Case Report

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Clinicopathological analysis of nongestational ovarian choriocarcinoma: A case report and review of literature

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Abstract:

Nongestational ovarian choriocarcinoma (NGOC) is a sporadic and aggressive malignant germ cell tumor, with fewer than 100 cases reported in the literature. We present the case of a 28-year-old woman diagnosed with NGOC, who underwent fertility-sparing surgery and adjuvant bleomycin, etoposide, and cisplatin chemotherapy, followed by a recurrence managed with the second-line chemotherapy and radiotherapy. This report highlights the diagnostic challenges, unique β-human chorionic gonadotropin profile, disease course, and treatment response.

Keywords:

Germ cell tumor, nongestational choriocarcinoma, ovary

Introduction

Ovarian germ cell tumors are rare, accounting for 1%–2% of ovarian malignancies.[1,2] According to the World Health Organization classification, they arise from germ cells or sex-stromal derivatives [Figure 1].

Ovarian Choriocarcinoma, an extremely rare subtype, is classified as gestational ovarian choriocarcinoma (GOC) or nongestational ovarian choriocarcinoma (NGOC). GOC is linked to ectopic pregnancy or metastasis from uterine or tubal choriocarcinoma, while NGOC arises from the germ cells with trophoblastic differentiation and is unrelated to pregnancy. NGOC may be pure or mixed with other germ cell elements, comprising <0.6% of germ cell tumors.[3] It typically affects young women, is highly aggressive, and lacks established treatment guidelines. Due to its rarity, standardized treatment guidelines are lacking. We report the case of a 28-year-old nulligravid diagnosed with NGOC, including diagnostic challenges, unique β-human chorionic gonadotropin (hCG) profile, disease course, and treatment response.

Case Report

A 28-year-old nulligravid woman with regular menses presented with a 3-month history of abdominal bloating, enlargement, and intermittent pain. She had no comorbidities, prior surgeries, or relevant personal, family, social, or sexual history. A transvaginal ultrasound revealed a normal uterus and right ovary with multiple follicles. The left ovary was replaced by a unilocular solid cystic mass measuring 27.9 cm × 24.8 cm × 15.6 cm, with a color score of 3, suggesting high vascularity. The International Ovarian Tumor Analysis Assessment of Different NEoplasias in the adneXa (IOTA-ADNEX) model estimated a 42.6% risk of malignancy. No preoperative tumor markers were obtained.

The patient underwent fertility-sparing laparotomy, including left salpingo-

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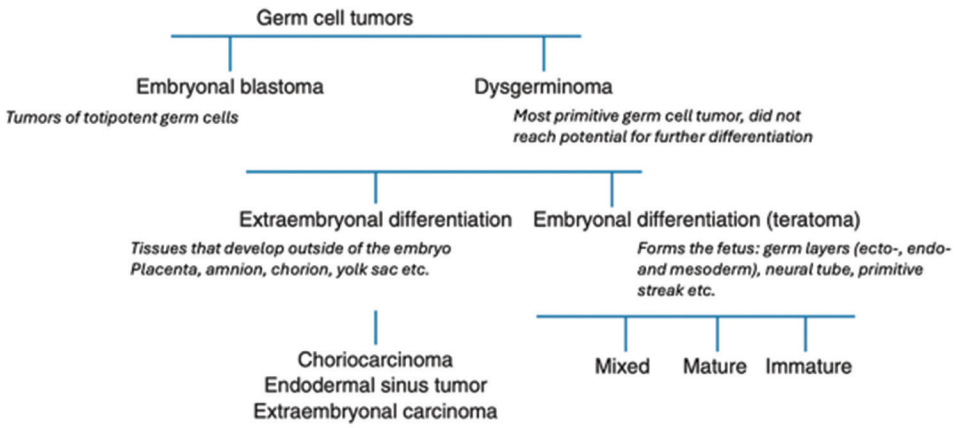


Figure 1: Classification schema of germ cell tumors of the ovary

oophorectomy, omentectomy, random peritoneal biopsies, and pelvic and para-aortic lymph node sampling. Intraoperatively, 100 cc of clear ascitic fluid was aspirated, and a large cystic left ovarian mass measuring 27.0 cm × 21.0 cm × 11.0 cm [Figure 2] and a grossly normal uterus and right adnexa were noted [Figure 3]. No residual macroscopic disease remained postoperatively.

Histopathological analysis of the ovarian mass revealed solid sheets of atypical round to spindle-shaped tumor cells, with surrounding hemorrhage and necrosis observed. Mitoses, including atypical forms, were present [Figure 4a and b]. Differential diagnoses included germ cell tumor, poorly differentiated carcinoma, and carcinosarcoma. All other surgical specimens, including peritoneal biopsies, omentum, lymph nodes, and fallopian tube, tested negative for malignancy. Immunohistochemistry (IHC) indicated tumor cells positive for hCG [Figure 5b], epithelial membrane antigen (EMA), and vimentin, but negative for OCT4 [Figure 5a], SALL4 [Figure 6a and b], Placental Alkaline Phosphatase (PLAP), Cluster of Differentiation 117 (CD117), and Carcinoembryonic antigen (CEA). These findings confirmed the diagnosis of nongestational choriocarcinoma.

Postoperatively, serum tumor marker levels were as follows: cancer antigen −125 at 20.4 U/mL, β-hCG at 14.96 mIU/mL, lactate dehydrogenase (LDH) at 198 U/L, and alpha-fetoprotein (AFP) at 1.2 ng/mL. The patient received four cycles of bleomycin, etoposide, and cisplatin (BEP) every 21 days. She tolerated chemotherapy well, experiencing no grade 3/4 toxicities. After the fourth cycle, β-hCG declined to 2.55 mIU/mL. Tumor marker levels remained stable, and she was monitored every 3 months.

At 12 months' postchemotherapy, the patient reported low back pain and hemoptysis. Computed tomography (CT) imaging revealed bilateral pulmonary nodules, para-aortic lymphadenopathy, and osseous lesions at T8 and the right iliac region. Surprisingly, β-hCG levels remained low (<1.2 mIU/mL) [Table 1]. CT-guided biopsy of a para-aortic lymph node

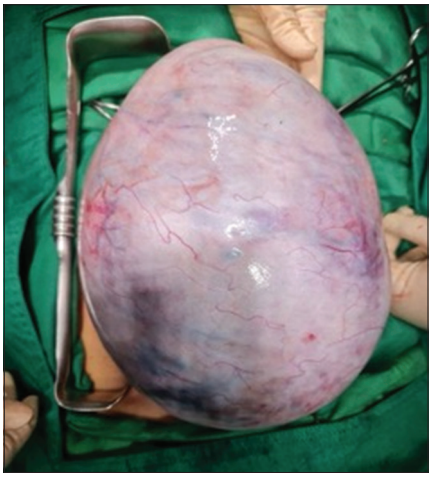


Figure 2: Ovarian new growth, left

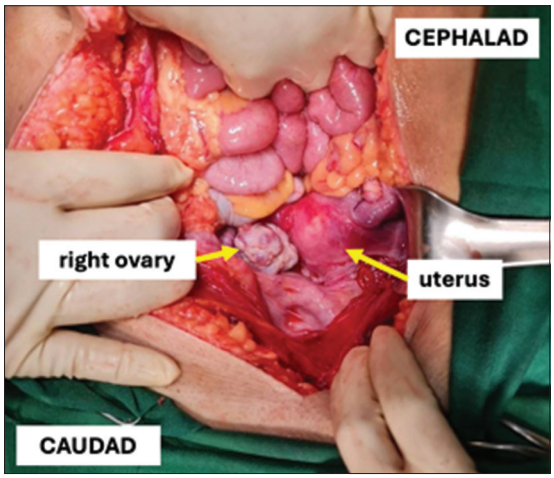


Figure 3: Grossly normal uterus and right ovary

revealed malignant round cells consistent with metastatic choriocarcinoma, morphologically similar to the original ovarian tumor [Figure 7a and b]. She was started on the second-line chemotherapy with Paclitaxel-Carboplatin every 21 days for 12 cycles, and received intensity-modulated radiotherapy (IMRT) to the para-aortic and osseous lesions. Zoledronic acid was initiated for bone metastases.

Posttreatment positron emission tomography (PET)/CT scan showed overall metabolic regression and stability of the lesions [Figures 8-11, a]. Although continuation of paclitaxel-carboplatin was recommended until disease progression or toxicity, the patient declined further chemotherapy due to logistical difficulties. Six months after completing treatment, repeat PET/CT showed stable disease [Figures 8-11, b] and tumor markers remained normal. She continues outpatient follow-up every 3 months, with annual imaging surveillance.

Table 1: Tumor markers post-operatively/ pre-bleomycin, etoposide and cisplatin I, after bleomycin, etoposide and cisplatin IV, during tumor recurrence and current disease stability

	Post-operative/ Pre-BEP I	Post-BEP IV	Recurrence	Disease stability
CA125 (U/mL)	20.4			
β-hCG (mIU/mL)	14.96	2.55	<1.2	<0.600
AFP (ng/mL)	1.2	2.11		
LDH (U/L)	198	227		2.99

BEP: Bleomycin, Etoposide, and Cisplatin, AFP: Alpha-fetoprotein, LDH: Lactate dehydrogenase, β-hCG: β- human chorionic gonadotropin, CA: Cancer antigen, I: 1st cycle, IV: 4th cycle

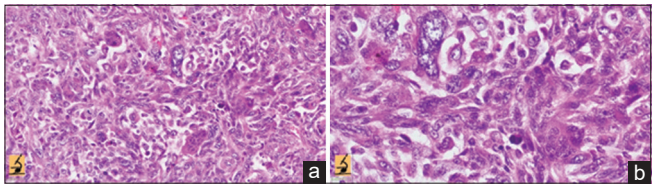


Figure 4: (a) Microscopic appearance of the left ovary on the scanning view (b) Higher magnification of the left ovarian mass with notable atypical spindle-shaped tumor cells and mitotic figures

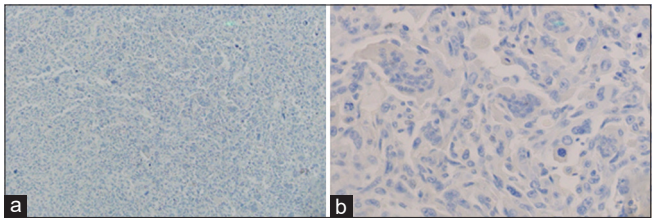


Figure 6: Supporting immunohistochemistry showing that the tumor is negative for SALL4: (a) ×10 (b) ×40

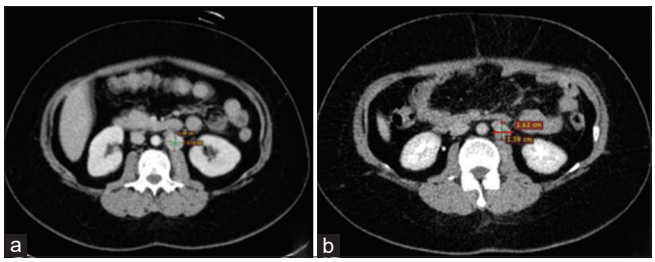


Figure 8: (a) Comparison of paraaortic lymph nodes after treatment (December 2023) and (b) 6 months after discontinuation of treatment (June 2024)

Discussion

NGOC is a rare and aggressive tumor with limited case documentation. They originate from trophoblastic differentiation of germ cells or through retro-differentiation of somatic tumors. They predominantly affect young women, with no identified risk factors. Prognosis is poor in advanced stages – 3-year survival rates drop from 100% in FIGO Stages I–III to 25% in Stage IV.[4]

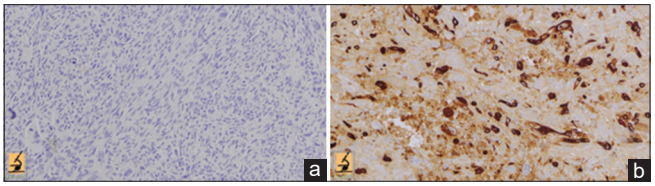


Figure 5: Supporting immunohistochemistry showing that the tumor is: (a) negative for OCT4, ×10 (b) positive for β-human chorionic gonadotropin, ×40

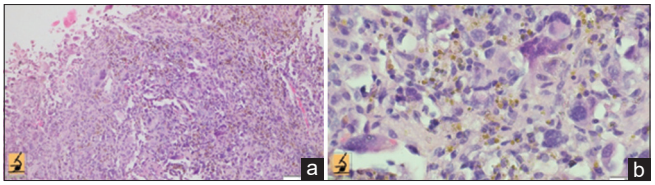


Figure 7: (a) Microscopic appearance of the para-aortic lymph node on the scanning view (b) Higher magnification showed atypical to round spindle cell tumor with hyperchromatic nuclei and atypical mitosis, morphologically compatible with the previous ovarian choriocarcinoma specimen

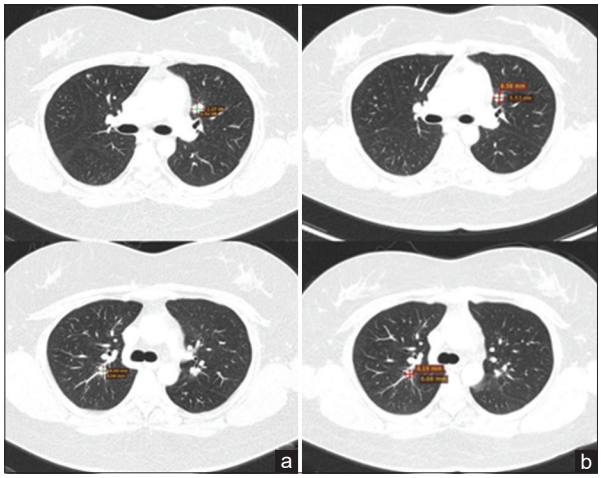
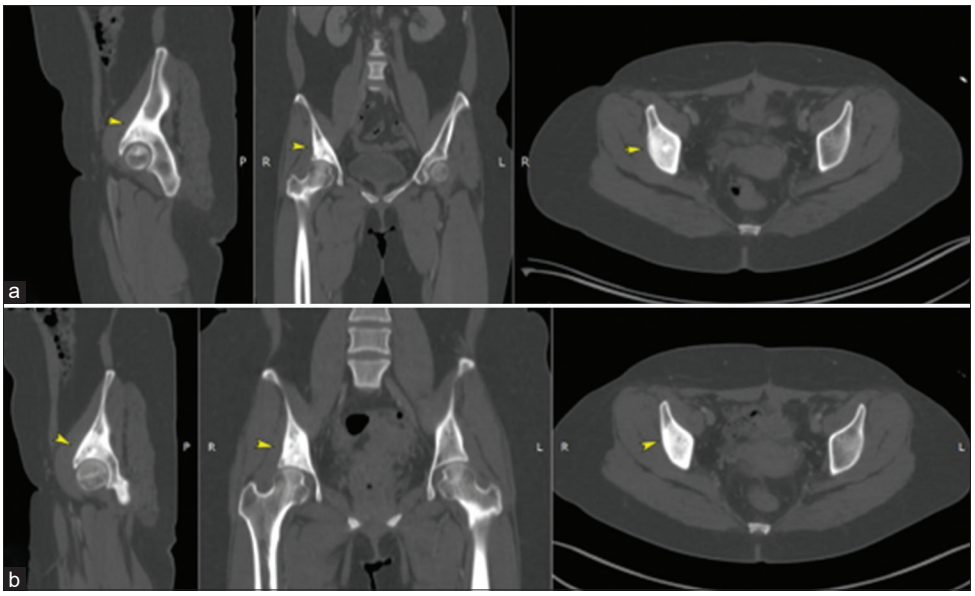


Figure 9: (a) Bilateral pulmonary nodules after treatment (December 2023) and (b) 6 months after discontinuation of treatment (June 2024)



Figures 10: (a) Right ilium sclerotic focus after treatment (December 2023) and (b) 6 months after discontinuation of treatment (June 2024)

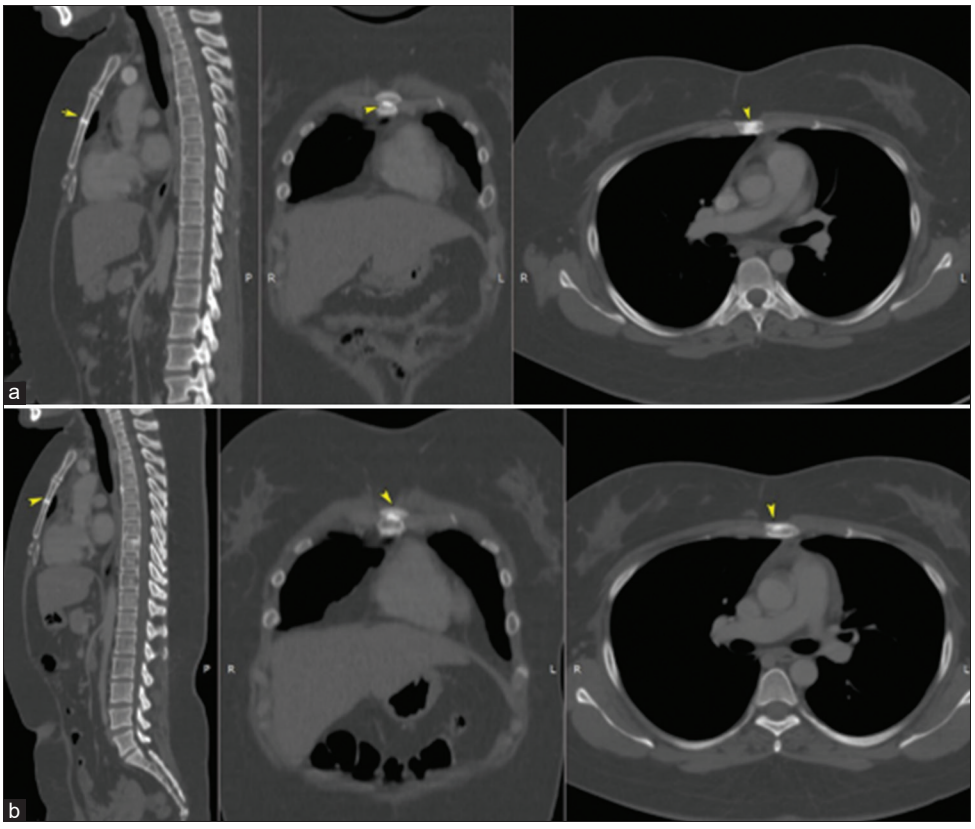


Figure 11: (a) Sternum sclerotic focus after treatment (December 2023) and (b) 6 months after discontinuation of treatment (June 2024)

Fewer than 100 cases of NGOC have been reported in the literature. Only two documented cases had a follow-up beyond 5 years: One by Hayashi *et al*. in a 10-year-old patient with 64 months' disease-free survival after salpingo-oophorectomy and BEP chemotherapy[5] and another by Choi *et al*. in a 33-year-old patient with 60 months' disease-free survival after surgery and EMA chemotherapy.[6] In the Philippines, only one case of pure NGOC has been previously published.[7]

NGOC typically presents in young women with nonspecific symptoms such as abdominal pain, bloating, or abnormal vaginal bleeding.[3] These mimic

more common conditions like ectopic pregnancy or tubo-ovarian abscess, leading to diagnostic delays.[8-10] In this case, the patient had vague abdominal symptoms and a large adnexal mass on ultrasound.

β-hCG levels for NGOC patients tend to be extremely elevated, as typically seen in GOCs. Interestingly, her serum β-hCG was only mildly elevated and remained low even during recurrence. This phenomenon may be attributed to the secretion of hCG variants not detected by conventional assays. hCG is a glycoprotein with variable glycosylation and commercial assays may miss nonstandard subunits or isoforms.[11] In addition to β-hCG, LDH, and α-FP were measured, following local guidelines recommending these markers for women under 40 with complex ovarian masses due to the risk of germ cell tumors. CA-125 is not recommended for NGOC monitoring, as it has low specificity and may be falsely elevated in conditions such as myoma, endometriosis, and pelvic infections.[12]

Histology remains critical in diagnosis. NGOC is characterized by the sheets of cytotrophoblasts and syncytiotrophoblasts with hemorrhage, necrosis, and a high mitotic index.[4] IHC is indispensable for confirmation, with positivity for hCG, EMA, and cytokeratin, and negativity for PLAP, SALL4, and OCT4, helping to rule out other germ cell tumors [Figure 12].[13] Molecular genetic analysis can distinguish NGOC from gestational choriocarcinoma by confirming the absence of paternal DNA, but is not widely available and was not done in this case.[14]

Transvaginal ultrasound is the preferred method for evaluating ovarian masses due to its superior sensitivity compared to transabdominal ultrasound. Choriocarcinomas typically appear as vascular solid tumors with cystic, hemorrhagic, and necrotic areas. CT and MRI do not offer additional sensitivity or specificity for detecting ovarian malignancies.[12,15]

Surgical resection improves overall and progression-free survival. Reported cases include performance of unilateral salpingo-oophorectomy, with or without hysterectomy, contralateral salpingo-oophorectomy, lymphadenectomy, and omentectomy.[3,10,16,17] Fertility-sparing procedures may be considered in young women without gross contralateral disease.[3,18] In a review by Lv *et al*., there was no significant difference with respect to either progression-free survival or overall survival in patients undergoing fertility-sparing surgery compared to those who underwent complete resection and staging. Postoperative residual tumor size was an independent prognostic factor for both overall survival and progression-free survival.[3] In this case, complete staging with fertility-sparing surgery was successfully performed.

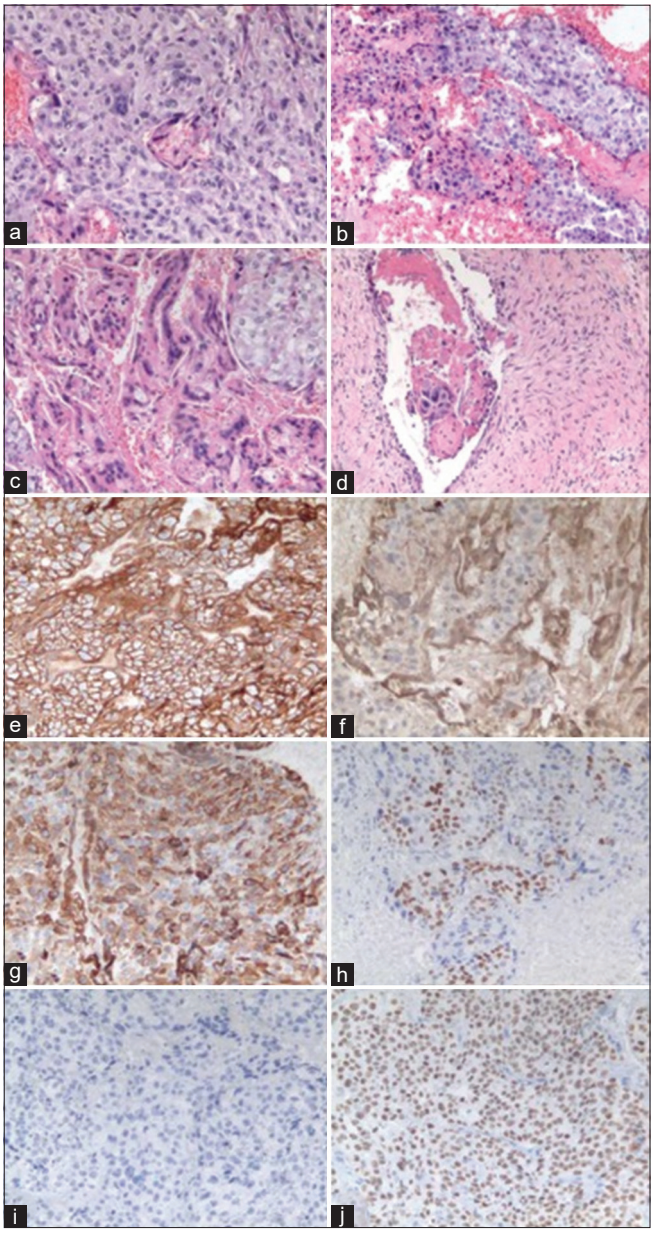


Figure 12: Nongestational choriocarcinoma of the ovary. The tumor consisted of two types of trophoblastic cells: (a) cytotrophoblast and (c) syncytiotrophoblast; with (b) hemorrhaging and (d) intravascular carcinoma thrombus. Immunohistochemical staining (×100) positive for (e) CK, (f) β-human chorionic gonadotropin, (g) human placental lactogen, (h) SALL4, and (j) Ki-67, (i) negative for epithelial membrane antigen

Given the guarded prognosis of NGOCs, in addition to optimal cytoreductive surgery, aggressive chemotherapy is advocated. While gestational choriocarcinomas respond to methotrexate-based regimens, NGOCs often require multiagent platinum-based chemotherapy.[4,18] BEP is the most widely used, with reported effectiveness as high as 93%.[16] Other treatment options as described by Lv *et al*. and Goswami (2001) include

methotrexate-actinomycin-D-cyclophosphamide (MAC); etoposide-methotrexate-actinomycin D/cyclophosphamide-vincristine (EMA/CO); ifosfamide-etoposide; and etoposide-methotrexate-actinomycin-D-cisplatin-etoposide.[3,17]

Management of recurrence remains poorly defined due to the rarity of the disease. Local guideline recommends regimen with Paclitaxel + Ifosfamide + Cisplatin, Cisplatin + Etoposide + Paclitaxel, Paclitaxel + Carboplatin, Paclitaxel + Gemcitabine, Paclitaxel + Ifosfamide, (Vincristine + Actinomycin + Cyclophosphamide), VelP (Vinblastine + Ifosfamide + Cisplatin), and VIP (Etoposide + Ifosfamide + Cisplatin).[18] Our patient responded well to Paclitaxel-Carboplatin.

The risk of ovarian toxicity is important to consider for patients in the reproductive age, especially with cisplatin and carboplatin (intermediate risk), while bleomycin and etoposide carry a lower risk.[18] The patient received BEP and paclitaxel-carboplatin but has resumed regular menstruation, indicating recovered ovarian function. Fertility often returns after fertility-sparing surgery and combination chemotherapy.[3]

Radiation therapy is rarely reported but may offer locoregional control in metastatic or recurrent disease. In the review by Lv *et al*., only two cases reported its use – one is chemoradiotherapy for an advanced disease that was followed by palliative surgery of residual disease and the other one is for cerebral metastasis.[3] In this case, IMRT was used for palliative management of bone lesions. Bisphosphonates such as zoledronic acid may be used for bone metastases, helping reduce skeletal-related events and improving quality of life.[19]

Given NGOC's aggressive nature and metastatic potential, close follow-up with clinical assessment, tumor markers, and periodic imaging is essential Our local guideline recommends physical examination every 2 months, imaging including chest and abdominal CT, MRI or PET/CT scan every 3–4 months and tumor markers every visit, if initially elevated.[4,18] Our patient is currently monitored with tumor markers (β-hCG, AFP, and LDH) every 3 months and PET/CT annually.

Conclusion

This case highlights the diagnostic and therapeutic challenges in NGOC, particularly with atypically low β-hCG levels. Despite initial remission after BEP chemotherapy, the patient experienced a distant recurrence but achieved disease stability with second-line chemotherapy and radiotherapy. NGOC management requires a multimodal approach and individualized treatment planning. More long-term data are needed to guide the optimal management of this rare malignancy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authorship contributions

Bernadette Cris L. Festejo-dela Cruz – Conceptualization, Formal Analysis, Writing-Original Draft, Review and Editing, Visualization.

Jericho Thaddeus P. Luna – Conceptualization, Formal Analysis, Writing- Original Draft, Review and Editing, Visualization, Supervision.

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Conflicts of interest

There are no conflicts of interest.

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