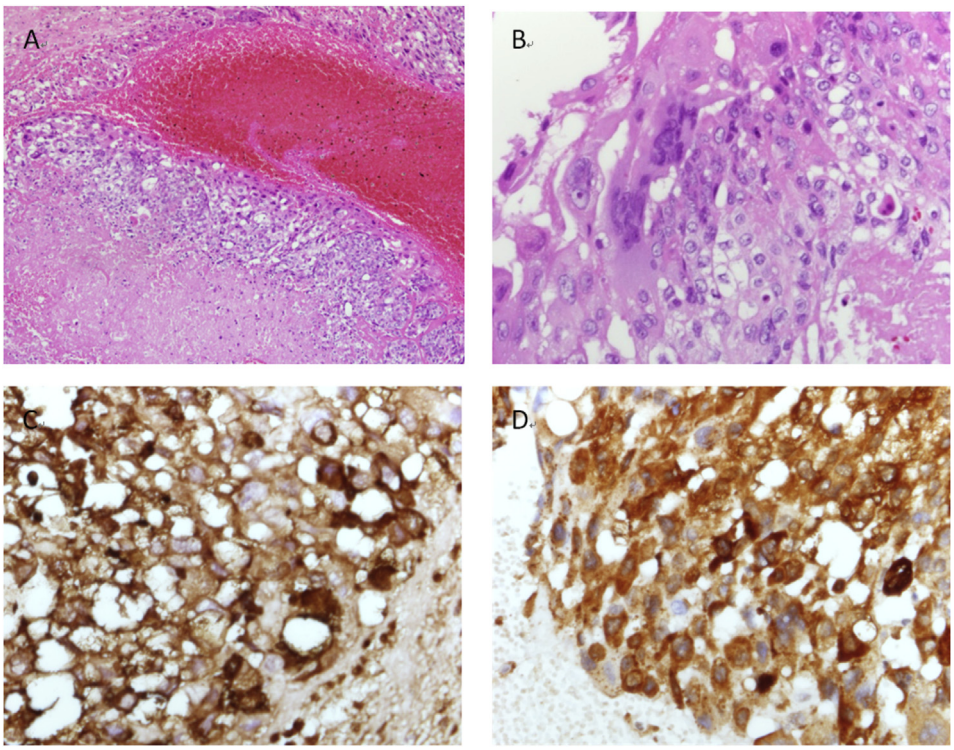

Figure 4. (A, B) Microscopic findings of the tumor. The tumor cells were characterized by marked nuclear atypia and hyperchromatism, and were arranged in a solid nest along with many giant cells, which were admixed with the blood clots and had infiltrated into the renal parenchyma. Focal renal pelvis invasion was observed, and some of the tumor cells had seeded and embolized into the large vessel wall. Marked hemorrhage, hematoma, and tumor necrosis were also identified [hematoxylin and eosin staining, (A) ×100 and (B) ×400]. (C) Immunoreactive for β-hCG immunostaining (β-hCG, ×400). (D) Immunoreactive for HSD3B1 immunostaining (HSD3B1, ×400). β-hCG = beta-human chorionic gonadotropin; HSD3B1 = 3-β-hydroxy-δ(5)-steroid dehydrogenase.

and leucovorin was applied because of the low total hCG concentration 2 weeks after nephrectomy (643 mIU/mL) and the desire to preserve renal function. Only one course of single-agent chemotherapy was initiated because of the elevated total hCG concentration after treatment. Under suspicion of disease progression, the therapy was replaced by multiagent chemotherapy using the EMACO regimen (etoposide 100 mg/m^2 on Days 1 and 2, methotrexate 300 mg/m^2 on Day 1, dactinomycin 0.5 mg on Days 1 and 2, cyclophosphamide 600 mg/m^2 on Day 8, and vincristine 1 mg/m^2 on Day 8). After two courses of the EMACO regimen, the serum total hCG concentration decreased from the highest value of 3253 mIU/mL to 603.9 mIU/mL.

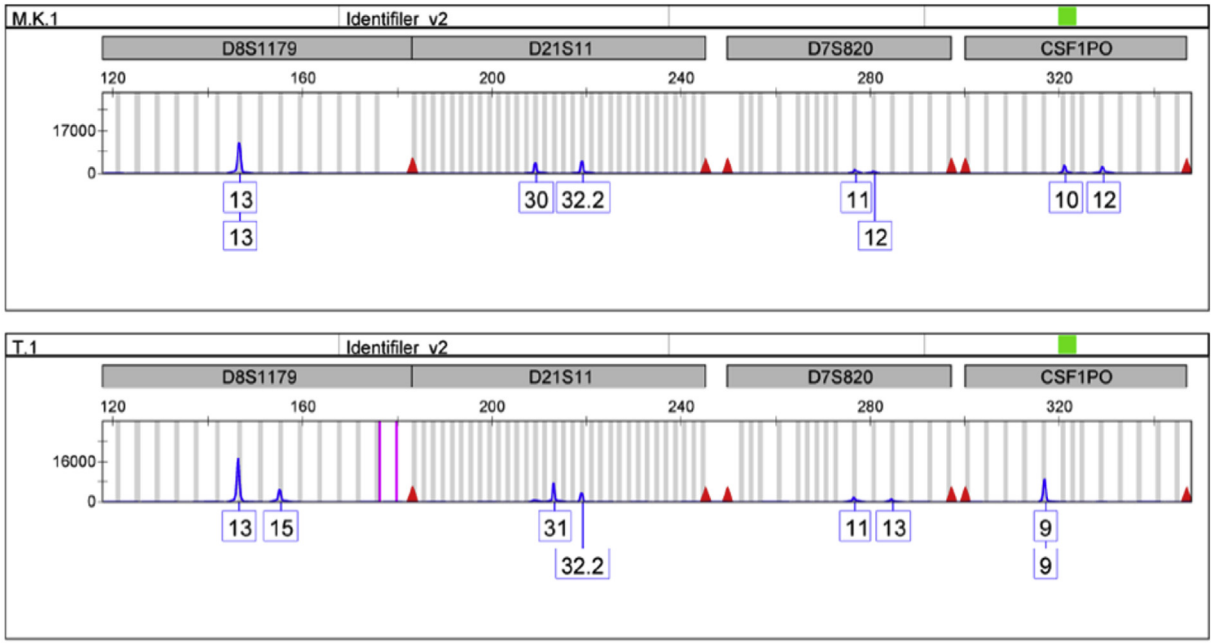

Figure 5. DNA studies revealed Y chromosomes in the tumor cell, which confirmed gestational choriocarcinoma with renal metastasis.

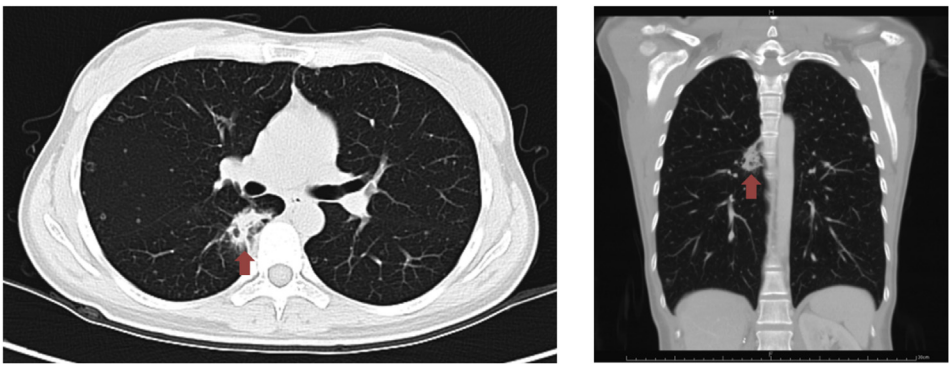

Figure 6. Computed tomography of the chest revealed an irregular mixed soft-tissue cystic lesion measuring approximately 3.2 cm in the superior right lower lobe (arrow) and multiple cavitary or cystic lesions with thick walls in all lobes of both lungs, which raised suspicion of lung metastases.

Unexpectedly, the total hCG concentration rebounded to 1308 mIU/mL during the third course of the EMACO regimen, which raised suspicion of therapy-resistant related disease progression. The therapy was shifted to the EMAEP platinum-based regimen (etoposide 100 mg/m^2 on Day 1, methotrexate 300 mg/m^2 on Day 1, dactinomycin 0.5 mg on Day 1, etoposide 150 mg/m^2 on Day 8, and cisplatin 75 mg/m^2 on Day 8). The patient remains under treatment.

Discussion

Gestational choriocarcinoma commonly begins in the uterus and can occur in any type of pregnancy. Extrauterine metastasis of gestational choriocarcinoma can occur in the absence of an existing primary uterine tumor because of spontaneous necrosis or complete regression of the primary tumor [3,5,6], which makes the diagnosis at the initial presentation more difficult. Due to the nature of the early dissemination and absence of a primary uterine origin, most patients exhibit one or more metastases at the time of diagnosis.

In our case, the patient presented with initial symptoms of refractory hematuria which were finally diagnosed as choriocarcinoma, FIGO Stage IV with renal and lung metastases. No primary neoplasia was found in the uterus to indicate choriocarcinoma. One limitation of this case study is that hCG concentration was not measured preoperatively because the urological manifestations developed at the beginning of the disease and did not raise concerns regarding GTN. Usually, this disease is discovered by experienced gynecologists, and most urologists do not encounter patients with this disease. Therefore, this case study may help clinical specialists to consider the possibility of GTN when a woman of reproductive age presents with unexplained hematuria [7].

As the gestational and nongestational choriocarcinoma cannot be differentiated based on the histological, immunohistochemical, and clinical manifestations, applying DNA analysis is critical to determining the origin of the tumor [3]. In this patient, DNA studies were used to distinguish the initial impressions of gestational choriocarcinoma and primary nongestational choriocarcinoma of the kidney. The results of the genetic analysis showed paternal Y chromosomes in the tumor cells, which helped to confirm the diagnosis of gestational metastatic choriocarcinoma of the kidney.

Identifying the gestational event associated with choriocarcinoma is an issue for debate. Choriocarcinoma commonly arises from a previous molar pregnancy, or more rarely, a nonmolar gestation within 1 year of the antecedent pregnancy [8]. The longest latent period reported in the literature is 23 years between a previous abortion and choriocarcinoma in a 53-year-old woman [9]. Our patient experienced a term pregnancy 5 years earlier, and she experienced spontaneous abortion at a gestational age of 4 weeks at the beginning of the disease. A pelvic ultrasound used to confirm the nature of the second pregnant event before the abortion showed an intrauterine gestational sac without the primary tumor, which may exclude molar pregnancy and uterine gestational choriocarcinoma. In addition, she reported experiencing regular menstruation with normal interval and duration before presentation. Taken together, these findings indicate that choriocarcinoma was more likely to have been associated with the term pregnancy 5 years earlier, although the possible association with the second pregnancy event cannot be excluded. Although the origin of this tumor is not clear, it may be resolved by DNA studies of the patient's child and the tumor.

In our case, the score of the Prognostic Scoring Index modified by the WHO was 9, which comprised 2 points for a term pregnancy, 4 points for >12 months from the index pregnancy, 1 point for tumor size, 1 point for renal metastasis, and 1 point for two metastases identified. This score is considered high risk. Patients with nonmetastatic (Stage I) and low-risk metastatic (Stages II and III, score < 7) GTN are recommended to receive single-agent chemotherapy, with resulting survival rates approaching 100%. Patients classified as having high-risk metastatic disease (Stage IV and Stages II or III with a score > 7) should be treated more aggressively with multiagent chemotherapy and adjuvant radiation or surgery, which may achieve cure rates of 80–90% [10]. Despite these recommendations, single-agent chemotherapy was applied because of the low total hCG concentration and the desire to preserve renal function. However, single-agent therapy failed, as shown by the increasing total hCG concentration.

Two similar cases of gestational choriocarcinoma with renal and pulmonary metastases have been reported in the recent literature [3,8]. The patients described in the two earlier cases and our patient were of reproductive age, were classified as having high-risk metastatic disease, and had received nephrectomy followed by postoperative chemotherapy. The patient mentioned by Vereczkey et al [3] received four cycles of multiagent chemotherapy with the BEP regimen (bleomycin, 30 mg/m^2; etoposide, 100 mg/m^2; cisplatin, 20 mg/m^2) and had a complete remission after the treatment. Karadeniz et al [8] reported on a patient who had received methotrexate-based chemotherapy, but the authors did not mention the detailed regimen or the patient's post-treatment outcome. In our case, the single-agent chemotherapy treatment failed.

A 2011 article in the “American Journal of Obstetrics and Gynecology” mentioned that one of the most common reasons for unsuccessful GTN treatment is the use of single-agent chemotherapy for patients with high-risk disease [10], which is consistent with the case presented here. In the treatment of our patient, the single-agent chemotherapy was replaced by multiagent therapy

using the EMACO regimen. Although this regimen appeared to be effective after two courses, the total hCG concentration rebounded in the third course, raising suspicion of drug resistance, and the multiagent chemotherapy was shifted to the EMAEP platinum-based regimen.

In Taiwan, there is no available statistical information regarding the incidence of gestational or nongestational choriocarcinoma. According to the statistical reports of the Health Promotion Administration, Ministry of Health and Welfare, in Taiwan, the average crude cancer incidence rate of choriocarcinoma (without age adjustment) from 2000 to 2010 was 0.12 per million in males and 1.27 per million in females.

In summary, we report a rare case of gestational choriocarcinoma with renal and pulmonary metastases lacking a primary uterine origin after a previous gestational event 5 years earlier. The only symptoms that helped in the diagnosis were refractory hematuria. The possibility of choriocarcinoma should be considered for women of reproductive age exhibiting unexplained hematuria.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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