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REVIEW

Gestational Trophoblastic Tumors

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Gestational trophoblastic disease is a spectrum of complexity. It has a malignant potential, but gestational trophoblastic tumor is a curable disease even in the presence of widespread metastases. Advanced knowledge about this disease is still emerging which will improve the treatment outcome.

The objective of this topic is to review the contemporary knowledge about this disease, emphasizing gestational trophoblastic tumor. Many different aspects will be discussed. Some aspects are well documented, some aspects are the organized different methods of management, and some aspects are still specific problems.

Definition

The terminology of this disease used in the literature creates considerable confusion. Usually gestational trophoblastic diseases (GTDs) refer to either conditions or tumors of allografts arising from a conceptus, which invade the tissues of the mother. Gestational trophoblastic disease is the terminological umbrella used to cover the spectrum of disease ranging form the hydatidiform mole (HM) through invasive mole (IM) and choriocarcinoma (CC) to placental site trophoblastic tumors (PSTT).[1] It can be divided into histopathological and clinical entities. As histological entities, HM, IM and CC arise from the trophoblastic epithelium, while PSTT arises from the trophoblast of the placental bed. As clinical entities, GTDs include the whole spectrum of disease and can be benign or malignant conditions.

HM has been separated into two clinical and genetic entities. The complete hydatidiform mole (CHM) is androgenetic in origin and has a diploid 46,XX karyotype, while partial hydatidiform mole (PHM) is mainly triploid or trisomic for a single chromosome.[2-4]

Gestational trophoblastic tumor (GTT) refers to a disease state with a malignant manner. It includes IM, CC, and persistent GTD after completion of pregnancy regardless of molar or non-molar type.

Gestational trophoblastic neoplasia (GTN) is the term applied to CC and related tumors. CHM and PHM have uncertain neoplastic potential and should be better considered as pathological conceptuses.

Epidemiology

There are many reports about the epidemiology of GTDs. The main obstacles in the interpretation of the differences among these reports are terms of definition, detection and identification of disease.[5] Due to the lack of internationally agreed upon terminology in the past, many reports lack precise and reproducible case definitions. At the present time, advanced diagnostic tools, such as color doppler

ultrasonography and magnetic resonance imaging, may have roles in anatomical diagnosis. In the future when precise cytogenetics of HM can be determined and applied in clinical service, the reclassification of the cases will be unavoidable.

Over or under reporting may be causes of different incidences between different populations. The over-reporting occurs in developing countries where data comes from hospital based studies. The under-reporting occurs in sub-optimal service communities.

To interpret the difference in incidence among the different reports, the source of data and the denominator should be compared. The source of data comes from hospital based or population based data. The denominator means pregnancies, deliveries, or live births. Among these, the best denominator is live births.

Pathology

In the era of ultrasonography, CHM is usually diagnosed early than in the past. Because of early evacuation of HM, the number of CHM with the classic symptoms and signs, such as uterine size larger than dates, hyperemesis gravidarum, toxemia, or hyperthyroidism, is decreased. The pathological criteria for HM is more applicable for advanced age HM. The differentiation between young age CHM and PHM may be problematic especially for pathologists whose experience with GTD are limited.

A common problem in pathological diagnosis of GTD is the differentiation between choriocarcinoma and early abortion or early HM. When the bizarre trophoblast is found and is undetermined, repeated curettage may be necessary. If the tissue yields a trophoblast without villous stroma, choriocarcinoma is more suspect, especially when the time at curettage is far beyond the last pregnancy. However, the clinical characteristic, the level of hCG, and ultrasonographic findings should be considered concomitantly.

Histopathological differentiation of trophoblastic metaplasia of the ovary, peritoneal cavity, and others viscera from CC sometimes proves difficult. These trophoblastic metaplasia can imitate the pattern of vascular invasion and the bilaminar structure of a villous trophoblast. In some cases they show a pattern consistent with adenocarcinoma, squamous carcinoma, or transitional carcinoma. The clues for suspicion of trophoblastic metaplasia are the intrinsic vessel, and the low level of hCG compared to tumor size. Nowadays, using polymerase chain reaction technique and molecular genetics study will solve this problem.[6-7]

The composition of bizarre mononuclear cells in the chemotherapy-resistant metastases of CC make them difficult to differentiate from PSTT.[8] The characteristics of hemorrhagic nodules, vesicular infiltration, and high mitotic rate will lead to suspicion of CC, and as a rule the level of hCG in CC is higher than hPL.

Cytotrophoblastic CC may be indistinguishable from PSTT. These tumors are composed of mononuclear cells and have an intravascular invasion rather than an interstitial mode of infiltration. They behave like a CC in the way that they form a hemorrhagic mass and early metastasis, but have a chemoresistant tendency like PSTT. Immunohistochemistry for hCG, hPL and placental alkaline phosphatase (PLAP) is helpful in these cases. Finding more positive cells for hPL than hCG suggest PSTT, and finding more hCG than hPL may indicate predominantly cytotrophoblastic CC.

Histopathological examination of the tissue obtained from endometrial curettage may be difficult to differentiate between placental site reaction and PSTT because of scanty tissues, extensive necrosis, or less confluent PSTT at the periphery.[8,9] Examination of the hysterectomy specimen makes it easier to differentiate between PSTT, placental site reaction and CC. The masses of PSTT have calcification, marked necrosis, but less hemorrhage.

There are difficulties in differentiating PSTT from placental site trophoblastic nodule (PSTN). The latter regresses spontaneously.[10-13] The regressing nodules of PSTN have marked hyalinization and necrosis and express more PLAP than hPL.[11] Urinary or serum hCG are not elevated in the patients with regressing PSTN.

Heterogenecity of hCG

Human chorionic gonadotropin is a glycoprotein hormone with 11 distinct antibody sites. It is synthesized mainly in syncytiotrophoblasts, and is stored in cytotrophoblasts. This hormone is composed of non-covalently joined α and β subunits. The α-subunit is similar to pituitary glycoproteins, whereas the β-subunit is unique from the other hormones.

The hormone hCG has multiples molecules which have heterogeneity in their peptide or carbohydrate moieties. This heterogeneity is more apparent in trophoblastic disease. There are high proportions of nicked hCG molecules, carbohydrate-variants of hCG, and hCG free β-subunits in GTT. Commercial kits for hCG assays or external testing laboratories should be chosen carefully for diagnosis or monitoring GTT. Each type of test has a different specificity. Some tests have high specificity for detection of intact hCG(non-nicked only), intact hCG plus free β, total hCG (intact plus nicked), total hCG plus free β, or total hCG (except hCG without C-terminal peptide segment) plus free β, etc. More than that the inter-assay variability has influence in hormone measurement. Both heterogeneity of the hormone and inter-assay variability produce an effect in the management of GTT.

Immunobiology of GTT

Gestational trophoblastic tumors have a characteristic of partial allograft, and therefore they induce a strength host immunologic response. The trophopblastic cells can also produce interferons,[14] the substances that enlarge the expression of class I human leukocyte. These reasons support the immunogenicity characteristics of this disease.

Activated lymphocytes and macrophages can inhibit proliferation and antigen expression of choriocarcinoma cells by producing many types of cytokines. The marked infiltration of the trophoblastic tumors by lymphocytes and macrophages is a good prognostic sign. In contrast, gestational trophoblastic tissues can suppress maternal immunologic responses. Molar villous fluid has an effect on the cytotoxic activity of mononuclear cells and lymphokine-activated mononuclear cells.[15] Molar decidua extracts suppress both interleukin-2-dependent and -independent responses.[16] These knowledge can lead to find therapies that have a potential to decrease or eliminate the immunosuppressive effects of molar trophoblastic tissues. The end result is a more favorable clinical outcome in patients with GTT.

Staging and classification system

The staging and classification systems are intended to group patients according to response to chemotherapy and diagnosis. They are proposed to encourage the uniform reporting of clinical data and to help physicians decide on optimal treatment. However, there is still confusion regarding the interpretation and application of various staging systems. The question is "which is the ideal staging system?"

There are 4 staging systems widely used nowadays. Hammond's clinical classification defines several "high-risk" factors that reduced the response rate and proposes the concept of primary combination agent therapy in the "poor prognosis" group.[17] The Bagshawe prognostic scoring system[18] gives different weighting to different risk factors. Most of the factors relate to tumor burden, sites of metastases, duration of disease, and degree of prior chemotherapy exposure. This scoring system also includes age, parity, ABO blood group, lymphocytic infiltration of the tumor, and immune status. The WHO prognostic scoring system[1] is a modification of Bagshawe's to be applicable worldwide. The total score has been shown to correlate with prognosis and response to therapy. The International Federation of Gynecologist and Obstetricians (FIGO) staging system has a basis in the anatomic distribution of disease. The revised system in 1992[19] includes two important clinical variables: the level of hCG and duration of disease, which is expected to give a more precise estimate of prognosis.

Although these referred systems have been used for many years, it has not been demonstrated as to which is the best evaluation system. The Hammond's clinical classification is more utilized by gynecologic oncologists because of its simplicity. An objection to FIGO staging is its inability to identify those

patients with advanced disease who require primary combination chemotherapy from those who respond to only a single agent chemotherapy. The WHO system, although more precise in prognosis, is also more complicated. Some factors in the WHO system may not be available and may be less significant.[20]

At the present time, the revised FIGO staging system is more acceptable. It correlates well with the WHO scoring system.[21] It is capable of predicting which patients will respond poorly to single agent chemotherapy, appears to reliably predict outcome and therefore can be used to help select appropriate treatment protocols.[22]

Follow-up after molar preganancy

The recommended follow-up scheme after molar evacuation is monitoring hCG levels weekly until non-detectable for three consecutive weeks and then monthly monitoring for six months. The basis for this scheme is that, patients whose hCG fell rapidly to normal by eight weeks following molar evacuation rarely have any further reactivation of the abnormal trophoblast.[23] The current question is whether this protocol should be used generally. Patients who have a slow decrease in hCG levels or who have high risk factors to develop post molar tumor should be followed-up for 6 months or much longer. Some institutes recommend a 2-year follow-up in patients whose hCG level are not normal level within 8 weeks.[24]

Clinical Features of GTT

In cases of GTT that occur after molar pregnancy, the diagnosis is usually straight-forward. Those patients who have locally invasive GTT may present with uterine hemorrhage of excessive duration, uterine subinvolution, persistent theca lutein cyst, and elevated hCG. The most common metastatic sites are lungs, vagina, liver and brain respectively. Some patients with metastatic GTT, especially those who have had no history of previous molar pregnancy, may have minimal gynecological symptoms. They have unexplained pulmonary or systemic symptoms and the GTT may not be diagnosed initially. The diagnosis of GTT should be considered in any women in the reproductive group who have multiple signs and symptoms of different organ systems.

The most common symptoms of PSTT are irregular vaginal bleeding or amenorrhea. In rare cases the presenting symptoms are virilization or nephrotic syndrome. Metastases of PSTT occurs in about 15% of cases. Cases with metastases have all presented with abnormal vaginal bleeding or gynecological symptoms. However there are reported cases of PSTT which presented initially with scalp metastases mimicking alopecia areata,[25] and others which presented initially as cervical lesion resembling cervical carcinoma.[26]

Post molar GTT

Post molar gestational trophoblastic tumor can occur in patient with both complete and partial molar preganancy. About 20% of patients develop post molar tumor after a complete mole.[27] The possible predictors of persistent tumors in these patients are high level of hCG, pathologic evidence of marked trophoblastic overgrowth, and age over 35 years.[28] Although the risk for persistent tumor after a partial mole is low,[29] all patients with partial mole still require hCG level monitoring to ensure complete remission.

The criteria for diagnosing persistent gestational trophoblastic tumor varies among centers. Most centers in the USA define persistent postmolar disease by the presence of re-elevation of or persistent plateau in hCG for at least three consecutive weeks. In the UK, the criteria is more stringent than the criteria in the USA. The selection criteria for treatment in the UK are serum hCG above 20,000 U/l for more than 4 weeks after evacuation, evidence of widespread metastases, and rising hCG values 4-6 months after evacuation.[24] It should be noted that not all small pulmonary metastases are associated with clinically progressive disease provided that the hCG is falling. In the UK only 7-8% of the patients with persistent trophoblastic tumor require chemotherapy compared to 20-30% of the same group in the USA.[24,30]

Investigation in GTT

The assessment of the extent of disease prior to treatment is mandatory in the management of GTT. The metastatic work-up should include chest radiography, ultrasound, or computed tomography (CT) scan of the abdomen and pelvis, and CT or magnetic resonance imaging (MRI) scan of the head.

Chest CT scans may demonstrate micrometastases in the presence of normal chest radiography. However, it has not been well documented about the prognostic significance of micrometastases in the lung detected by CT of the chest. In addition Ngan et al. reported that micrometastases in the lung do not affect the clinical outcome of patients with FIGO stage IA disease.[31] CT of the thorax is not essential in the staging of this disease.

Ultrasound is the examination of choice for initial diagnosis of GTD. It may be useful in detecting extensive uterine involvement and identifying sites of resistant uterine tumor. With transvaginal ultrasonography examination there is a relation between hCG levels and tumor volume, uterus length and theca lutein cyst, and can be used in the monitoring of treatment of patients with persistent gestational trophoblastic disease.[32] Doppler ultrasound can assess the vascularity of the GTT. A low pulsatility index in the uterine arteries as measured by doppler ultrasound correlated with the development of drug resistance in the tumor.[33] Thus, the assessment of the uterine arteries using the pulsility index may be helpful in predicting poor response of the treatment.

Magnetic resonance imaging has been shown to accurately define the degree of uterine invasion by GTT. It is also useful for monitoring tumor responsiveness to therapy. However, there seems to have no correlation between MRI changes and hCG level or specific histologic types of GTD.[34]

Cerebrospinal fluid hCG estimations are useful in detecting tumor involvement of the central nervous system, as well as for monitoring therapeutic response. The ratio of plasma/CSF hCG tends to less than 60 in the presence of cerebral metastases. The interpretation should be performed with care, because the hCG in the plasma changes rapidly. A single value may be misleading.

Management of GTT

The treatment of GTT depends upon prognostic variables. Chemotherapy is the main treatment of GTT. Usually, the low-risk patients are treated with single chemotherapy, while the high-risk patients are treated with combination chemotherapy. Radiotherapy and surgery may have a role in specific circumstances. However, there are some variations between the regimen which depend upon the treatment centers and classification system. The variation of the treatment protocols can be categorized in to three groups and is summarized in Table 1.

In the first group, the patients are classified by FIGO anatomical staging system. Methotrexate (MTX) is used as the single drug chemotherapy agent. The time interval between the course of the drug is not fixed. Further chemotherapy is withheld as long as the hCG is still falling. The second course is administered when the hCG level plateaus for more than 3 consecutive weeks or begins to rise again, or the hCG level does not decline by 1 log within 18 days after completion of the first treatment. In the case of unsatisfactory response, the dosage of MTX should be increased, or actinomycin-D(Act-D) should be substituted. If the patients is still resistant to Act-D, the combination chemotherapy of EMA-CO(etoposide, methotrexate, actinomycin-D, cyclophosphamide, vincristine) is the protocol of choice. In those patients with evidence of brain metastasis whole-brain irradiation is instituted immediately.

In the second group, the patients are classified by Hammond's clinical system. MTX or Act-D are used as the single drug chemotherapy. The time interval between the course is fixed at 7 days. The drug is continued until the hCG titer is normal. In the case of MTX reistance, the drug is switched to Act-D. The combination chemotherapy of MAC (methotrexate, actinomycin-D, chlorambucil) is considered before EMA-CO. Whole-brain irradiation is performed in cases of cerebral metastasis.

In the third group, the patients are classified by a prognostic scoring system. MTX is still the drug of choice in low-risk patients. The drug free interval is 6 days. Etoposide, hydroxyurea, MTX with folinic acid, mercaptopurine, and ACT-D are alternately prescribed in medium-risk patients. EMA-CO is preferred in high-risk or in single drug resistant patients. Intrathecal MTX is recommended as central nervous system (CNS) prophylaxis in patients with pulmonary metastasis. It is given with the first three course of chemotherapy. Patients with CNS involvement need special management. Initial craniotomy is suggested in the case of isolated, superficial brain lesion. The dose of MTX as well as folonic acid is increased in EMA-CO regimen. Intrathecal MTX is prescribed in the CO part of the EMA-CO schedule and is continued until both serum and CSF hCG concentrations are normal.

Table 1. Summary of variations in treatment protocol of GTT

Classification system	Interval of drug administration	MTX resistant	Combination chemotherapy	Brain metastasis
FIGO staging system	Not fixed time interval	: Increased dose of MTX : Act-D	EMA-CO	Whole brain irradiation
Hammond's clinical system	Fixed	Act-D	MAC If resistant, EMA-CO is considered	Whole brain irradiation
Prognostic scoring system	Fixed	Etoposide, hydroxyurea, mercaptopurine, Act-D	EMA-CO	Intrathecal MTX for prophylaxis and treatment

Drug administration

Methotrexate and actinomycin-D are the basis of treatment for GTT. Traditional therapy consists of MTX administered intramuscularly or intravenously at 0.4 mg/kg per day for five days, or Act-D administered intravenously at 10-12 μg/kg per day for five days. Signs of toxicity with MTX administration include alopecia, mucositis, neutropenia, as well as cutaneous toxicity. The most common adverse effects of Act-D are nausea and vomiting.

High-dose methotrexate-folinic acid rescue usually consists of 1 mg/kg MTX given on days 1, 3, 5, and 7 alternating with intramuscular folinic acid 0.1 mg/kg on days 2, 4, 6, and 8. The rationale for folinic acid administration is to protect the normal tissue from the dihydrofolate reductase block induced by MTX, allowing a higher dose of MTX to be administered. However this regimen yields a higher peak concentration but also results in subtherapeutic and subtoxic levels of MTX.

In nonmetastatic GTT, weekly intramuscular MTX is equally effective and less toxic than the eight-day MTX-folinic acid regimen.[35] The dose of MTX is 40 mg/M^2. This protocol has minimal toxicity and hospitalization.

Actinomycin-D can be used as a single intravenous bolus dose 40 μg/kg every two weeks. The total dose of Act-D in this protocol is equivalent to the traditional 5-day courses. The bolus Act-D represents a cost-effective chemotherapy with an acceptable remission rate but slightly higher toxicity than weekly MTX.[36]

Etoposide has been confirmed as an active single agent in the treatment of GTT, especially in the patients who were resistant to MTX.[37] However, etoposide induces an increased risk of secondary tumors including myeloid leukemia and colon and breast cancer.[38] Therefore it should not be used as an initial drug for GTT but should be reserved for patients who are likely to be resistant to either MTX or Act-D.

Etoposide, MTX, Act-D/cyclophosphamide, vincristine (EMA/CO) regimen is effective and well tolerated for patients with high-risk GTT as well as those who are resistant to MTX. This schedule requires only one night of hospitalization with each complete cycle.[39]

Drug resistant

Most of the patients with GTT are cured by either single agent therapy or EMA/CO schedule. However, there is a small number of patient with ultra-high-risk factors who will become drug resistant. These are combination of brain and liver metastases, long interval from the antecedent pregnancy, prior term pregnancy, or metastatic PSTT.[40] Salvage therapy consists of EP/EMA (etoposide, cisplatin/etoposide, MTX, Act-D) schedule and resection of the active site of disease. The other approach is high-dose chemotherapy and autologous bone marrow transplantation.[41,42]

New drugs that may have a role in ultra-high-risk patient include taxanes and camptothecins. The former group is paclitaxel and docetaxel and the latter is topotecan and irinatecan. Paclitaxel has an activity against previously treated germ cell tumors.[43] The mechanism of action of camptothecins is to inhibit topoisomerase I. Both topotecan and irinatecan have significant antitumor activity against many cancers.[44,45] Other potential drugs are gemcitabine and temozolomide.

Role of surgery

The indications for hysterectomy in patients with GTT are controlling of severe uterine hemorrhage and eliminating the persistent foci of the disease in the uterus. In addition, from this, geriatric, multiparous women who have a disease confined in the uterus will benefit from hysterectomy. In order to minimize the risk of trophoblastic embolization during hysterectomy, the vessels draining the uterus should be ligated at the beginning, and the uterus should be gently handled.

In young nulliparous women whose fertility has to be preserved, a local excision of the uncontrollable bleeding site from the uterus may be unavoidable. This type of surgery combined with concurrent chemotherapy can cure the disease. The other option is internal iliac arteries ligation. The disadvantage of this procedure is that after the ligation, pelvic angiography may be impossible.

Bleeding is the most common major problem in GTT. It is the result of arteriovenous malformations within the untreated or poorly controlled tumor or the results of arteriovenous fistular or aneurysm of the vascular space previously filled by tumor. By using the selective angiographic embolization, the bleeding, especially from the tumor in the vagina, can be well controlled.[46]

To increase the cure rate of GTT, salvage surgery is attempted to eradicate the residual resistant disease. In these selected patients, the full range of current technique may be needed. MRI of the brain and CT of the thorax and abdomen as well as ultrasonography of the pelvis and liver are mandatory. Unfortunately, in this group of patients multiple radiographic abnormalities are commonly found. To identify the sites of active disease, scanning with ^{131}I-labeled antibody to hCG, or, more recently18 F fluorodeoxyglucose positron emission tomography scanning can be helpful.[47] After salvage surgery, extensive chemotherapy should be given to solidify the remission.[40]

Subsequent reproductive performance

Subsequent reproductive outcomes in patients treated for GTD are comparable to that of the general population.[48] However, the time between cure and the next pregnancy is longer than in the case of miscarriage. The reasons are that it takes a longer time for the normalization of the hCG and the need of

contraceptive usage during the 1-year period of follow-up.

The results of reproductive function after treating GTT are still controversial. There is a possibility that the chemotherapy will affect the reproductive function. The cytotoxic drugs have more potential for causing sterility than antimetabolites. The effects of these drugs in the ovaries are follicle destruction and ovarian fibrosis which causes an alteration of hormonal production. The final result is temporary or permanent amenorrhea. However, a long-term study of subsequent pregnancy outcomes in treated GTT report that chemotherapy does not influence later pregnancies.[48,49] These patients can be reassured that in general they can anticipate a normal future reproductive outcome.

Etoposide is one of the most effective anticancer drugs for GTT. However, it can causes gonadal toxicity. Recently, it was confirmed that this complication is not related to the amount of prior etoposide exposure, but rather it seems to be age related. Ovarian cycles can resume to normal after cessation of treatment in patients under 40 years old. In contrast, etoposide causes irreversible impairment in older women.[50]

Chemotherapy in the patients with GTT can accelerate menopause by 3 years.[51] Although it has a slight practical importance, the timing of pregnancy should be considered appropriately. These women should not become pregnant during the period of 1-year follow up because early pregnancy will mask serological diagnosis of relapse. However, they should not delay pregnancy too much as they are at risk of early menopause.

Psychological consequences and psychological sequelae of GTT

The diagnosis of GTD is perplexing to both the patient and her husband. The stresses include pregnancy loss, a serious disease, surgical treatment with or without chemotherapy, and delay of future pregnancy. The couples will face a rapid change of their situation from being cheerful and happiness due to a pregnancy to a potentially life threatening condition.

The GTT have an effect in 2 aspects of psycho-social consequences. The first aspect is femininity and gender identity, which is dependent on reproductive capacity. The second aspect is disruption in sexuality and self-image, which arises from malignancy diagnoses. The emotional response among these women are fear, sense of pessimism, depression, and insecurity related to their future. Research about this issue on Western patients and those on Asian patients yield similar results.[52,53]

The psychological sequelae in patients with GTT is emotional disturbance. Many women become most depressed soon after chemotherapy. The explanation of this phenomenon is that of difficulty in organizing their lives after prolonged duration of stress. Early warning of these patients will be helpful.

Problems in management of GTT in Thailand

Although the patients with GTT usually have successful outcomes in Western countries, there are still many problems in management of GTT in Thailand. To achieve the optimal result, the following components are required. First is a well organized registration and follow-up system. Second is the centralization of expertise to provide optimal and contemporary treatment. The last is good compliance by the patients, which depends on the level of their knowledge and awareness of the malignant potential of this disease as well as economic status.

In Thailand, there has been no well organized registration and follow-up system for GTD patients. The report of incidence comes from hospital-based data, which has a tendency to over-report. This disease is different from other cancer in that a pathological specimen is not necessary for diagnosis. Levels of βhCG and clinical information may be sufficient for diagnosis. Although, our country has a tumor registry, which is a population data, it is based on pathological classification. Thus, the accuracy of registration of this

disease may be obscured.

The characteristic of health service of GTT in Thailand is decentralization. The GTD patients usually receive the treatment first at a provincial hospital and are referred to the tertiary-care hospital when the disease is advanced or complicated. The pitfalls of management of GTT always happened with less experienced physicians. Even in a tertiary-care hospital, there are limitations in some capacities in providing optimal treatment, such as radiological intervention, sophisticated tomography scanning, a bone marrow transplantation unit, and a well-trained surgical oncologist who is accustomed to this type of patients. Moreover, most of the physicians pay concentrate on eradicating the disease, that is, normalizing the level of hCG. The psychosocial sequences and psychological sequelae are less considered.

The compliance of the patient is very important. A long follow-up period with frequent examinations time usually results in these patients being lost to follow-up. Intense patient education to make them recognized this potentially life threatening disease is usually inadequately provided. The financial burden is another important reason that has a great effect to the compliance of the patients.

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