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Gestational trophoblastic neoplasia coexisting with cervical carcinoma: A case report

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Abstract:

Gestational trophoblastic neoplasia (GTN) with a concurrent cervical malignancy is very rare, making the case both a diagnostic dilemma and a therapeutic challenge. Currently, there has only been one reported case worldwide. We present a case of GTN Stage I:11 with non-keratinizing squamous cell carcinoma of the cervix Stage II-B. Initial treatment, in the form of chemotherapy, was directed toward the GTN, as this appeared to be the more aggressive disease. Surgery was not feasible during diagnosis due to the cervical carcinoma. However, the GTN proved resistant to chemotherapy due to the increasing beta human chorionic gonadotropin titers. An attempt to decrease the size of the cervix for surgery to be possible through chemoradiation was instituted, but due to complications and tumor progression to the lungs, she succumbed to the malignancy.

Keywords:

Cervical cancer, gestational trophoblastic neoplasia, human chorionic gonadotrophin

Introduction

Gestational trophoblastic neoplasia (GTN) with coexisting cervical cancer is almost unheard of. A literature search using various engines, namely, PubMed, Medline, Ovid, Scopus, Google Scholar, and Science Direct, revealed one reported case.

Because of the rarity of GTN with coexisting cervical cancer, there is no existing diagnostic and treatment protocol for the management of the patients. We report a case of a 51-year-old Filipina who consulted at a tertiary government hospital due to on-and-off vaginal bleeding for 2 months. This paper aimed to discuss the challenges in arriving at the correct diagnosis, as well as the therapeutic dilemmas encountered.

Case Report

A 51-year-old, Gravida 3 Para 2 (2012), Filipina, consulted at our institution due to a 2-month history of on-and-off vaginal bleeding. She has hypertension with good compliance with medications. Her first coitus was at 24 years old, with two lifetime sexual partners. Her husband works as a security guard with known extramarital affairs. She had her first pregnancy at 24 years old, which was carried to term and delivered through cesarean section for an unrecalled indication. Her second pregnancy was a spontaneous abortion at 30 years old, with no curettage and histopathology done. After 2 years, she had her third pregnancy, which was carried to term and delivered via repeat cesarean section. She did not use any form of contraception.

Two months before admission, the patient had on-and-off vaginal bleeding associated

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with crampy, hypogastric pain radiating to the flank area with an increase in urinary frequency and dysuria. There was no postcoital bleeding, foul-smelling vaginal discharge, weight loss, and anorexia. Due to the persistence of vaginal bleeding, she sought consult at the outpatient department of our institution. Pregnancy test was done, which revealed a positive result. She was then referred to the emergency room (ER) for further work-ups.

At the ER, she was afebrile with stable vital signs and a normal body mass index. A 10 cm × 10 cm, firm, movable, nontender hypogastric mass was palpated. On pelvic examination, the cervix was bulky, measuring 5 cm × 5 cm and was slightly deviated to the right. The uterus was symmetrically enlarged to 18 weeks' size, without adnexal mass and tenderness noted. On rectovaginal examination, she had intact rectal vault, a good sphincter tone with no masses noted. The left parametrium was smooth and pliable, whereas the right parametrium was nodular and fixed. The initial serum beta-human chorionic gonadotropin (βhCG) was elevated to 3347.18 mIU/ml. Transvaginal ultrasound showed a 4.1 cm × 5.2 cm × 4.2 cm cervical mass with full stromal invasion and extension to the uterine isthmus and right parametrium. There was also a heterogeneous endometrial mass measuring 6.3 cm × 5.3 cm × 2.7 cm with <50% myometrial invasion. Normal ovaries and bilateral pelvic lymphadenopathies were seen. The chest X-ray [Figure 1a], chest computerized tomography (CT) scan, and whole abdominal ultrasound yielded normal results. Cervical punch biopsy was done, which revealed squamous cell carcinoma, non-keratinizing [Figure 2a and b]. Because of the rarity of concomitant GTN and cervical cancer, several immunohistochemical studies were done to confirm the histopathologic reading. These included: P16, which was positive in more than 50% of tumor cells; P63 stain was positive in 30% of tumor cells; βhCG and inhibin, which stained positive in <5% scattered cells [Figure 2c-f]. These findings were most consistent with squamous cell carcinoma. However, the findings did not rule out the presence of a secondary tumor, given a separate endometrial mass with <50% myometrial invasion and an elevated βhCG titer. The working diagnosis at this time was GTN Stage I with the WHO prognostic score of 10, cervical cancer Stage II-B, squamous cell carcinoma, nonkeratinizing. The patient was then admitted for further management.

On admission, she was referred to the Section of Gynecologic Oncology for comanagement. It was suggested to start chemotherapy with methotrexate and concurrent pelvic external beam radiation therapy (EBRT) to target both the GTN and cervical cancer. However, treatment was not readily instituted due to financial constraints. A repeat transvaginal ultrasound done after a month of no treatment showed an increase in the size of the cervical mass to 4.5 cm × 5.9 cm × 5.8 cm with extension to the upper third of the vagina. Moreover, the hypervascular endometrial mass was now seen to be prolapsing into the cervical canal. Serum βhCG also showed an increasing trend [Figure 3a]. It was decided to start her with mthotrexate 0.4 mg/kg/day intramuscularly for 5 days while awaiting funds for EBRT. Before chemotherapy, her βhCG was already at 80,004.01 mIU/mL. After the first cycle of methotrexate, chemoresistance was encountered with a rise of βhCG to 132,340.56 mIU/mL. Chemotherapy was then shifted to Etoposide and Cisplatin. However, chemoresistance was again noted, with the βhCG titer rising further to 284,211.50 mIU/mL. The patient was then shifted to multiple-agent chemotherapy in the form of etoposide-methotrexate-actinomycin-cyclophosphamide-oncovin (EMACO) regimen. Because of the anticipated toxicities that may arise with the EMACO regimen, pelvic EBRT was temporarily deferred. An adequate response after the first cycle with EMACO was noted. Serum βhCG decreased to 54,865.14 mIU/mL. However, the patient encountered several toxicities, such as granulocytopenia and multiple electrolyte imbalances. She also developed furuncles in both labia. After treatment of all her

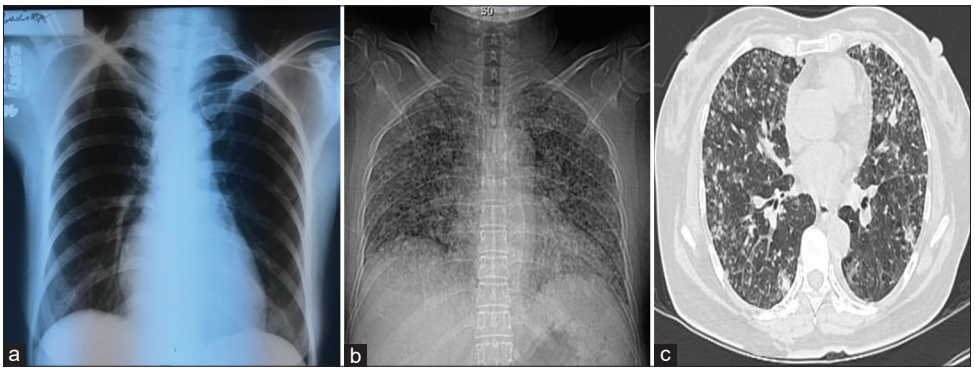

Figure 1: Images of the lungs during admission. (a) Chest X-ray (CXR) on admission which showed no significant chest findings. (b) CXR on the 15th day of external beam radiation therapy showed Innumerable ill- to fairly-defined various-sized, noncalcified, enhancing pulmonary nodules (c). Cross-sectional section of the chest computerized tomography scan showed pulmonary masses with spiculated borders scattered throughout both lungs

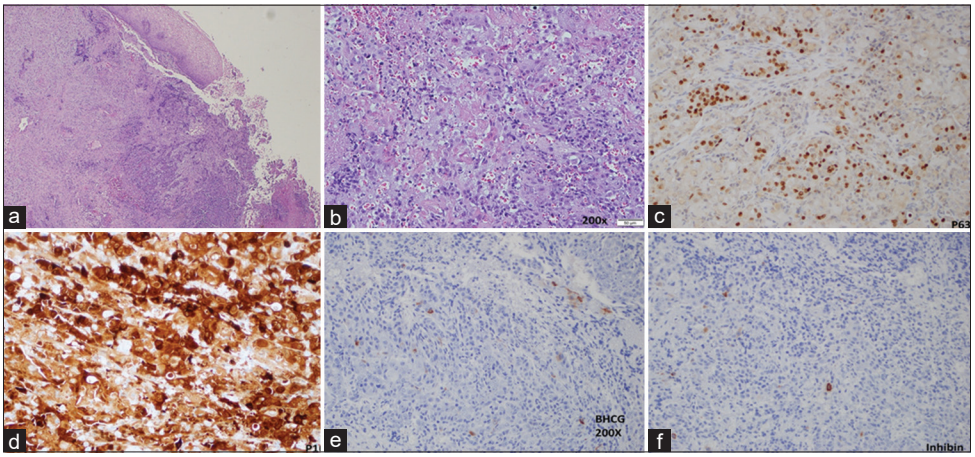

Figure 2: Photomicrographs of the cervical punch biopsy (a). Scanner view shows neoplastic squamous cells invading the cervical stroma. (b). At ×200 magnification, the individual cells are seen to have moderately pleomorphic polygonal nuclei with occasionally prominent nucleoli and scant to variable eosinophilic cytoplasm. (c). Immunohistochemical (IHC) Stain with P16 which showed staining in more than 50% of tumor cells (d) P63 IHC showing positive staining in 30% of tumor cells (e) beta human chorionic gonadotropin IHC was positive in less than 5% scattered cells (f). Inhibin stained positive in less than 5% scattered cells

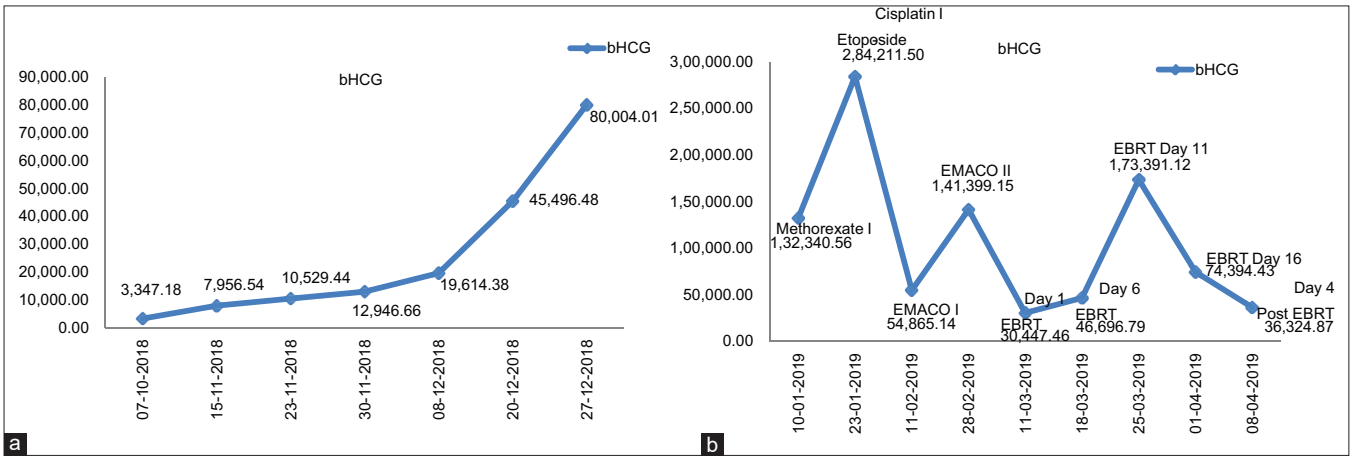

Figure 3: ß-human chorionic gonadotropin (ßhCG) trends. (a) Beta-HCG trend before chemotherapy (b). Beta HCG trend during chemotherapy

toxicities, the second cycle of EMACO was given after 2 weeks. Chemoresistance was again encountered, with βhCG increasing to 141,399.15 mIU/mL. Multiple toxicities, namely anemia, granulocytopenia, leukopenia, hypokalemia, hyponatremia, hypocalcemia, and hypomagnesemia, were again noted. Repeat pelvic examination revealed an increase in the size of the cervical mass from 5 cm × 5 cm to 8 cm × 8 cm. Uterus remained at 18 weeks size, with no adnexal masses and tenderness noted. The left parametrium was still smooth and pliable, whereas the right parametrium was nodular and fixed. A multidisciplinary conference was held. It was decided to put the EMACO chemotherapy on hold and to start chemoradiation with the hope of shrinking the cervical mass to make surgery feasible, thereby decreasing the tumor load of the GTN before resuming chemotherapy. Weekly cisplatin (40 mg/m^2) and pelvic EBRT for 25–28 days were started after correcting and treating her toxicities. Serum βhCG was monitored regularly while on chemoradiation. Despite the weekly cisplatin and daily pelvic EBRT, the βhCG levels were still elevated [Figure 3b]. On the 34th hospital day, day 15 of pelvic EBRT, the patient had cough associated with hemoptysis. Tumor bleeding from lung metastasis was considered. Chest X-ray was requested, revealing diffuse reticulonodular opacities in both lungs, which was considered a metastatic process given the known primary malignancy. Chest CT scan with contrast showed innumerable ill- to fairly-defined various-sized, non-calcified, enhancing pulmonary nodules with spiculated borders scattered throughout both lungs [Figures 1b and c]. Sputum cultures and sputum acid- fast bacilli were both normal. Repeat speculum examination revealed a pale pink cervix without gross lesions and masses, absence of vaginal masses, and scanty vaginal bleeding. On internal examination, the cervix was firm and nodular, but the size decreased from 8 cm × 8 cm to 4 cm × 4 cm. The uterus was still enlarged to 18 weeks size. The right parametrium was still nodular and fixed on rectovaginal

examination. The βhCG at this time was still elevated at 74,394.43 mIU/mL. Pelvic EBRT was continued for the next 4 days.

On the 38th hospital stay, day 19 of pelvic EBRT, the patient still experienced cough associated with hemoptysis and dyspnea. Pallor and cardiorespiratory distress were noted. She also had anemia and thrombocytopenia. The pelvic EBRT was deferred. A family conference was done to appraise relatives of the patient's condition and prognosis. Dyspnea further progressed on her 39th hospital stay. Desaturations were observed despite administration of positive airway pressure.

On her 40th hospital stay, despite the progressive cardiopulmonary distress, the patient refused intubation and resuscitation. She then succumbed to acute respiratory failure secondary to multiple lung metastasis. An autopsy was advised, but relatives refused the procedure.

Case Discussion

The term GTN encompasses the spectrum of trophoblastic diseases that are locally proliferative with the ability to invade normal tissue and the potential to spread outside of the uterus. It includes invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT).[1] GTNs are uncommon and account for <1% of all gynecologic malignancies.[2]

In this report, we presented the case of GTN occurring with cervical carcinoma. This condition is very rare, with only one reported case of histologically proven coexisting cervical carcinoma and GTN to date. This was a case of a 60-year-old postmenopausal woman who had an ETT coexisting with a mucinous adenocarcinoma of the cervix.[3] Because of the rarity of the condition, our index case imposed a diagnostic challenge as well as a treatment dilemma.

We are presented with a case of a 51-year-old G3P2 (2012) Filipina with a 2-month history of on and off vaginal bleeding associated with hypogastric pain, increase in urinary frequency and dysuria. No post-coital bleeding, foul-smelling vaginal discharge, weight loss, and anorexia were noted. She had normal vital signs and was afebrile. On abdominal examination, a hypogastric mass was palpated. Pelvic examination revealed a bulky cervix and uterine enlargement. No adnexal masses and tenderness were noted. On rectovaginal examination, the left parametrium was smooth and pliable, while the right parametrium was nodular and fixed. Pregnancy test was positive. Initial serum βhCG was elevated at 3347.18 mIU/ml. Transvaginal ultrasound showed a cervical mass with full stromal invasion and extension to the uterine isthmus and right parametrium. There was also a heterogeneous endometrial mass with <50% myometrial invasion. Normal ovaries and bilateral pelvic lymphadenopathies were also seen. The baseline chest X-ray, chest CT scan with contrast, and whole abdominal ultrasound were normal.

The βhCG is an excellent tumor marker for the diagnosis, management, and posttreatment monitoring of GTN. However, the pretreatment level among the different gestational trophoblastic disease entities greatly varies from one another. Since both PSTT and ETT are characterized by the neoplastic proliferation of intermediate trophoblastic cells, patients often present with βhCG elevations that are much lower than choriocarcinoma and invasive mole.[4-6] In a study published by Santoro *et al*., the βhCG level of patients with PSTT ranged from 2 to 22,065 mIU/ml, with a mean of 607.64 mIU/ml. Cases with a value higher than 10,000 mIU/ml were very rare.[6] Serum βhCG levels of ETT range from 12 to 148,000 mIU/ml but are usually only slightly to moderately elevated (665–2500 mIU/ml).[5] Cervical carcinomas can also present with low levels of βhCG, usually not exceeding 60 mIU/ml. Mustafa *et al*. attributed the βhCG elevation in cervical carcinoma to the ectopic secretion of the cancer cell line.[7]

The initial serum βhCG level of our index case was 3,347.18 mIU/ml. Our considerations at this point were an ETT or a GTN occurring concomitantly with cervical carcinoma. ETT was considered, given the modest elevation of βhCG titer despite a large uterine tumor. In addition, among the four histologic types of GTN, ETT is the one that is known to mimic a cervical carcinoma due to its predilection to develop in the lower uterine segment and the cervix.[5,8,9] Around 31% of cases may present with the primary disease in the cervix.[10] Grossly, it presents as a solid to well-defined cystic mass that deeply invades the cervix or myometrium. Cut surface of the solid areas is typically tan to brown with varying amounts of hemorrhage and necrosis.[8,9] Most cases that have been reported would initially be diagnosed as a cervical cancer, but histopathological and immunohistochemical studies will point to the correct diagnosis. Jordan *et al*. reported a case of a 39-year-old multigravid who was initially diagnosed with cervical cancer. Treatment with concomitant cisplatin and radiotherapy plus single-dose methotrexate was unsuccessful. Histopathology, immunohistochemistry, and genetic studies proved that the cervical mass was an ETT.[11] Similarly, Narita *et al*. reported on the case of a 53-year-old woman who was initially diagnosed with cervical cancer on cervical punch biopsy. The patient underwent a radical hysterectomy. Histopathology and immunohistochemical studies showed an ETT.[12]

To establish the diagnosis, our patient underwent a cervical punch biopsy, which was read as squamous cell carcinoma, nonkeratinizing type. Immunohistochemical staining was likewise done, which revealed results consistent with squamous cell carcinoma, nonkeratinizing. However, given the elevated βhCG titer, and the presence of an endometrial mass, a concurrent GTN, probably a choriocarcinoma, was considered. Diagnosis at this point was GTN I:11 with squamous cell carcinoma of the cervix, nonkeratinizing type stage II-B. The diagnosis of cervical carcinoma was based on the tissue biopsy and immunohistochemical results. On the other hand, histopathology is not mandatory in the diagnosis and treatment of GTN. The diagnosis was based on the patient's clinical history, elevated serum βhCG titer, and evidence of an endometrial mass with myometrial invasion.

Currently, there are no existing guidelines on how to treat a GTN coexisting with cervical carcinoma. Radiation with concomitant cisplatin chemotherapy is the treatment of choice for patients with cervical carcinoma stage II-B. On the other hand, chemotherapy remains to be the cornerstone in the management of patients diagnosed with GTN. The utilization of the combined FIGO staging system [Table 1] and WHO prognostic scoring system [Table 2] has enabled physicians to properly categorize patients and determine the appropriate chemotherapeutic agent based on the disease severity. Patients classified as having either nonmetastatic or metastatic, low-risk disease are given single-agent chemotherapy in the form of methotrexate or actinomycin-D.[13,14] On the other hand, patients with metastatic high-risk disease are given multiagent chemotherapy, most commonly in the form of EMACO, which is composed of etoposide, methotrexate, actinomycin-D, Cyclophosphamide, and Oncovin.[14-16] Recent reports have shown a very good cure rates, with values approaching 100% for those with low-risk disease and 80%–90% for those with high-risk disease.[13,15-17]

In consultation with the Section of Gynecologic Oncology, it was decided to proceed with EBRT with concomitant methotrexate to address the two clinical conditions present in the patient. Methotrexate was the chemotherapeutic agent chosen since she had a nonmetastatic GTN. Moreover, a previous study has shown that methotrexate given at 25–50 mg at weekly intervals, is an effective palliative treatment for recurrent or metastatic carcinoma of the cervix.[18] In this regard, it was hoped that methotrexate will be not only effective for the GTN but for the cervical carcinoma as well. It was unfortunate that, due to financial constraints, treatment was not immediately instituted and serum βhCG continued to increase rapidly. At this point, the biological behavior of the two tumors was primarily taken into consideration. Compared to cervical carcinoma, which has a more indolent clinical course, GTN is known to be a highly aggressive tumor if treatment is withheld. As such, management was directed to address the GTN first.

Being categorized as a nonmetastatic disease, the patient was started on single-agent chemotherapy in the form of methotrexate. However, the patient presented with resistance after one cycle of methotrexate. The patient was not shifted to actinomycin-D, which is the usual recommendation following resistance to methotrexate given the unique condition of our patient. Instead, she was started on a combination of etoposide and cisplatin. This regimen was preferred due to the known sensitivity of GTN to cisplatin as well as its effectiveness as a sensitizer to radiation therapy for cervical cancer. A study on concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer revealed that regimens of radiotherapy and chemotherapy that contain cisplatin improve the rates of survival and

Table 1: 2000 FIGO staging system

Stage	Description
Stage I	Disease confined to the uterus
Stage II	GTN extends outside the uterus but is limited to the genital structures (adnexae, vagina, and broad ligament)
Stage III	GTN extends to the lungs with or without genital tract involvement
Stage IV	All other metastatic sites

GTN: Gestational trophoblastic neoplasia, FIGO: The International Federation of Gynecology and Obstetrics

Table 2: The World Health Organization prognostic scoring system

Prognostic factors	Score			
	0	1	2	4
Age (years)	<40	≥40		
Antecedent pregnancy	Mole	Abortion	Term	
Interval months from index pregnancy	<4	4–<7	7–<13	>13
Pretreatment hCG (mIU/mL)	<1000	1000–<10,000	10,000–<100,000	>100,000
Largest tumor size (including the uterus) (cm)	<3	3–<5	>5	
Site of metastases	Lung	Spleen, kidney	Gastro-intestinal	Liver, brain
Number of metastases		1–4	5–8	>8
Previous failed chemotherapy			Single drug	2 or more drugs

hCG: Human chorionic gonadotropin

progression-free survival among women with locally advanced cervical cancer.[19] However, chemoresistance was also noted with the etoposide-cisplatin regimen. Because of the persistently increasing βhCG levels, it was decided to shift to a multiagent chemotherapy in the form of EMACO. Unfortunately, after the second cycle of EMACO, chemoresistance was again encountered and the cervical mass was also noted to further increase in size. At the point, hysterectomy to decrease the tumor load and remove the focus of drug resistance was contemplated.

Surgery is considered an adjuvant treatment in the management of GTN. Hysterectomy is an option for patients who do not respond to first- or second-line chemotherapy, especially in those with no desire to retain their reproductive capacity.[17,20] The procedure has the advantage of decreasing hospital stay and the number of chemotherapeutic cycles.[17] For our patient, the size of the cervical mass prohibited the performance of the procedure. Pelvic external beam radiotherapy (EBRT) was then instituted with concomitant cisplatin chemotherapy to shrink the size of the cervical mass to make surgery feasible.

Despite the numerous chemotherapy and pelvic EBRT that were administered, the patient's condition worsened. Several toxicities were encountered that prevented the institution of treatment as scheduled. The tumor was highly aggressive, as shown by the rapidly increasing βhCG titer and enlarging cervical and endometrial masses. Tumor progression to the lungs was observed in our index patient, and she eventually succumbed to acute respiratory failure secondary to multiple lung metastasis.

Summary

GTN with cervical carcinoma is a rare disease that poses a diagnostic challenge and therapeutic dilemma. Due to its rarity, there are no current treatment guidelines on the proper management of such a case. GTN is a highly curable disease, especially if it is diagnosed in the early stage. It is unfortunate that there was a delay in the management of this patient due to financial constraints. In addition, the patient had a highly aggressive tumor that had resistance to the various chemotherapeutic regimens given to her.

Declaration of the patient's consent

The authors certify that they have obtained all appropriate consent forms. Since the patient in this report succumbed to her illness, the husband gave consent for his wife's images and other clinical information to be reported in this journal. The husband understands that his wife's name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Authorship contributions

Agnes L. Soriano-Estrella, MD - conceptualization, wrote some parts of the manuscript, final editing.

Julie Ann B. Bolastig-Canson, MD, Ginessa Grace G. Rendaje, MD, May Delight G. Galingan, MD - wrote some parts of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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