Research Article

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Gestational Choriocarcinoma

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ABSTRACT

Gestational choriocarcinoma is a malignant tumor with a high potential for angioinvasion and metastasis that is defined within Gestational Trophoblastic Diseases. The incidence is variable, with the presence of a complete molar pregnancy as the main risk factor, however, it has the capacity to develop from any type of gestational event. The clinical manifestations will depend on the involvement and extent of the pathology, so in the case of metastatic disease the organ mainly affected will be the lung, while in local disease the common finding is irregular vaginal bleeding. Diagnosis is based on measurement of serum beta-hCG levels accompanied by a complete medical history, an exhaustive physical examination and the performance of imaging aids such as transvaginal or transabdominal ultrasound. Central medical management consists of the administration of cycles of chemotherapy with one or more drugs depending on the extent of the condition. Finally, the prognosis is usually favorable, however, it depends to a great extent on the opportune recognition of the case, therefore, Through this document, we seek to provide an updated vision of the problem in question in order to facilitate comprehensive medical management and, therefore, contribute to the reduction of epidemiological figures related to morbidity and mortality.

KEYWORDS: Choriocarcinoma; Gestational; Metastasis; beta-hCG; Chemotherapy; Prognosis; Morbidity and mortality

INTRODUCTION

Gestational trophoblastic disease (GDT) comprises a heterogeneous group of lesions generated from the trophoblastic epithelium of the placenta that are classified as neoplastic (invasive moles, choriocarcinoma, placental trophoblastic tumor, and epithelioid trophoblastic tumor) or non-neoplastic (partial or complete hydatidiform mole) affecting approximately 1 in 1,000 pregnancies [1,2].

Choriocarcinoma (CCA) can be classified into three subtypes as: gestational when it develops from any event related to pregnancy, non-gestational when they are derived from germ cells or somatic

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cells, and finally, intraplacental when their presence within the placenta is defined, correlated with metastasis in mother and fetus [3]. Gestational choriocarcinoma represents 95% of malignant choriocarcinoma cases. It was identified that approximately 50% derives from molar pregnancy, 25% from term pregnancies, 22% abortions and only 3% from ectopic pregnancy [4].

The gestational CCAas a malignant epithelial tumor derived from chorionic villi, it is included in the spectrum understood as gestational trophoblastic neoplasia (GNT) defined by the International Federation of Gynecology and Obstetrics (FIGO) as a condition in which levels of the human chorionic gonadotropin hormone (hCG) do not decrease correctly in the absence of a normal pregnancy. This entity is classified from a combination between the Staging System established by FIGO (Table 1) with the Classification system of the Forecast of the World Health Organization (Table 2) allowing to observe the anatomical distribution based on the extension of the disease description of the risk of resistance to monotherapy. Low-risk GTN is one that is in FIGO stages I, II, or III with a WHO score of less than 7, while high-risk GTN is when stages I, II, or III are found with a WHO score. greater than or equal to 7 as well as that of stage IV. According to Brenes et al. [5] patients with a score greater than or equal to 13 will present premature death resulting from hemorrhagic sequelae.

Table 1: FIGO layering for NTG.

STAGE I	Tumor limited to the uterine body
STAGE II	Tumor extends to adnexa, broad ligament, or vagina, but limited to genital structures
STAGE III	Pulmonary metastases visible on chest x-ray with or without extension to genital structures (uterus, pelvis, or vagina)
STAGE IV	Distant metastatic disease outside the lungs, pelvis, or vagina

Table 2: WHO risk scoring system for GTN. Bassrisk with scoresless than or equal to 6. High risk scores greater than 6 less than 13. Very highrisk in scoresolder than 13.

FIGO Score	0	1	2	4
Age	<40	>40	-	-
Previous pregnancy	cool	abortion	Normal	-
Interval since last pregnancy (Months)	<4	6-Apr	12-Jul	>12
Serum HCG level (IU/mL) Before treatment	<10 3	>103- <104	>104- <105	>105
Upper tumor size (CMS)	-	4-Mar	>=5	-
Site of metastasis	Lung	Spleen	Gastrointestinal tract	Brain
		Kidney		Liver
Number of metastases	-	4-Jan	8-May	>8
Failure to prior treatment (chemotherapy)	-	-	single drug	2 or more drugs

CCA is a rare condition with a variable incidence that occurs mainly in women of reproductive age. The pathogenesis is related to an alteration in the regulation of the invasion of the trophoblast cells into the decidua [6] with the main risk factors being a history of hydatidiform mole, advanced maternal age, ethnicity, and the use of oral contraceptives [7]. The signs or symptoms are non-specific and in most cases are related to the associated metastatic commitment, with the lung as the main organ affected; however, in non-metastatic disease the manifestation reported in up to 75% of all cases is the persistent and irregular vaginal bleeding [8-10]. The diagnosis is made from the quantification of serum beta-hCG levels, however, since it usually represents a challenge for the clinician, it is vitally important to maintain a high index of suspicion.to since medical management will depend on the type and stage of the disease being chemotherapy the initial intervention. Other valid medical procedures include dilation and curettage, hysterectomy, or even a combination of techniques [11].

Finally, the prognosis of the patients is usually favorable, however, this depends on multiple factors including tumor size, beta-hCG values, changes in the immune response and the existence or not of timely diagnosis, since in those cases late survival rates and associated complications increase drastically [12].

METHODOLOGY

To carry out this article, a systematic review of articles was carried out in the different scientific databases such as ScienceDirect, Pubmed, Elsevier, Scielo and Medline, for which the following keywords were used: “choriocarcinoma”, “trophoblastic”, “neoplasia”, “gestational” and “placenta”. Articles in English and Spanish, published since 2010, which clearly and precisely address the topic to be dealt with, were selected, obtaining a total of 30 articles, among which review articles and case reports stand out. All those articles published before 2010 or that did not provide sufficient or adequate information to address the topic to be dealt with were excluded from the review.

RESULTS AND DISCUSSION

Gestational CCA is a malignant and aggressive tumor considered to be the condition with the highest incidence within NTG. It occurs in women of reproductive age with an estimated incidence of 1 in

40,000 pregnancies in North America and Europe or 9.2 and 3.3 per 40,000 pregnancies in Southeast Asia and Japan respectively. It has the capacity to develop after any type of pregnancy, with complete molar pregnancy being the risk factor mainly associated, since Espinoza, Fernández [9] comment that although 80% of moles are considered benign and regress spontaneously, 15-20% persist and 2-3% become malignant. This is also confirmed by various authors who comment that CCA is 1,000 times more likely to develop after a molar pregnancy than any other gestational event [11-13]. Other related risk factors are black race, null or multiparity, maternal age (>35 years or <17 years), smoking and the use of oral contraceptives for more than 7 years, however, this The latter still generates great discussion [14].

Regarding the pathophysiology, it is important to mention that gestational CCA develops from the proliferation of the villous cytotrophoblast and syncytiotrophoblast, which is subjected to a process of hyperplasia and anaplasia, becoming a tissue with a high potential for angioinvasion and even the generation of distant metastasis since it produces significant levels of angiogenic growth factors and remodeling of the uterine vasculature [15]. The clinical manifestations can be subtle, however, they are related to the location and the presence or absence of metastatic involvement. In the case of contained disease, irregular and persistent vaginal bleeding is considered the most frequent sign. In addition, in those cases presented during an ongoing pregnancy, it should be taken into account that approximately 50% of the patients will present a higher uterine height than expected for gestational age and 30% of them increase in size in one or both ovaries [16]. Other less specific symptoms or signs are vomiting, abdominal pain, anemia, and hyperthyroidism.

On the other hand, Coronado et al. [3] comment that CCA within GTN is the condition with the greatest invasive capacity and that the lung is the main organ affected (60-95%) followed by the vagina (50%), cervix or vulva (15%), brain or liver (5-15%) and finally uterine tubes, kidney and even choroid in 0.2% of all cases [15-17]. The clinical manifestations of metastatic disease depend on the affected site, the most frequent being those coming from the respiratory system (cough, hemoptysis, chest pain or respiratory distress). Other possibly related symptoms include headache, altered state of consciousness, seizures, visual disturbances, abdominal pain, and hematuria.

Timely diagnosis is essential to establish a satisfactory response in medical management and the patient's prognosis, so despite the fact that it can be difficult on many occasions, healthcare personnel must maintain a high index of suspicion that is based on the completion of a complete clinical history including specific data on the disease. The physical examination must be exhaustive and include speculoscopy with bimanual palpation of the uterus to search for an adnexal mass due to the high frequency of vaginal dissemination. The main extension paraclinical is the quantification of serum beta-hCG since, as mentioned by Song et al. [16] the persistent elevation of this hormone after any molar or non-molar pregnancy, spontaneous abortion, ectopic, preterm or term can trigger the process. In this part, the criteria established by FIGO for the diagnosis of GTN must be taken into account. Jorgensen et al. [18] also comment that the production of beta-hCG by GTN is considerably higher in invasive mole and choriocarcinoma, reaching serum levels greater than 1,000,000 mUl/mL.

The use of imaging aids is a fundamental part of the diagnostic process, however, even today various debates have been generated about what should be definitively included in the routine assessment. According to Jorgensen et al. [18] ultrasound (abdominal or transvaginal) should be performed in patients with persistently elevated b-hCG levels after initial dilation and suction evacuation of a molar pregnancy to rule out a new pregnancy, measure the uterine volume and assess the spread of the disease within the pelvis. Since this allows us to characteristically demonstrate the presence of a non-specific intrauterine focal mass that can have any echogenicity, being hyper vascular on Doppler, being related to areas of necrosis and hemorrhage and even, in patients with more extensive disease, it may demonstrate invasion through the myometrium or beyond the uterus into the parametrium, vagina, and other pelvic organs (Figure 1); [19]. Coronado et al. [3] also mentions that ultrasound in combination with clinical history and hormone levels are the first line of diagnosis.

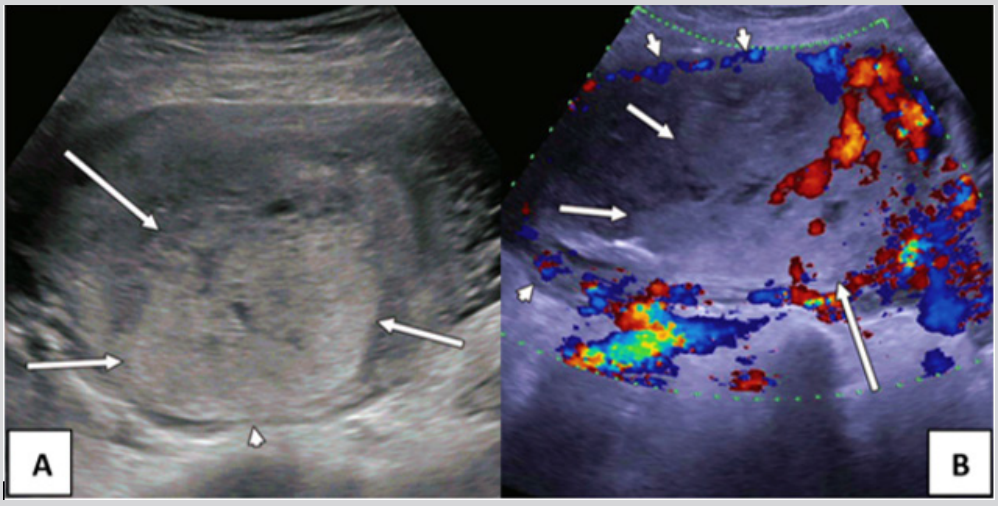

Figure 1: Choriocarcinoma. A. Transabdominal ultrasound showing a large hyperechogenic uterine mass (long arrows) invading the posterior myometrium (short arrow) reaching the serosal surface. B. Transabdominal Doppler imaging with a large, heterogeneous, predominantly hyperechoic vascular mass (long arrows) surrounded by highly vascularized myometrium (short arrows).

Chest X-ray is useful to evaluate pulmonary metastasis by finding rounded densities with alveolar pattern or even pleural effusion with embolic pattern secondary to pulmonary artery occlusion. Thoracoabdominal or pelvic computed tomography (CT) has a limited role for the study of the primary tumor; however, it is useful for the evaluation and staging of metastatic disease, mainly at the pulmonary level, where there are numerous pulmonary nodules surrounded or not by halos. ground glass opacity secondary to the presence of peritumoral hemorrhage (Figure 2); finally, nuclear magnetic resonance (NMR) is necessary to determine the involvement of the central nervous system. On the other hand, Brenes et al. [5].

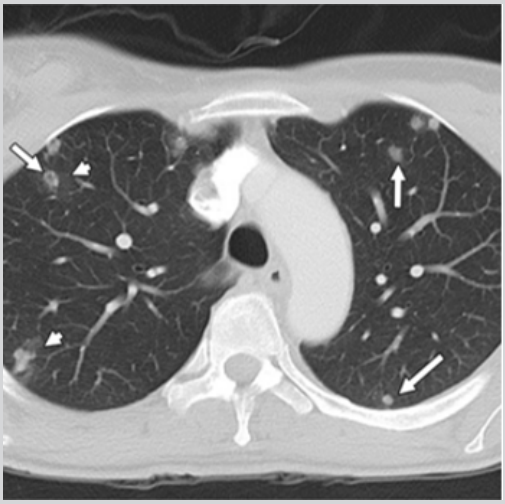

Figure 2: CT lung window of a woman with CCA with lung metastasis. Pulmonary nodules (long arrows) some surrounded by a halo of illustrated glass opacity (short arrows).

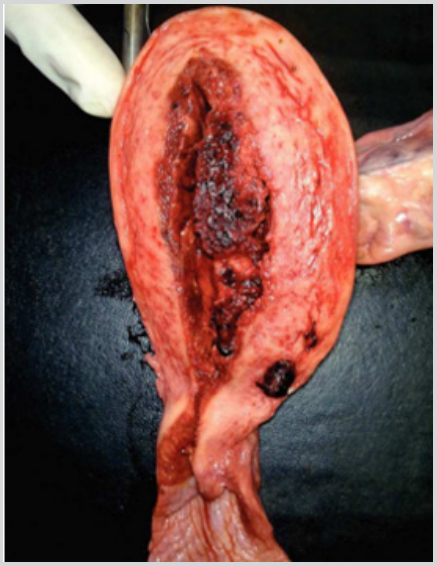

Figure 3: Sagittal section of the uterus with choriocarcinoma demonstrating intramural thrombosis.

Histological study has become a useful tool for the diagnosis, surveillance and detection of recurrence in case of drug resistance. Macroscopically, a single or multiple irregular uterine mass is found that presents extensive necrotic or hemorrhagic areas (Figure 3), while microscopically, a diffuse infiltrative or solid destructive growth is observed that affects the endometrium through tumor cells that contain villous trophoblasts. Chorionic cells of various types with biphasic or triphasic growth patterns with sheets of mononuclear tumor cells surrounded by multinuclear syncytiotrophoblastic cells (Figure 4). Hui [20] also ensures that marked cytological pleomorphism, nuclear enlargement, and intense mitotic activity will always be found. various authors. The medical management of CCA should be directed through staging and classification, however, in general, chemotherapy is the main focus, which must be used quickly and effectively. This is supported by various authors, including Braga et al. [1] who conducted a Brazilian multicenter study that addressed the role of chemotherapy in a specific subgroup comprised of 199 women diagnosed with CCA without evidence of metastatic disease of which 152 were treated with immediate initiation of chemotherapy and 47 with expectant management. It was intended to demonstrate that expectant management was safe and could prevent chemotherapy toxicity, however 44.7% of patients (21/47) required initiation of the drug [22].

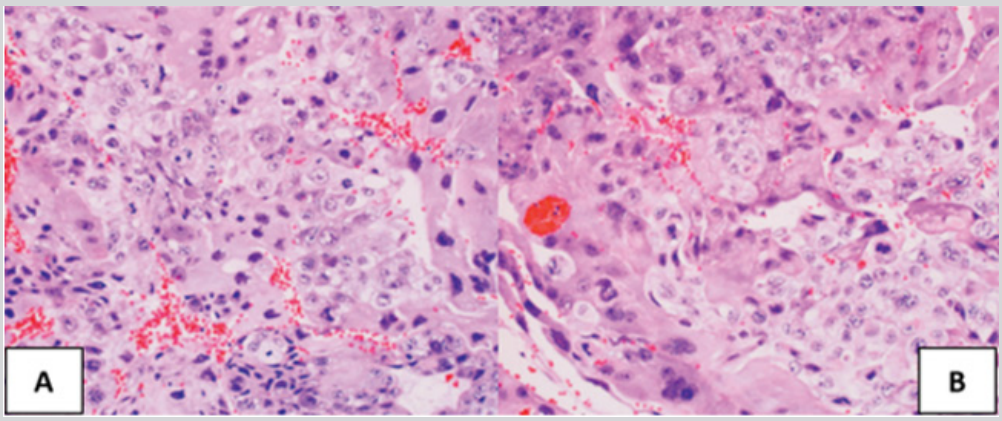

Figure 4: Histological study of CCA. A. Tumor cells in biphasic or triphasic proliferation surrounded by syncytiotrophoblast. B. Marked cellular atypia.

In low-risk disease, the general indication is to start therapy with methotrexate or actinomycin D, obtaining 10-year survival rates of up to 100% in stage I and 85% in stage II or III [7,26]. However, Agustín (11) comments that since there are more than 14 types of established therapeutic regimens, the decision will largely depend on local institutional protocols, making it clear that in those cases in which an inadequate response is found due to toxicity or increased beta-hCG should be modified from the initial regimen. Gabilondo [23] comment that in an analysis carried out in 2016 it was determined that actinomycin D leads to higher cure rates than methotrexate as monotherapy, however, in the case of high-risk disease, chemotherapy is based on the administration of multiple pharmacological agents, among which the EMA-CO regimen stands out, recognized as the first line of treatment due to high survival rates as well as low toxicity when using high doses. of methotrexate, folic acid, actinomycin D, cyclophosphamide and vincristine [24-27]. The duration of drug administration will also depend on the type and stage of the disease since, in cases of low-risk disease, remission is defined as the moment in which undetectable beta-hCG levels are obtained for at least 3 weeks while, in high-risk cases.

In ultra-high-risk patients with massive disease, standard chemotherapy could cause sudden tumor collapse with severe hemorrhage, metabolic acidosis, myelosuppression, sepsis, and multiple organ failure, so in order to avoid the above, low-dose drugs should be started [28]. Other medical interventions are chemotherapy (limited to TGD metastatic to the brain or liver) or surgical processes such as hysterectomy and even curettage, however their performance must be decided upon individualizing each case according to age, desire for parity and associated risk factors, as that massive, life-threatening hemorrhages could occur. Sahily et al. [24] recommend performing most of these procedures in case the initial management is not successful. During the medical management stage, beta-hCG should be measured weekly until the moment of remission, then every month for one year and then annually for 5 years [29]. The previously mentioned scheme is the one indicated in patients with low-risk disease, however, in those with high risk the scheme should be monthly for 18 months, every 6 months for 2 years and finally every year for 5 years. In some patients, the measurement of beta-hCG every 6 months until the end of life is suggested, emphasizing that effective contraceptive measures should be established. The risk of relapse after completion of chemotherapy is approximately 3% in the first year and then decreases to less than 1%. Finally, the prognosis of the patients depends on multiple factors such as tumor size, hormone values, changes in the immune response and the existence or not of an opportune diagnosis (less than 6 months), taking into account that in case of disease there is no metastatic survival is 85-94% with a significant decrease in the percentage depending on the organ affected in the metastasis (70% brain, 27% liver, 10% both). In addition, commented that 83% of patients with CCA manage to conceive despite having received prior chemotherapy with favorable prognoses regardless of the agents used and risk stratification.

CONCLUSION

Choriocarcinoma is a rare malignant neoplasm that is generated from the trophoblastic epithelium of the placenta due to errors in the differentiation and cell proliferation stages. The prognosis is usually favorable despite the fact that it is a pathology with a high potential for dissemination and a fatal outcome; however, it is conditioned by the establishment of an opportune diagnosis as well as the beginning of comprehensive medical management, therefore, the health must maintain a high index of suspicion that is accompanied by the measurement of b-hCG levels and the use of imaging studies that allow establishing confirmation of the condition and the effective reduction of variables related to preventable complications attributed to diagnostic errors, therapeutic and follow-up.

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