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REVIEW ARTICLE

GESTATIONAL TROPHOBLASTIC DISEASE

JP Deep [1]*, LB Sedhai [1], J Napit [1] and J Pariyar [2]

[1] Department of Obstetrics and Gynecology, Chitwan Medical College Teaching Hospital, Bharatpur-10, Chitwan, Nepal.

[2] Gynecologic Oncology Unit, BP Koirala Memorial Cancer Hospital, Chitwan, Nepal.

***Correspondence to :** Dr Jagat P Deep, Chitwan Medical College Teaching Hospital, Bharatpur-10, Chitwan, Nepal. Email: jpdeep@hotmail.com*

ABSTRACT

Gestational trophoblastic disease (GTD) is a group of tumors that arise from placental tissue and secrete β-hCG. GTD is a combination of benign or invasive mole and malignant known as Gestational Trophoblastic Neoplasia (GTN). Prevalence, diagnosis and treatment of GTD have drastically changed in recent years.

Key Words: *Chemotherapy, Gestational Trophoblastic Disease (GTD), Gestational Trophoblastic Neoplasia (GTN), Hysterectomy & Molar Pregnancy.*

INTRODUCTION

Gestational trophoblastic disease (GTD) comprises a group of interrelated conditions that arise from placental trophoblastic tissue after normal or abnormal fertilization. It comprises a spectrum of clinical entities ranging from non-invasive molar pregnancy, to metastatic gestational trophoblastic neoplasm (GTN), and is characterized by a distinct tumor marker (β-subunit of human chorionic gonadotrophin, β HCG). Hippocrates was probably the first to describe gestational trophoblastic disease around 400 BC in his description of dropsy of the uterus. [1] GTDs are classified as at least five distinct groups on the basis of histopathology, cytogenetic, and clinical features: hydatidiform mole (HM) which includes complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM), invasive mole, choriocarcinoma(CCA), placental site trophoblastic tumor(PSTT), and miscellaneous trophoblastic lesions. [2] However current WHO classification [3] of GTD is presented as follows:

Classification of gestational trophoblastic diseases.

1. Hydatidiform moles:
   a. Complete hydatidiform mole (CHM)
   b. Partial hydatidiform mole (PHM)
2. Invasive hydatidiform mole
3. Gestational choriocarcinoma (CC)
4. Placental site trophoblastic tumor (PSTT)
5. Epithelioid trophoblastic tumor (ETT)
6. Tumor-like conditions:
   a. Exaggerated placental site reaction (EPS)
   b. Placental site nodule (PSN)
7. Unclassified trophoblastic lesions

Pathology of Gestational Trophoblastic Disease

All type of gestational trophoblastic disease is derived from the placenta. GTD is a combination of benign and malignant or invasive disease. Hydatidiform moles and choriocarcinoma arise from villous trophoblast while placental-site trophoblastic tumors from interstitial trophoblast. Most of complete and partial hydatidiform moles have distinctive morphological characteristics, although diagnostic criteria have changed because evacuation is done earlier in gestation. [4]

Hydatiform Mole (HM)

Trophoblasts are specialised epithelial cells, derived from the outermost layer of the blastocyst that originates in early embryonic differentiation. Trophoblasts can be classified into three distinct groups: cytotrophoblasts, syncytiotrophoblasts, and intermediate trophoblasts. HM is a trophoblastic lesion characterized by a hydropic (ie,vacuolar) swelling of the chorionic villi and trophoblastic proliferation (Figure 1). It is classified as a CHM or a PHM on the basis of histopathological features and karyotype (Table 1). [2,5]

CHM is characterized by the diffuse hydropic swelling and trophoblastic (syncytio, cyto, and intermediate trophoblasts) hyperplasia on the chorionic villous surfaces [6] (Figure 1). Most CHM are cytogenetically diploid with a 46XX karyotype with both sets of chromosomes of paternal origin (2:0). CHM develops from the fertilization of an anuclear ovum by a haploid (23X) sperm, which then undergoes duplication. About 4–15% of CHMs has a 46XY or 46XX karyotype that arises from the fertilization of an "empty" ovum by two spermatozoa [3] (Table 2)

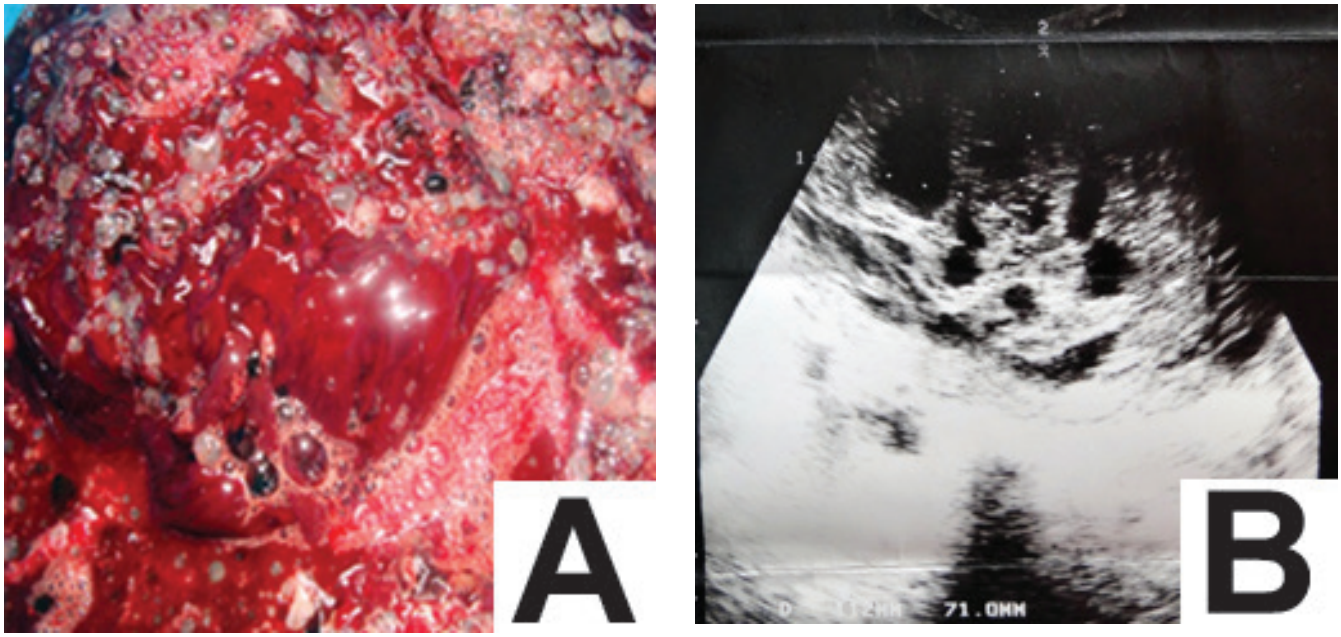


Figure 1: A. Complete hydatidiform mole, gross specimen. Note the diffuse hydropic placental villi, which make up almost the entire specimen.
B. Pelvic B-mode ultrasound of complete hydatidiform mole with characteristic vesicular pattern of multiple echoes, hypoechoic lesion within placenta.

Table 1: Histopathological and cytogenetic features of complete and partial moles and choriocarcinoma

Characteristic	**Complete mole**	**Partial mole**	**Choriocarcinoma**
Karyotype 46xx (90%)	Paternal origin 46xx (90%) 46xy (10%)	Maternal /Paternal origin 69xxy(58%) 69xxx(40%) 69xyy(2%)	Aneuploid
Chorionic Villi Trophoblastic Hyperplasia Trophoblastic cell type	Diffuse Oedema Diffuse Syncytio,Cyto, intermediate	Focal Oedema Focal Syncytio, Cytotroblasts	Absent Diffuse,necrotic, hemorrhagic Syncytio, cyto, intermediate

PHM presents two populations of chorionic villi, one with normal morphology, and the other with scattered hydropic villi and focal trophoblastic (syncytio and cyto) hyperplasia. PHM occurs when an ovum with 23X haploid set (2:1) of chromosomes is fertilized by two spermatozoa that carry either of the sex chromosomes. It results in a zygote with a total of 69 chromosomes, both maternal and paternal, with a sex chromosomes configuration of XXY, XXX, or occasionally XYY [2] (Table 2).

Invasive mole

An invasive mole is a HM that is characterized by the presence of enlarged molar villi that penetrate deeply into the myometrium. A local invasive mole has a similar histological feature as a CHM with a variable degree of trophoblastic hyperplasia. Invasive mole histopathology may closely mimic that of choriocarcinoma, with the production of secondary metastatic lesions, particularly in the vagina and lungs, but, unlike choriocarcinoma, an invasive mole can regress spontaneously.[2] Morphologically, an invasive mole is distinguishable from choriocarcinoma by the presence of villi, which are generally absent in choriocarcinoma. Cytogenetically invasive moles are mostly diploid but some are aneuploidy. [5]

Choriocarcinoma (CCA)

Choriocarcinoma is an invasive malignant neoplasm of the trophoblastic epithelium of the placenta. It is characterized by masses of cells invading adjacent tissues and permeating vascular spaces. Microscopically, the neoplasm is composed of an avillous invasive proliferation of syncytiotrophoblasts and cytotrophoblasts surrounded by necrosis and hemorrhage. Intermediate trophoblastic multinucleated giant cells are present and have enlarged nuclei and abnormal mitotic. Most choriocarcinomas seem to be cytogenetically aneuploidy.5 Malignant transformation in GTD is likely to be a multistep process involving a series of genetic changes including activation of oncogenes and inactivation of tumor suppressor genes. 5However, because trophoblastic cells are, by nature, rapidly dividing and invasive, with direct invasion into the myometrium and vascular invasion resulting in spread to distant sites, most

commonly to the lungs, brain, liver, pelvis and vagina, kidney, intestines, and spleen has been well documented in literatures.

Placental site trophoblastic tumor (PSTT)

This type of tumor generally presents microscopically as trophoblastic infiltration confined to the endometrium and myometrium of the placental implantation site. A placental site trophoblastic tumor seems to follow sequentially from intermediate trophoblastic cells of the placental bed after a full-term pregnancy or a non-molar abortion, and is primarily composed of sheets of intermediate trophoblastic cells, with lesions of low or high-grade malignancy. The pattern of cellular invasion is characterized by single or small groups of cells infiltrating the muscle fibers, without producing extensive necrosis. [7] When this tumor is malignant; it is fairly resistant to chemotherapy. Unlike other forms of GTD, PSTT is characterized by low beta-hCG levels because it is a neoplastic proliferation of intermediate trophoblastic cells.

Miscellaneous and unclassified trophoblastic lesions

Exuberant placental site trophoblastic lesions are described as non-neoplastic proliferation of intermediate trophoblasts at the site of implantation of the embryo. [7] Unclassified trophoblastic lesions are characterized by the invasion of spiral arteries by intermediate trophoblasts and by extensive areas of hyalinization. Placental site nodule and plaque composed of intermediate trophoblastic cells embedded in hyalinised material with little mitotic activity affect the endometrium and superficial myometrium. Unclassified trophoblastic lesions include lesions with gross features of a HM, but lack abnormal trophoblastic activity, or lesions with abnormal trophoblastic proliferation without a villous component. [7]

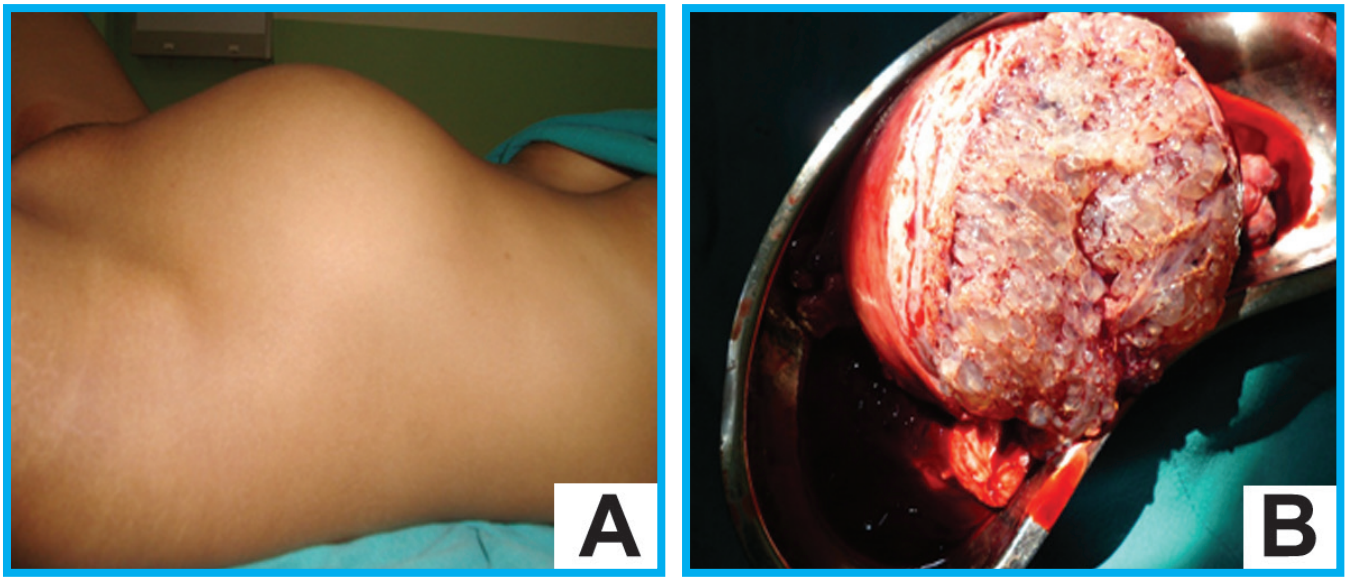
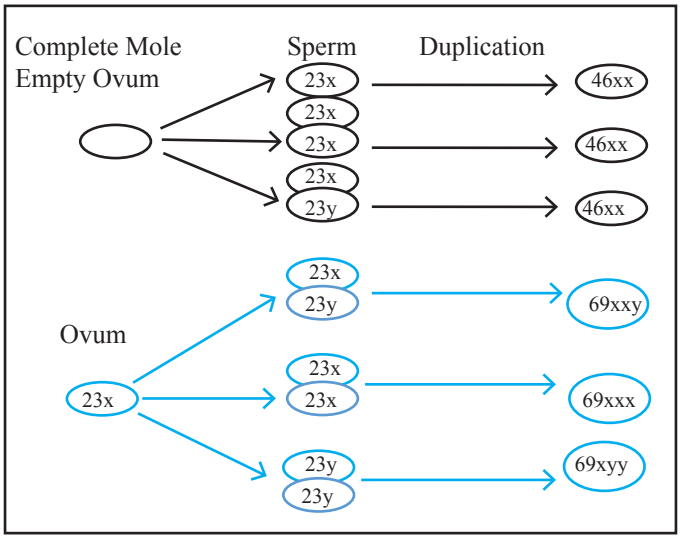


Figure 2. A. Uterus is larger than size B. Gross specimen in a patient treated for complete hydatidiform mole with primary hysterectomy

Table 2: Chromosomal origin of complete and partial hydatiform mole



Epidemiology and risk factors:

Incidence rates of GTD differ throughout the world, but the extent to which differences are attributable to definitions used and diagnosis is unclear. [7] However GTD is more prevalent in Asia than in North America or Europe, [8,9] which could be due to differences in prevalence, discrepancies between hospital-based and population-based data, or disparity in availability of central pathology review. Risk factors for HM are maternal age,previous history of HM, [7] and the risk seems to increase to about 25% in women who have had more than one previous HM. [10] Reproductive factors on the risk of GTD remains unclear while abortion is associated with a modest increased risk of GTD in at least seven studies, with relative risks ranging from 1.1 to 3.3. [11,12] No difference in risk was reported for spontaneous or induced abortions. Parental blood group shows relative risks for GTD according to maternal and to maternal and paternal blood groups (AB0). Women with group A or AB blood seemed to have a higher risk of HM compared with women with group B or O blood (relative risk 0.9–4.8). The data also suggested a higher risk for persistent GTD and for CHM compared with PHM. [12]

Oral contraceptives use is generally associated with an increased risk of GTD, with relative risks ranging from 1.11 [2] to 2.6. [13] The risk generally increased with duration of use. Environmental and lifestyle factors: there is limited information on other possible etiological risk factors for GTD, such as smoking habits, alcohol consumption, diet, socioeconomic status, and herbicide exposure. Some studies shows smoking is relative risk for HM and Choriocarcinoma after a long periods. [13] However two other studies found no association between smoking and CHM [13] or GTD. [14] Infections such as sexually transmitted agent is involved in the etiology of GTD has been suggested. [15] The presence of HPV 18 has been reported in trophoblastic cell of HM and Choriocarcinoma. [16] No associations have been found for other types of infective agents, including herpes simplex virus, hepatitis viruses, measles, rubella, mumps, chicken pox, infectious mononucleosis, or venereal diseases during pregnancy. [2] A few studies, however, have reported a positive association between GTD and pulmonary tuberculosis (relative risk 5.6; 95% CI 1.6–19.1). [17]

Clinical presentation and diagnosis:

Different type of GTD may have different presentation and diagnosis criteria. Abnormal pregnancy is the most common cause of a raised ß-hCG in women whereby abnormal placental tissue proliferates in the absence of a fetus, and therefore complicated pregnancy is frequently diagnosed in patients with GTD. The most common presenting symptom is abnormal vaginal bleeding usually occurring at 6-16 weeks of gestation in 80-90% of cases with a palpable uterus that is larger [6] than the gestational age (Figure 2) according to the last normal menstruation period. Molar pregnancy can also present with hyperemesis gravidarum, anemia, hyperthyroidism, very high levels of ß-HCG and pre-eclampsia before 20 weeks of gestation. Some patients present with a history of passing hydropic vesicles or grape-like pieces of tissue. [18] The elevated levels of ß-hCG, especially in those women with enlarged uteri between 14 to16 weeks sizes can give rise to complications such as theca lutein cysts, severe hyperemesis gravidarum and subclinical hyperthyroidism. [19] Ultrasound has become the most important diagnostic tool in diagnosing molar pregnancy, especially CHM.The ultrasound picture shows a mixed echogenic pattern (Figure 1B), comprising hydropic villi, an absent fetus and no amniotic fluid, exhibiting “snow storm pattern” with or without theca lutein cysts. [20] However, the ultrasound appearance is non-specific, and therefore molar pregnancies are frequently misdiagnosed as incomplete miscarriages. As is the case with other forms of complicated pregnancy, ultrasound findings need to be interpreted against the background of the ß-hCG value. Suspicious ultrasound findings, together with an abnormally raised ß-hCG must be regarded as highly suggestive of molar pregnancy. Where ultrasound is available for patients who book early to confirm their pregnancy, the diagnosis will often be made before onset of symptoms typically experienced in complicated pregnancy. [21] Ultrasound finding in cases of PHM, includes a fetus (sometimes growth restricted), amniotic fluid and focal areas of anechogenic spaces in the placenta. Theca lutein cysts are absent. [21] It can be difficult to distinguish between a complete and partial hydatiform mole on ultrasound findings alone, and the diagnosis is usually confirmed after histo-pathological examination. Accurate diagnosis is not essential as the management of both PHM and CHM remains the same. In the absence of vaginal metastases, vaginal ultrasound can be performed to conform and exclude invasive hydatiform mole, where the interface between abnormal trophoblastic tissue and normal myometrium is carefully examined with the aid of high resolution. [21]

Diagnosis of GTN:

Following a molar pregnancy which is mostly a benign disease, GTN is diagnosed based on criteria presented by FIGO consensus statement of 2000. [22]

i. When the plateau ß-hCG lasts for 4 measurements over a period of 3 weeks or longer, that is on day 1, 7, 14, 21.

ii. When there is a rise of ß-hCG of three weekly consecutive measurements or longer, over at least a period of 2 weeks or more days 1, 7, 14.

iii. When the ß-hCG level remains elevated for 6 months or more.

iv. GTN is diagnosed if there is a histological diagnosis of choriocarcinoma.

Once the diagnosis of GTN is conformed, the patient must then be investigated for staging. Chest X- ray or CT chest is appropriate for lung survey, USG and CT can be used in liver metastasis while CT or MRI scan can be used for brain metastasis. After the diagnostic investigations have been performed the patient is then staged according to the FIGO anatomical staging [22] (Table 3) and allocated a prognostic score using the modified WHO prognostic scoring system (Table 4).

Table 3: The FIGO anatomical staging for GTN.

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

Management:

Dilatation and suction evacuation is the standard treatment of all patients presenting with a possible diagnosis of molar pregnancy. Before evacuation the following investigations should be performed: Full blood count, coagulation profile, renal function assessment, liver function test, thyroid functions, quantitative ß-HCG level, and blood group compatibility, chest X-ray and CT scan in selected cases. Evacuation, usually under general anesthesia and preferably under ultrasound guidance, should be performed as soon as possible after the patient has been assessed and stabilized. After adequate dilatation of the cervix, a suction

cannula is placed just beyond the internal os, suction is applied and the uterus allowed to contract as the products are being aspirated after commencing an intravenous oxytocin infusion. Suction curettage is safer than sharp curettage and more effective than medical or non-surgical methods of evacuation. [23] As heavy bleeding can be encountered, it is always good practice to have blood for transfusion readily available. Patients with uteri larger than 14 to 16 weeks are prone to develop respiratory complications at time of evacuation. Respiratory distress can occur due to trophoblastic embolization and cardiac failure due to anemia, hyperthyroidism or pre-eclampsia. Iatrogenic fluid overload can cause pulmonary oedema. [18,19] In selected elderly gravida where preservation of fertility is not required, hysterectomy could be an alternative treatment to dilatation and suction curettage with the advantage of not requiring future contraception. The risk of GTN after hysterectomy is 3–5%, and therefore post-operative monitoring of ß-hCG remains crucial. Theca lutein cysts will resolve completely in weeks or months, and will seldom need surgical intervention. [19] The laboratory must use an appropriate hCG assay that is able to detect not only the ß-hCG secreted in normal pregnancy, but also the variants associated with GTD (hyperglycosylated hCG, nicked hCG, and nicked hCG missing the C-terminal extension on beta-hCG). Dilutions should also be performed to avoid false positives and negatives. [24] Choriocarcinoma is versatile type of GTD and can present with the symptoms and signs of the organ affected by metastases. Patients can present respiratory symptoms and haemoptysis due to metastatic lung lesions or with neurological deficient or symptoms in brain metastasis eg. intracerebral bleeding. It should also be on the differential diagnosis of patients presenting with carcinoma of unknown primary.[19] A history and general examination is mandatory. A pelvic examination must be performed to rule out vaginal and/or pelvic metastases. Apart from the imaging studies already mention elsewhere. Metastases to other sites are rare without respiratory metastases. Up to 40% of patients with negative findings for lung metastases on chest radiograph will have metastases diagnosed on CT scan of the chest. [19] The FIGO staging and prognostic scoring system is useful in making treatment decisions. Women with stage I disease generally have low risk scores and about 90% of these women will go in remission following single agent chemotherapy. Stage II and III with a low risk score (< 7) can be treated with single agent chemotherapy while those with a high risk score (≥ 7) as well as stage IV disease will require more than single agent chemotherapy. [25]

Table 4. Modified WHO prognostic scoring system as adapted by FIGO

Score	0	1	2	4
Age	< 40	> 40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval months from index pregnancy	< 4	4- <7	7- <13	> 13
Pre-tretment β-HCG (iu/I) level	<103	<103-104	104- <105	> 155
Largest tumor size (including uterus) (cm)	-	3- <5	> 5	-
Site of Metastases	Lung	Spleen, Kidney	GI tract	Liver, Brain
Number of metastases	-	1-4	5-8	> 8
Previous failed chemotherapy	-	-	Single drug	2/more drugs

Table 4 shows the modified WHO prognostic scoring system as adopted by FIGO. [22] In order to stage and allot a risk factor score, a patient's diagnosis is allocated to a stage as represented by a Roman numeral I, II, III and IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals, e.g. Stage II:4, Stage IV:9. A score of 0–6 is regarded as low risk and a score of 7 or higher as high risk. [26]

Chemotherapy:

GTN is very sensitive to chemotherapy and high cure rates are achievable with many patients requiring only single agent treatment. Stage of disease, risk score and previous exposure to chemotherapy will influence the decision of chemotherapeutic regimen. Indication for chemotherapy is given in Table 5. [3]

Table 5: Indications for chemotherapy

* Brain, liver, gastrointestinal or lung metastases >2 cm on chest X-ray
* Histological evidence of choriocarcinoma
* Heavy vaginal bleeding or gastrointestinal/intraperitoneal bleeding
* Pulmonary, vulval or vaginal metastases, unless the hCG level is falling
* Rising hCG in two consecutive serum samples
* Serum hCG>20,000 IU/l more than 4 weeks after evacuation
* hCG plateau in three consecutive serum samples after evacuation
* Raised hCG level 6 months after evacuation even if it is falling

Single agent chemotherapy:

Methotrexate is still the most widely used single agent treatment. It can be administered as a single dose, eight day course or a weekly regimen until the ß-hCG levels return to normal. The different treating regimens are probably equally effective. [27] Ten to thirty percent of patients will require a second treatment course if the serum beta-hCG does not fall by one log within 18 days, or if the value plateaus for more than two weeks before returning to normal. According to some data pulsed dactinomycin is more effective than methotrexate as a single agent with comparable toxicity. [28] Dactinomycin is also a very useful agent in patients where methotrexate is contraindicated. Etoposide and 5-fluorouracil are also drugs that are being used as single agents. Single agent chemotherapy alone can achieve remission in over 90 percent of patients with stage I disease, and over 80 percent of women with low risk stage II and III disease.

Multiagent chemotherapy:

Women diagnosed with high risk GTD or women who are refractory to single agent chemotherapy will require combination chemotherapy. The combination of etoposide, methotrexate and dactinomycin followed by cyclophosphamide and vincristine (EMA/CO) is the most widely used regimen for initial treatment of high-risk GTD in most countries. The regimen is repeated every two weeks until normalization of ß-hCG and disappearance of all radiographically evident disease, and then continued for an additional three cycles (six weeks).29 Besides alopecia, this well tolerated regimen is not associated with serious toxicity. [30] Other multiagent regimens include EMA and MAC [triple therapy with methotrexate, dactinomycin plus either chlorambucal (original regimen) or cyclophosphamide (modified regimen)]. There are no randomized trials comparing the different regimens. Second line chemotherapy is indicated in patients who are resistant to initial chemotherapy (20–25%), can't tolerate the initial regimen, or develop recurrent disease after chemotherapy. Most patients with relapsed stage I or low-risk disease, and 60 to 70% of high-risk patients who relapsed, can be successfully salvaged with additional chemotherapy. [31,32] Patients who fail to have an initial response to treatment have a worse outcome than do those who relapse after an initial response. [33] MAC, EMA and EMA combined with etoposide and cisplatin (EMA/EP) are frequently used in this setting. [34] Paclitaxel alone or in combination with ifosfamide, carboplatin, or cisplatin plus etoposide are other multiagent salvage chemotherapy.

Post treatment monitoring:

All women with GTD should be monitored with weekly serial measurements of serum ß-hCG during treatment. Remission is defined as three consecutive normal hCG values over 14 to 21 days. After remission is achieved, serum ß-hCG should be measured monthly until the patient has had normal ß-hCG levels for one year (at least 6 months). After remission, the risk of tumor relapse in patients treated for persistent GTN is 3 to 9%. A significant number of patients with recurrent disease can be cured, and such cases should always be offered treatment with curative intent. [35] Assays used for monitoring ß-hCG levels after treatment should be able to measure the ß-hCG variants. Failure to measure variant ß-hCG molecules associated with GTN may result in a false negative test as these are the major (and sometimes the only) sources of ß-hCGimmunoreactivity. 24

Surgery:

Repeat evacuation is associated with risks of uterine perforation, hemorrhage, infection, intrauterine adhesions, and anesthetic complications. The efficacy and benefit of repeat evacuation is doubtful and should only be performed if there is evidence of retained tissue in the uterus. Hysterectomy is indicated in the following cases, women diagnosed with choriocarcinoma who do not desire future fertility. Hysterectomy can be performed before chemotherapy, as this prevents the persistence of drug-resistant local disease, and can shorten the duration and amount of chemotherapy required to achieve remission. [36] Primary therapy for stage I or II placental site trophoblastic tumor as it is usually limited to the uterus and the response to chemotherapy is variable. Women with resistant chemotherapy and residual disease limited to uterus only could have hysterectomy. Persistent uncontrolled uterine bleeding or ongoing sepsis due to infection of necrotic tumor may be another indication for hysterectomy. There is no proven benefit to performing a hysterectomy if the uterus has no disease demonstrable on imaging. Thus, radiographic imaging, with MRI and/or ultrasonography, should be performed prior to hysterectomy in women where hysterectomy is being considered. Local excision is an option in women who need to retain fertility. Successful treatment of localized disease by hysterotomy, local tumor excision and uterine reconstruction has been described.

Treatment of metastases:

Brain metastases are a relatively rare occurrence. Cranial radiotherapy given concurrently with the initiation of

chemotherapy to shrink the tumor and to attempt to minimize intracranial bleeding can be used. Alternatively, high-dose EMA/CO with or without intrathecal methotrexate can also be used. [37,38] Craniotomy and resection of drug-resistant lesions is very rarely indicated and then only for patients who do not have metastatic disease elsewhere. Patients with hepatic metastases have a poor prognosis. Combination chemotherapy can induce a partial response in most cases. Hepatic resection and/or selective embolization of the hepatic arteries may help in some cases to control bleeding or remove resistant tumor. [39] A solitary chemoresistant pulmonary nodule can be treated with a thoracotomy and wedge resection. Other systemic metastases must first be ruled out and serum ß-hCG concentration should be less than 1500 mIU/mL. [40] Vaginal metastases can cause heavy bleeding which can be controlled by packing, followed by a wide local excision if necessary. Alternatively, embolization of the vaginal branch of the hypogastric artery can be considered.

Contraception and future pregnancies:

Contraception is essential during the whole duration of treatment and hCG surveillance. Non-hormonal method of contraception is preferable; however, it is associated with higher failure rate. Oral contraception can be used after serum hCG returns back to normal. Intrauterine devices are contra-indicated due to the risk of uterine perforation. Pregnancy should be avoided for at least one year following treatment for GTN. Women who conceive within a year have a good prognosis, but diagnosis of relapse is likely to be delayed in the presence of a pregnancy. Chemotherapy in general does not impact adversely on future fertility and does not increase the risk of congenital abnormalities in future pregnancies. [41]

CONCLUSION

GTD is an entity associated with abnormal proliferation of placental-type tissue resulting after fertilization. Diagnosis of GTD is based upon clinical features, quantative evaluation of serum BhCG, radiological findings, karyotype and histopathology of the evacuated tissue. GTD was once a potentially fatal disease. However, with better understanding about the disease, availability of very sensitive diagnostic tools (radiology and tumour marker), and with the introductions of highly effective chemotherapies GTD now has favorable prognosis. Although potentially curable, the unsupervised or untreated cases may present with life-threatening bleeding, progression into systemic disease and malignancy which often could be very challenging to treat because of late presentation and drug resistance. GTD should preferably be managed at specialized unit or center following standard treatment protocol for the optimum outcome.

Consequently, novel therapies with improved efficacy and reduced toxic effects need to be identified. Therefore, a new prognostic test at the time of initial GTD diagnosis is needed to identify those who might develop malignant disease, of course, if residual complete hydatidiform mole acquires additional genetic evaluation after evacuation, such a test might never be possible. However, evidence comparing early versus delayed evacuation of complete hydatidiform mole alone and in pregnancies with a healthy twin suggests that delayed termination has no increased risk of malignant disease. [42,43] This finding suggests that hydatidiform moles are probably pre-programmed to behave malignantly at an early stage of development and before uterine evacuation. The optimum management strategy for women with repetitive molar pregnancies to allow healthy pregnancy is unknown; even though the causative gene has been identified for many cases, its function is unknown.

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