Critical Situations in Gestational Trophoblastic Diseases

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14.1 Introduction

Gestational trophoblastic diseases (GTD) are a group of heterogenous disease that arise from trophoblast; and range from premalignant conditions like partial and complete hydatidiform moles to malignant lesions like invasive hydatidiform moles, choriocarcinoma and the rarer placental site trophoblastic and epithelioid tumours [1–7]. The malignant forms of the disease that will need chemotherapy are collectively called gestational trophoblastic neoplasms (GTN) [1].

The incidence of GTD is higher in Asian (1 in 500) and African (1 in 1000) than European or American (1 in 1500) population [3, 4, 7]. The incidence of molar pregnancy in India is 1 in 400 pregnancies [8]. About 80% of GTDs are hydatidiform moles. Risk factors for the development of hydatidiform moles include extremes of age, ethnicity, history of spontaneous miscarriage and dietary deficiencies [9]. Women between 21 and 35 years of age have a lower incidence than women younger than 21 years or older than 35 years [10]. The etiopathology, diagnosis, presentation and management of GTDs have been described previously. This chapter will outline the critical situations encountered with GTDs.

14.2 Critical Events

GTDs entail a variety of presentations secondary to their endocrine, secretory, angiogenic and other properties. Presentations may sometimes be extremely perplexing and not fit into any clinical situation. Presentation may be sometimes so

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acute that GTD is occasionally diagnosed for the first time in ICU. The presentation is often acute or subacute and clinicians need to keep a high risk of suspicion of GTDs in all women in the reproductive age group [11].

14.2.1 Haemorrhage

Excessive vaginal bleeding is known to occur with GTDs [11]. This may be due to the production of high levels of angiogenic growth factors which remodel the uterine vasculature and lead to the formation of arteriovenous malformation. Although more commonly seen in choriocarcinoma, abnormal uterine bleeding may be seen in complete hydatidiform mole and placental-site trophoblastic disease [11]. Due to the chance of significant bleeding during procedures like suction evacuation of hydatidiform mole, RCOG guidelines (2010) advocate the presence of a senior surgeon (Fig. 14.1) [12]. Blood should also be kept cross-matched in the event of sudden post-procedure haemorrhage. Bleeding and shock does sometimes occur remote from the procedure. Hence proper counselling for a strict followup and appraisal of complications that could ensue will go a long way in reducing the preventable morbidity and mortality.

The use of oxytocics before the evacuation of molar pregnancy is not recommended because of the theoretical concern of the trophoblastic material embolising through the uterine venous plexus into the systemic veins [12]. However, to control life-threatening bleeding, infusions of oxytocics may be required. Similarly, preparation of the cervix with prostaglandins and use of sharp curettage is also not recommended [13]. Apart from major bleeding during the evacuation of molar pregnancy,

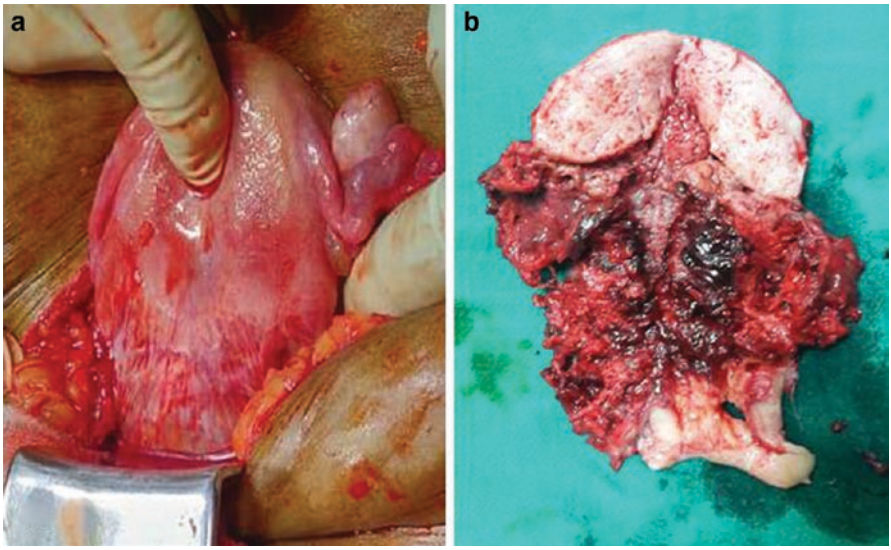

Fig. 14.1 Invasive mole—Patient had torrential haemorrhage during attempted suction and evacuation. (**a**) Emergency laparotomy and (**b**) cut open gross specimen showing invasive mole

acute cardiopulmonary distress and adult respiratory distress syndrome have also been reported after suction evacuation in 27% of cases.

Haemorrhage may not be only confined to vaginal bleeding. Excessive haemorrhage has also been reported in the gastrointestinal tract and patients may present with excessive haematemesis and melena or lower gastrointestinal tract bleeding [14, 15]. Unexplained anaemia is often seen in these patients and may or may not be associated with masses in the small bowel or colon [16]. Rarer manifestations include recurrent epistaxis along with abnormal vaginal and rectal bleeding [11]. Bleeding leading to a painful eye with decreased visual acuity has also been reported [11]. Torrential bleeding may happen from suburetrhral nodule (Fig. 14.2). Stitches may be difficult to fix. Styptics , local and systemic, with packing may be helpful at times. Hence biopsy from such nodules is not only unnecassary but may be lethal at times.

14.2.2 Perforation and Spontaneous Uterine Rupture

There are case reports of spontaneous uterine perforation in patients with choriocarcinoma [17, 18]. The possible mechanisms are invasion of blood vessels by the trophoblastic cells leading to uterine infarction at multiple sites due to thrombosis, aneurysm formation and tumoral bleeding [11]. Other possible causes of uterine rupture are invasion of the uterine endometrium and myometrium by tumour cells or tumour necrosis due to chemotherapy [11]. Such patients may present with signs and symptoms of acute abdomen and emergency hysterectomy may have to be performed. Massive hemoperitoneum occurring days after suction and evacuation procedure may occur when the invasive component of the disease has been missed or may accrue after the procedure (Fig. 14.3). Hence, thorough counselling of patients for strict follow-up is the onus of the consultant. Treatment is always surgical. Segmental resection is the treatment of choice. The patient is often hemodynamically unstable and hence needs utmost attention.

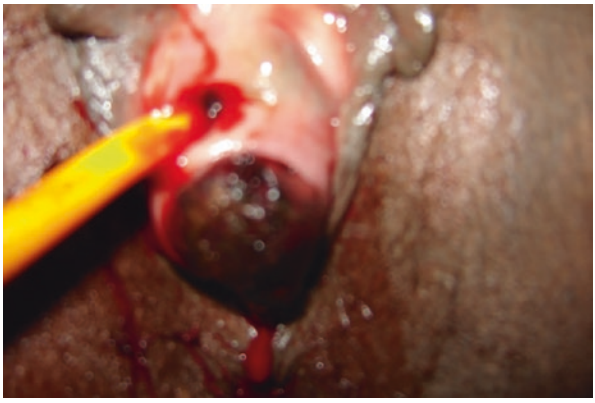

Fig. 14.2 Vaginal nodule in GTD

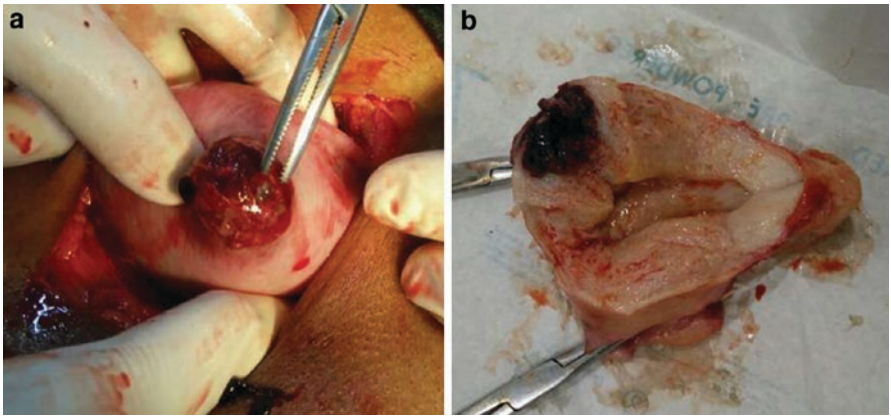

Fig. 14.3 Woman presented in emergency after 1 month of molar evacuation with massive hemoperitoneum where laparotomy with hysterectomy was performed. (**a**) Fundal perforation is seen and (**b**) cut section of specimen showing the perforation

14.2.3 Systemic Signs of Tumour Metastasis

The lung parenchyma is the most common site of metastasis in patients with choriocarcinoma and patients may present with signs and symptoms of acute respiratory failure like dyspnoea, acute chest pain with or without haemoptysis [19] and sudden onset of pulmonary hypertension due to pulmonary embolism (Fig. 14.4) [20]. In fact, the differential diagnosis of choriocarcinoma should be kept in mind in a young woman presenting with sudden onset of pulmonary hypertension due to pulmonary embolism without any other antecedent risk factors [11]. Women may land up in pulmonary medicine department leading to delay in treatment and detorioration, which is sometimes acute and sudden. Hence a element of suspicion in women of reproductive age group is worth a life.

Central nervous system involvement occurs in 10% of patients with choriocarcinoma and has varied manifestations [11]. Tumour metastasis to the central nervous system is also common which manifests as raised intracranial pressures and seizures [11]. Surgical intervention in the form of emergency craniotomy to release intracranial pressure has been done with encouraging results. Sudden onset of stroke-like symptoms have also been reported with hemiparesis and facial palsy due to multiple intracerebral haemorrhages from aneurysmal vessels in the brain [21]. Though challenging, treatment of seemingly hopeless cases does benefit in majority of cases.

14.2.4 Acute Abdomen

Acute abdomen has been reported in patients with GTDs due to rupture and haemorrhage, intussusception and extrauterine sites of implantation mimicking ruptured

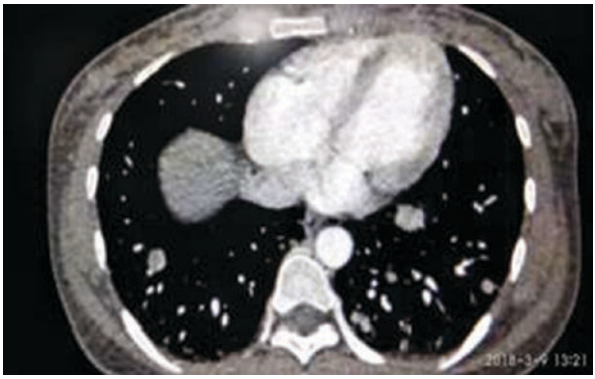

Fig. 14.4 CECT thorax showing multiple lung metastases in a patient of GTN presenting with haemoptysis where chest X-ray was inconclusive

ectopic pregnancy [11, 22]. Massive intraperitoneal haemorrhage has also been reported but may be due to variable aetiology like ruptured liver or spleen or a ruptured blood vessel [11]. Involvement of the kidney causes symptoms and signs of acute flank pain with hematuria and renovascular hypertension [23]. In fact, on many occasions, the abdomen has been opened suspecting ruptured ectopic or intestinal perforation and has been later found to be GTD [11]. GTD of fallopian tubes may present exactly like ruptured ectopic and proved only by a postoperative histopathologic study of the removed appendage.

14.2.5 Thyrotoxicosis

The similar structure of the human chorionic gonadotrophin (hCG) and thyroid-stimulating hormone causes hCG to exert a thyrotrophic action and signs and symptoms of thyrotoxicosis such as hypertension, tachycardia, atrial fibrillation and congestive cardiac failure has been reported in these patients (Fig. 14.5) [24]. So, the differential diagnosis of GTDs should always be kept in mind in a woman after any pregnancy event presenting with signs and symptoms of thyrotoxicosis and both serum hCG as well as thyroid hormone assay should be performed [11].

14.2.6 Acute Vascular Events

Due to the presence of a hypercoagulable state, venous and arterial thromboembolism may occur [25]. Activation of platelets and factors XII and X due to tumour cell–macrophage interaction causes the release of cytokines like TNF-alpha and interleukins leading to endothelial damage. Other risk factors may be the toxicity of chemotherapeutic agents [11].

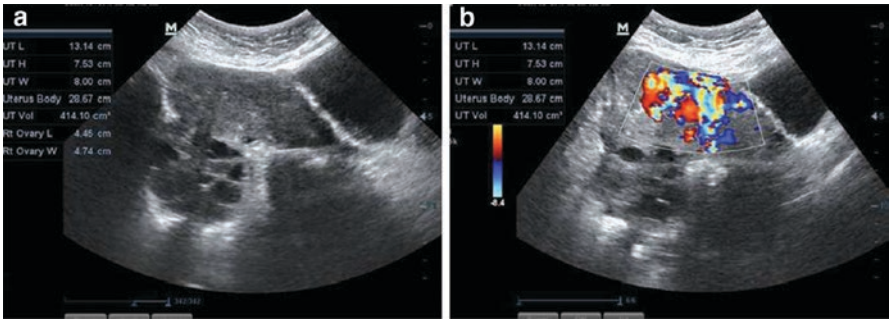

Fig. 14.5 Case of GTN which presented with features of thyrotoxicosis. (**a**) Grey scale 2D ultrasonography showing uterus with theca-lutein cyst of ovary and (**b**) colour Doppler image showing increased vascularity inside the uterus

14.2.7 Sepsis

Clostridium perfringens induced sepsis has been reported in a case of invasive molar pregnancy. The necrotic tumour tissue creates hypoxic and ischaemic conditions that allow the proliferation of this anaerobic Gram-positive bacillus leading to the formation of gas gangrene [26]. In this particular case, the sepsis is resolved after hysterectomy leading to removal of the septic foci [26]. Similarly, previous reports exist of association of clostridium infections in patients with choriocarcinoma [27].

14.2.8 Ovarian Hyperstimulation Syndrome

This condition is typically seen in patients following ovulation induction and consists of enlarged ovaries, with multiple follicular cysts and acute fluid shifts from intravascular space to the extracellular space, causing haemoconcentration, oedema, electrolyte disturbances and massive pleural effusion, ascites and pericardial effusions in severe cases leading to acute thromboembolic events and even death. Although sometimes seen in twin pregnancy, ovarian hyperstimulation syndrome has been reported 3 days after molar pregnancy evacuation [28]. It is likely that the high levels of hCG cause bilateral ovarian stimulation and enlargement. Young women presenting with ascites and enlarged ovaries and raised B HCG may be mistaken for germ cell tumour of ovaries and careful decision needs to be taken along with a history of recent termination of pregnancy.

14.2.9 Chemotherapy

Occasionally very high-risk cases with large tumour burden may present with an acute serious illness due to tumour lysis and haemorrhage. Though seemingly hopeless, careful management of these cases will help them survive as they are potentially

curable. Alternatively, low-dose Etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 (EP) induction chemotherapy for patients with high-volume disease is a better and safer option. Ensuring adequate hydration, commencing therapy with allopurinol or rasburicase and special attention to electrolyte balance and renal function has reduced the rates of early deaths [29]. Fatal pulmonary haemorrhage may occur due to positive pressure ventilation as the vessels are very friable; hence, low pressure is recommended. Tumour lysis may sometimes lead to multiorgan failure and death. Life-threatening myelosuppression is sometimes a crisis to manage vigourously.

14.2.10 Critical Situations During Surgery

There is a chance of embolisation of the trophoblastic tissue; hence, minimal manipulation and prophylactic or perioperative CT is proposed by some to be another method to prevent embolisation. Patients are usually anaemic and hemodynamically unstable and need added attention and precaution. Extensive vascular supply and the friable nature of the uterus may lead to extensive intra-op blood loss that has to be handled properly and fast. Sometimes, unrecognised extrauterine disease may pose a challenge. DIC, though rare, should be kept in mind. Hence, it is always advisable to handle surgery in GTD by an experienced surgical team along with an adequate blood transfusion facility and ICU backup.

14.2.11 Unstable Patients

An extensive metastatic burden and hCG levels of over 500,000 IU/L behave unpredictably. An initial treatment with MTX infusion/leucovorin rescue or Etoposide 100 mg/m^2 ± cisplatin 50–75 mg/m^2 is sometimes given to avoid catastrophic haemorrhage from high-risk sites of metastases. EMA/CO is initiated as soon as the condition improves.

14.2.12 Adnexal Torsion and Theca Leutin Cyst Rupture

Present with acute abdomen and need immediate treatment.

14.2.13 Thyroid Crisis

High levels of HCG are typically required for the development of clinical hyperthyroidism. Iodinated substances can trigger a crisis (**Jod Basedow phenomenon).** Rarely the thyroid stimulation can have potentially life-threatening consequences. Carbimazole and β-blockers for symptom relief appear to be effective. Thyroid function normalises rapidly with treatment of the underlying GTD and the consequent fall in HCG levels [30].

14.3 Conclusion

GTDs constitute a clinical conundrum and often the first presentation to the hospital is because of an acute or subacute crisis. Clinicians will likely encounter such women in their practice and therefore need to be aware of the varied critical events that may manifest in these women. Often, the diagnosis may not be readily apparent as the heterogeneity of the disease leads to signs and symptoms that are present in other organs. Therefore, a high index of suspicion of GTDs should be kept in mind while attending to women in the reproductive age group presenting with an acute or subacute crisis. Overall, definitive care for GTN is the purview of the gynaecologist but the emergency physicians should be aware of the risks and be able to recognise the patient with this potentially lethal but curable disease.

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