

Primary non-gestational pure choriocarcinoma arising in the ovary: A case report and literature review

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Abstract. Pure non-gestational choriocarcinoma is a primary germ cell neoplasm that has been defined as a tumor without other germ cell elements. The current study presents an extremely rare case of non-gestational pure choriocarcinoma in a postmenarcheal young female and describes details of the tumor, including the clinicopathological findings. The patient was a 10-year-old female who underwent salpingo-oophorectomy. Histologically, the extensive hemorrhagic tumor was composed of choriocarcinoma without additional germ cell tumor components. The tumor cells were immunohistochemically positive for epithelial markers, including cytokeratins and epithelial membrane antigens, and there was a positive cytoplasmic reaction for β -human chorionic gonadotropin in the syncytiotrophoblasts. Furthermore, numerous tumor cells were immunohistochemically positive for the β 2-microglobulin antibody. The patient received adjuvant cisplatin, etoposide and bleomycin chemotherapy, and is currently disease-free without evidence of recurrence or metastasis subsequent to 62 months of follow-up.

Introduction

A malignant tumor of the ovary with trophoblastic differentiation may be a gestational or non-gestational choriocarcinoma and may be a primary tumor or a metastasis from other organs. Predominantly, non-gestational choriocarcinoma occurs as a component of a mixed germ cell tumor (1,2).

Pure non-gestational choriocarcinoma is an extremely rare primary germ cell neoplasm, with reports of only a few cases at the time of the present case (3,4). Pure choriocarcinoma has been defined as a tumor that does not include other germ cell tumor elements (1). It is necessary to distinguish between cases of non-gestational or gestational choriocarcinoma of the ovary, as cases of non-gestational choriocarcinoma have a poorer prognosis compared with gestational cases, and the treatment regimen for the two diseases differs. In general, the non-gestational type has only been clinically diagnosed in patients who were sexually immature, unable to conceive or had never had sexual intercourse (5). In the absence of clinical information, it is difficult to differentiate the two diseases morphologically. The current study reports a rare case of non-gestational pure choriocarcinoma in a postmenarcheal young female and describes details of the tumor, including the clinicopathological findings. Furthermore, a differential diagnosis between non-gestational and gestational choriocarcinoma of the ovary, based on immunohistochemical differences, is discussed. Consent was obtained from the family of the patient.

Case report

In June 2004, a 10-year-old Japanese female presented to Dokkyo University School Hospital (Tochigi, Japan) with abdominal pain and a mass. The patient had experienced diarrhea alternating with constipation and low-grade fever for the previous two months. Furthermore, weight loss of 8 kg had been exhibited over the previous three months, with decreased food intake. The patient experienced the first menarche six months prior to presenting, and the periods of menstruation were irregular. The medical history and the family history were non-contributory.

Upon physical examination, an uneven, firm mass (20 cm in diameter) was palpable in the abdomen. The remaining systemic examination was unremarkable. The serum β -human chorionic gonadotropin (hCG) and serum α -fetoprotein levels were 6,600 ng/ml (normal, <0.1 ng/ml) and <5 ng/ml (normal, <10 ng/ml), respectively. Magnetic resonance imaging showed the pelvic mass, which exhibited

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Table I. Clinicopathological characteristics of 32 cases of non-gestational pure ovarian choriocarcinoma.

Variable	Value
Mean age, years	13.8±4.2
Duration of abdominal pain, weeks	3-16
Side, %	
Right	68
Left	32
Stage, %	
I	49
II	17
III	17
IV	17
Surgery, %	
UO/SO	71
AH+BSO	20
BSO	4
hCG, mU/ml	0.034-200,000
Pregnancy test, n	5
Treatment, n	
Bone marrow transplant	2
Chemotherapy	
Methotrexate-based	11
Vinblastin, bleomycin and cisplatin	3
Cisplatin, etoposide and bleomycin	3
Outcome, %	
Succumbed	35
Alive	65

UO/SO, unilateral oophorectomy/salpingo-oophorectomy; hCG, human chorionic gonadotropin; BSO, bilateral salpingo-oophorectomy; AH, abdominal hysterectomy.

high intensity with a septal structure on T1-weighted images and irregular high intensity on T2-weighted images, with peripheral enhancement for gadolinium-diethylenetriamine pentaacetic acid.

The patient was diagnosed as having an ovarian tumor and underwent a celiotomy. Intraoperatively, bloody ascitic fluid was observed in the peritoneal cavity, together with a dark red fudge-like and fragile 18x15x10-cm mass, weighing 1,110 g and involving the right ovary. A small number of tumor nodules were disseminated in the Douglas pouch. The intra-peritoneal fudge-like mass was macroscopically resected by right salpingo-oophorectomy.

Upon gross inspection, the mass predominantly consisted of hemorrhagic coagulation necrosis, however, viable areas were observed in certain regions of the tumor (Fig. 1). Histological specimens were randomly prepared from 80 sections taken from various sites, followed by routine staining and

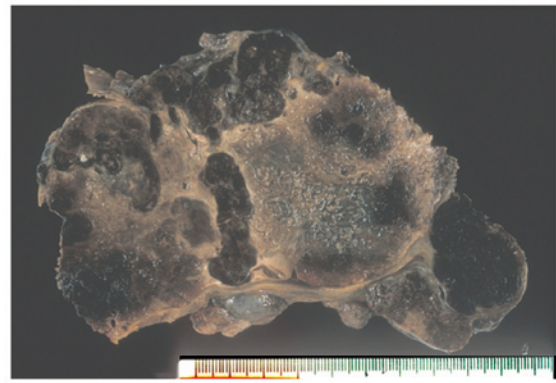


Figure 1. Fudge-like and fragile mass revealing extensive hemorrhagic necrosis.

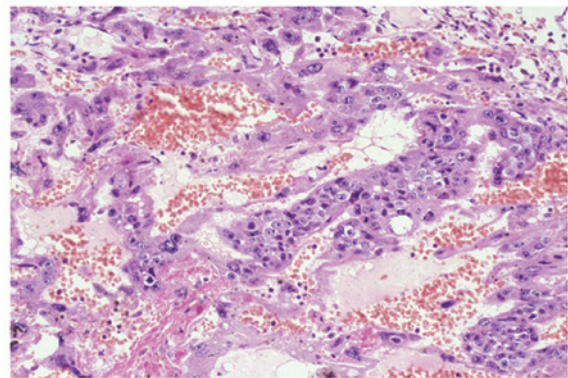


Figure 2. Tumor showing the biphasic appearance of mononuclear cytotrophoblasts and multinucleated syncytiotrophoblasts with hemorrhage.

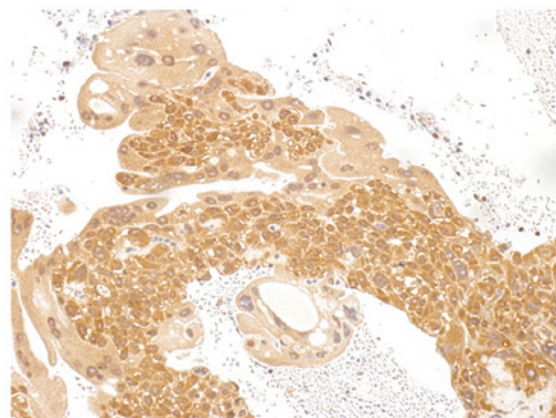


Figure 3. Positive immunoreactivity for β2-microglobulin in the cytotrophoblast and syncytiotrophoblast tumor cells.

immunohistochemistry. Microscopically, viable tumor cells were present in the periphery of the mass and were aggregated with one another. The tumor cells were characterized by an intimate admixture of two cell types, mononuclear and multinuclear giant cells, which occasionally exhibited a plexiform pattern. The mononuclear cells were medium in size, polygonal or round, with clear or amphophilic cytoplasm, and exhibited a well-defined cell border. The nuclei of these cells were round and hyperchromatic, with conspicuous nucleoli. Numerous

mitotic cells were observed. These findings indicated cytotrophoblastic cells. Conversely, the multinuclear giant cells varied in shape and size, and were irregularly-shaped cells with abundant dense amphophilic or vacuolated cytoplasm, and multiple hyperchromatic nuclei without mitosis. These multinuclear cells were regarded as syncytiotrophoblasts (Fig. 2). No evidence of other germ cell elements or chorionic stroma was observed. Immunohistochemically, although positive cytoplasmic staining was observed in the syncytiotrophoblasts for β -hCG (rabbit polyclonal antibody; Nichirei, Tokyo, Japan), no reaction was observed in the cytotrophoblasts. Additionally, positive staining was observed for epithelial markers, such as cytokeratin AE1/AE3 (AE1+AE3; Dako, Carpinteria, CA, USA) and epithelial membrane antigen (E29; Dako) in the two cell types. Furthermore, the cells were also histochemically positive for the β 2-microglobulin (BMG) antibody (rabbit polyclonal antibody; Dako) (Fig. 3).

One week after surgery, the patient received three cycles each lasting three weeks, of chemotherapy: cisplatin (33 mg/m², days 1-3), etoposide (167 mg/m², days 1-3) and bleomycin (15 U/m², day 1) (PEB). The post-therapeutic period was favorable, with no major complications. The serum hCG level returned to normal (0.1 ng/ml) five months after the PEB chemotherapy. Furthermore, the patient is currently disease-free without evidence of recurrence or metastasis subsequent to 62 months of follow-up.

Discussion

Two forms of ovarian choriocarcinoma, gestational and non-gestational, have been reported. Gestational choriocarcinoma of the ovary may be the result of metastasis from a uterine trophoblastic disease, or, rarely, it may follow an ovarian pregnancy. The non-gestational type is a primary germ cell neoplasm differentiating along the extraembryonic chorionic tissue. The majority of the tumors occur in combination with other germ cell neoplasms. Pure choriocarcinoma of the ovary has been defined as a tumor that occurs in the absence of all other germ cell tumors. No additional components of germ cell tumors were found in association with the present tumor. Furthermore, the α -fetoprotein levels were normal. Pure ovarian choriocarcinoma is extremely rare (1,2), and based on an extensive search of the English literature, it can be observed that only a few cases of this type of choriocarcinoma have been previously described (Table I) (3,4). This tumor most commonly occurs in young individuals, and ~50% of cases are identified at a relatively early stage. In addition, in ~66% of patients chemotherapy improves prognosis.

The present case exhibited the required pathological characteristics, as described in the previously reported cases, to determine a diagnosis of pure choriocarcinoma (1). No other carcinomatous or germ cell tumor elements were identified in addition to the trophoblastic cells. Furthermore, the histological examination revealed no similar tumors in other organs. However, it was difficult to determine morphologically whether the case was a non-gestational or gestational tumor. The majority of studies have suggested that the diagnosis of pure non-gestational choriocarcinoma should be limited to premenarcheal patients (1-3,5).

Differentiation between non-gestational and gestational choriocarcinoma is required, as the chemotherapy and prognosis differ for the two tumor types. A study of the tumor characteristics has been previously performed *in vitro* by the genetic analysis of cell lines. Tanaka *et al* (6) reported a lack of effective messenger RNA for BMG in gestational human choriocarcinoma cell lines, as well as the presence of messenger RNA for BMG in non-gestational choriocarcinoma. Several previous studies have also investigated the high expression levels of BMG in choriocarcinoma. Kato *et al* (7) investigated choriocarcinoma cells that produced moderate amounts of surface and secreted BMG. Norman *et al* (8) also reported that the serum BMG level was elevated in patients with choriocarcinoma. The study indicated that BMG may be clinically used as a serum marker for this disease. In the present study, BMG was detected in each of the two types of tumor cells using immunohistochemistry. By contrast, there have been no previous studies to immunohistochemically confirm the expression of BMG in the trophoblastic tumor; to the best of our knowledge, the current case study is the first to present this point. Based on the immunohistochemical findings and previous studies, a diagnosis of primary, pure non-gestational choriocarcinoma of the ovary was suggested. This study indicates that BMG may be clinically used as a serum marker for non-gestational choriocarcinoma in the future. However, the cause of the BMG expression in non-gestational choriocarcinoma remains unclear.

In conclusion, the current study presents a case of primary pure ovarian choriocarcinoma, which was successfully treated with surgery and a PEB regimen. Further pathological and biological techniques for the differentiation of gestational and non-gestational tumors is required for the efficient treatment of choriocarcinoma in the future.

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