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Case Report

Intracerebral hemorrhage as initial presentation of nongestational choriocarcinoma: a case report and literature review

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Abstract: Intracerebral hemorrhage as initial presentation of nongestational choriocarcinoma is extremely rare. The therapy includes surgery, chemotherapy and radiotherapy. Nongestational metastatic choriocarcinoma has a poor treatment effect and a dismal prognosis. This study is to report a rare case of intracerebral hemorrhage as initial presentation of unknown primary of nongestational choriocarcinoma in order to familiarize its diagnosis and treatment, and review the relative reference to enhance the knowledge of it.

Keywords: Choriocarcinoma, intracerebral hemorrhage, brain metastasis, hCG, treatment

Introduction

Nongestational choriocarcinoma originates in the trophoblastic differentiation [1, 2] and has a poor prognosis [3-6]. It metastasizes by lymphatic or blood vessels in early stages of the disease [7]. It is extremely rare that intracranial hemorrhage as the first symptom of nongestational choriocarcinoma. This paper describes a rare case of intracerebral hemorrhage as initial presentation of unknown primary of nongestational choriocarcinoma. Intracerebral hemorrhage resulting from ruptured pseudoaneurysm was suspected. Emergent surgery was performed in order to evacuate of the hematoma. Pathologic examination of the specimen showed metastatic choriocarcinoma. After 1 courses of BEP (bleomycin, etoposide, and cisplatin), the levels of hCG returned to normal. Nongestational choriocarcinoma with brain metastasis has a poor prognosis and the management of these patients requires a multimodal approach. Then she continued to doreceivechemotherapy and radiotherapy. At present, the patient recovers menstruation, and a right limb function is gradual recovery but memory is still poorwith ten months of follow-up. The diagnosis, treatment and prognosis of nongestational choriocarcinoma were discussed by reporting this case and reviewing the relative references.

Materials and methods

A 26-year-old Chinese woman presented at the Gynecology Out-Patient Clinic at Fei county people's hospital, complaining of menopause over the previous two months and low-grade headache over the previous three days with the history of no pregnancy and only two months of sexual life. Laboratory work-up showed markedly elevated serum hCG (human chorionic gonadotropin) (>10,000 mIU/ml). Transvaginal ultrasounds demonstrated normal appearance of uterus and bilateral ovaries. She obtained conservative treatment with a preliminary diagnosis ofpregnancy.

Three days later, the patient was sudden convulsions with unconsciousness about several minutes, along with right limbs activity obstacle, vomiting for gastric contents. Craniocerebral CT showed left ventricular hemorrhage, causing significant midline shift, basal ganglia region high density shadow (**Figure 1**). Intracerebral

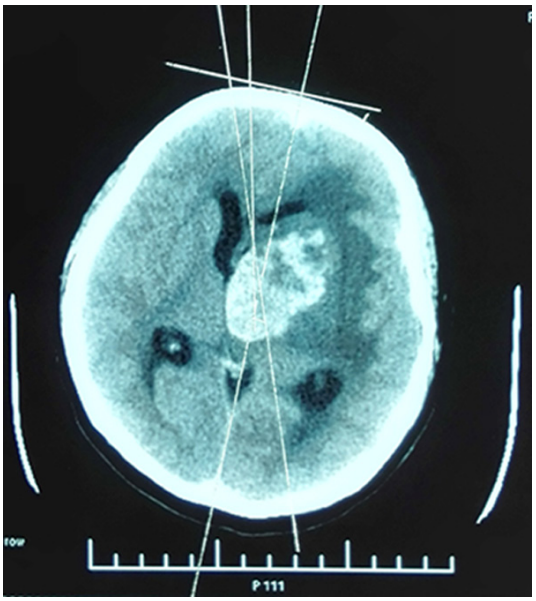

Figure 1. CT image prior to surgery.

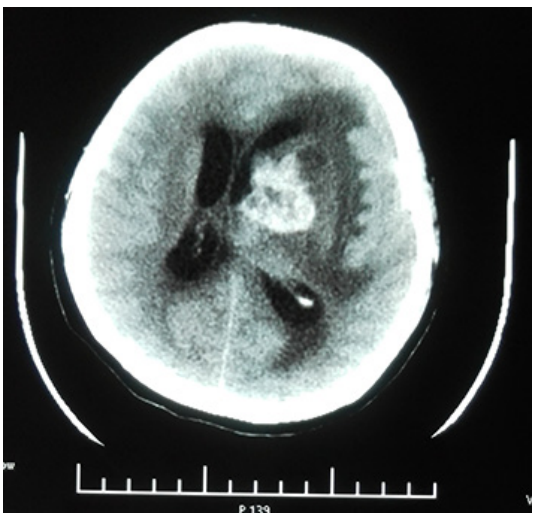

Figure 2. CT image posterior to the first surgery.

hemorrhage resulting from ruptured pseudoaneurysm was suspected. Her condition was not stable, so that she did not obtain further examination. The patient went external ventricular drainage via the parietal craniotomy to evacuate of the hematoma. Postoperative effect is not ideal (**Figure 2**). Magnetic resonance imaging (MRI) of the brain: the left basal ganglia region showed a irregular abnormal signal with hematoma dimensions 5.5 × 3.9 × 3.7 cm; right frontal lobe, corpus callosum knee, brain stem see flake abnormal signal with infarction

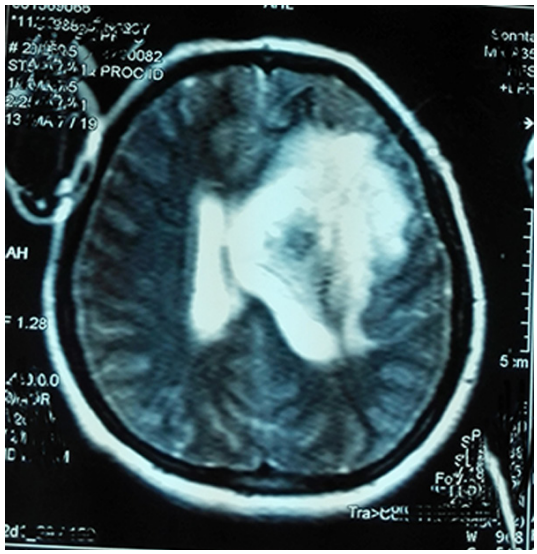

Figure 3. MR image prior to the second surgery.

(**Figure 3**). Grossly raised serum hCG was detected (3338.00 mIU/ml). Pelvic examination was unremarkable. It was also normal that neck, chest, abdominal and pelvic CT and transvaginal ultrasonography. Lining left thalamic lesion resection, intraoperative probe: seeing and removing brain tissue yellow dye, finding brain tumor about 4 × 4 cm in size with grey red color, blood supply of medium and the quality of a material medium. After surgery, she was sedated and mechanically ventilated for neuroprotection, while continuous monitoring of her intracranial pressure. Osmotic diuretics were used for control of intracranial hypertension. Her general status gradually got better. Pathologic examination of the specimen showed metastatic choriocarcinoma (immunohistochemical: CK+, HCG+, HPL+, Ki-67 70%, P63-, GFAP-) (on the left side of the thalamus). Although all the pelvic imaging was normal, the diagnosis of metastatic nongestational choriocarcinoma was made. The patient presented at Shandong Cancer Hospital, and hCG level dropped to 135 mIU/ml. She started on chemotherapy with regimen of bleomycin, etoposide, and cisplatin (BEP). Then her hCG level returned to normal (1.28 mIU/ml). She sequentially received 3 courses of BEP with tri-week and brain intensity modulated radiotherapy in a dose range of 5000 cGy. After the treatment, FDG-PET had not shown any remarkable hypermetabolic foci in any other locations. A review of the literature was performed to discuss the

Table 1. Nongestational choriocarcinoma: summary of cases

Age	Metastasis	β-hCG	Surgery	CTx	Radiotherapy	Outcome
54 [25]	Liver, lung	High	RH	BEP	Whole-brain	D9
15 [26]	No	N	LSO+OM	NS	No	NS
55 [24]	Lung	High	TAH+BSO	BEP	No	A20
10 [27]	No	NS	LSO+POM	PVB	No	NS
22 [28]	No	High	RS+RBL (first)	EMA-EP	No	A26
		RO+OM (second)				
23 [29]	No	High	LSO	MTX, EMA-EP, BEP	No	A22
28 [30]	No	High	RM	MTX, EMA-CO	No	A24
33 [31]	No	High	LS+LOC	EMA	No	A5
25 [32]	No	ND	RM	EMA-CO, BEP, VIP	No	A9
54 [1]	Lung, brain	ND	RH+BSO+PLND	AP, MEA	No	D12
62 [2]	Lung, spleen	High	TAH+BSO	ND	No	D8
	Bilateral gland					
	Brain					

A: alive; AP: doxorubicin cisplatin; β-hCG: β-human chorionic gonadotropin; B: bilateral; BL: broad ligament; BEP: bleomycin, etoposide, cisplatin; CTx: chemotherapy; D: dead; EMA-CO: etoposide, methotrexate, leucovorin, dactinomycin, cyclophosphamide, vincristine, EMA-EP (etoposide,metotrexate, actinomycin D, leucovorin, and cisplatin); F: female; L: left; MEA: methotrexate, etoposide, dactinomycin; MTX: methotrexate; NS: not stated; ND: not done; N: normal; O: oophorectomy; OM: omentum majus; OC: ovarian cyst; PVB: vinblastine, bleomycin, cisplatin; POM: part omentum majus; PLND: pelvic lymph nodes dissection; R: right; RH: radical hysterectomy; RM: removal mass; S: salpingectomy; SRH: semi-radical hysterectomy; TAH: total abdominal hysterectomy; VIP: etoposide, ifosfamide, and cisplatin.

diagnosis, treatment and prognosis of nongestational choriocarcinoma.

Results

The patient underwent emergent surgery. Pathologic examination showed metastatic choriocarcinoma. After 1 courses of chemotherapy (bleomycin, etoposide, and cisplatin) (BEP), the levels of hCG returned to normal, and she continued to accept 3 courses of BEP and brain intensity modulated radiotherapy in a dose range of 5000 cGy. At present, the patient recovers menstruation, and a right limb function is gradual recovery but memory is still poor. Meanwhile, reexamination hCG is in the normal range.

Discussion

Nongestational choriocarcinoma is very few in the literature and their characteristics are showed in **Table 1** since 2005. Only three of those cases had brain metastasis in late stage, and they did not have intracerebral hemorrhage. Raffaele Longo et al. described the case of a primary nongestational choriocarcinoma of the uterine cervix involving the liver, lungs, abdominal lymph nodes and brain metastasis (after six cycles of chemotherapy) in a 54-year-old postmenopausal woman. T. Seki et al. reported a rare case of uterine endometrial carcinoma with trophoblastic differentiation with lung metastases and brain metastases (after eight cycles of chemotherapy) in a 54-year-old postmenopausal woman. Yingmei Wang et al. presented a case of nongestational uterine choriocarcinoma involving the lung, spleen, bilateral adrenal gland, and brain. In all above mentioned cases, preoperative serum levels of hCG are not available in the second case, while the others are high. Grossly raised serum hCG was detected in our case. It is clear to diagnosis the metastatic nongestational choriocarcinomas of brain, but its primary tumor is unknown. Intracerebral hemorrhage as an initial presentation of nongestational choriocarcinoma has not been described so far. Its causes may include the lower incidence of nongestational choriocarcinoma and being included in other studies.

Nongestational choriocarcinoma is a mixed germ cell tumor which is from gonadal or extragonadal midline locations (mediastinum, retroperitoneum or pineal gland) [8] or other epithelial cancers such as lung, stomach, and bowel [9]. The origin of disease in our case is

unknown until now. The patient had only two months of sexual life without menopause ago. Afterwards, she showed menopause over the previous two months, so that it was impossible to transport from chorionic cells from a previous pregnancy, and gestational sac did not seek out by imaging examination including neck, chest, abdominal and pelvic CT and transvaginal ultrasonography before and after surgery, at the same time she also appeared menstrual after surgery. After treatment, FDG-PET had not shown any remarkable hypermetabolic foci in any other locations. The disease could develop from some location that later spontaneously regresses or smaller lesions do not find by imaging examination. Prior to treatment, FDG-PET is not available; otherwise, it might find the origin of disease in our case. The accurate origin is impossible in this case.

Choriocarcinomas of paraneoplastic can secrete hCG, which can lead to a erroneous pregnancy test. Other sources of false-positive pregnancy test result include ectopic hCG secretion such as congenital defects or other ovarian tumors, iatrogenic or self-administration of hCG, heterophile antibodies, or rheumatoid factor. Its cause is choriocarcinomas in this case. For the childbearing age of woman, pregnancy is not the only cause of elevated urine hCG level and amenorrhea. Height of serum hCG is one of the characteristic clinical findings and is an important symbol of brain metastasis. Measurement of hCG concentrations in cerebral spinal fluid (CSF) is a more sensitive and reliable indicator of tumor presence [10]. As long as hCG in CSF is abnormal. Quantification of the hCG in CSF is conducive to guide treatment and monitor response to treatment of these tumors [11]. It is a pity that our case does not detect hCG in CSF. False negative urine hCG may be described in choriocarcinoma patients because of the high concentration of the antigen. Mehra et al showed a case of choriocarcinoma whose urine hCG test is negative [12]. Dilutions of urine samples from 1:10 to 1:1000 are helpful us overcome the hook effect [13, 14]. Some studies [15] defined outcome on the basis of the serum hCG levels. Once hCG is normal, 3 consolidation chemotherapy are required [16]. Our patient obtained complete remission with 3 consecutive normal serum hCG levels (<2 mIU/ml). HCG tests cannot rule out choriocarcinoma completely. Hence, it must be continued to screen in special clinical situations.

Mostly patients usually remained asymptomatic [17]. On account of nongestational choriocarcinomas being perfused by fragile vessels, invading and eroding vessel wall. Bleeding at metastatic foci is frequent symptoms of metastases like our patient. Intracerebral hemorrhage is the most common symptoms of cerebral involvement and may develop acute focal neurologic deficits. Cerebral hemorrhage makes most of the patients died [18, 19]. Life-threatening bleeding, surgery should be performed, though surgery with a high incidence of hemorrhagic complications. Craniotomy could provide acute decompression or control bleeding.

For childbearing age of patients, the diagnosis of nongestational choriocarcinoma is very difficult according the clinical and radiological findings. We should be extensive sampling to identify choriocarcinomas of different origins by pathologic morphologic analysis and biochemical examination, but it is not easy. PET scan could help find occult metastatic lesions. DNA polymorphism analysis is a new way to identify [15, 20-22]; however, their clinical applicability is limited. Although our case was not performed DNA analysis, we diagnosed according to the diagnostic criteria of Saito et al [23] (absence of disease in the uterine cavity, pathological confirmation of disease, and exclusion of molar pregnancy and of intrauterine pregnancy) it was fulfilled.

Nongestational choriocarcinoma is a highly chemosensitive tumor. So, chemotherapy is a wise choice for nongestational choriocarcinomas patients. Due to the infrequency of nongestational choriocarcinomas, there is still no consensus chemotherapy regime. Recent literature indicates that it is responsive to multi agent chemotherapy which includes VAC (vincristine, actinomycin D, cyclophosphamide) or BEP (bleomycine, etoposide, cisplatin) [24]. The use of routine cranial radiation to reduce the chance of cerebral hemorrhage and recurrence are appropriate; however, which could induce intellectual impairment over the long term.

Nongestational metastatic choriocarcinoma has a poor treatment effect and a dismal prognosis. In above mentioned three cases, overall survival is 8 months, 9 months, 12 months and respectively. In our case, normal FDG-PET may be a good prognostic sign after treatment. After radiation and chemotherapy, the patient recov-

ers menstruation, and a right limb function is gradual recovery but memory is still poor. Meanwhile, reexamination hCG is in the normal range.

Conclusion

In summary, we report a rare case of intracerebral hemorrhage as initial presentation of unknown primary of nongestational choriocarcinoma. Our report may provide some revelations that it may represent an underlying neoplasm for women at childbearing age presenting with intracranial hemorrhage. Metastatic nongestational choriocarcinoma could be a cause of cerebral haemorrhage for reproductive age of patients. The knowledge of understanding nongestational choriocarcinoma would make earlier diagnosis, better treatment and improve the outcome.

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Disclosure of conflict of interest

None.

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