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Bizarre presentation of choriocarcinoma: A case report

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Abstract:

Choriocarcinoma is a malignant subtype of gestational trophoblastic disease that follows any type of pregnancy. It is characterized by rapid hematogenous spread to multiple organs, associated with high human chorionic gonadotropin levels with good response to chemotherapy. We present the case of a 31-year-old Filipina who initially presented with severe headaches and blurring of vision 3 years after an unremarkable term pregnancy. The transvaginal ultrasound was normal. After a series of diagnostic tests, the initial working impression was a primary brain tumor with metastases to the lungs, adrenal, kidney, and vulva. Emergency craniotomy was done due to deteriorating status secondary to an intracranial hemorrhage. The histopathology report showed choriocarcinoma. Chemotherapy using Etoposide-Methotrexate-Actinomycin D-Cyclophosphamide-Vincristine with high-dose methotrexate and concomitant whole-brain irradiation was then instituted with good response. This case highlights the importance of having a high index of suspicion for gestational trophoblastic neoplasia to prevent the performance of unnecessary procedures, leading to a delay in diagnosis and the institution of the appropriate treatment.

Keywords:

Brain metastasis, etoposide-methotrexate-actinomycin D-cyclophosphamide-vincristine, gestational trophoblastic neoplasia, metastatic high-risk disease

Introduction

Choriocarcinoma is a rare, highly malignant type of gestational trophoblastic neoplasia (GTN) characterized by rapid trophoblastic proliferation and invasion of surrounding tissue. This may occur during or after any type of pregnancy, with 25% of cases following a normal-term pregnancy.[1-3]

This tumor demonstrates rapid hematogenous spread to multiple organs. Approximately 30% of choriocarcinoma patients exhibit metastasis at the time of diagnosis, which may be attributable to the high affinity exhibited by trophoblastic cells for blood vessels. The most common presenting symptom is vaginal bleeding, but in some, the presentation may be misleading due to the absence of a demonstrable tumor in the uterus. Instead, patients present with symptoms referable to the site of metastasis.[3,4]

We report a case of choriocarcinoma in a 31-year-old Filipina who was initially diagnosed with a case of primary brain tumor. Several diagnostic tests were done, which failed to confirm the diagnosis, leading to a delay in the institution of the appropriate. An emergency craniectomy led to the correct diagnosis and eventual successful treatment.

Case Report

This is the case of a 31-year-old, gravida 1 para 1 (1001), Filipina, who had an uncomplicated normal spontaneous delivery 3 years before admission. She took combined oral contraceptive pills for a total of 6 years. Her condition started 6 weeks before admission at our center when she experienced the sudden onset

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of constant, gnawing, right-sided, and nonradiating headache with Visual Analog Scale ranging from 5 to 10 out of 10. There was no known aggravating symptom and it was minimally relieved by various analgesics. Headache was associated with occasional vomiting and constant left-sided blurring of vision. This prompted a consult with an ophthalmologist, which revealed essentially normal findings. She then consulted a neurologist. Magnetic resonance imaging of the brain was requested, which revealed a conglomeration of at least six peripherally enhancing nodules involving the right occipital lobe, with the largest measuring 1.3 cm, associated with moderate surrounding vasogenic edema compatible with an infectious or inflammatory process [Figure 1]. She was then advised admission for further work-up and management.

On admission at another private tertiary hospital, X-ray and computed tomography (CT) of the chest [Figure 2] were done, which both showed pulmonary masses. On whole-abdomen CT, a heterogeneously enhancing mass in the upper pole of the right kidney measuring 4.9 cm × 3.6 cm × 3.9 cm was seen. A percutaneous CT-guided biopsy was then performed on the pulmonary and renal masses. She was discharged while awaiting histopathologic results, which eventually revealed malignant cells with cytomorphologic features consistent with adenocarcinoma. In the interim, still with the persistence of moderate-to-severe headache associated with blurring of vision on the left eye.

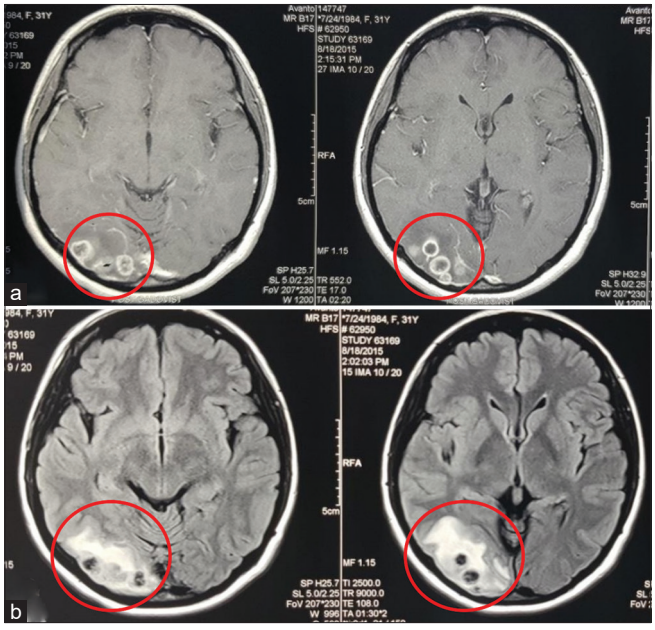

Figure 1: (a) Brain MRI revealing a conglomeration of at least six peripherally enhancing nodules (red circle) involving the right occipital lobe with the largest measuring 1.3 cm, (b) the MRI FLAIR showing moderate surrounding vasogenic edema. The imaging characteristics of these contrast enhancing nodules (red circle) were interpreted as compatible with an infectious or inflammatory process, of which tuberculosis was the usual suspect. However, other parasitic etiologies, such as toxoplasmosis, schistosomiasis, and cryptococcosis may likewise be entertained. MRI: Magnetic resonance imaging, FLAIR: Fluid‑attenuated inversion recovery

Four weeks before admission to our institution, the patient noted four erythematous, nontender papules on her left labia majora. No consultation was done.

Three weeks before admission, she suddenly complained of a sharp, left flank pain, radiating to the left lower quadrant, rated as 7 out of 10 in the pain scale. She also experienced diplopia, and the vulvar lesions were noted to coalesce. These prompted her to seek consultation at the emergency department of the previous private tertiary hospital, and she was subsequently readmitted. On physical examination, there was a blind spot on the left lower quadrant of the left eye on the confrontational visual field test. Abdominal examination revealed direct tenderness on the left lower quadrant with no palpable mass, rebound tenderness or guarding. There was no costovertebral angle tenderness. An erythematous, elongated, nontender vulvar lesion with ill-defined borders measuring 2 cm × 1 cm was noted. Neurologic examination was unremarkable.

An abdominal CT scan with contrast was done [Figure 3], which showed a large hyperdense mass in the left adrenal gland measuring 6.88 cm × 3.7 cm × 5.69 cm, interpreted as a hematoma. The previously visualized hyperdense mass in the upper pole of the right kidney now measured 4.52 cm × 4.94 cm × 4.47 cm with a fluid density in the inferior subcapsular region of the right kidney believed to be a hematoma from the previous biopsy. There was minimal ascites in the left posterior pararenal space, minimal pleural effusion on the left lower lung, and a pulmonary nodule on the posterior basal segment of the right lower lung measuring 0.59 cm × 0.76 cm × 0.74 cm.

She then underwent a left adrenal arteriogram which showed a hypervascular mass at the left adrenal gland supplied by the left superior adrenal artery, which was noted to arise from the left inferior phrenic arteries with few neovascularities [Figure 4a]. Embolization was subsequently done [Figure 4b].

One week before admission, she developed sudden onset of sharp, nonradiating right flank pain rated as 7/10, associated with gross hematuria. Furthermore, the previously noted left labial mass is now firm, tender, measuring 4 cm x 6 cm with ill-defined borders and oozing surfaces. This prompted a referral to an obstetrician and gynecologist. Pressure packing with unmedicated gauze was placed on the area. Foley catheter was inserted. Cystoclysis was done with the drainage of sanguinous fluids with blood clots.

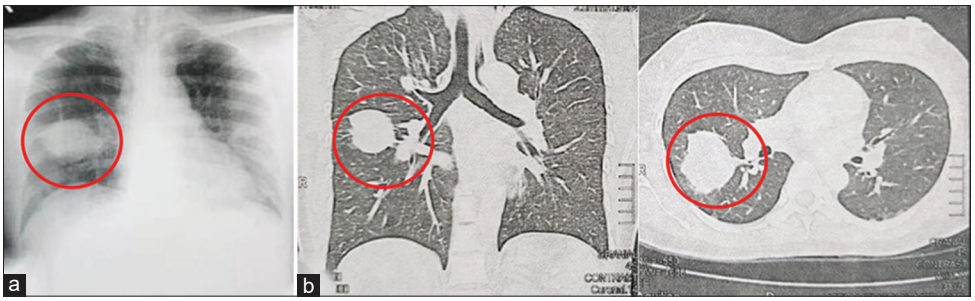

Figure 2: Imaging studies on the chest which included (a) Chest x-ray revealing a rounded homogenous opacity at the right middle lung zone, denoting a pulmonary mass (red circle) (b). Contrast enhanced CT scan showing a large peripherally enhancing mass (red circle) with irregular margins measuring 2.8 x 3.2 x 3.1 cm in the right middle lung with a satellite nodule in its inferolateral aspect measuring 0.88 cm in diameter

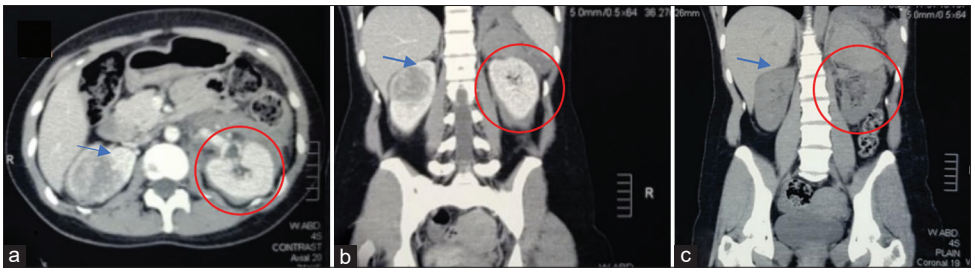

Figure 3: CT scan of the Abdomen. (a) Axial view with contrast showing the hyperdense mass (blue arrow) in the upper pole of the right kidney now measured 4.52 x 4.94 x 4.47 cm (previously 4.9 x 3.6 x 3.9 cm) and a large hyperdense mass (red circle) in the left adrenal gland mass measuring 6.88 x 3.70 x 5.69 cm (b) Coronal view with contrast showing hyperdense (c) Coronal view of the plain CT scan showing the lesions

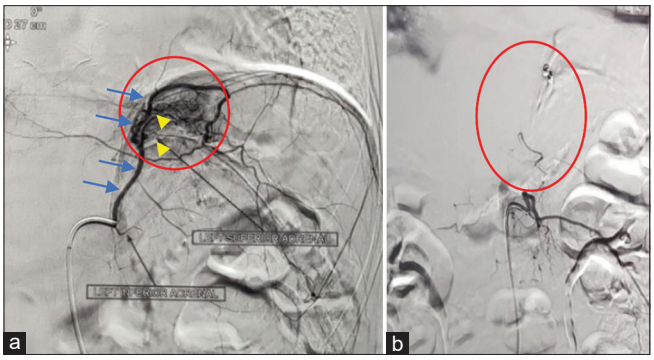

Figure 4: Pre- and post-embolization angiogram. (a) Renal angiogram showed a solid homogenous hyperechoic mass with well-defined margin in the mid-to-upper pole of the right kidney measuring 3.48 x 3.0 x 3.02 cm, a left adrenal hypervascular mass (red circle), supplied by the left superior adrenal artery (yellow arrowhead) noted to arise from left inferior phrenic arteries (blue arrows) with neovascularities.(b) Angiogram after embolization of the left inferior phrenic and superior adrenal arteries

A transvaginal ultrasound was done, which revealed a normal uterus and ovaries.

A repeat CT scan of the whole abdomen revealed an increase in the size of the right renal mass with extension to the renal hilum, resulting in caliectasis with blood clot formation. On the other hand, there was a decrease in the size of the left adrenal hematoma [Figure 5].

A few hours after the procedure, she had sudden onset of generalized severe, crushing headache, anisocoric pupils, medial deviation of the left eye, and weakness on the left upper and lower extremities with deteriorating neurological status with Glasgow Coma Scale of 10 (E2V5M3). A cranial CT scan with contrast revealed hemorrhagic cranial metastasis in the right occipito-parieto-temporal lobe [Figure 6]. Emergency craniectomy was done with total excision of the tumor without complications. The patient remained stable postoperatively with an unremarkable stay at the intensive care unit for 4 days. The rest of the previously noted neurologic symptoms resolved. CT scan done postoperatively showed complete resection of the brain tumor [Figure 7]. Brain tumor specimen was sent for epidermal growth factor receptor mutation test for metastatic lung carcinoma confirmation; however, it was negative.

A day before admission to our institution, there was bleeding from the labial mass which was controlled by pressure dressing. On examination, the left labial mass now measured 10 cm × 8 cm with varicosities. It was at this point when a serum human chorionic gonadotropin (hCG) was requested, which revealed a value of 90,909 mIU/ml. Cell blocks of the brain tumor were sent for histopathology, which revealed malignant, highly pleomorphic features consistent with choriocarcinoma. The patient was immediately referred to a trophoblastic disease specialist and transferred to our institution.

Transvaginal ultrasound with Doppler velocimetry on admission showed a left labial mass described as irregular, solid, heterogeneous, and multilobulated, measuring

9.9 cm × 8 cm × 6.98 cm, the depth of which was limited to the subcutaneous area and outer periurethral area. Color mapping showed marked vascularity, branching, high-flow, and low resistance indices. The anorectum, urinary bladder, urethra, and vagina are uninvolved. These findings were consistent with choriocarcinoma. The rest of the reproductive organs were unremarkable.

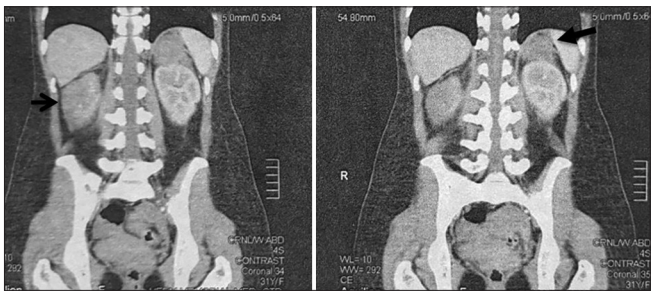

Figure 5: Contrast-enhanced CT scan of the abdomen (coronal view). Arrow: Increase in size of the right renal carcinoma measuring 5.06 cm × 5.47 cm × 5.46 cm (previously 4.52 cm × 4.93 cm × 4.47 cm) with extension to the renal hilum resulting to disruption and splaying of the pelvicalyceal system; Full arrowhead: decrease in size of the left adrenal hematoma measuring 6.4 cm × 6.4 cm × 8.8 cm (previously 6.88 cm × 8.37 cm × 5.69 cm) with resorption of the left subcapsular hematoma. CT: Computed tomography

Diagnosis at this point was GTN IV: 20. Chemotherapy was immediately instituted using the etoposide-methotrexate-actinomycin D-cyclophosphamide-vincristine (EMACO) regimen with high-dose methotrexate and concomitant whole-brain irradiation. Following the second cycle of chemotherapy, the patient developed febrile neutropenia, severe diarrhea, markedly elevated liver enzymes, and mucocutaneous lesions characteristic of methotrexate adverse reaction. Methotrexate was thus removed from her regimen. There was a complete resolution of the vulvar lesions after the fourth cycle of chemotherapy [Figure 8]. The patient eventually achieved remission after eight cycles of chemotherapy inclusive of three consolidation therapies [Figure 9]. Serial posttreatment surveillance of her lungs, abdomen, and brains showed no evidence of disease. She has remained disease free for the past 6 years.

Discussion

GTN is a rare group of malignancies characterized by abnormal trophoblastic proliferation and elevated hCG titers. This includes invasive mole,

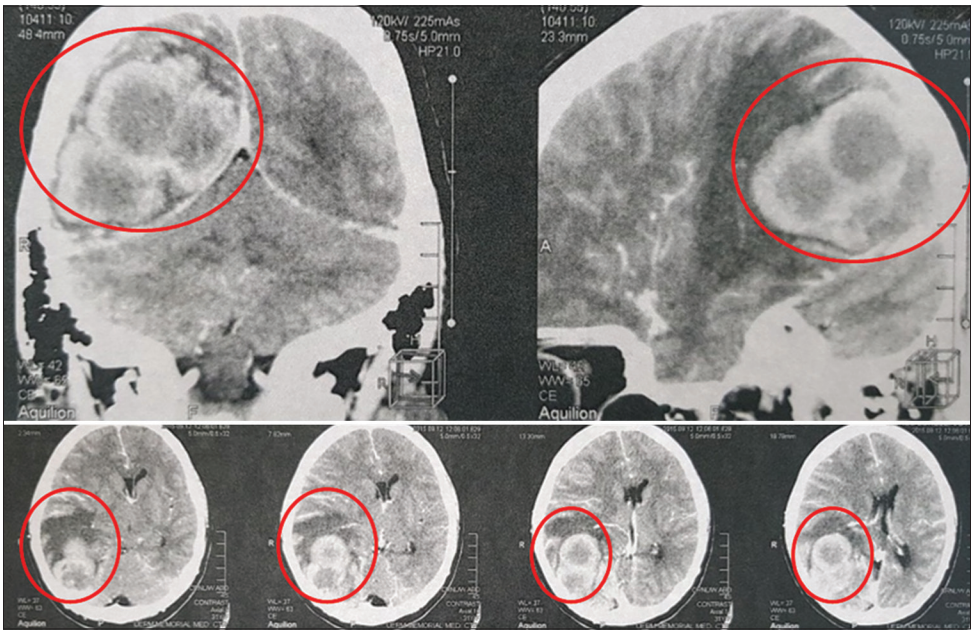

Figure 6: Contrast-enhanced cranial CT scan (coronal and axial view). Hemorrhagic intracranial metastases in the right occipito-parieto-temporal lobe (red circle) with surrounding edema and mass effects

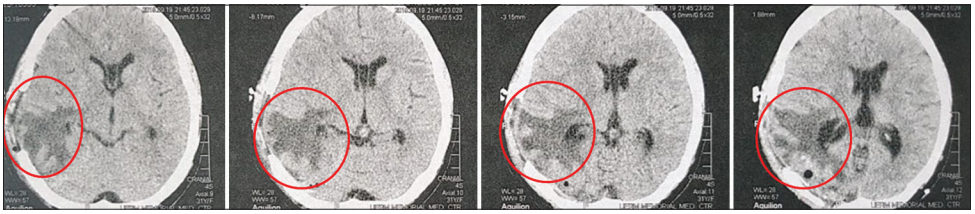

Figure 7: Plain cranial CT-Scan. Complete gross-resection of right occipital-parietal and temporal lobe tumors (red circle) with resolution of mass effects and residual post-operative changes

choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. These malignancies can occur weeks or years following any pregnancy but occur most commonly after a molar pregnancy.[5,6]

Wide variations exist in the reported incidence. It affects 1 in 20,000–40,000 pregnancies in the United States and 3–9/40,000 pregnancies in Southeast Asia and Japan. About 50% of all choriocarcinomas arise from a complete molar gestation, 25% following a normal pregnancy, and 25% after a spontaneous miscarriage or ectopic pregnancy.[2,7] Based on the accumulated data from accredited hospitals by the Philippine Obstetrical and Gynecological Society, the prevalence rate of choriocarcinomas and other GTNs in the Philippines has remained almost constant at 0.56/1000 pregnancies.[8]

Data on etiologic factors for choriocarcinoma are lacking due to the rarity of the tumor. Maternal age and history of the hydatidiform mole are the only two established risk factors, although studies have speculated on the risks of oral contraceptives and other exogenous hormones.[5,9] However, in the current retrospective database study, no association has been found between hormonal contraception and the development of GTN.[9] Race may also a risk factor due to the higher prevalence reported from Asia, the Middle East, and Africa, with the highest incidence from Southeast Asia.[2,7,10]

The clinical presentation is diverse. Abnormal vaginal bleeding remains to be the most common symptom, which occurs in 66.6% of cases. Other relatively frequent presentations are respiratory symptoms (11.1%) or a persistently positive pregnancy test (5.5%).[11] Approximately 30% of choriocarcinoma patients exhibit metastasis at the time of diagnosis. The most common metastatic sites are the lungs (80%), vagina (30%), pelvis (20%), liver (10%), and brain (10%).[12,13]

Brain metastasis portends a poor prognosis. Cerebral involvement can cause increased intracranial pressure and bleeding, which often leads to neurological

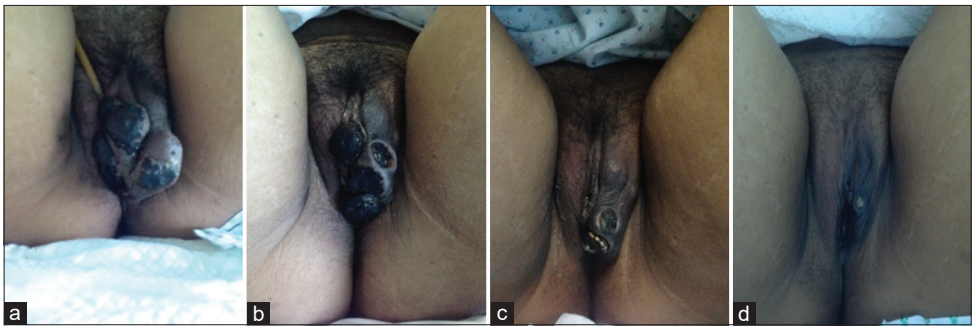

Figure 8: Regression of vaginal metastasis during treatment. (a) Lesion on admission at our institution, (b) lesion after EMACO I, (c) further regression in the size of the lesion after EMACO II, (d) vaginal lesion almost gone following EMACO III. EMACO: Etoposide-methotrexate-actinomycin D-cyclophosphamide-vincristine

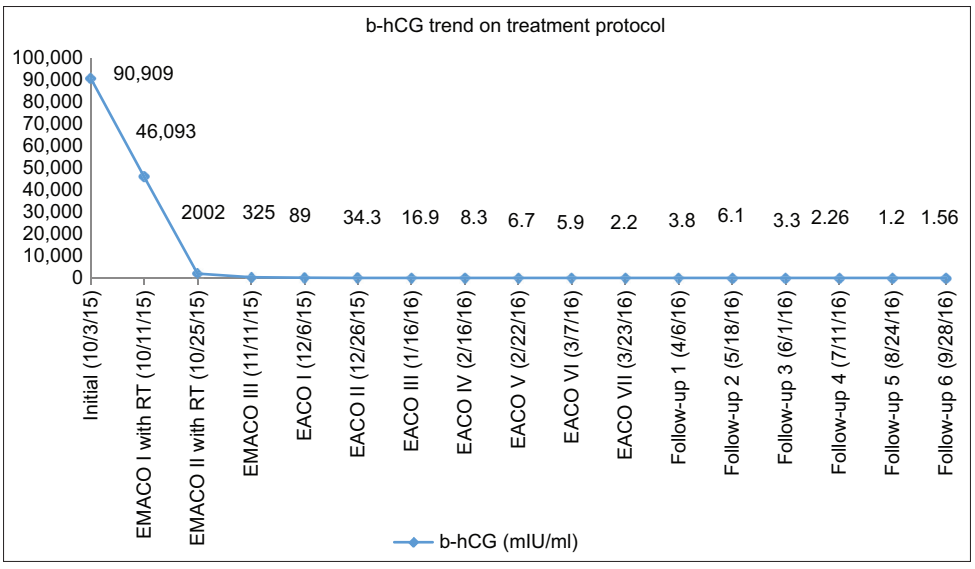

Figure 9: Trend of hCG of patient while on treatment and follow-up. hCG: Human chorionic gonadotropin

symptoms, including nausea, vomiting, headache, seizures, slurred speech, visual disturbances, or hemiparesis. In the index case, neurologic symptoms were the initial manifestations without the evidence of any gynecologic symptom or sonologic finding. Severe headache and blurring of vision on the left eye, in the absence of any gynecologic symptoms, may not have aroused any suspicion of choriocarcinoma to the clinician, especially since the antecedent pregnancy was a normal pregnancy 3 years ago.

Diagnosis of choriocarcinoma is made based on the clinical presentation, serum hCG level, and typical ultrasonographic findings. Unfortunately, the atypical sequence of events manifested by the patient, along with the late gynecologic manifestations and normal findings on transvaginal ultrasound led to misdiagnosis and subsequent delay in treatment. A histopathological diagnosis is not essential for the diagnosis and treatment of GTN. It was fortunate that biopsy was not done on the suspicious labial mass, which would have caused profuse and potentially lethal bleeding due to the hypervascularity of trophoblastic tumors. Craniectomy is not usually warranted unless the patient presents with intracerebral bleeding with deteriorating neurological status. In our case, the craniectomy not only improved the condition of the patient but also became the tool that led to the eventual diagnosis of the disease. Therefore, in the presence of unexplained systemic symptoms in any reproductive-aged woman, it is prudent to obtain serum hCG titers even in the absence of abnormal uterine bleeding or any gynecologic symptoms. Correlation with the serum hCG titer may give a hint to the diagnosis, which was initially neglected in this case. A high index of suspicion, accurate and thorough clinical history, and physical examination are crucial to mitigate unnecessary procedures and clinch the diagnosis early.

After a complete metastatic work-up, patients are staged using the FIGO 2000 staging system and scored using the modified WHO prognostic scoring system. This system allows the stratification of patients into low-risk, high-risk, and ultrahigh-risk diseases, which guides physicians as to the chemotherapeutic regimen that is most appropriate for patients.[5] Our patient was diagnosed with GTN IV: 20.

Despite having widespread disease and rapid progression, choriocarcinoma is now one of the most curable malignancies. Chemotherapy remains to be the foundation of treatment. The EMACO regimen, composed of Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, and Vincristine (Oncovin), is now the most commonly used regimen for the treatment of high-risk GTN due to its good efficacy and tolerability profile. The survival rate of high-risk patients treated with the EMACO regimen is 88%, and 76% of these patients were alive with no evidence of disease after 5.5 months.[14]

Patients with central nervous system lesions are typically considered among the ultrahigh-risk subgroup that benefits from coordinated multimodal therapy. Systemic chemotherapy in the form of methotrexate, etoposide, actinomycin D, cyclophosphamide, and vincristine is the optimal treatment of choice with concomitant whole-brain irradiation to limit acute hemorrhagic complications from brain metastases. Whole-brain irradiation combined with systemic chemotherapy results in cure rates up to 75% among patients who initially present with brain metastases with approximately 70%–85% long-term survival in contemporary studies.[11,15] Our patients were given high-dose EMACO with concomitant whole-brain irradiation therapy to achieve hemostasis and tumor shrinkage.

Even with intense chemotherapy, craniectomy may also play a role in therapy for high-risk diseases as a means of controlling tumor hemorrhage or dealing with other life-threatening complications. However, craniectomy for the sole purpose of doing a biopsy to obtain a histopathologic diagnosis is not recommended.[16]

Recently, selective angiographic embolization has become a part of multimodal therapy, which is employed to control tumor bleeding instead of surgical intervention.[17] Our patient had angiographic embolization of the left inferior phrenic and superior adrenal arteries from a different metastatic site, which spared her from further extensive surgical intervention.

In the index case, the patient achieved complete remission following multimodal treatment with systematic multiagent chemotherapy, whole-brain radiation therapy, resection of the brain lesion, and selective arterial embolization of metastatic sites. This case demonstrates the importance of rapidly initiating chemotherapy and radiotherapy for FIGO stage IV gestational choriocarcinoma following diagnosis. Ninety percent of patients with choriocarcinoma achieve complete or prolonged remission following treatment with multiagent chemotherapy regimens; hence, an accurate and prompt diagnosis is immensely important.

Conclusion

One of the challenges in making the diagnosis of GTN is the variability in clinical presentation. This article reports the paradoxical manifestation of choriocarcinoma where the patient manifested with neurological symptoms and widespread metastasis in the absence of gynecologic

symptoms and sonologic findings. The initial diagnosis was primary brain tumor. An emergency craniectomy was done for surgical decompression. Although this procedure eventually paved the way for the histologic diagnosis of choriocarcinoma, this would have been prevented if there was a suspicion of a possible GTN on the initial presentation. The patient was eventually treated with high-dose EMACO chemotherapy and concomitant whole-brain irradiation. This case highlights the importance of a high index of suspicion for a possible GTN to prevent unnecessary procedures, ensure timely diagnosis, and institute early treatment.

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

Krizia Marie M. Cornel, MD - involved in the conceptualization, data curation, writing of the original draft, review and editing, visualization.

Agnes L. Sorina-Estrella, MD - involved in conceptualization, validation, resources, data curation, review and editing of the draft, visualization, supervision, project administration.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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