Intra-operative cytodiagnosis of primary ovarian choriocarcinoma with Ki67 immunoexpression

ABSTRACT
Primary ovarian choriocarcinoma is a rare neoplasm that can be gestational and non-gestational in origin. It accounts for one in 369 million pregnancies. Both types present with similar clinical, histomorphological and ultrastructural findings. But, it is essential to differentiate the two because the gestational type has a better clinical course and responds to single-agent chemotherapy. Usually, the gestational ovarian choriocarcinoma is metastatic from uterine choriocarcinoma and follows antecedent pregnancy and is seen in females of 40 years or older. DNA polymorphism analysis showing the presence of paternal genes in the tumor establishes the gestational origin of choriocarcinoma. We present the intra-operative cytological findings of a case of primary ovarian choriocarcinoma in a 25-year-old lady arising from ectopic pregnancy with Ki67 immunostain.

Key words: Intraoperative cytology; Ki67; ovarian choriocarcinoma

Introduction
Choriocarcinoma is a highly aggressive malignant human chorionic gonadoprotein-producing neoplasm with usually an intrauterine location and can be gestational or non-gestational in origin.[1] Extrauterine choriocarcinomas are very rare and can be seen in other parts of the female genital tract like fallopian tube, ovary and cervix. The estimated incidence of gestational ovarian choriocarcinoma is one in 369 million pregnancies, associated with coincident or antecedent gestation.[2,3] We report a case of primary gestational ovarian choriocarcinoma in a young lady where the diagnosis was rendered by intra-operative cytology and the proliferative potential was estimated by Ki67 immunohistochemistry.

Case Report
A 25-year-old female presented with pain abdomen and bleeding per vaginum for 25 days. She was febrile and anemic with occasional bouts of vomiting. She had a past history of right-sided ectopic gestation 1 year back. Abdominal examination revealed a soft, non-tender palpable lump in the right iliac fossa. Her hemoglobin level was 8.6 gm%. Her urine tested negative for βhCG and the serum level was slightly increased to 3080 mIU. The chest radiograph was normal. Ultrasonography showed a right-sided tubo-ovarian mass. The ovary was enlarged and showed a hyperechoic heterogeneous mass. The uterus was normal appearing without intrauterine pregnancy or gestational sac. On laparotomy, the right ovary was replaced by a hemorrhagic,
Friable and necrotic mass. The uterus and fallopian tubes were found to be normal. A portion of the ovarian mass was immediately removed for intra-operative cytology. Imprint cytosmears were prepared from the mass and fixed with absolute alcohol and stained with Papanicolaou stain and hematoxylin and eosin (H and E) stain. Two cytopathologists examined the smears, which showed small clusters of pleomorphic and hyperchromatic cells with clear to pale eosinophilic cytoplasm over a hemorrhagic and necrotic background [Figure 1a and b]. Occasional multinucleated giant cells (syncytiotrophoblasts) were also seen. There was conspicuous absence of other cellular elements. Considering the clinical presentation, a provisional diagnosis of choriocarcinoma was given. The patient then underwent total hysterectomy with right-sided salpingo-oophorectomy. We received the gross specimen as cut-opened uterus with cervix and a large hemorrhagic and friable mass. The ovarian mass measured 10 cm × 8 cm × 6 cm. It was grayish white to hemorrhagic and necrotic [Figure 2a]. Sections were taken from different areas of the ovarian mass along with uterine wall and cervix and stained with H&E stain after processing. Histopathology revealed mostly areas of hemorrhage and necrosis with a biphasic tumor tissue comprising of pleomorphic cytotrophoblasts and syncytiotrophoblasts. The sections were also subjected to Ki67 immunostain and were found to be positive with diffuse and intense staining (in more than 50% of cytotrophoblasts) showing high proliferative index of the tumor cells [Figure 2b]. In contrast, the syncytiotrophoblasts were negative for Ki67. The uterine wall showed non-secretory endometrium over unremarkable myometrium. Therefore, a final diagnosis of primary gestational ovarian choriocarcinoma was given.

Discussion

Ovarian choriocarcinoma is a highly malignant tumor characterized by the presence of malignant trophoblastic cells histopathologically and a raised serum βhCG level biochemically. It can be gestational or non-gestational in origin. The distinction between the two is difficult, but necessary, as the non-gestational type has bad prognosis.[4] Most of the ovarian choiocarcinomas are usually gestational. Gestational ovarian choriocarcinomas are commonly metastatic from uterine or fallopian tube lesions. The patients are 40 years or older, present with abnormal uterine bleeding and have a very high serum βhCG level. The above-said patient was a young female of 25 years with a past history of ectopic gestation 1 year back, had a mild increase in the serum βhCG level and had no abnormality in the uterus or fallopian tube. She was treated with methotrexate-based chemotherapy (methotrexate, etoposide and actinmycin-D) and her βhCG level came down to normal after two cycles of chemotherapy, and is doing well till date. Ki67 was applied here to study the proliferative index of choriocarcinoma, which was high (more than 50% of cytotrophoblasts) and also strong in intensity of staining. Also, it can be used to determine the therapeutic response after treatment by comparing with the present index. This can be used as a prognostic indicator in the present case. But, in other situations where the diagnosis is not so straightforward, it can be used to differentiate from other gestational trophoblastic diseases like hydatidiform mole (complete type) and placental site trophoblastic reaction and tumor.

Histomorphologically, it is impossible to differentiate gestational from non-gestational choriocarcinoma. There are no unique ultra-structural or immunohistochemical features to distinguish either of them.[5] DNA polymorphism analysis can be utilized to distinguish pure non-gestational choriocarcinoma of the ovary from gestational choriocarcinoma. Genetic analysis showing whether a paternal contribution is present in the genome or not can be a useful modality in determining the origin of the choriocarcinoma.[6] Human leukocyte antigen typing for paternal antigen in trophoblastic elements can also be used to determine the gestational etiology. Markedly elevated levels of serum human chorionic gonadoprotein levels are commonly found with gestational tumors but
are not very reliable. The majority of patients with non-gestational ovarian choriocarcinoma are younger than 20 years. About 50% of patients demonstrate precocious puberty whose lesions arise prior to menarche. While most gestational choriocarcinomas show hematogenous spread, the non-gestational choriocarcinoma tend to follow the lymphatic system. The staging depends on the original site of the tumor, like for gestational (metastatic or primary) choriocarcinoma — standard choriocarcinoma staging applies and for non-gestational choriocarcinoma — staging is performed by ovarian cancer staging system. Because this patient was a young female presenting with gestational choriocarcinoma of the ovary, she was treated with radical surgery with preservation of contralateral ovary and followed by methotrexate-based chemotherapy.

We are reporting this case as it is rare and also because one should be aware of the cytologic findings of choriocarcinoma so as to give a correct diagnosis during operation to help the surgeons in the proper management of such lesions.

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Conflicts of interest
There are no conflicts of interest.

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