Case Report

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A series of missing primaries: Pulmonary metastasis in Gestational Trophoblastic Neoplasia in the absence of uterine tumors

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Abstract:

Gestational trophoblastic neoplasias (GTN) are extremely aggressive tumors derived from placental trophoblasts. These tumors are always the sequalae of a pregnancy. Choriocarcinoma, which is the most common of these, is typically characterized by early extra-pelvic hematogenous spread. Since the progression of illness is rapid, timely diagnosis and treatment will favor improved chances for cure, whereas late commencement of therapy will make resolution difficult. The diagnosis of GTN is straightforward with an elevated beta-human chorionic gonadotropin (β-hCG) and distinct sonographic features of the tumor inside the uterus. However, very rarely, this disease may occur in the absence of uterine tumors. Practicing physicians must be mindful that GTN may initially manifest with pulmonary symptoms and/or radiographic evidence of metastatic lung lesions. In this series, the features pertaining to the clinical course of three patients are described, all of whom presented with pulmonary masses, elevated β-hCG, and normal transvaginal sonograms.

Keywords:

Choriocarcinoma, gestational trophoblastic neoplasia, pulmonary metastasis

Introduction

Gestational trophoblastic neoplasia (GTN) represents a spectrum of proliferative abnormalities of trophoblasts associated with pregnancy.[1] The World Health Organization (WHO) classification of GTN includes invasive mole, choriocarcinoma, placental site trophoblastic tumor, epithelioid trophoblastic tumors, and miscellaneous and unclassified trophoblastic lesions. Choriocarcinoma is the most common malignant form, which acts as a highly aggressive tumor due to the rich vascularity and affinity of trophoblasts for blood vessels. Although its most frequent site of metastasis is the lung, gestational choriocarcinoma rarely presents as a pulmonary mass in the absence of a primary uterine tumor.

This paper presents a series of three patients with choriocarcinoma who consulted for evaluation of abnormal clinical and radiologic chest findings.

Cases

Case 1 is a 27-year-old gravida 6 para 6 (6006) who was admitted for the weakness of all extremities. She had continuous vaginal spotting and hemoptysis after delivering a term infant 4 months before admission. Computerized tomography (CT) scan revealed brain and multiple unilateral lung metastases. Ultrasonography showed

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no evidence of uterine tumor. Impression was GTN Stage IV: the WHO prognostic score of 18. She had good response to chemotherapy with etoposide, methotrexate, actinomycin (EMA), cyclophosphamide, and oncovin (EMACO) with concomitant whole-brain irradiation until the fourth cycle when serum beta-human chorionic gonadotropin (β-hCG) titers started to increase. Metastatic workup revealed resolution of the brain lesion on CT scan but with persistence of the multiple lung foci. Salvage chemotherapy in the form of EMA, etoposide, and cisplatin (EMA/EP) was started. After the first cycle of EMA/EP, the patient underwent surgery. The planned operative intervention was a pulmonary resection followed by exploratory laparotomy and total hysterectomy. However, because of extensive pulmonary parenchymal involvement of the tumor, left upper lobectomy, resection-anastomosis of the left pulmonary artery, and left lower lung wedge resection were performed. Intraoperatively, the patient became hemodynamically unstable, thus, the plan for pelvic exploration was deferred. Administration of chemotherapy was delayed for 3 weeks to allow adequate postoperative recovery and healing. Weekly postoperative serum β-hCG titers showed a decreasing trend. Postoperative chest CT scan showed clearing pulmonary nodules. However, on the 3rd week following surgery, serum β-hCG began to rise. Repeat metastatic survey revealed negative results. The second cycle of EMA/EP yielded a good response. After the third cycle, the serum β-hCG increased again. A hysterectomy was performed. This resulted to a decrease in the β-hCG titer despite the absence of any uterine abnormality by histopathology. Chemotherapy was continued but with poor response. The patient refused further treatment eventually succumbing to the disease.

Case 2 is a 43-year-old gravida 10 para 8 (8028) who was admitted due to elevated serum β-hCG titers. She had a molar pregnancy 5 years before admission for which a hysterotomy was done. Two months after the surgery, she experienced profuse vaginal bleeding. She was admitted and given an unrecalled "chemotherapeutic agent" intramuscularly. Serum β-hCG titers were monitored until normal results were achieved. The vaginal bleeding resolved and resumption of regular menstruation ensued. Four months before admission, she had increasing frequency of chest pains, accompanied by cough, and hemoptysis. The general and pelvic examinations were unremarkable. Transvaginal sonogram revealed normal results [Figure 1]. Serum β-hCG was markedly elevated at 102,748 mIU/mL. Chest radiograph showed a mass on the superior segment of the left lower lobe of the lung [Figure 2]. Further workups did not demonstrate metastasis to other sites. She was subsequently admitted with an impression of GTN Stage III with a WHO prognostic score of 14. She achieved remission after adequate responses to EMACO and completing consolidation courses [Figure 3].

Case 3 is a 19-year-old gravida 1 para 0 who was admitted due to elevated β-hCG levels. She had a curettage for an abortion 9 months before the diagnosis of GTN. Histopathologic analysis of the specimen revealed decidual tissue. She reported abnormal uterine bleeding postcurettage. Despite a postoperative ultrasound revealing a thin endometrium and normal ovaries [Figure 4], the β-hCG levels were persistently elevated at 153,900 mIU/mL. Chest radiography showed a pulmonary mass at the right upper lobe [Figure 5]. She was then referred to a tertiary hospital where further metastatic workups showed no demonstrable lesions in other organs. On the day of admission, she had one episode of hemoptysis. The general and pelvic examination findings were unremarkable. She was diagnosed as a case of GTN Stage III with a WHO prognostic score of 10. Multiagent chemotherapy using EMACO was initiated. Monitoring of β-hCG titers during treatment [Figure 6] revealed adequate response, and she achieved a normal level after seven cycles of chemotherapy. She is for three cycles of consolidation therapy.

Discussion

GTN comprises a group of disorders arising from placental trophoblastic tissue after fertilization.[1] The WHO classification of GTN includes invasive mole, choriocarcinoma, placental site trophoblastic tumor, epithelioid trophoblastic tumors, and miscellaneous trophoblastic lesions. The various types of GTN have varying potentials for local invasion and metastases and they generally respond to chemotherapy.

Overall, GTN is a rare disease, with its incidence varying greatly in different parts of the world.[1] In the Philippines, the prevalence rate of GTN from the years 2002 to 2008 has remained constant at 0.56/1000 pregnancies or 857/1,531,453 pregnancies.[2] Diagnosis is based on elevated serum β-hCG coupled with a highly vascular, invasive uterine mass. Pulmonary metastasis is present in over 80% of cases.[3] Rarely, cases of GTN are diagnosed due to elevated serum β-hCG associated with lung metastasis but in the absence of a uterine mass. The three patients presented in this paper represent the only three cases of metastatic GTN without evidence of gynecologic lesions that were encountered at the Division of Trophoblastic Diseases of the Philippine General Hospital from the years 2000–2015.[4]

Choriocarcinoma is the most common form of GTN. It is histologically characterized by a malignant proliferation of the Langerhans cells and syncytial cells

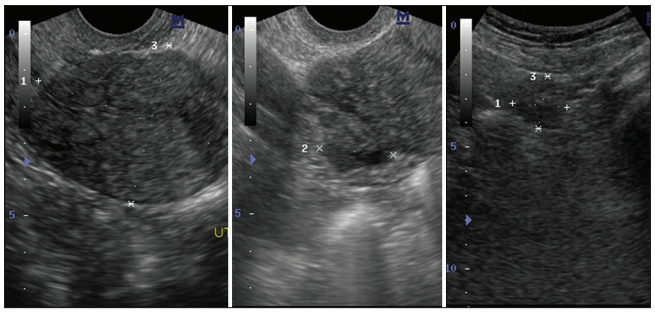

Figure 1: Transvaginal sonogram of Case 2 depicting normal results

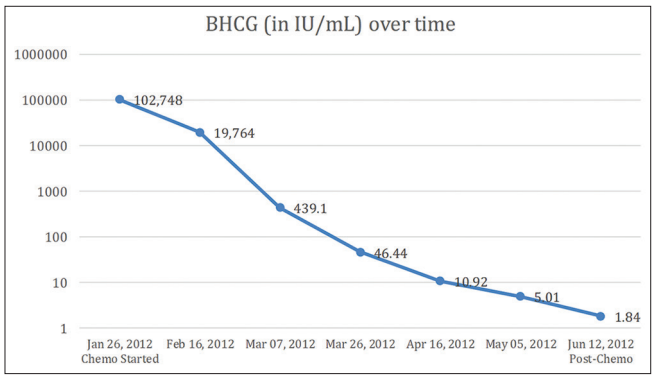

Figure 3: Beta-human chorionic gonadotropin titers of Case 2 showing adequate response to chemotherapy

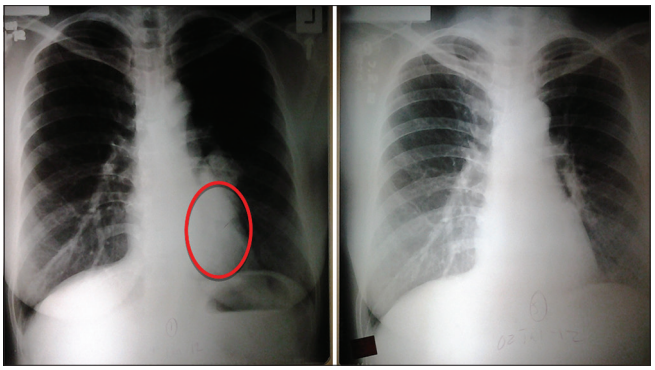

Figure 2: Chest radiograph of the Case 2 showing a 6.5 cm × 4.5 cm mass at the superior segment of the left lower lobe (left) and clearing of said mass (right) after chemotherapy

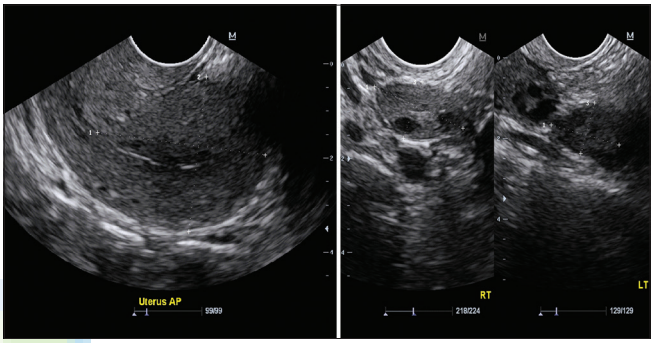

Figure 4: Transvaginal sonogram of Case 3 showing normal results

of trophoblastic origin that is normally situated in the female genital tract after a gestational event.[5-7] Several years may elapse between the antecedent pregnancy and disease presentation. Its clinical presentation is varied and is dependent on the involved organ. Vaginal bleeding remains to be the most common symptom.[3] The ability to eradicate these tumors with chemotherapeutic methods depends on detecting their presence as soon as possible after the antecedent pregnancy.[8]

When confronted with a patient presenting with a pulmonary mass, determining its etiology is a diagnostic challenge. Proper interpretation of the information obtained from a thorough clinical history and physical examination will dictate the appropriate battery of diagnostic examinations and subsequent course of management. Occasionally, gynecological features are absent at the time of the initial presentation of choriocarcinoma. A high index of suspicion is necessary for the diagnosis. Hence, its possibility should always be kept in mind in all reproductive-aged women presenting with unusual chest radiographs.[9]

In all three cases, patients presented with a radiographically documented pulmonary mass with accompanying lower respiratory symptoms. The clinician must account for all other etiologies that may produce mass lesions in the lungs. Primary pulmonary carcinoma is an entity that must first be ruled out since diagnostic and therapeutic management options would differ from that of metastatic choriocarcinoma– the former is diagnosed utilizing visualization and histopathologic sampling of the mass through bronchoscopy, while biopsy is avoided in the latter because of its high vascularity and its morbid propensity to cause massive pulmonary hemorrhage. In terms of cure, the standard in pulmonary carcinoma is surgical resection, whereas chemotherapy is the principal mode of treatment for metastatic choriocarcinoma.

hCG is a hormone normally produced by the syncytiotrophoblast after conception. It is a glycoprotein composed of 237 amino acids with mass of 25.7 kDa. It has an α (alpha) and a β (beta) subunit. Malignant neoplasms may cause pathologic production of this hormone.[10] The beta subunit of hCG (β-hCG) is currently being utilized as a tumor marker for choriocarcinomas, germ cell tumors, hydatidiform moles, teratomas with elements of choriocarcinoma, and islet cell tumors.[11] Serum titers of β-hCG were elevated in all our index cases.

Careful interpretation of pulmonary masses in the background of elevated titers of β-hCG is warranted, as a very close differential, primary pulmonary choriocarcinoma (PPC), a tumor of lung origin, also presents as such. These cancers are unusual because of their nongestational, extra-gonadal origin. Primary

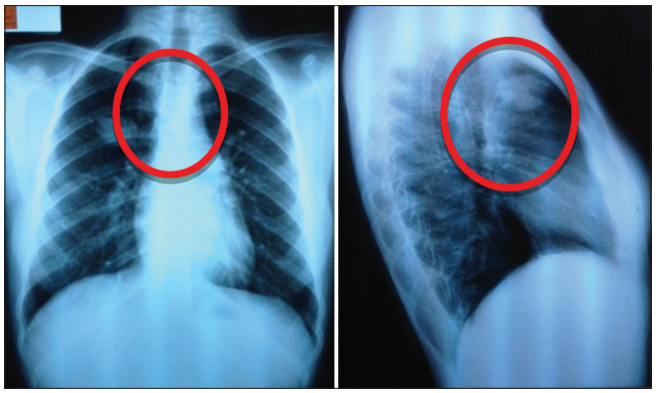

Figure 5: Chest radiographs of Case 3 on admission showing a well-defined mass measuring approximately 2.8 cm × 3.8 cm at the anterior segment of the right upper lobe

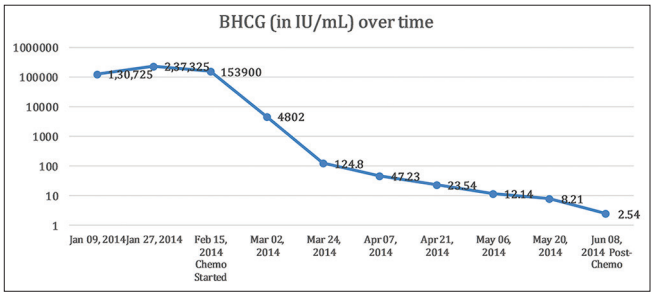

Figure 6: Serum beta human chorionic gonadotropin of case 3 showing adequate response to chemotherapy

nongestational choriocarcinoma may arise from the mediastinum, the midline retroperitoneum, or intracranially. Although metastasis to the lung is not infrequent, unique trophoblastic tumors originating from the lungs are extremely rare with their histological features similar to those of choriocarcinomas arising elsewhere. The rarity of PPC is emphasized by the publication of only 25 cases in all available world literature. The exceptionally scant occurrence of PPC and the small size of tumor samples make it challenging to diagnose either by cytology or bronchoscopy-guided biopsy alone. Committing to a diagnosis entails the exclusion of metastatic spread from GTN. The diagnostic criteria include the lack of a previous gynecologic malignancy, presence of a lung lesion in the absence of a gonadal primary site and a raised serum hCG titers that become normal after surgery or chemotherapy, and pathologic confirmation of the disease.[12]

Despite histologic similarity, the reason that may explain why PPC behaves differently from GTN is unknown. The prognosis of PPC is usually grave. No successful protocol has been proven for this disease. Surgery is of little value because of its invasiveness and rapid growth. Radiation therapy has been disappointing as PPC is radiotherapy-resistant. Despite its limited value, surgical resection followed by adjuvant multi-agent chemotherapy appears to be the plausible treatment for PPC.[6,7] This is in contrast to metastatic GTN, in which chemotherapy remains the standard of care with surgical intervention as an adjunct. In all the cases presented, despite fulfilling the diagnostic criteria of PPC based on the presenting pulmonary manifestations of the illness, the elevated β-hCG titer, and the absence of gynecologic lesions, the disclosure of antecedent pregnancies, occurrence of abnormal uterine bleeding, and good responses to chemotherapy, greatly favor a gestational etiology.

At present, there is no accepted definite pathophysiology for the occurrence of metastasis in the absence of a primary tumor in GTN. The most plausible mechanism is the vascular invasion of trophoblastic emboli to the lungs, with concurrent and unprompted regression of the intrauterine tumor.[13] This so-called "burn out" hypothesis signifies a unique feature of GTN – that it is likely to become metastatic even before the primary lesion is detected.

GTNs are generally responsive to chemotherapy. Parameters that influence prognosis involve the patient's age, type, and interval from an antecedent pregnancy, presenting β-hCG level, tumor size, sites, and number of metastasis, and previous chemotherapy.[14] In the first case, pulmonary and cranial metastasis led to the classification of a Stage IV, high-risk illness, which carried poor prognosis. The succeeding two cases are high-risk Stage III diseases that fared comparatively better.

The standard treatment for GTN is chemotherapy, using either a single or multiagent chemotherapeutic regimen, depending on the stage and prognostic score of the patient. Planning the course of treatment is based on the patient's pretreatment FIGO 2000 classification and WHO prognostic scoring system.[14] Women with scores ≤6 are classified as low-risk and are treated with single-agent chemotherapy while women with scores ≥7 are considered high risk and are treated with multiagent chemotherapy. Consolidation chemotherapies are given in all cases following normalization of β-hCG titer. The cure rate for women with low-risk GTN approaches 100% and 95% for women with high-risk GTN.

The main indication for surgical intervention in cases of GTN is removal of a chemotherapy-resistant focus. However, hysterectomy may be also done to decrease tumor load to decrease the number of chemotherapeutic cycles. This may be offered to patients who have a completed family size and is no longer desirous of future pregnancy. The decision to remove the adnexa depends on the patient's age and involvement of the ovaries. In the absence of gynecologic lesions, and with a good response to chemotherapeutic agents, the clinician may opt not to

pursue surgery, as with the last two cases presented. The patient's plan for future fertility was likewise put into consideration in managing the third case.

In instances of chemotherapy-resistant pulmonary lesions, resection of metastasis appears to be viable. The criteria to perform pulmonary surgery in metastatic GTN are as follows: the patient must be fit for surgery, the primary site of malignancy must be controlled, there is no evidence of metastasis elsewhere and the metastasis involves only a singular lung.[15] Thoracic surgery has significantly contributed to the management and outcome of complicated GTN patients.

It is inevitable that some patients, despite aggressive and timely institution of treatment, fail to attain remission. In this group, palliative care should be considered. The primary goals of palliative care are relief of the patient's suffering and provision of the best possible quality of life. Involvement of specialty palliative care providers may provide a holistic approach in managing these patients. Given the lack of proven overall survival benefit associated with chemotherapy-resistant disease, a clinician may opt to consider palliation in lieu of more invasive yet medically futile treatment. The patient in the first case is an ideal candidate for palliative care intervention.

Overall, the cases presented in this report were diagnosed and managed as early as the circumstances permitted. In addition to illustrating the unusual metastatic course of GTN, the first case also highlights the autonomous nature of the human individual and that the ultimate decision to pursue treatment ultimately lies on the patient herself. The patient in the second case is now under the remission phase. The patient in the last case is completing treatment with a very good chance of achieving remission. The favorable outcome in two of the three cases may be attributed to the clinicians' high index of suspicion, timely management, and initiation of definitive treatment at the earliest possible time. It is unfortunate that the first case sought treatment at a relatively advanced clinical state leading to late commencement of treatment and the poor response to therapy.

Conclusion

It is imperative for any clinician to have a high index of suspicion, backed by a thorough analysis of the clinical findings, to appropriately diagnose and treat patients with choriocarcinoma. Ample recognition of the various manifestations of metastatic choriocarcinoma and greater use of assays for hCG should result in prompt diagnosis and an improved long-term prognosis in these patients. Varied forms of treatment are available. Based on sound judgment, the clinician must decide which of these will best attain the treatment goals set the patient and the physician.

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.

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Conflicts of interest

There are no conflicts of interest.

References

1. Altieri A, Franceschi S, Ferlay J, Smith J, La Vecchia C. Epidemiology and aetiology of gestational trophoblastic diseases. Lancet Oncol 2003;4:670-8.
2. Cagayan MS. Changing trends in the management of gestational trophoblastic diseases in the Philippines. J Reprod Med 2010;55:267-72.
3. Savage P. Clinical features of molar pregnancies and gestational 21 trophoblastic neoplasia. In: Hancock BW, Seckl MJ, Berkowitz RS, 22 editors. Gestational Trophoblastic Diseases. 4th ed. London, UK: 23 International Society for the Study of Trophoblastic Diseases; 2015. c10p12.
4. Section of Trophoblastic Diseases, Philippine General Hospital, Compilation of Annual Reports form 2000-2015 (Unpublished Data). University of the Philippines,Manila, 2015.
5. Serno J, Zeppernick F, Jäkel J, Schrading S, Maass N, Meinhold-Heerlein I, *et al*. Primary pulmonary choriocarcinoma: Case report and review of the literature. Gynecol Obstet Invest 2012;13:171-6.
6. Berthod G, Bouzourene H, Pachinger C, Peters S. Solitary choriocarcinoma in the lung. J Thorac Oncol 2010;5:574-5.
7. Di Crescenzo V, Laperuta P, Napolitano F, Carlomagno C, Garzi A, Vitale M. An unusual case of primary choriocarcinoma of the lung. BMC Surg 2013;13 Suppl 2:S33.
8. Magrath IT, Golding PR, Bagshawe KD. Medical presentation of choriocarcinoma. Br Med J 1971;2:633-7.
9. Lazovic B, Milenkovic V. Gestational choriocarcinoma with hemorrhagic pleural effusion. Arch Oncol 2010;18:86-7.
10. Canfield RE, O'Connor JF, Birken S, Krichevsky A, Wilcox AJ. Development of an assay for a biomarker of pregnancy and early fetal loss. Environ Health Perspect 1987;74:57-66.
11. Gregory JJ Jr., Finlay JL. Alpha-fetoprotein and beta-human chorionic gonadotropin: Their clinical significance as tumour markers. Drugs 1999;57:463-7.
12. Kini U, Babu MK. Primary pulmonary choriocarcinoma: Is it still an enigma? Indian J Chest Dis Allied Sci 2007;49:219-26.
13. Seetharaman ML, Arora R, Arora VK. Gestational choriocarcinoma with haemorrhagic pleural effusion. Indian J Chest Dis Allied Sci 1991;33:39-42.
14. Ngan HY, Bender H, Benedet JL, Jones H, Montruccoli GC, Pecorelli S, *et al*. Gestational trophoblastic neoplasia, FIGO 2000 staging and classification. Int J Gynaecol Obstet 2003;83:175-7.
15. Tomoda Y, Arii Y, Kaseki S, Asai Y, Gotoh S, Suzuki T, *et al*. Surgical indications for resection in pulmonary metastasis of choriocarcinoma. Cancer 1980;46:2723-30.