

Clinical features of a Chinese female Non-gestational Choriocarcinoma cohort: a retrospective study of 37 patients

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Abstract

Background

Choriocarcinoma is a rare malignant neoplasm, classified as gestational choriocarcinoma and non-gestational choriocarcinoma. The purpose of this study is to demonstrate the clinical characteristics of Chinese female non-gestational choriocarcinoma patients and introduce our experience of treating this rare disease.

Results

We conducted a single-centered retrospective study on a sample of 37 non-gestational choriocarcinoma patients who were diagnosed and treated at Peking Union Medical College Hospital from March 1982 to March 2020. Their demographic, clinical, laboratory, and therapeutic data were collected. Detailed information were available for all individuals in our sample of 37 patients. The primary lesions included 34 in ovary, 2 in pituitary and 1 in stomach. The mean of onset age was 22.8 years. The mean follow-up period spanned 87.5 months. Lung (40.5%) were the most commonly observed metastatic sites. All subjects were treated by surgeries and multi-drug chemotherapies with a mean of 5.8 courses to achieve complete remission. The overall complete remission rate, relapse rate, 3-year and 5-year survival rates are 81.1%, 16.7%, 80.0%, and 75.5%.

Conclusions

Non-gestational choriocarcinoma could be managed well with surgeries and multi-drug chemotherapies, but the overall outcome was still worse than gestational ones. Both ovary cancer and gestational choriocarcinoma classification could be applied for ovary non-gestational choriocarcinoma. Mixed non-gestational choriocarcinoma seems to have similar therapeutic effects compared with pure ones.

Background

Choriocarcinoma is a rare and aggressive malignant tumor composed of biphasic cellular components of mononuclear cytotrophoblasts and multinucleated syncytiotrophoblasts [1]. The two significant choriocarcinoma subtypes, namely: gestational choriocarcinoma (GC) and non-gestational choriocarcinoma (NGC), have relatively different etiology, biological activity and prognosis [2]. GC could arise following any type of pregnancy, including hydatidiform mole, term or preterm pregnancy, ectopic pregnancy, and abortion. GC is also chemosensitive and overall cure rate in these tumors is currently >90% [3]. On the contrary, NGC may develop under two possible scenarios: it may arise from germ cells in gonads or extra-gonadal locations, or it could rarely occur in parenchymal organs due to dedifferentiation of somatic carcinoma [1]. The former subset is classified as a type of germ cell tumor.

Owing to the rarity of NGC, its clinical characteristics remain unclear. Germ cell tumor NGC occurs in ovary and midline locations, such as mediastinum, retroperitoneum, and pineal gland. Uterus, cervix,

stomach, pancreas and rectum were also illustrated to have NGC with or without somatic carcinoma components in case reports [4-8]. Some studies conclude that NGC is less sensitive to chemotherapy and has relatively poor prognosis, compared with GC [9]. In those case reports, the responses of therapy varied. Further large NGC cohorts are still needed to verify those conclusions.

As far as we know, there is no NGC cohort reported from other medical center. Except we have previously reported a clinical analysis of 21 non-gestational ovary choriocarcinoma in 2009 [10]. Our previous study on cases from March 1982 to October 2008 indicated that the complete remission (CR) rate and 5-year overall survival rate were 76.2% and 79.4%, respectively. Due to gradually accumulated understanding of this disease, several new NGC cases were diagnosed in the past 11 years.

In this study, we reviewed the medical records of all NGC patients treated at our institution. The purpose of this study is to demonstrate the clinical characteristics of Chinese female non-gestational choriocarcinoma patients and introduce our experience of treating this rare disease.

Methods

This study adopted modified Saito's diagnostic procedures [11]. Patients should meet all of the following inclusion criteria: (1) absence of disease in the uterine cavity, (2) pathological confirmation of choriocarcinoma with persistent elevated serum level of β -human chorionic gonadotropin (β -hcg) (3) exclusion of molar pregnancy, and (4) exclusion of coexistence of intrauterine pregnancy. Exclusion criteria are as follows: (1) previous ectopic pregnancies history, and (2) lesions were only observed in lung.

We retrospectively reviewed the medical records of all the NGC patients recruited between March 1982 and March 2020 at Peking Union Medical College Hospital (PUMCH). Written informed consent was obtained from each patient, and this study was approved by the Institutional Review Board of PUMCH.

Detailed demographic and clinical data were collected. Any initial symptoms, sexual contact history, previous medical history, and family history, if found during careful inquires, were listed in detail. The laboratory values of β -hcg, alpha-fetoprotein (AFP) were reviewed as available. Therapeutic modalities included surgery, chemotherapy and radiotherapy. Number of chemotherapy courses were carefully calculated.

Based on their response to each therapeutic modality, we categorized all patients into the following subsets, complete remission (CR), partial remission (PR), progressive disease (PD) and relapse. A CR was defined as complete elimination of all clinical syndromes and laboratory or imaging abnormality. PR was noted as an alleviation but a lesser degree of partial persistence of clinical, laboratory or imaging abnormalities continue to persist. PD is defined as a rising hCG level with development of previous lesions or occurrence of new metastases during treatment. Relapse was listed for patients with elevated β -hcg after reaching CR with a treatment-free interval of at least 3 months.

All data were recorded and analyzed in SPSS statistics software version 22. Descriptive data were expressed in numbers (%) for categorical variables, and mean (SD) for continuous variables. Student's t test were used for continuous and categorical variables. All tests were two-sided and a p-value of less than 0.05 was considered to be statistically significant. Kaplan and Meier methods were applied for survival analysis.

Results

Demographic data

A total of 37 NGC patients were recruited, all of Chinese origin. The mean age at onset of disease was 22.8 (9.6, range 9-44) years. As in March 2020, the follow-up period of this cohort amounted to 87.5 (82.4, range 1-269) months. Twenty-three patients had no pregnancy history, including 7 premenarchal girls. Twenty of them declared no previous sex life history. (Table 1)

Clinical presentations

For 37 NGC patients, ovary was the most commonly affected location with an 11:22:1 ratio of left/right/bilateral. Two patients had NGC in pituitary, another one had NGC in stomach. Twenty-one (56.8%) patients had metastatic lesions of which lungs were the most commonly observed (40.5%) locations. Brain and liver metastasis were found in two patients. Another 4 patient had extensive lesions in abdomen cavity.

Symptoms of these NGC patients were relatively not specific. Abdominal pain was reported by 24 patients. Six of them had acute abdomen and were underwent emergency surgery. Sixteen postpuberal patients had abnormal uterine bleeding, such as irregular menstruation and amenorrhea. Two pituitary patients were affected with insipidus. Other tumor-related manifestations, such as fever, pregnancy symptoms, palpable mass, headache, cough, hemoptysis, and melena were only rare conditions. No choriocarcinoma or any other type of tumor history of primary relatives were reported by these 37 NGC patients.

Serum β -hcg levels of each patient was regularly measured. The mean of each patient's highest value of serum β -hcg during the whole disease course was 77278 (121363, range 89.1-386274) mIU/ml. AFP was tested in 13 patients. Only one mixed germ cell tumor NGC with dysgerminoma and embryonal carcinoma patient had elevated AFP.

Seven patients had histopathologically confirmed mixed NGC (1 in pituitary, 5 in ovary, 1 in stomach). Apart from choriocarcinoma, other components include dysgerminoma, embryonal carcinoma, teratoma and adenocarcinoma. A Student's t test shows that mixed NGC and pure NGC had little differences between onset age ($p=0.283$), choriocarcinoma staging ($p=0.245$), ovary cancer staging ($p=0.507$, only for 34 ovary NGC patients), β -hcg level ($p=.0311$), having metastasis or not ($p=0.523$), overall courses of chemotherapy ($p=0.836$), courses to reach CR ($p=0.262$), and CR rate ($p=0.277$). (Table 1 & Figure 1)

Therapeutic modalities

Treatments include chemotherapy, surgery, radiotherapy and intrathecal injection. All patients received multiple-drug combined chemotherapy. The main regimen chosen are EMA/CO (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, Vincristine, for 20 patients), FAEV (Floxadine, Actinomycin-D, Etoposide, Vincristine, for 15 patients), BEP (Bleomycin, Etoposide, Cisplatin, for 7 patients), PVB (Bleomycin, Vincristine, Cisplatin, for 4 patients), and ICE (Ifosfamide, Carboplatin, Etoposide, for 2 patients). Nine patients received chemotherapy before surgery. The overall mean courses and courses to reach CR were 9.9 and 5.8, respectively. For 7 mixed NGC patients, 2 took mainly BEP protocol and another 3 used EMACO protocol, all with a CR response. BEP, EMACO and FAEV protocols were prescribed for another ovary mixed NGC patients but was unable to control her disease. The stomach mixed NGC patient obtained CR after FAEV therapy but had disease relapse after 2 years.

Myelosuppression was commonly observed adverse effect of chemotherapy, but only one patient had life-threatening myelosuppression. Other conditions such as liver injury, dental ulcer, anorexia were rarely reported by sporadic patients.

All 37 patients underwent surgery and thus had a histopathological confirmation of choriocarcinoma. For 34 ovary NGC patients, 16 underwent cytoreductive surgery and 18 received fertility-preserving surgery. For 16 cytoreductive surgery patients, 6 was initially underwent fertility-preserving procedures. However, a debulking surgery was performed in our medical center because of unsatisfactory drop of β -hcg or disease relapse. Even though 15 patients had lung metastases, only three of them received pulmonary lobectomy.

Assisting chemotherapy, one pituitary NGC patients completed 25 times of radiotherapy treatments (total 45 Gray). Another patient with cerebral metastasis received 3 methotrexate intrathecal injections. (Table 2)

Outcomes

For all 37 NGC patients, 30 (81.1%) achieved CR, 4 (10.8%) achieved PR. Three (8.1%) patients had PD and were died. One patient was diagnosed in 1980s and received nonstandard multi-drug combined chemotherapy. She gave up treatment after 44 months of unsuccessful decline of hCG. Another subject had mixed NGC with teratoma and dysgerminoma components. She underwent debulking surgery and received FAEV, BEP and EMACO chemotherapy for 23 months. The last patient died of chemoresistance. Succession regimen of FAEV, PVB, ICE and EMAEP (Etoposide, Methotrexate, Actinomycin D, Cisplatin) were unable to decline β -hcg to normality.

For 34 CR and PR patients, 8 patients were lost of follow-up, including 4 CR and 4 PR patients. With a mean of 87.5 months of follow-up, the overall 1-year, 3-year and 5-year survival rates are 86.2%, 80.0% and 75.5%.

Five (16.7%) of the CR patients had disease relapse during follow-up. Four were affected by ovary NGC and initially received fertility-preserving procedures. After disease relapse, three underwent another debulking surgery and subsequent chemotherapies. One girl only received another 6 courses of EMACO. All of them four obtained CR again. The stomach NGC patient showed multiple metastases in abdomen 2 years after reaching CR and died of chemoresistance.

Discussion

NGC had seldom been reported because of its low incidence. Publications available are mostly case reports and occasionally case series of patients. We conducted a retrospective study of 37 NGC patients, and their clinical, demographic data and treatment plans were detailed reviewed. Managed with surgeries and multi-drug chemotherapies, the overall 3-year and 5-year survival rates for NGC are 80.0% and 75.5%.

It is hard to discriminate a subject is GC or NGC, due to similar macroscopic appearances, histopathological features, and elevated serum level of β -hcg [1]. Notably, a higher serum β -hcg level does not ensure choriocarcinoma components of a mixed germ cell tumor [12, 13]. Except for Saito's criteria proposed in 1960s, two more exclusion criteria were added for this study to exclude some possible GC patients. Firstly, due to hematogenous spread of GC, primary lesions in uterine cavity may regress spontaneously but metastasis in lungs may still exist [14-16]. On the other hand, since lung was not common site of germ cell tumor, patients with solitary lesions in lungs were most likely to be GC and were excluded accordingly. Secondly, there is a small possibility that some ovary NGC may originate from ectopic pregnancies. Even though ovarian pregnancy is one of the rarest forms of ectopic pregnancy having incidence of 1/7000-1/40,000 in live births and only 0.5-3% of all ectopic gestations, patients with previous ectopic pregnancy were also excluded [17].

Some studies insisted NGC patients should have no pregnancy history [1]. A choriocarcinoma must be NGC, if technically excluded history of pregnancies and even previous sex life. However, most NGC belongs to germ cell tumor. The pathogenesis of germ cell tumor has no relationship with pregnancy or not [18]. So patients may have previous pregnancy not related to NGC. The diagnostic criterion of no pregnancy is strict indeed, but not comprehensive enough and may omit some gonadal or extragonadal germ cell tumor NGC. In this study, only 14 NGC patients reported previous sex life.

DNA polymorphism analyses was also an important tool for diagnosis. Gnotyping could identify the presence of a parental allele thus confirm a diagnosis of GC, since NGC has only maternal allele. Based on this distinguishing feature, genetic analysis was applied by more and more studies and considered with low controversy [19, 20]. However, since genetic analysis is not widely put into use for choriocarcinoma patients, clinical diagnosis should still be the mainstream.

Because of the rarity, staging of NGC remains unclear. For ovary NGC, both ovary cancer and choriocarcinoma staging classification could be adopted. For 34 ovary NGC subjects in this study, 14 were in stage I, 2 in stage II, 2 in stage III, and 16 in stage IV according to International Federation of Gynecology and Obstetrics (FIGO) 2013 standard of ovary cancer, with a 5-year survival rate of 92.9%,

100%, 0% and 72.2%, respectively. In view of FIGO 2000 classification of choriocarcinoma, 14 were in stage II, 11 in stage III, and 10 in stage IV. The CR rates were 92.9%, 81.8%, and 40.0%, respectively, which were a bit lower than those of GC (CR rates: 99.3%, 89.4%, and 79.0% for stage II, III, and IV, respectively) [21]. The reported survival rate of stage IV ovary germ cell tumor was 14-54% [22]. Our results were relatively higher. Strikingly, eleven of those ovary NGC patients had lung metastases, thus were classified as stage III of choriocarcinoma and stage IV of ovary cancer. Nine achieved CR, while one died because of irregular chemotherapy and one were lost of follow-up after 4 months treatment. So the overall prognosis of NGC with lung metastases was favorable. In consideration of the features of NGC, such as high rate of lung metastases (40.5% in this cohort), therapeutic effects, and optimistic prognosis, ovary NGC should also be accepted to be staged by choriocarcinoma classification. However, the WHO prognostic scoring system for malignant gestational trophoblastic diseases was not suitable for NGC, because two items, antecedent pregnancy and interval from index pregnancy, were inapposite to be evaluated.

Currently there is no standard therapies for NGC, but instead, treatments mainly follow that of GC [23]. NGC is regarded to originate from the patient itself, so surgical procedures along with chemotherapies are required in most cases [24]. EMA/CO and FAEV regimen were the mainly chosen multiple-drug combined chemotherapies in this cohort, showing good tolerance and effectiveness for NGC. Neoadjuvant chemotherapies should also be considered for patients with high β -hcg level. Both BEP and EMA/CO regimen seem to be effective to control mixed germ cell tumor with choriocarcinoma components, and the overall CR rate and survival rate were not different between mixed choriocarcinoma patients and pure ones. Since NGC mainly affect young premenopausal women who have not completed childbearing, every effort is made to minimize the long-term effects of cancer treatment. Fertility-preserving surgeries for patients with localized lesions could also be considered.

This study had some limitations. Firstly, it was a retrospective study and that may implicate recall and missing data bias, so we conducted different methods to gather information. Secondly, the number of patients in our cohort was still relatively small, even given that NGC is such a rare disease globally. Lastly, as a top national medical center in China, patients from all over China would come for us, and we might be presented with more cases too severe to be clinically representative.

Conclusions

In summary, the sample in this study is a Chinese non-gestational choriocarcinoma cohort. We have provided detailed demographic and clinical data of these patients. Ovary and lung are the most commonly observed primary and metastatic sites. Both ovary cancer and gestational choriocarcinoma classification could be applied for ovary NGC. Mixed NGC seems to have similar therapeutic effects compared with pure NGC. NGC could be managed well with surgeries and multi-drug chemotherapies, but the overall treatment response is still worse than GC. Our cohort adds to the disease spectrum of trophoblastic disease and hopefully helps researchers to deepen their understanding of this type of illness.

Abbreviations

gestational choriocarcinoma	GC
non-gestational choriocarcinoma	NGC
complete remission	CR
β -human chorionic gonadotropin	β -hcg
Peking Union Medical College Hospital	PUMCH
alpha-fetoprotein	AFP
partial remission	PR
progressive disease	PD
Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, Vincristine	EMA/CO
Floxuridine, Actinomycin-D, Etoposide, Vincristine	FAEV
Bleomycin, Etoposide, Cisplatin	BEP
Bleomycin, Vincristine, Cisplatin	PVB
Ifosfamide, Carboplatin, Etoposide	ICE
Etoposide, Methotrexate, Actinomycin-D, Cisplatin	EMAEP
International Federation of Gynecology and Obstetrics	FIGO

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from each patient, and this study was approved by the Institutional Review Board of Peking Union Medical College Hospital.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

SYM analyzed and interpreted the patient data and drafted the manuscript. XY designed the study. JF, PBJ, WXR, YJJ, FFZ, RT, ZJ were also contributors in acquisition, interpretation and analysis of the data. All authors read and approved the final manuscript

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Tables

Table 1. Demographic and clinical characteristics of the 37 patients with non-gestational choriocarcinoma

Demographic characteristics	N=37
Age at diagnosis, mean (S.D.), years	22.8 (9.6)
<15 years old	9 (24.3%)
16-20 years old	9 (24.3%)
21-25 years old	5 (13.5%)
25-30 years old	5 (13.5%)
>30 years old	9 (24.3%)
Duration of follow-up, mean (S.D.), months	87.5 (82.4)
Primary location	
Ovary	34 (91.9%)
Left	11 (32.3%)
Right	22 (64.7%)
Bilateral	1 (2.9%)
Pituitary	2 (5.4%)
Stomach	1 (2.7%)
Metastatic lesion	
Lung	15 (40.5%)
Brain	2 (5.4%)
Pelvic metastases	4 (10.8%)
Abdominal metastases	6 (16.2%)
Initial symptoms	
Abdominal pain	24 (64.8%)
Acute abdomen	6 (25.0%)
Abnormal uterine bleeding	16 (43.2%)
Inspidus	2 (5.4%)
Pregnancy symptoms	3 (8.1%)
Palpable abdominal mass	2 (5.4%)
Hemoptysis	1 (2.7%)
Cough	1 (2.7%)
Fever	1 (2.7%)
Headache	1 (2.7%)
Melena	1 (2.7%)
Laboratory tests	
Serum β -hcg, mean (S.D.), mIU/ml	77278 (121363)
AFP, elevated	1/13 (7.7%)

β -hcg: β -human chorionic gonadotropin; AFP: alpha-fetoprotein

Table 2. Treatment and outcome of the 37 patients with non-gestational choriocarcinoma

Surgical operations	
Laparotomy	31 (83.8%)
Laparoscopic surgery	4 (10.8%)
Craniotomy	2 (5.4%)
Chemotherapy	
Total number of courses, mean (S.D.)	9.9 (8.4)
Number of courses before CR, mean (S.D.)	5.8 (5.3)
Outcome	
CR	30 (81.1%)
Relapse	5 (16.7%)
PR	4 (10.8%)
PD	3 (8.1%)

CR: complete remission; PR: partial remission; PD: progressive disease

Figures

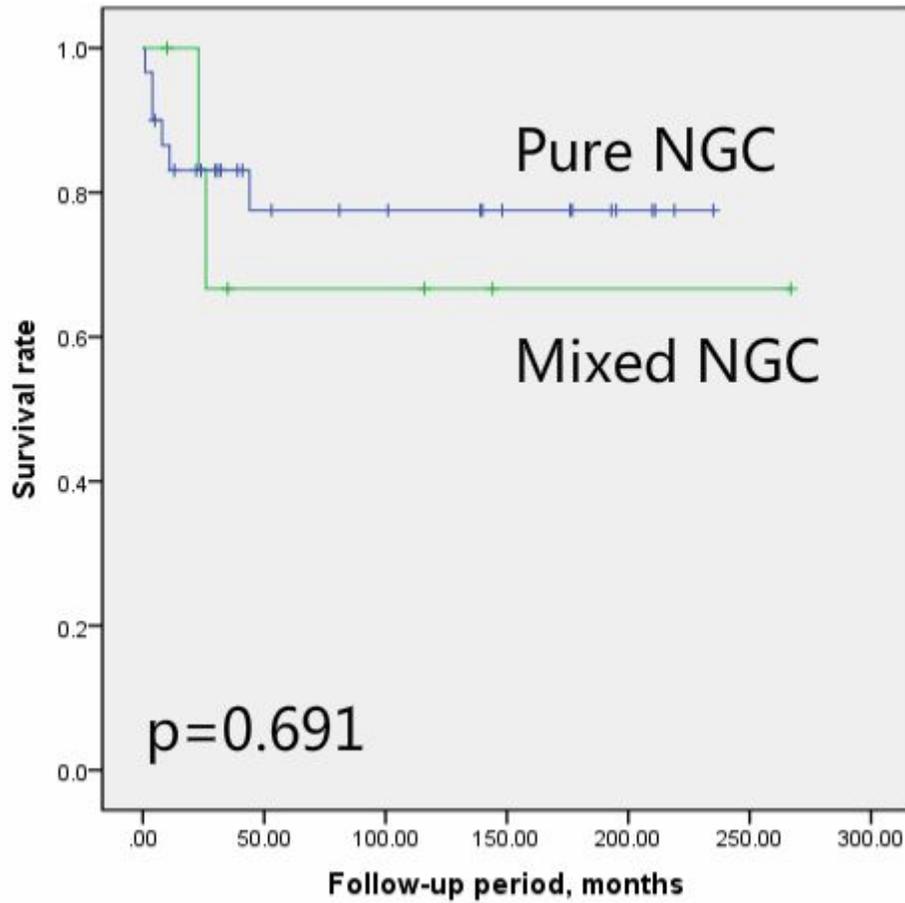


Figure 1

Survival rates of mixed non-gestational choriocarcinoma patients and pure ones NGC: non-gestational choriocarcinoma