Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 1–8

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Review Article

Unusual clinical presentations of choriocarcinoma: A systematic review of case reports

Mishu Mangla [a, *], Deepak Singla [b], Harpreet Kaur [a], Sushmita Sharma [a]

[a] Department of Gynecology and Obstetrics, GianSagar Medical College and Hospital, Banur, Punjab, India
[b] Department of Anesthesia, BPS Govt. Medical College, Khanpur Kalan, Sonipat, Haryana, India

ARTICLE INFO

Article history:
Accepted 20 May 2015

Keywords:
choriocarcinoma
clinical presentation
review

ABSTRACT

Choriocarcinoma (CC) is a highly malignant tumor originating in the trophoblastic tissue. The clinical presentation of CC is so much varied that every case may be one of its kinds and thus can be a diagnostic challenge. Numerous case reports have been published in various journals regarding the unusual clinical presentations of this cancer. Therefore, we conducted a systematic review of all case reports in English language on gestational CC published in PubMed-indexed journals from 1998 to 2015. The main aim was to provide a summary and critical analysis of all the data and evidence published regarding the atypical clinical presentations of CC in recent years. In total, 121 case reports pertaining to unusual clinical manifestations of gestational CC were analyzed. The age of patients in whom cases were reported ranged from 17 to 67 years, and the time period between the index pregnancy and development of CC varied from 4 weeks to as long as 25 years. Cardiopulmonary complaints (20.66%) followed by gastrointestinal (18.43%) and central nervous system manifestations (17.67%) were found to be the most common. Through this review, the authors have made an attempt to discuss various manifestations with which a patient with gestational CC can present to clinician so that early diagnosis and timely management can be initiated, thus improving clinical prognosis.

Introduction

Choriocarcinoma (CC) is a highly malignant tumor originating in the trophoblastic tissue. Majority of cases of CC arise due to malignant transformation of a complete molar pregnancy, although it has been reported following term pregnancy, spontaneous abortion, and even after ectopic pregnancy [1]. It is known to occur in 1 in 5333 tubal pregnancies and 1 in 1.6 million normal intrauterine pregnancies [2]. Although only 0.76–4 % cases of CC develop in ectopic locations, they are usually more aggressive and associated with distant metastasis [3,4]. It can develop anytime between 5 weeks and 15 years after gestation or even after menopause [5,6]. Cases have been reported to occur even 23 years after menopause [7].

Approximately 30 % cases of CC have metastatic disease at the time of diagnosis. Lungs (80%) are the most common site of metastasis, followed by vagina (30%) and liver (10%). Metastatic CC involves the brain in 3–28% of patients [8]. The clinical presentation of CC is so much varied that every case may be one of its kinds and thus can be a diagnostic challenge. Another problem leading to a delay in diagnosis is that sometimes the history of antecedent pregnancy may not be elicited or the presentation may be so delayed that the patient may not recollect such history. Such patients present advanced metastatic disease due to a delay in the diagnosis which can prove fatal.

Early diagnosis and prompt initiation of chemotherapy is a well-known determinant of prognosis of CC. A knowledge regarding the variations from its classic clinical presentation is, therefore, a must to any practicing clinician. The main aim of this systematic review was to provide a summary and critical analysis of all the data and evidence published regarding the atypical clinical presentation of CC in recent years and thus help the practicing clinicians in early diagnosis and timely treatment of CC, thus improving prognosis. A special emphasis was given to nongynecologic and atypical clinical manifestations which pose a real diagnostic challenge.

* Corresponding author. Department of Gynecology and Obstetrics, GianSagar Medical College and Hospital, Banur, Punjab 140401, India.
E-mail address: deepak10.4u@gmail.com (M. Mangla).

http://dx.doi.org/10.1016/j.tjog.2015.05.011

Materials and Methods

An electronic search of Pubmed database was conducted for case reports regarding unusual clinical presentations of CC, published in English from 1998 to 2015, i.e., last 17 years. The electronic search strategy was done using keywords, such as "choriocarcinoma" and "clinical manifestation", "choriocarcinoma" and "unusual presentation", and "choriocarcinoma" and "case reports". Two authors independently analyzed the title and abstracts of all case reports found from the initial search. The data thus extracted was double checked to avoid duplication. Any disagreements between the two authors were resolved through discussion.

Clinical manifestation was defined as patient-level finding gathered during medical interview, physical examination, or through diagnostic studies. Patients reporting to health care practitioner with any clinical manifestation, other than the following common signs and symptoms [9], were regarded as unusual: (1) enlarged uterus; (2) abnormal uterine bleeding; (3) persistence of theca lutein cysts in the ovaries; and (4) plateau or rising serum human chorionic gonadotropin (hCG) concentrations measured during postmolar follow-up after uterine evacuation.

This systematic review was planned according to PRISMA guidelines. The articles pertaining only to unusual clinical manifestation of gestational CC were included in the present review. Only female patients with cases reported by authors as gestational CC, which they confirmed by beta hCG or histopathology, were included in the review. Studies and reports of fatal cases were also included if the condition causing death was attributed to CC or its related complications. Case reports with nongestational CC, case reports of male patients with CC, and articles focusing predominantly on the management of CC were excluded. Any article that was not a case report, i.e., review article, original article, clinical trial, or commentary was also excluded from the present review.

Of all the case reports finally included in the review, one author extracted information such as geographical distribution or country of occurrence of the case, year of publication, age of the patient at the time of presentation, relationship with pregnancy or abortion, diagnostic modality used to confirm CC, and its final prognosis. The details regarding the antecedent pregnancy event and the time interval between index pregnancy and detection of choriocarcinoma was also extracted. The data thus collected was entered in an excel sheet and organized into system-wise manifestations of CC cases. Descriptive statistics was used to calculate simple frequency, percentage, and proportion out of the total case reports.

Results

Data collection

In total, 750 case reports pertaining to the unusual clinical manifestations of CC were found on electronic data search of PubMed database from 1998 to 2015. After excluding the duplicates and case reports on nonhuman subjects, we were left with a total of 722 articles. Furthermore, 572 articles were excluded as they were pertaining to either testicular CC, nongestational CC, or were not in English language. Additionally, 29 articles were excluded as they focused mainly on the management of CC, newer treatment options available for the same, and did not highlight the clinical manifestation. Considering all the inclusion and exclusion criteria, a total of 121 case reports were finally analyzed (Figure 1).

Case distribution

Cases have been reported from all over the world. Geographical distribution of the cases has been shown in Figure 2. Majority of cases have been reported from Asia (47.1%) and Europe (26.44%). Additionally, 14.04% cases were from North America and 3.3 % from South America. Two cases have been reported from Australia, three cases from Africa, and six cases from Eurasia. The distribution of articles according to the year of publication has been shown in Figure 3. It is interesting to note that the number of cases being reported has increased from 2006 onward as shown in Figure 3. Maximum number of cases were reported in 2006 (13 cases), followed by 2009 (12 cases). In 2011 and 2013, 10 cases each were reported (Figure 3).

The age of the patients in whom CC was reported varied from 17 to 67 years, with the majority of patients (84.29%) aged 20–40 years. There were two patients aged < 20 years and five patients aged > 50 years.

Antecedent pregnancy

In 50 out of 121 case reports, antecedent pregnancy was full term pregnancy, 18 cases followed abortion, 8 followed molar pregnancy, 7 ectopic gestations, and 1 case followed partial mole. In 10 case reports, the details regarding antecedent pregnancy were either not available or not mentioned; however, as the authors had reported them to be gestational CC, they were included in the present review. The time period between the index pregnancy and development of CC varied from 4 weeks to as long as 25 years.

Out of all the reported cases, 15 patients succumbed to disease, mainly because of late presentation or delay in diagnosis, whereas 106 patients showed remission. The diagnosis of CC in these case reports was made by authors on the basis of histopathology in majority of patients (73.55%), by fine needle aspiration cytology in one patient, after autopsy in one patient, and on clinical grounds in the remaining patients.

Clinical manifestations

Maximum number of patients (20.66%) in the reported cases came to clinical attention due to cardiopulmonary complaints, followed by gastrointestinal (18.43%) and central nervous system manifestations (17.67%). Furthermore, 9.91% cases were detected due to feto maternal hemorrhage and 5.28% and 4.95% cases due to renal and ocular manifestations, respectively. Other manifestations that brought the patient to clinical attention are shown in Figure 4. A brief summary of the various clinical presentations of this great clinical masquerader has been shown in Figure 5.

Atypical gynecologic and obstetric manifestations

Abnormal vaginal bleeding is known to be the most common gynecological presentation of CC [8]. Gestational CC has been reported to present as both primary as well as secondary postpartum hemorrhage [10]. It can present any time after the termination of index pregnancy, but patients who present early have a better prognosis. Other symptoms included severe pelvic pain, isolated vaginal nodule [11], and vulvovaginal swelling mimicking an infected and neglected Bartholin cyst or a hematoma [12]. It also presents itself as necrotic and hemorrhagic cervical mass [13]. Although there are not many cases reported in literature, cervical CC is thought to arise from either a malignant transformation of a cervical ectopic pregnancy or from cervical metastasis of a primary tumor of uterine origin which later spontaneously regressed or by transport of malignant chorionic cells to the cervix after a dormant period following previous pregnancy [14–16].

Interestingly, a few cases of spontaneous uterine rupture due to CC have also been reported in literature [17]. Okamoto et al [18] have even reported a case of spontaneous rupture of the uterus

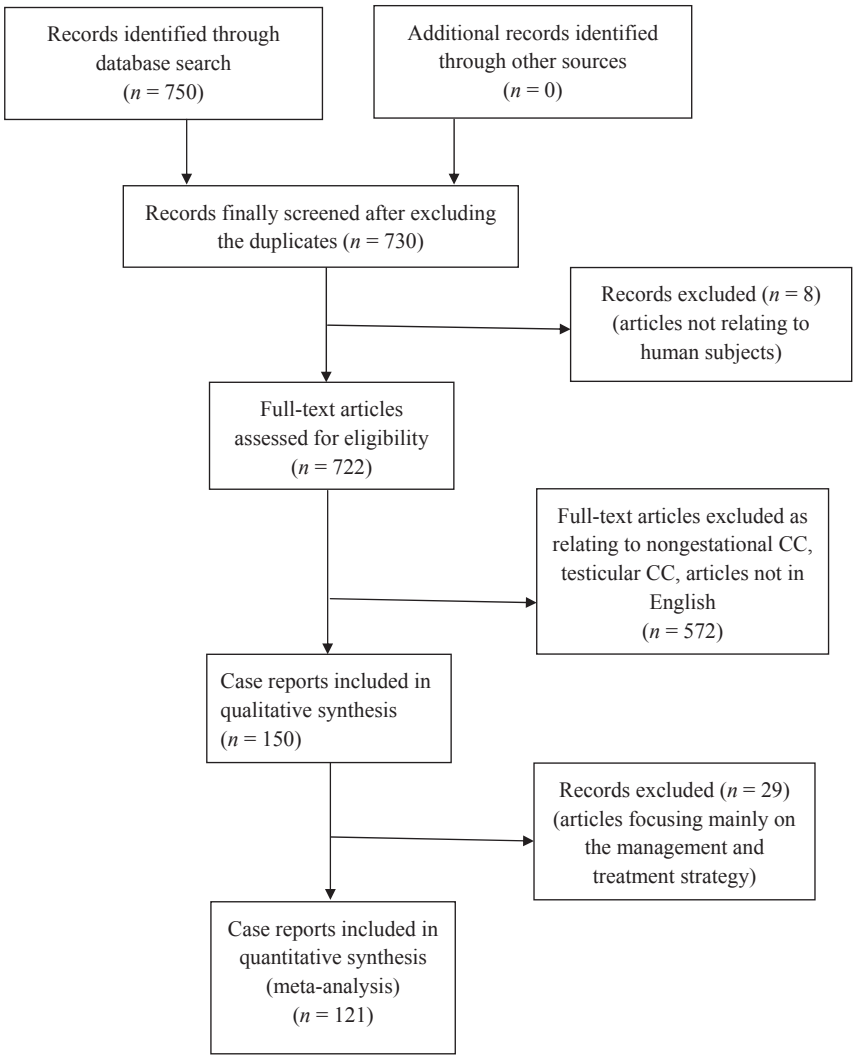

Figure 1. PRISMA flow chart of the screening process.

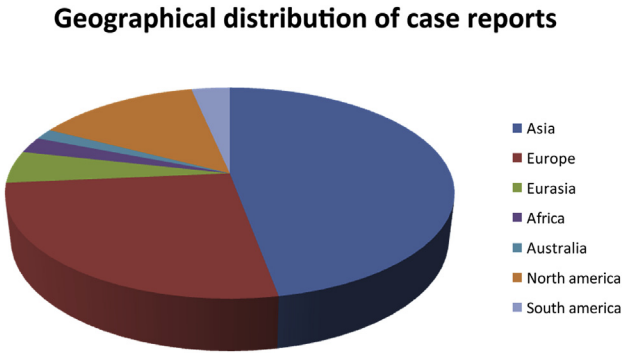

Figure 2. Area-wise distribution of analyzed case reports.

23 years after an elective abortion. Many theories have been proposed explaining the etiopathology. Invasion of the blood vessels by trophoblastic cells, leading to multiple site infarction of the uterus due to thrombosis, formation of vascular aneurysms and intratumoral bleeding is one such theory [17]. Myometrial invasion [19] and rapid necrosis of the tumor cells due to chemotherapy leading to perforation are other possible etiologies [20]. There have been case reports in literature showing spontaneous perforation of uterus even after good response to combination chemotherapy, as evident by satisfactory fall in hCG titers. The patient thus presented with signs of acute abdomen due to intraperitoneal hemorrhage [20] during the course of chemotherapy.

Intraplacental CC in association with a live pregnancy has a reported incidence of 1 in 50,000 to 1 in 1,60,000 depending on the ethnicity [21]. It is associated with a poor prognosis because of the delay in diagnosis, thus increasing the possibility of widespread dissemination [22–24]. The clinical presentation in pregnancy has been in the form of early onset pre-eclampsia or antepartum hemorrhage [25,26]. In 2002, Lam et al [27] reported two cases of feto maternal hemorrhage during antenatal period due to CC. Massive feto maternal hemorrhage even led to sudden and unexplained intra uterine fetal demise or a fetus being born with life-threatening anemia that even led to cardiac failure. Although a high index of suspicion and knowledge about such a rare presentation can be helpful, there is not much a gynecologist can do in preventing such obstetric catastrophes. Thus, Kleihauer–Betke test and a detailed histopathological examination of placenta should be performed as a routine in all cases of unexplained death of the fetus *in utero*, and any suspicious case should be kept on beta hCG monitoring till negative [28].

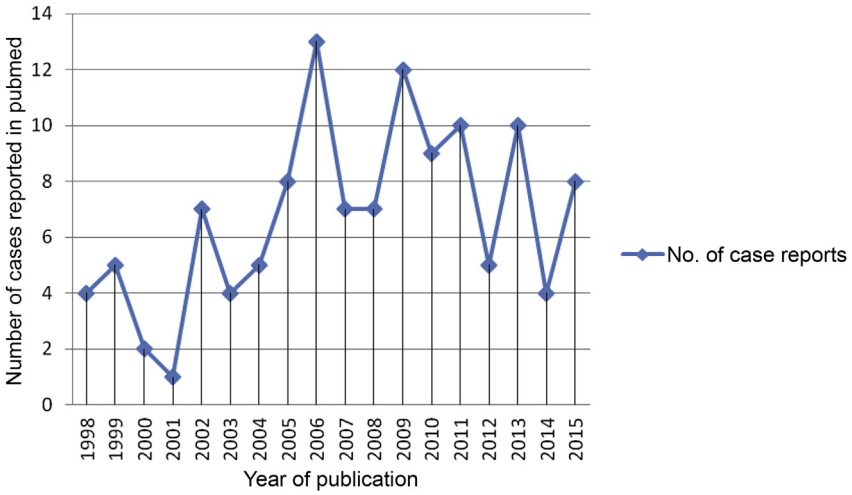

Figure 3. Distribution of articles according to the year of publication.

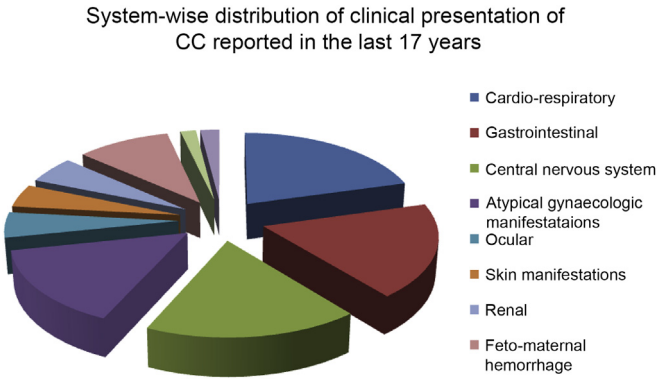

Figure 4. System-wise atypical manifestations of choriocarcinoma reported from 1998 to 2015. CC = choriocarcinoma.

There are cases reported in literature showing mother to fetal transmission of CC [29]. Thus, both the gynecologist and pediatrician need to be aware of such possibility of transplacental transmission, and beta hCG monitoring has been recommended as a routine even in babies of mothers detected with postpartum CC. On the other hand, mothers whose babies develop CC should be kept on hCG follow-up even in the absence of symptoms. Although there are no specific and clear cut recommendations at present, but assuming that a majority of cases occur within 6 months of delivery, measurement of beta hCG every 2 weeks for the first 6 months and monthly thereafter up to 2 years in the neonate has been recommended [30].

Cardiopulmonary manifestations

Lung is probably the most preferred site of metastasis in patients with CC [8]. The main symptoms in the patients with pulmonary metastasis were hemoptysis, dyspnea, pleuritic chest pain, and cough with or without hemoptysis. In a case report by Gangadharan et al [31], pulmonary artery hypertension was the only manifestation. Thus, CC should be kept in the differential diagnosis, especially in case of young women presenting with pulmonary embolism or sudden onset of pulmonary artery hypertension as this may be the sole manifestation of disease [31]. Another rare cardiopulmonary manifestation reported is a reproductive age women presenting with cardiac intracavitary mass. Although rare, but cases with cardiac metastasis of CC have also been reported [17,32]. These can later metastasize to any organ through blood vessels.

Neurologic

Central nervous system involvement is present in approximately 10% of the patients with CC [8]. Presenting symptoms have been diverse. It is presented in the form of intra or extra axial hemorrhage [33] due to oncotic aneurysm formation and its subsequent rupture [34], infarction or even in the form of subdural hematoma requiring decompressive craniotomy [35]. It has once been reported to come to attention as bleeding from carotid-cavernous fistula. Daniel et al [36] have reported a case of CC presenting in a stroke-like manner with right-sided facial nerve palsy and hemiparesis of right upper limb [36]. The computed tomography findings of multiple intracerebral hemorrhages were explained by vascular fragility and rupture of oncotic aneurysms. Signs and symptoms of increased intracranial pressure due to brain metastasis have been the only presenting symptom in some cases.

Gastrointestinal

Involvement of the gastro intestinal tract is not very common in cases of CC [8]. Only about 5% of the patients with CC are known to develop small bowel metastasis [8]. It presents in the form of acute or sub acute intestinal obstruction secondary to an intussusception [37]. There are case reports showing spontaneous perforation of small bowel even at multiple points, presenting with acute abdomen and vomiting [38]. Massive intraperitoneal hemorrhage has been reported in many patients, but the etiology of the same is widely variable, such as due to ruptured spleen [39], ruptured liver [40], or the rupture of a major blood vessel. Sometimes cases taken up for laparotomy with a clinical diagnosis of ruptured ectopic or small intestinal perforation have later been found to be due to CC. CC has presented itself with profuse upper gastrointestinal bleeding in the form of hematemesis or malena [41] or in the form of massive lower gastrointestinal bleeding [42], and also in the form of unexplained severe anemia which may or may not be associated with polypoidal masses in small bowel and colon [43]. CC has even caused isolated renal manifestations like profuse and life-threatening hematuria and co-existent enlargement of single or both kidneys due to metastatic disease. The primary uterine foci

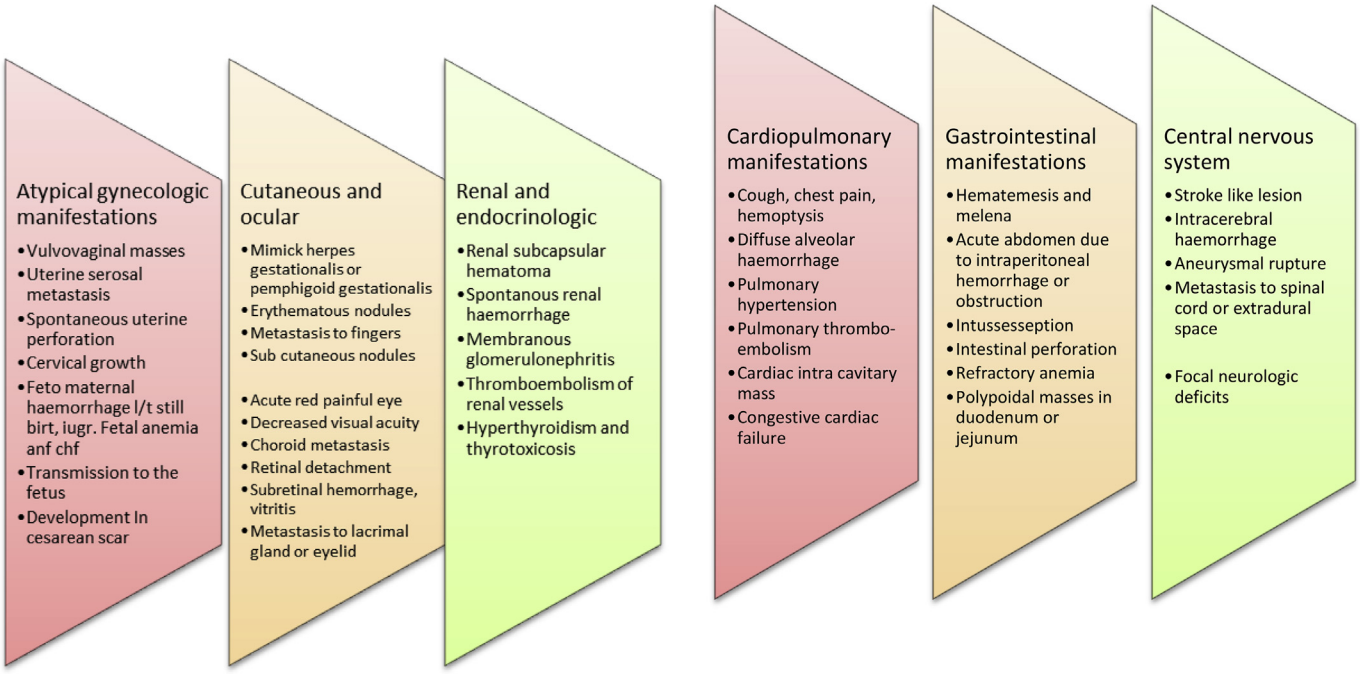

Figure 5. A brief summary of unusual clinical presentations of choriocarcinoma reported in the last 17 years.

in some cases were not identifiable [44,45]. Tumor emboli have been reported to cause obstruction of the renal artery, presenting in the form of flank pain, hematuria and renovascular hypertension [46]. Occasionally, the diagnosis has been revealed only after pathologic examination of specimen obtained after surgery for some other cause, such as specimens of radical nephrectomy [47].

Endocrine and skin

Due to the similar structure of hCG and thyroid-stimulating hormone (TSH), hCG is known to exert a thyrotrophic action, and thyrotoxicosis has been a presenting symptom of gestational CC [48]. Therefore, a woman presenting with symptoms of secondary hyperthyroidism of sudden onset, especially after pregnancy needs a measurement of hCG along with TSH to rule out CC.

Skin is an uncommon site of metastatic cancer, and the incidence of cutaneous metastasis in cases of visceral malignancy has been reported to vary between 1.4% and 10.4% depending on the type of malignancy being studied [49–52]. Biopsy of the skin lesion in case of a primary malignancy of unknown origin has given valuable clues to diagnosis; for example, mucin-containing cells in cases of colon cancer, bile-containing glandular structure in patients with hepatoma, and cytotrophoblasts and syncytiotrophoblasts in cases of CC. Erythematous and extremely vascular deposits over the skin in association with other signs and symptoms of metastatic disease have been reported as the initial presenting symptoms, and thus, the patients with CC are first presented to the dermatologist [53]. CC has even been reported to present in the same clinical presentation as herpes gestationalis [54], subcutaneous masses on chest wall [55], or rubbery hard nodule with a ragged external surface [56].

Hypercoagulability

The association between cancer and hypercoagulability was known even as back as 1865, and a combination of the two is called as Trousseau syndrome. Patients either reporting with arterial and venous thrombosis as their initial presentation or even developing such complications during the course of therapy have been reported in literature [57]. The activation of platelets and factors XII and X due to interaction between tumor cells and macrophages and release of cytokines like TNFa, IL-1, and IL-6 causing endothelial damage have been implicated in etiopathology [58]. Apart from the frequent use of central venous catheters and need of total parenteral nutrition, the toxicity of chemotherapeutic drugs also contributes to thromboembolism in these patients. A very interesting presentation in the form of isolated bone marrow metastasis along with toe gangrene due to hypercoagulability has been reported from India [59].

Eye and ent

Another very rare and interesting presentation of CC has been reported from Turkey in the form of recurrent epistaxis, abnormal vaginal bleeding, rectal bleeding, and presence of subcutaneous nodules on both thighs and forearms along with a maxillary sinus mass with intranasal invasion [60]. A painful red eye along with decreased visual acuity has been reported to be the only presentation [61]. Ocular manifestations in the form of intraocular hemorrhage, swelling, or decreased acuity of vision, have also been reported to be the initial manifestations of CC. Cases initially reported as vitritis, retinal detachment, or chorioretinal deposits on fundus examination have been later attributed to CC. Although favored sites of metastasis include choroid and uvea [61,62], isolated cases have been reported to metastasize to lacrimal gland [63] and even the eyelid [Mangla et al, unpublished data].

Transmission through organ transplantation

Overall, the incidence of malignant tumors of donor origin in recipients of solid organ transplant has been reported to vary from 0.2% to 2% [64–66]. CC of donor origin has also been reported to be transmitted to recipients of solid organ transplants. Detry et al [67] have reported CC following the transplant of kidney and liver [66].

Although rare, but it is important to keep in mind that a screening for CC should be undertaken in each potential woman donor at child-bearing age. Absence of localization of intrauterine pregnancy in the presence of elevated levels of beta hCG should arouse suspicion. It is always preferable to exclude such donors from the list because the data regarding the prognosis of such tumors is not widely available in the context of current chemotherapy protocols. Although recurrent bacteremia is an expected complication of chemotherapy due to immune suppression and side effects of drugs, recurrent bacteremia has been reported as the only clinical presentation of CC in an otherwise healthy patient [68].

Discussion

This systematic review aimed to highlight and discuss various atypical gynecologic and unusual systemic clinical manifestations with which a patient with gestational CC can approach a clinician. This review was inspired by the fact that although this disease is highly responsive to chemotherapy, the main reason that has led to poor prognosis in the majority of cases is late diagnosis due to its highly varied and atypical clinical presentation. By the time diagnosis is confirmed, the disease is already widespread and in advanced clinical stage.

Authors from different countries from all over the world have reported cases regarding the unusual clinical manifestations of gestational CC; however, majority of case reports did not highlight the way the differential diagnosis of gestational CC from nongestational CC was confirmed. Although a majority of cases of CC after pregnancy are gestational in origin, differentiation from nongestational variant is important because of difference in the treatment strategy. The differentiation of gestational CC from its nongestational variant is actually difficult, except in patients who are sexually immature, unable to conceive, or those who have never had sexual intercourse [69]. As there are no distinctive ultra structural or immunohistochemical differences between gestational or nongestational CC, examination of genetic polymorphism from the tumor and their comparison with those found in the patient and her sexual partner to define the presence or absence of paternal DNA is necessary to establish its origin [70]. Human leukocyte antigen typing for antigens of paternal origin in trophoblastic elements also has an application in determining its gestational origin [71].

Extra uterine CC is a rare entity in itself. Cases have been reported to arise from cervix, ovary, fallopian tube, vulva, vagina, and even in cesarean scar [72]. Since the antecedent pregnancy may go unnoticed, these are to be taken as gestational CC, especially in females of reproductive age group unless proved otherwise. The criteria used for the diagnosis of primary extra uterine origin of CC are as follows [73]: (1) absence of disease in uterine cavity; (2) pathologic confirmation of diagnosis; (3) exclusion of molar pregnancy; and (4) exclusion of a co-existent intrauterine pregnancy.

Nongestational CC has its origin either from multipotent cells left behind during the process of embryogenesis or from dedifferentiation of neoplastic cells [74]. Isolated cases have been reported to arise from pineal gland, lungs, urinary bladder, or gastrointestinal system [75]. Sometimes the antecedent pregnancy may even go unnoticed, thereby leading to misdiagnosis of gestational CC as nongestational.

Beta hCG levels have been known to be both of diagnostic and prognostic value in patients with CC. Although the clinical presentation of CC is so much varied, a problem further confusing the clinical diagnosis is false negative report of hCG. The condition referred to as the “high-dose hook effect” is primarily due to a very high level of the analyte which overwhelms the assay system, preventing the formation of color change in pregnancy detection kits and thereby leading to false negative tests [76,77]. This can be overcome by measuring serum beta hCG levels after dilution. Still adding further to the diagnostic dilemma is an entity called “phantom HCG” [78]. Persistent low levels of hCG in patients without any history of trophoblastic disease may actually be misleading and diagnosis of CC in such patients should be made with caution. Laboratory should be requested to show dilutional parallelism in the hCG results, and urine also should be checked for beta hCG at the same time.

CC probably one of those rare neoplasms that is completely curable by chemotherapy even in the presence of widespread metastasis. Although chemotherapy is the treatment of choice, massive life-threatening vaginal bleeding may mandate surgery exceptionally in the form of hysterectomy even in reproductive age women [79]. CC is one of those rare malignant tumors that can be effectively managed by single- or multiple-agent chemotherapy and has a remission rate as high as 87.5% if the time interval from index pregnancy to initiation of chemotherapy is less than 4 months [80]. However, some women still succumb to this fatal malignancy due to late presentation and delayed diagnosis. Its highly atypical presentation may be the reason for delayed diagnosis in some cases. CC should be kept in the differential diagnosis in all women of reproductive age group presenting with hemorrhagic manifestations in any organ system, unexplained systemic symptoms, and particularly in those patients with metastatic symptoms with primary malignancy of unknown origin.

The present systematic review and analysis of case reports/case series had certain limitations. First, the frequency of various clinical presentations of CC might have been significantly influenced by underreporting of relatively more frequent common clinical presentations and over reporting of unusual, infrequent, and interesting clinical presentations. Second, restriction of the period of study to only articles published in the last 17 years, and third, articles published in PubMed database only, could have been responsible to our missing out on important clinical data. Therefore, more such studies with more extensive sample sizes are thus needed to provide a comprehensive knowledge regarding the clinical presentation of CC.

Conclusion

A good and complete knowledge regarding the clinical presentation of this great masquerader, especially among primary care physicians, can thus go a long way in decreasing the adverse outcomes related to this highly malignant but curable malignancy.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

References

[1] Meddeb S, Rhim MS, Zarrouk W, Bibi M, Yacoubi MT, Khairi H. Unusual gestational choriocarcinoma arising in an interstitial pregnancy. Int J Surg Case Rep 2014;5:787–8.
[2] Rettenmaier MA, Khan HJ, Epstein HD, Nguyen D, Abaid LN, Goldstein BH. Gestational choriocarcinoma in the fallopian tube. J Obstet Gynecol 2013;33:912–4.
[3] Chen MJ, Yang JH, Lin MC, Ho HN, Yang YS. An unusual gestational choriocarcinoma occurring primarily in the surface of subserous leiomyoma. BJOG 2004;111:188–90.
[4] Salleh S, Arthrur I. Persistent peritoneal trophoblastic implantation following salpingotomy, salpingectomy and Methotrexate for ectopic pregnancy. Gynecol Surg 2005;2:195–6.
[5] Hassadia A, Kew FM, Tidy JA, Wells M, Hancock BW. Ectopic gestational trophoblastic disease: a case series review. J Reprod Med 2012;57:297–300.
[6] Soper JT, Mutch DG, Schink JC. American college of Obstetricians and Gynaecologists diagnosis and treatment of gestational trophoblastic disease; ACOG practice bulletein no. 53. Gynecol Oncol 2004;93:575–85.

[7] Desai NR, Gupta S, Said R, Desai P, Dai Q. Choriocarcinoma in a 73-year-old woman: a case report and review of the literature. J Med Case Rep 2010;4:379.
[8] Berkowitz RS, Goldstein DP. Gestational Trophoblastic Disease. In: Berek J, editor. Berek & Novak's Gynecology. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 1581–603.
[9] Goldstein DP, Berkowitz RS. Current management of gestational trophoblastic neoplasia. Hematol Oncol Clin North Am 2012;26:111–31.
[10] Dobson LS, Gillespie AM, Coleman RE, Hancock BW. The presentation and management of post-partum choriocarcinoma. Br J Cancer 1999;79:1531–3.
[11] Samantaray S, Rout N, Kakkar S, Pattanayak L. Choriocarcinoma presenting as a vaginal nodule: a rare presentation diagnosed by fine needle aspiration cytology. Acta Cytol 2009;53:364–5.
[12] Bhattacharyya SK, Saha SP, Mukherjee G, Samanta J. Metastatic vulvo-vaginal choriocarcinoma mimicking a Bartholin cyst and vulvar hematoma two unusual presentations. J Turk Ger Gynecol Assoc 2012;13:218–20.
[13] Mitrovic SL, Arsenijevic PS, Kljakic D, Djuric JM, Milosavljevic MZ, Protrka ZM, et al. Gestational choriocarcinoma of the cervix. Arch Iran Med 2014;17:783–5.
[14] Kairi-Vassilatou E, Papakonstantinou K, Grapsa D, Kondi-Paphiti A, Hasiakos D. Primary gestational choriocarcinoma of the uterine cervix: Report of a case and review of the literature. Int J Gynecol Cancer 2007;17:921–5.
[15] Maestá I, Michelin OC, Traiman P, Hokama P, Rudge MV. Primary non-gestational choriocarcinoma of the uterine cervix: A case report. Gynecol Oncol 2005;98:146–50.
[16] Wang D, He Y, Hu Y, Xie C, Yin R. Placental site trophoblastic tumor with unusual presentation in the uterine cervix. Eur J Obstet Gynecol Reprod Biol 2010;148:100–1.
[17] Bozaci EA, Taşkin S, Gürkan O, Atasoy C, Ersoy ZG, Erekul S, et al. Intracavitary cardiac metastasis and pulmonary tumor emboli of choriocarcinoma: the first case diagnosed and treated without surgical intervention. Gynecol Oncol 2005;99:753–6.
[18] Okamoto T, Nomura S, Nakanishi T, Yamada S, Tomoda Y. A case of uterine choriocarcinoma with spontaneous rupture twenty-three years following the antecedent pregnancy. J Obstet Gynaecol Res 1997;23:189–95.
[19] Ma Y, Xiang Y, Wan X, Chen Y, Feng F, Lei C, et al. The prognostic analysis of 123 postpartum choriocarcinoma cases. Int J Gynecol Cancer 2008;18:1097–101.
[20] Xie C, Zheng L, Li Z, Zhao X. Spontaneous uterine perforation of choriocarcinoma with negative beta-human chorionic gonadotropin after chemotherapy. Med Princ Pract 2011;20:570–3.
[21] Berkowitz RS, Goldstein DP, Bernstein MR. Choriocarcinoma following term gestation. Gynecol Oncol 1984;17:52–7.
[22] Bagshawe KD. Risk and prognostic factors in trophoblastic neoplasia. Cancer 1976;38:1373–85.
[23] Tidy JA, Rustin GJ, Newlands ES, Foskett M, Fuller S, Short D, et al. Presentation and management of choriocarcinoma after nonmolar pregnancy. Br J Obstet Gynaecol 1995;102:715–9.
[24] Aso K, Tsukimori K, Yumoto Y, Hojo S, Fukushima K, Koga T, et al. Prenatal findings in a case of massive fetomaternal hemorrhage associated with intraplacental choriocarcinoma. Fetal Diagn Ther 2009;25:158–62.
[25] Luna Russo MA, Multani SS, Ridgway M, Martin Jr JN. Second trimester presentation of preeclampsia and choriocarcinoma in a primigravida with live birth. J Matern Fetal Neonatal Med 2015;28:889–91.
[26] Steigrad SJ, Cheung AP, Osborn RA. Choriocarcinoma co-existent with an intact pregnancy: case report and review of the literature. J Obstet Gynaecol Res 1999;25:197–203.
[27] Lam CM, Wong SF, Lee KW, Ho LC, Yu VS. Massive feto-maternal hemorrhage: an early presentation of women with gestational choriocarcinoma. Acta Obstet Gynecol Scand 2002;81:573–6.
[28] Lee KW, Ho LC. A case of massive fetomaternal haemorrhage at term associated with choriocarcinoma. Aust NZ J Obstet Gynaecol 1999;39:274–6.
[29] Bolze PA, Weber B, Fisher RA, Seckl MJ, Golfier F. First confirmation by genotyping of transplacental choriocarcinoma transmission. Am J Obstet Gynecol 2013;209:e4–6.
[30] Blohm ME, Göbel U. Unexplained anaemia and failure to thrive as initial symptoms of infantile choriocarcinoma: a review. Eur J Pediatr 2004;163:1–6.
[31] Gangadharan VP, Chitrathara K, Sivaramakrishnan R, Satishkumar K, Nair MK. Pulmonary hypertension– a rare presentation of choriocarcinoma. Acta Oncol 1993;32:461–2.
[32] Kishore AG, Desai N, Nayak G. Choriocarcinoma presenting as intracavitary tumor in the left atrium. Int J Cardiol 1992;35:405–7.
[33] Wang J, Wang R, Zhao J. Ruptured cerebral aneurysm from choriocarcinoma. J Clin Neurosci 2013;20:1324–6.
[34] Toyama K, Tanaka T, Hirota T, Misu N, Mizuno K. A case report of neoplastic aneurysm due to metastatic choriocarcinoma. No ShinkeiGeka 1986;14:385–90.
[35] Rocque BG, Başkaya MK. Spontaneous acute subdural hematoma as an initial presentation of choriocarcinoma: a case report. J Med Case Rep 2008;2:211.
[36] Daniel CN, Ango IG, Nwobodo EI. Choriocarcinoma with cerebral metastasis presenting as a stroke like lesion. Sahel Med J 2015;18:16–9.
[37] Martínez-Ordaz JL, Gómez-Jiménez LM, Ballinas-Oseguera G. [Jejunal metastasis from choriocarcinoma. A three-case report]. Rev Gastroenterol Mex 2012;77:143–7.
[38] Balagopal P, Pandey M, Chandramohan K, Somanathan T, Kumar A. Unusual presentation of choriocarcinoma. World J Surg Oncol 2003;1:4.
[39] Mitták M, Samlík J, Satinský L, Foltys A. Metastatic choriocarcinoma as a cause of hemorrhage in the digestive tract and abdominal cavity. Rozhl Chir 2001;80:538–40.
[40] Mittal S, Aird I, Haugk B. Gestational choriocarcinoma in liver mimicking ruptured ectopic pregnancy. J Obstet Gynaecol 2012;32:499.
[41] Villet WT, Du Toit DF, Conroy C. Unusual presentation of choriocarcinoma. A case report. S Afr Med J 1979;55:96–8.
[42] Suski E, Pavlides C, Matsumoto T. Massive lower gastrointestinal bleeding: unusual presentation of metastatic choriocarcinoma. Int Surg 1979;64:53–5.
[43] Chaturvedi M, Vaideeswar P, Pandit A. Metastaic Choriocarcinoma: An unusual cause of severe anemia. J Postgrad Med 2005;51:230–1.
[44] Ogunbiyi OA, Enweren EO, Ogunniyi JO. Unusual renal manifestations of choriocarcinoma. Afr J Med Med Sci 1986;15:93–7.
[45] Devasia A, Nath V, Abraham B, Gopalkrishnan G, Nair S. Hematuria, renal mass and amenorrhea: indicators of a rare diagnosis. J Urol 1994;151:409–10.
[46] Usta TA, Karacan T, Ozyurek E, Naki MM, Omeroglu SN, Demirkiran F. Primary renal artery choriocarcinoma causing secondary renovascular hypertension. Int J Surg Case Rep 2014;5:1197–9.
[47] Regis C, Taieb S, Lesoin A, Baranzelli MC, Blehaut T, Leblanc E. Uncommon clinical presentation of a gestational choriocarcinoma. Gynecol Obstet Fertil 2006;34:716–9.
[48] O'Reilly S, Lyons DJ, Harrison M, Gaffney E, Cullen M, Clancy L. Thyrotoxicosis induced by choriocarcinoma a report of two cases. Ir Med J 1993;86:124–7.
[49] Odom RB, James WD, Berger TG. Andrew's diseases of the skin. 9th ed. Philadelphia: W.B. Saunders; 2000.
[50] Spencer PS, Helm TN. Skin metastases in cancer patients. Cutis 1987;39:119–21.
[51] Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: A retrospective study of 4020 patients. J Am Acad Dermatol 1993;29:228–36.
[52] Johnson WC. Metastatic carcinoma of the skin. In: Elder D, Elenitsas R, Jaworsky C, Johnson Jr B, editors. Lever's histopathology of the skin. Philadelphia: Lippincott-Raven; 1997. p. 1011–8.
[53] Park SG, Chang JY, Kim SH, Bang D. Cutaneous metastasis of choriocarcinoma: a case report. J Korean Med Sci 2005;20:683–6.
[54] Djahansouzi S, Nestle-Kraemling C, Dall P, Bender HG, Hanstein B. Herpes gestationis may present itself as a paraneoplastic syndrome of choriocarcinoma-a case report. Gynecol Oncol 2003;89:334–7.
[55] Chama CM, Nggada HA, Nuhu A. Cutaneous metastasis of gestational choriocarcinoma. Int J Gynaecol Obstet 2002;77:249–50.
[56] Razi T, Yaghoobi R, Feily A, Jazayeri N, Razi S, Mohammadbeigi M. Cutaneous metastasis of postpartum choriocarcinoma: case report. Acta Dermatovenerol Croat 2011;19:69–70.
[57] Cyriac S, Sagar TG, Mahajan V. Choriocarcinoma with arterial and venous thrombosis. Neurol India 2009;57:505–7.
[58] Bick RL. Cancer associated thrombosis. N Engl J Med 2003;349:109–11.
[59] Singh S, Sardhana M, Sharma S, Chitralkar P. Choriocarcinoma presenting as an isolated bone marrow metastasis-a case report. Ecancermedicalscience 2014;8:393.
[60] Alici S, Bavbek SE, Eralp Y, Argon A, Basaran M, Aydiner A, et al. An atypical presentation of metastatic gestational choriocarcinoma with maxillary sinus and subcutaneous involvement; report of a case with literature review. J BUON 2002;7:373–6.
[61] Yoon A, Verma S, Birnbaum A. Exudative retinal detachment caused by metastatic choriocarcinoma to the choroid. J Emerg Med 2013;44:617–9.
[62] Hazan A, Katz MS, Leder H, Blace N, Szlechter M. Choroidal metastases of choriocarcinoma. Retin Cases Brief Rep 2014;8:95–6.
[63] Ahamed NA, Sait K, Anfnan N, Farwan K, Nizamuddin SH, Baeesa SS. Gestational Choriocarcinoma Presenting with Lacrimal Gland Metastasis: A First Reported Case. Case Rep Obstet Gynecol 2015;2015:879538.
[64] Weir B, Macdonald N, Mielke B. Intracranial complications of choriocarcinoma. Neurosurgery 1987;2:138–42.
[65] Birkeland SA, Storm HH. Risk for tumor and other disease trans- mission by transplantation: A population-based study of unrecognized malignancies and other diseases in organ donors. Transplantation 2002;74:1409–13.
[66] Garrido G, Matesanz R. The Spanish National Transplant Organiza- tion (ONT) Tumor Registry. Transplantation 2008;85:61–3.
[67] Detry O, Detroz B, D'Silva M, Pirenne J, Defraigne JO, Meurisse M, et al. Misdiagnosed malignancy in transplanted organs. Transpl Int 1993;6:50–4.
[68] Holt P, Nicholas R. Recurrent bacteraemia: an unusual presentation of choriocarcinoma. Br Med J (Clin Res Ed) 1981;282:1835–6.
[69] Park SH, Park A, Kim JY, Kwon JH, Koh SB. A case of non-gestational choriocarcinoma arising in the ovary of a postmenopausal woman. J Gynecol Oncol 2009;20:192–4.
[70] Yammamoto E. Ovary: Choriocarconoma. Atlas Genet Cytogenet Oncol Haematol 2009;13:683–5.
[71] Bhatia K, Vaid AK. Diagnostic dilemma: non-gestational or gestational choriocarcinoma of the ovary. J Assoc Physicians India 2008;56:1001–2.
[72] Qian ZD, Zhu XM. Caesarean scar choriocarcinoma: a case report and review of the literature. Eur J Med Res 2014;19:25.
[73] Saito N. On ectopic choriocarcinoma. World Obstet Gynecol 1965;17:459–84.
[74] Grammatico D, Grignon DJ, Eberwein P, Shepherd RR, Hearn SA, Walton JC. Transitional cell carcinoma of the renal pelvis with choriocarcinomatous differentiation. Immunohistochemical and immunoelectron microscopic

assessment of human chorionic gonadotropin production by transitional cell carcinoma of the urinary bladder. Cancer 1993;71:1835–41.
[75] Hara S, Ito K, Nagata H, Tachibana M, Murai M, Hata J. Choriocarcinoma of the renal pelvis: a case report. Hinyokika Kiyo 2000;46:117–21.
[76] Pang YP, Rajesh H, Tan LK. Molar pregnancy with false negative urine hCG: the hook effect. Singapore Med J 2010;51:e58–61.
[77] Namburi RP, Kancherla V, Ponnala AR. High dose hook effect. J NTR Univ Health Sci 2014;3:5–7.
[78] Cole LA. Phantom hCG and phantom choriocarcinoma. Gynecol Oncol 1998;71:325–9.
[79] Topuz S, Iyibozkurt C, Mete O, Akhan S, Salihoğlu Y, Bengisu E, et al. Life-saving hysterectomy in choriocarcinoma: presentation of two cases. Eur J Gynaecol Oncol 2008;29:664–5.
[80] Ghaemmaghami F, KarimiZarchi M. Early onset of metastatic gestational trophoblastic disease after full-term pregnancy. Int J Biomed Sci 2008;4:74–7.