Primary Bilateral Ovarian Choriocarcinoma in a 33-year-old, G3P3(3003) Female: A Case Report

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ABSTRACT

This is a case of a 33-year-old, G3P3(3003) female patient with a clinical presentation of vaginal bleeding associated with on and off hypogastric pain. The patient was diagnosed and managed as a case of tubo-ovarian abscess and subsequently underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO). Microscopic sections of both ovaries, however, showed dual population of tumor cells composed of medium-sized, mononucleated cells admixed with multinucleated giant cells with marked pleomorphism, extensive hemorrhage and necrosis. Immunohistochemistry studies using beta-hCG was diagnostic of ovarian choriocarcinoma, favoring non-gestational in origin. Classification of non-gestational choriocarcinoma (NGOC) was established using diagnostic criteria for NGOC established by Saito et al., and Mangla et al. DNA analysis, however, remains to be the gold-standard for differentiating between gestational (GOC) and non-gestational (NGOC) etiology.

Key words: choriocarcinoma, germ cell malignancy, ovary, non-gestational

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INTRODUCTION

Ovarian choriocarcinomas are highly aggressive form of ovarian malignancy composed of trophoblastic cells, which are broadly classified into gestational and non-gestational subtypes.[1–5] While gestational choriocarcinoma (GOC) arise from molar or ectopic pregnancies, non-gestational choriocarcinoma (NGOC) can develop independently within the ovary without prior gestational event, often arising from malignant germ cell tumors or high grade somatic carcinomas.[3,4,6] Both forms are exceedingly rare, with a reported prevalence of 1 in 5,335 ovarian pregnancies for gestational choriocarcinoma and 1 in 369 million ovarian carcinomas for non-gestational choriocarcinoma in Eastern countries.[6] Collectively, ovarian choriocarcinoma account for less than 5% of all ovarian malignancies in Western population[4] with prevalence of non-gestational origin at <1%.[7,8] In the Philippines, the prevalence of ovarian choriocarcinoma remains unknown due to its extreme rarity, with only seven documented cases reported locally.[9]

The clinical manifestations of these tumors are similar regardless of origin, often nonspecific, with most common symptoms being abnormal vaginal bleeding in 89-97% of cases, and abdominal or pelvic pain in 39-54%.[2-5] Adult patients may present with symptoms related to ectopic pregnancy, whereas prepubertal children, may present with symptoms of precocious puberty.[2,3,6,7,10] The nonspecific nature of these symptoms may ultimately lead to a misdiagnosis preoperatively.[4] A markedly elevated serum β-hCG levels may aid clinicians in the diagnosis.[11]

Imaging studies using transvaginal ultrasound may yield nonspecific results while pelvic ultrasound may show highly vascular, echogenic non-homogenous mass with a normal uterus. Further imaging studies using CT scans may aid in evaluating the disease and determine presence of other hemorrhagic lesions.[7]

Grossly, ovarian choriocarcinomas typically present as unilateral, large, solid, hemorrhagic masses with extensive necrosis,[2,9] and bilateral ovarian involvement are exceedingly rare occurrence.[7] Histologically, these tumors are composed of mononucleated trophoblastic cells (cytotrophoblasts and intermediate trophoblasts) with clear cytoplasm, admixed with multinucleated syncytiotrophoblastic cells characterized by bizarre nuclei and abundant amphophilic cytoplasm. Tumor cells frequently form solid sheets and may occur as pure choriocarcinomas or in combination with other germ cell elements.[1-3,5,9,10] In the event of a mixed histology, the other germ cell elements typically surround the choriocarcinomatous elements resulting in small nodules that are associated with hemorrhage,[2] a feature that is not observed in this case.

Immunohistochemistry staining with beta-hCG, may provide a definitive diagnosis of choriocarcinoma.[1,2] Other IHC studies with CD30, PLAP, SALL4 and AFP may also aid in demonstrating the presence of other germ cell elements.[7]

Identification of these tumors is of utmost importance due to its aggressive nature and high metastatic potential.[1–5] Furthermore, distinguishing these neoplasm between its origin is crucial due to the difference in prognosis, management approach and treatment outcomes with gestational choriocarcinoma (GOC) having a more favorable prognosis and response to treatment.[6,10] In contrast, non-gestational choriocarcinoma (NGOC) is associated with a higher metastatic potential, poorer prognosis and a more aggressive clinical course, often requiring multi-drug therapy.[3,7]

This case report underscores the critical need to maintain an index of suspicion for malignant etiologies, even in the face of benign clinical and radiological findings; and highlights the importance of employing appropriate ancillary studies, such as tumor markers, immunohistochemistry, and molecular studies, to accurately diagnose rare and aggressive malignant tumors. Moreover, this case exemplifies the challenges posed by diagnostic limitations in the practice of pathology in a resource-constrained setting.

CASE

This case involves a 33-year-old, G3P3(3003) female who presented with a chief complaint of vaginal bleeding four months prior to admission, accompanied by intermittent hypogastric pain. Persistence of symptoms prompted the patient for consult at the obstetrics and gynecology department.

Initial imaging study using transvaginal ultrasound revealed a 2.4 x 2.0 x 2.0 cm unilocular cyst containing low-level echogenic fluid with a reticular pattern, along with an adherent 6.8 x 4.9 x 5.45 cm complex mass, including a solid area measuring 5.8 x 4.8 x 3.7 cm. The ultrasound impression suggested a tubo-ovarian abscess.

A review of the patient's laboratory results showed a positive serum pregnancy test with elevated serum beta-hCG at 541,149.90 mIU/mL (reference range: 1.2–5.0 mIU/mL), cancer antigen 125 (CA-125) at 199 U/mL (reference range: 0–35 U/mL), and lactate dehydrogenase (LDH) at 361 U/L (reference range: 120–246 U/L). Other laboratory results were unremarkable.

The patient was admitted as a case of tubo-ovarian abscess and subsequently underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO).

On gross examination, a previously sectioned TAHBSO specimen (Figure 1) was received with a highly irregular, poorly defined adnexa and enlarged right and left ovaries measuring 8.5 x 7.5 x 5.5 cm and 5.0 x 5.0 x 2.5 cm, respectively. The cut section of both ovaries shows a dark-brown, heterogenous, solid, hemorrhagic cut surface with extensive necrosis. Fallopian tubes were unidentifiable grossly (Figure 2).

Microscopic sections of both ovaries revealed extensive hemorrhage and necrosis with tumor cells arranged in sheets, composed of medium-sized, mononucleated cells with open coarse chromatin and clear cytoplasm, admixed with multinucleated giant cells with abundant, vacuolated, somewhat basophilic cytoplasm with marked pleomorphism (Figure 3). Also observed were bizarre mitotic figures and increased mitotic activity. Gross and microscopic sections of the uterine cervix and uterine corpus were unremarkable.

The primary diagnosis for this case was ovarian choriocarcinoma, with the following differential diagnoses: high-grade serous carcinoma, high-grade endometrioid carcinoma, and malignant germ cell tumors.[2,12-14]

Immunohistochemical analyses demonstrated the following findings: strong, diffuse cytoplasmic expression of beta-hCG; strong, diffuse membranous expression of CK7 in neoplastic cells; focal positive cytoplasmic expression of inhibin; and focal, weak positive nuclear expression of SALL4. No expression was observed for p53, WT1, PAX8, ER, CD30, and AFP (Figure 4).

The strong, diffuse, cytoplasmic expression on beta-hCG confirms the trophoblastic composition of the neoplastic cells. This result is also supported by the focal positive expression of inhibin. The diffusely membranous expression of CK7 indicates that the tumor cells originated in the female genital tract.

The lack of observed expression using p53, WT1 and PAX8, on the other hand, rules out high-grade serous carcinoma as a diagnosis. High-grade endometrioid carcinoma was ruled out due to non-expression of neoplastic cells on PAX8 and ER. Furthermore, malignant germ cell tumor was also ruled out due to negative staining on CD30 and AFP, as well as weak, focal positive expression on SALL4. In a study by Mei et al., SALL4 exhibits strong expression in all cases of dysgerminoma, embryonal carcinoma, and yolk sac tumors, but only shows weak to focal staining in 1 out of 3 choriocarcinoma cases with no expression observed on the remaining 2 cases.[15,16]

Elevated serum beta-human chorionic gonadotropin (beta-hCG) levels are a hallmark of choriocarcinoma.[1-5,7,8] And

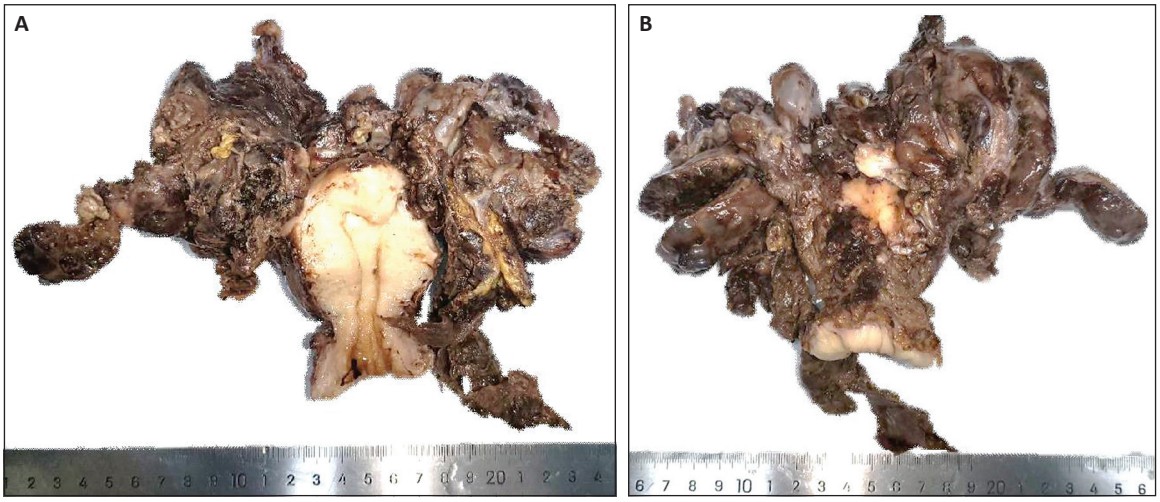

Figure 1. Gross appearance of the TAHBSO specimen. **(A)** Anterior view of the previously sectioned specimen with prominent bilateral hemorrhagic and irregularly enlarged adnexae. **(B)** Posterior view of the specimen.

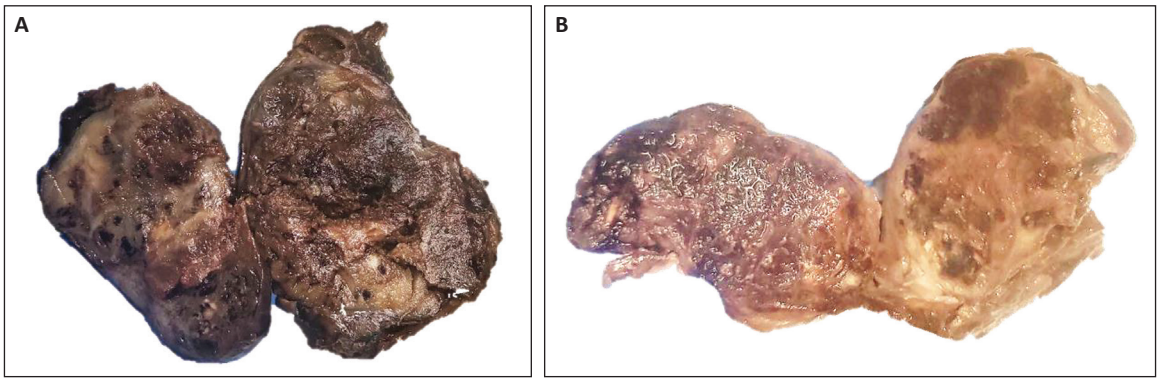

Figure 2. Cut sections of the right **(A)** and left **(B)** ovaries showing a dark-brown heterogenous, solid cut surface with extensive hemorrhage and necrosis.

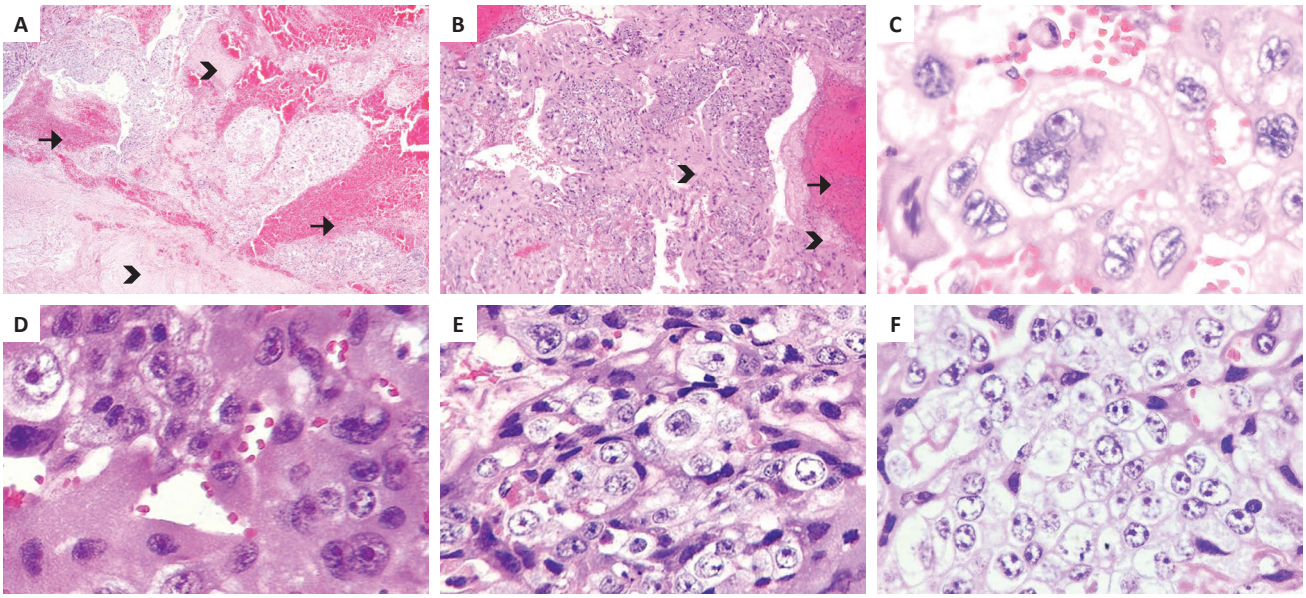

Figure 3. Representative microscopic sections of the right **(A, C, and E)** and left **(B, D, F)** ovaries, respectively. **(A)** and **(B)** show tumor cells in sheets with intervening extensive necrosis *(arrowhead)* and hemorrhage *(arrow)* (H&E, 40x). **(C)** and **(D)** show multinucleated cells with markedly pleomorphic nuclei, irregular cellular outline, open chromatin, prominent nucleoli and vacuolated, eosinophilic to amphophilic cytoplasm (H&E, 400x). **(E)** and **(F)** show medium-sized, mononucleated cells with open chromatin, prominent nucleoli, open chromatin and clear eosinophilic cytoplasm; also noted hyperchromatic nuclei and bizarre mitotic figures (H&E, 400x).

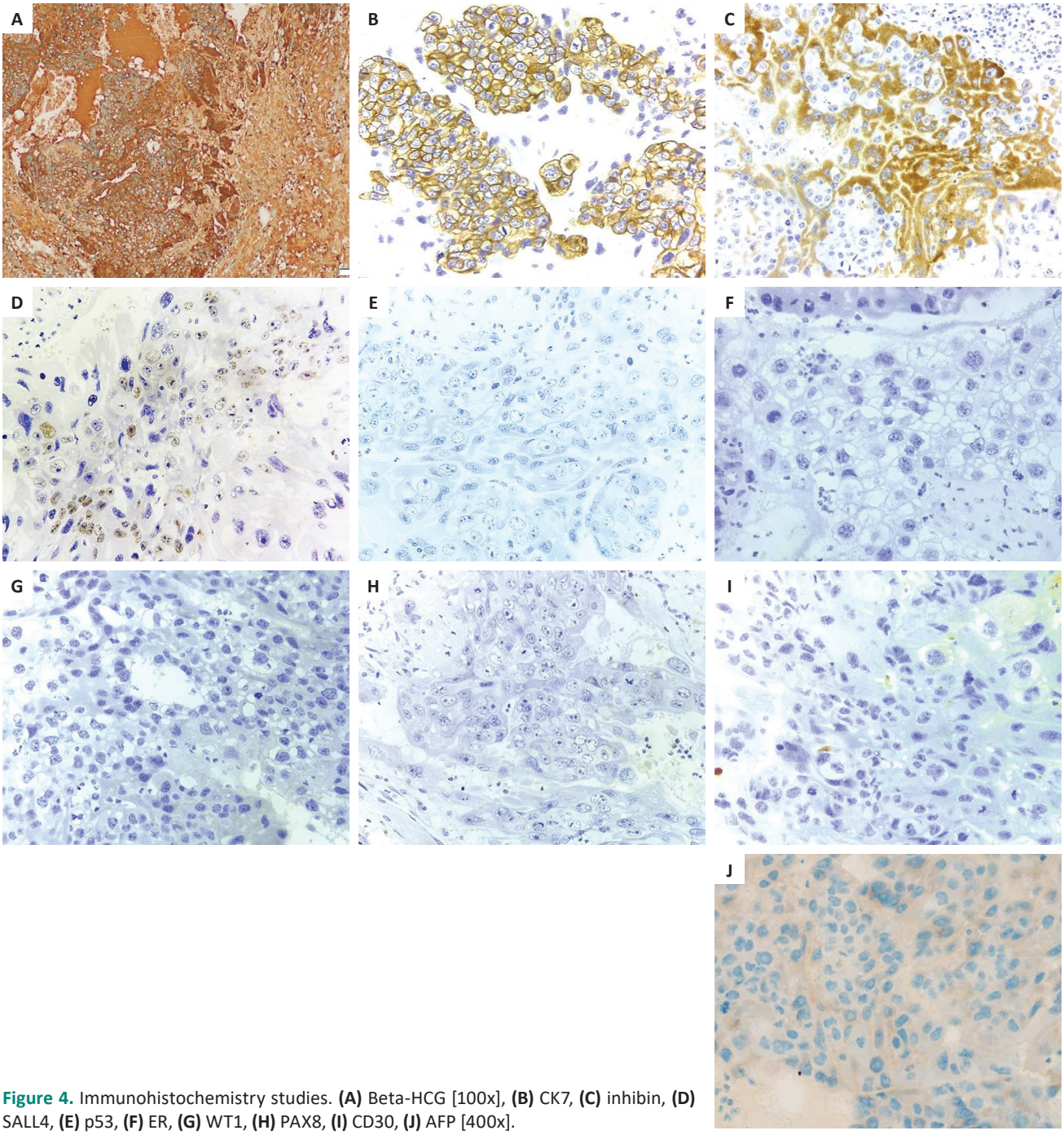

Figure 4. Immunohistochemistry studies. **(A)** Beta-HCG [100x], **(B)** CK7, **(C)** inhibin, **(D)** SALL4, **(E)** p53, **(F)** ER, **(G)** WT1, **(H)** PAX8, **(I)** CD30, **(J)** AFP [400x].

while this phenomenon may be observed in other ovarian malignancies, such as high-grade serous carcinoma,[13] dysgerminoma with syncytiotrophoblast, and embryonal carcinoma,[2] values exceeding 100,000 mIU/mL are highly suggestive of choriocarcinomatous etiology.[11]

Based on the careful consideration of the patient's clinical presentation, gross findings of the specimen, histomorphologic features and immune profile, a diagnosis of bilateral ovarian choriocarcinoma was established.

A metastatic work-up was conducted after the release of the final immunohistochemistry results using CT-scan showing no other lesion or mass, radiographically, indicating that the tumor is primary ovarian in nature. The patient was scheduled for completion surgery and further management; however, the patient was lost to follow-up.

Another dilemma posed by this case was the classification between gestational and non-gestational etiology, due to current unavailability of DNA analysis in the country. Nevertheless, this case most likely favors non-gestational etiology, due to the following salient features: no past or present history of abortion, molar or ectopic pregnancy, absence of corpus luteum microscopically, absence of disease in the uterus and other parts of the female genital tract, absence of neoplasm in the midline structures and the absence of other somatic malignancies.

DISCUSSION

Non-gestational choriocarcinoma is an exceedingly rare ovarian malignancy accounting for less than 0.6% of malignant ovarian germ cell tumors[7] and less than 1% of all ovarian neoplasm.[8] Gestational and non-gestational choriocarcinomas share identical histomorphologic features, clinical presentations, and immuno-profiles, making the differentiation between the subtypes a diagnostic conundrum. Detection of a corpus luteum microscopically, can aid in diagnosis, wherein, when observed, indicates the tumor to be of gestational in origin,[6,7,10] meanwhile, absence of trophoblasts in the uterus is suggestive of non-gestational origin.[5] Other factors to consider are the age of onset, history of molar pregnancy, history of ectopic or presence of current intrauterine pregnancy.[5-7,10]

Non-gestational choriocarcinoma is more likely to occur in prepubertal children, younger reproductive age women,[7] or postmenopausal women[2] with a mean age of diagnosis at 12 to 25 years old.[7] Distinguishing GOC and NGOC in women in reproductive age, however, may be considerably difficult, given the sexual and obstetric history.[2,7]

To further aid in distinguishing the origin of these tumors, a diagnostic criteria was established, by Saito et al., in 1963[17] based on the patient's detailed history, as follows: (1) absence of disease in the uterine cavity; (2) pathological confirmation of choriocarcinoma with the persistence of elevation in beta-HCG; (3) exclusion of history or current diagnosis of molar pregnancy; and (4) exclusion of coexisting intrauterine pregnancy.[7] This diagnostic framework was further expanded by Mangla et al., in 2023.[3] In Mangla et al.,'s criteria, germ cell origins were further classified into gonadal and extra-gonadal tumors. The criteria for gonadal or primary ovarian tumors shared similar criteria to those established by Saito et al., while extra-gonadal tumors, which are typically found to arise from midline structures have the following minimum diagnostic criteria: 1) radiographic evidence of a midline tumor; 2) no prior history of ovarian malignancy; and 3) elevated serum beta-hCG levels. Additionally, Mangla et al., also included criteria to determine non-germ cell origins arising from other somatic malignancies, as follows: 1) the presence of malignancy in other parenchymal locations, including the lungs, liver, or uterus, and 2) pathologic confirmation of a somatic malignancy (Figure 5).

The exact pathogenesis of ovarian choriocarcinoma remains unclear;[3,4,16] however, recent studies have identified specific genetic alterations. In gestational choriocarcinoma, overexpression of *TP53*, *CDKN1A*, *RB1*, *EGFR*, *ERBB2*, *c-MYC*, *BCL2*, *NANOG*, and *H19* genes has been observed, along with downregulation of *NECC1*, *TIMP3*, *DOC-2/hDab2*, *RASSF1A*, *CDKN2A*, *CDH1*, *IGF2*, *OCT4*, and *SOX2*. Additionally, genetic aberrations such as deletion of 7p12–7q11.2, amplification of 7q21–q31, and loss of 8p12–21 have been implicated. In contrast, non-gestational choriocarcinoma is associated with gain of 12p and overexpression of *p53*, *CGB5*, *CGA*, *NANOG*, *STELLA*, and *GDF3* genes.[3,7,18-20] Another study showed variations in the copy number, as well as significant amplifications of Her2, IKZF3, PGAP2 and c-Myc, in non-gestational ovarian choriocarcinoma which are not demonstrated in the gestational counterpart. These genes are believed to cause poorer immunogenicity of NGOC, contributing to a poor response to chemotherapy.[9]

Non-gestational choriocarcinoma is associated with a poorer prognosis and a more aggressive clinical course, often requiring multi-drug therapy.[3] Due to the aggressive nature and rapid growth of NGOC, metastasis occurs early. A review of 39 NGOC cases showed that 80% of patients had metastasis to the lungs, 30% to the pelvis, 20% to the vagina, and 10% to the liver. Furthermore, the overall survival rate of NGOC significantly drops to 25% over 3 years at FIGO stage IV compared to 100% for FIGO stages I, II and III.[7] Nevertheless, chemotherapy regimens containing cisplatin, such as the combination of cisplatin, etoposide, and bleomycin (PEB), have shown promising improvements in survival and prognosis of non-gestational choriocarcinoma.[2,7]

While diagnostic criteria may aid in the diagnosis of NGOC, definitive differentiation between the origins relies on paternal DNA analysis.[1-5,7,8] In this case, however, due to the unavailability of DNA testing, both diagnostic criteria were utilized to determine this case to be Non-gestational, primary ovarian in origin.

CONCLUSION

This report examines a case of primary bilateral ovarian choriocarcinoma in a 33-year-old, G3P3(3003) female patient who was initially diagnosed and managed as a case of tubo-ovarian abscess and benign ovarian neoplasm.

This case presented a diagnostic dilemma due to its rarity and the discrepancy between clinical diagnosis and microscopic findings. The strong, diffuse cytoplasmic immunoreactivity of beta-hCG confirms the trophoblastic composition of the neoplastic cells establishing the diagnosis of ovarian choriocarcinoma. Due to the unavailability of paternal DNA analysis, the non-gestational origin was determined through a comprehensive review of the literature using diagnostic criteria established by Saito et al., and Mangla et al., Nonetheless, DNA testing remains to be the gold standard for the diagnosis of non-gestational ovarian choriocarcinoma, indicating a need for molecular advancement in the country.

This case further underscores the significance of histological assessment of surgical specimens and the utilization of different diagnostic modalities, alongside a comprehensive review of the relevant literature to establish a pathologic diagnosis.

ETHICAL CONSIDERATIONS

Patient consent was obtained before the submission of the manuscript.

STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

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