

Case Report

Primary Anterior Medistinal Choriocarcinoma in Male with Lung Metastasis and Pituitary Microadenoma: A Case Report

Dong Liu Qingjian Ye Minjuan Ye Yuebo Yang

Department of Gynaecology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Keywords

Anterior mediastinal choriocarcinoma · Male · Chemotherapy · Gynecomastia

Abstract

The authors report a case of a 29-year-old male presented with bilateral breast enlargement with no significant past medical history or estrogen exposure. Serum β -human chorionic gonadotropin (HCG) was 14,306.60 mIU and positron emission tomography-computed tomography discovered a malignant mass on the right side of anterior superior mediastinum. Magnetic resonance imaging demonstrated pituitary microadenoma. Pathological biopsy showed poorly differentiated pituitary adenoma and immunohistochemical staining displayed that CK(+), PLAP(-), AFP(-), HCG(+), CD30(-), Oct3/4(-), CK7(+), TTF-1(-), CD117(-), Ki 67(80+), CK5/6(-), EMA(partial+), inhibin(partial+). A diagnosis of primary anterior mediastinal choriocarcinoma metastasis to bilateral lungs accompanied with pituitary microadenoma was confirmed. Then the patient received chemotherapy combined with immunotherapy. But serum β -HCG level was still above the normal, and unfortunately, the patient died 6 months after his diagnosis. This case inspires us to think of the possibility of choriocarcinoma when a man presents gynecomastia or lung metastatic symptoms, adding Opdivo to the chemotherapy might not improve the poor treatment outcomes.

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Correspondence to:
Dong Liu, liudong8@mail.sysu.edu.cn
Yuebo Yang, yueboyang001@163.com

Introduction

Choriocarcinoma is an aggressive tumor, which is usually gestation-associated and occurs in female population, sometimes occurs in the testicles of males. Extragonadal choriocarcinoma in male is extremely rare and it is characterized by easily being misdiagnosed, early hematogenous spreading, poor response to therapy, and short survival time. The current study presents a case of primary choriocarcinoma of anterior mediastinum metastasis to bilateral lung accompanied with pituitary microadenoma in a 29-year-old male. The aim of this report was to explore the accurate diagnosis and optimal treatment of primary choriocarcinoma of anterior mediastinum.

Case Presentation

A 29-year-old male with no significant past medical history presented gradually bilateral breast enlargement for last 2 months accompanied with pain exacerbated when touched, with no galactorrhea, redness, or swelling. He denied history of exposure to systemic or topical exogenous estrogenic compounds. His weight was 65 kg, height was 171 cm, and body mass index was 22 kg/m². On examination, patient had Tanner II breast development on both sides. Testicles were equal in size and pubic hair development was Tanner V and the penis was 8 cm when flaccid.

Patient was afebrile with a heart rate of 82 bpm (beats per minute), respiratory rate of 16/min, and blood pressure of 102/70 mm Hg. The cardiac and abdominal examinations were unremarkable. Pectoral auscultation and percussion were normal. Pathological reflex was negative. His medical and family history was not significant. The results of GnRH stimulation test were as follows: luteinizing hormone 0.15 - 0.15 - 0.22 - 0.26 - 0.25 - 0.57 mIU/mL, follicle-stimulating hormone <0.050<0.050<0.050<0.050–0.06 mIU/mL, testosterone 29.85–27.84–30.95–32.86–31.73–29.0 ng/mL, estradiol 2 (E2) 530–525–522–541–516–539 pg/mL. Serum β -human chorionic gonadotropin (HCG) was 14,306.60 mIU. Breast ultrasound showed hyper echo under mammilla, which was considered as breast development. The results of routine laboratory examinations were all normal. Positron emission tomography-computed tomography revealed solid-appearing mass on the right side of anterior superior mediastinum, extending to pleura and pericardium, whose metabolic activity was classified as malignant (Fig. 1). There were also extensive and multiple bilateral pulmonary nodules with metabolically active, which are deemed as lung metastases. Magnetic resonance imaging of pituitary gland demonstrated pituitary microadenoma. Patient underwent resection and biopsy of right middle lung nodules under thoracoscopy under general anesthesia. The microscopic pathological examination showed that the center of the neoplasm was composed of necrotic and hemorrhagic areas. Cells surrounded were arranged in nests flake, cellular atypia, abundant cytoplasm, nuclear vacuoles, visible nucleoli, and nuclear fission (Fig. 2). Immunohistochemical staining results were as follows: CK(+), PLAP(-), AFP(-), HCG(+), CD30(-), Oct3/4(-), CK7(+), TTF-1(-), CD117(-), Ki 67(80+), CK5/6(-), EMA(partial+), inhibin(partial+), indicating choriocarcinoma. Based on the above findings, a diagnosis of primary anterior mediastinal choriocarcinoma metastasis to bilateral lung accompanied with pituitary microadenoma was confirmed (Table 1).

Treatment and Outcome

The patient received four cycles of T-BEP [1, 2] scheme consisting of Taxol (300 mg/m², intravenous [IV] drip d1), cisplatin (30 mg/m², IV drip d1-5), etoposide (170 mg/m², IV drip d1-5), bleomycin (30 mg/m², IV drip d2, 8, 15). Patient developed a fever after using

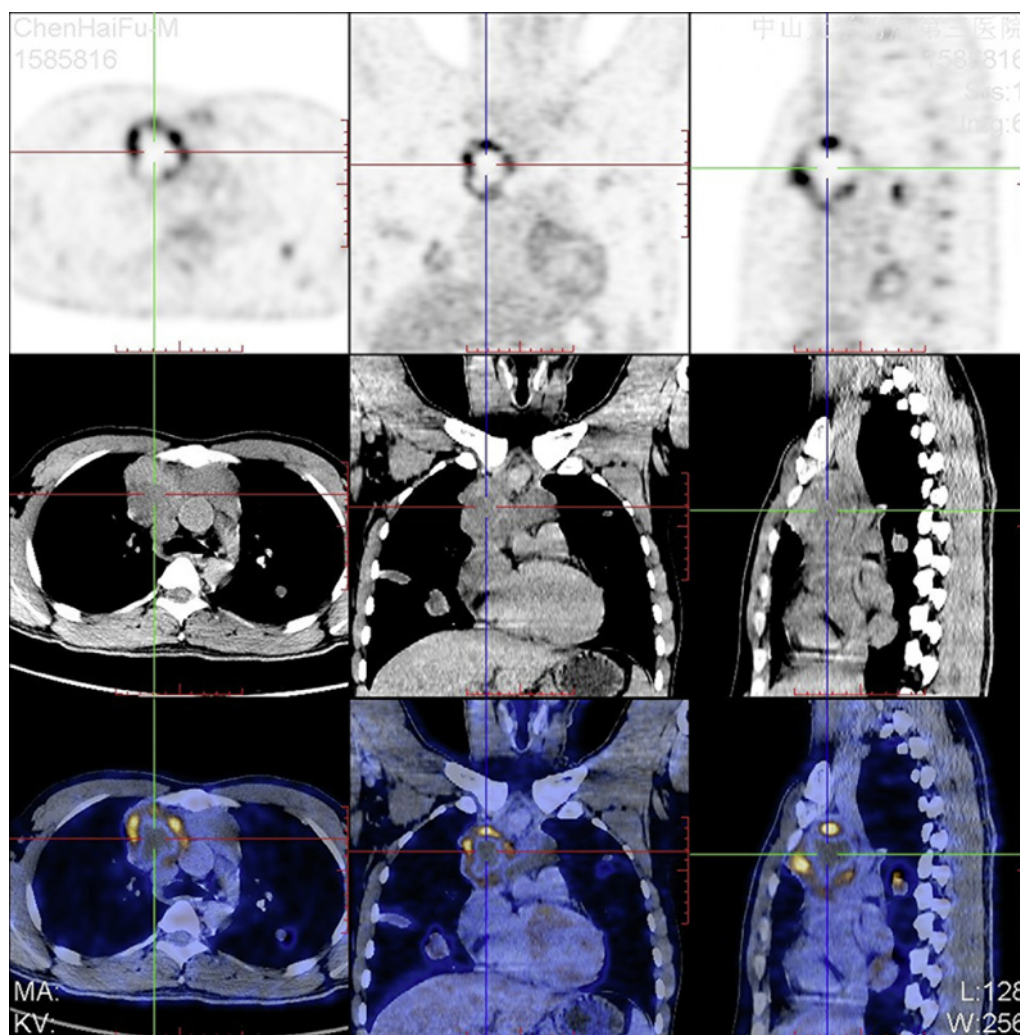


Fig. 1. PET-CT revealed solid-appearing mass on the right side of anterior superior mediastinum, extending to pleura and pericardium, whose metabolic activity was classified as malignant. PET-CT, positron emission tomography-computed tomography.

bleomycin and the patient's temperature dropped to normal after symptomatic treatment. After the first course of chemotherapy, patient developed IV grade myelosuppression, so we injected recombinant human granulocyte colony-stimulating factor (G-CSF) and the suppression was alleviated. The patient also received three times of lumbar puncture and intrathecal methotrexate 12 mg. Since the second course of chemotherapy, we did prophylactic recombinant human G-CSF injection and patient had not had any fever or myelosuppression. After the patient finished four cycles of T-BEP scheme, radiology examination revealed that solid-appearing mass on the right side of anterior superior mediastinum became smaller and metabolic activity decreased (Fig. 3). Some of the metastatic bilateral pulmonary nodules began to shrink, while others became larger and there were also new nodules appeared. The metabolic activities were mild to moderate. Serum β -HCG was 10.27 mIU. Because there were still residual cancer focus, we changed chemotherapy scheme to classic EMA/CO scheme, consisted of etoposide (170 mg/m^2 , IV drip d1-2), methotrexate (170 mg/m^2 , IV drip), actinomycinD (0.5 mg/m^2 , IV drip d1-2), cytotoxin ($1,000 \text{ mg/m}^2$, IV drip d8), and vincristine (1.7 mg/m^2 , IV drip d8). Patient was in good condition during this

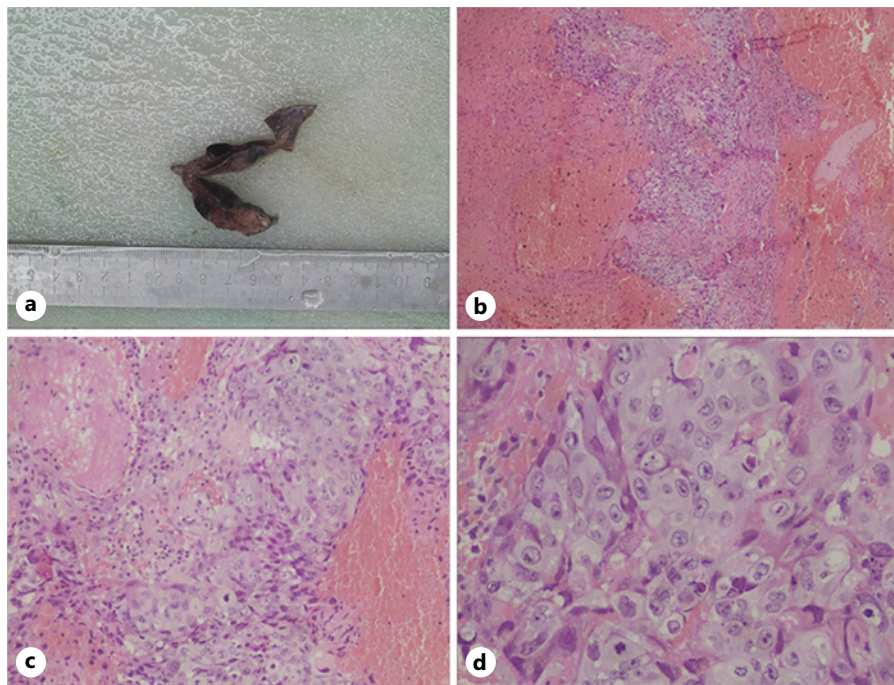


Fig. 2. Macroscopic and histologic features of the tumor: **a** A few purple and black nodules on right middle lung. **b, c** At lower magnification, tumor cells grow in cluster with a large area of hemorrhage and necrosis (**d**).

course but Serum β -HCG did not decrease. So, after one cycle treatment, we changed the scheme to GOP scheme consisted of gemcitabine (1.3 mg/m^2 , IV drip d1), Taxol (120 mg/m^2 , IV drip d1), and oxaliplatin (220 mg/m^2 , IV drip d1). Since immunohistochemical staining results showed PD-L1 was 80–90% positive, we added immunotherapy and changed the scheme to classic EMA/CO scheme, including opdivo (180 mg/m^2 , IV drip d0), etoposide (170 mg/m^2 , IV drip d1-2), methotrexate (170 mg/m^2 , IV drip), actinomycinD (0.5 mg/m^2 , IV drip d1-2), cytotoxin ($1,000 \text{ mg/m}^2$, IV drip d8), and vincristine (1.7 mg/m^2 , IV drip d8). Chemotherapy combined with immunotherapy continued until the patient died of complications (Table 1). Secondary anemia accompanied by granulocyte maturation disorder in patients during chemotherapy, so hematopoietic stem cell transplantation was recommended. However, when all the prerequisites for cell transplantation are ready, the patient experienced a sudden death (Fig. 4).

Discussion

Choriocarcinoma is generally gestational related, which often occurs with spontaneous abortion, hydatidiform moles, ectopic pregnancy, or normal delivery. Based on the data, it affects 1–9.2 in 40,000 pregnancies and 1 in 40 hydatidiform moles. Nongestational choriocarcinoma is rare, and the incidence ratio of gestational choriocarcinoma to nongestational choriocarcinoma was 79:1. Nongestational choriocarcinoma can occur in both male and female and a ratio of male-to-female is 13:33 among patients according to the statistics by Jiang et al. [3, 4] In males, choriocarcinoma is generally considered a non-seminomatous germ cell tumor, which represents less than 5% of all germ cell tumors in males [5]. The median age of nongestational choriocarcinoma in male is 30 years old and the

Table 1. Chronological patient treatment process

Date	Event
13 Aug 2018	Hospitalization for bilateral breast enlargement
24 Aug 2018	Resection and biopsy of right middle lung nodules under thoracoscopy
4 Sep 2018	Checked β -HCG level: 33,191.5 mIU
5 Sep 2018	The first cycle of T-BEP started Taxol (300 mg/m ² , intravenous [IV] drip d1) cisplatin (30 mg/m ² , IV drip d1-5) etoposide (170 mg/m ² , IV drip d1-5) bleomycin (30 mg/m ² , IV drip d2,8,15)
7 Sep 2018	Fever, T _{max} = 39.5°C, no coughing or other infectious symptoms, DXM was used and temperature dropped to normal
10 Sep 2018	Blood routine: WBC: 10.65 × 10 ⁹ /L, PLT: 312 × 10 ⁹ /L, Hb: 106 g/L, CRP: 29 μ g/L, UA: 443 μ mol/L
13 Sep 2018	Blood routine: WBC: 1.65 × 10 ⁹ /L, Hb: 103 g/L, patient developed IV grade myelosuppression, we injected recombinant human granulocyte colony-stimulating factor (G-CSF), and the suppression was alleviated. The first cycle of chemotherapy was finished
18 Sep 2018	Blood routine: WBC: 14.25 × 10 ⁹ /L, PLT: 165 × 10 ⁹ /L, Hb: 98 g/L, CRP: 29 μ g/L, UA: 604 μ mol/L, β -HCG: 1641.8 mIU, PA: 174 mg/L
20 Sep 2018	Lumbar puncture+intrathecal drug injection: MTX
25 Sep 2018	Blood routine: WBC: 9.69 × 10 ⁹ /L, PLT: 208 × 10 ⁹ /L, Hb: 108 g/L, β -HCG: 341.7 mIU, ALT: 38 U/L, GLOB: 24 g/L
26 Sep 2018	The second cycle of T-BEP started
6 Oct 2018	Blood routine: WBC: 3.69 × 10 ⁹ /L, PLT: 147 × 10 ⁹ /L, Hb: 86 g/L
9 Oct 2018	Blood routine: WBC: 9.07 × 10 ⁹ /L, PLT: 127 × 10 ⁹ /L, Hb: 93 g/L
12 Oct 2018	The second cycle of T-BEP was finished
5 Sep 2018	Taxol (300 mg/m ² , intravenous [IV] drip d1) cisplatin (30 mg/m ² , IV drip d1-5) Etoposide (170 mg/m ² , IV drip d1-5) Bleomycin (30 mg/m ² , IV drip d2,8,15)
18 Oct 2018	The third cycle of T-BEP started
31 Oct 2018	The third cycle of T-BEP was finished
9 Nov 2018	The fourth cycle of T-BEP started
23 Nov 2018	Blood routine: WBC: 6.54 × 10 ⁹ /L, PLT: 89 × 10 ⁹ /L, Hb: 73 g/L, GLOB: 19.2 g/L The fourth cycle of T-BEP was finished
11-27	β -HCG: 10.27 mIU, PET-CT scan showed that compared with 2018-08-20, some of the metastatic bilateral pulmonary nodules began to shrink, while others became larger and there were also new nodules appeared. The metabolic activities were mild to moderate
29 Nov 2018	The fifth cycle of chemotherapy started and the protocol changed to EMA/CO. Etoposide (170 mg/m ² , IV drip d1-2) Methotrexate (170 mg/m ² , IV drip) actinomycinD (0.5 mg/m ² , IV drip d1-2) Cytotoxin (1000 mg/m ² , IV drip d8) Vincristine (1.7 mg/m ² , IV drip d8)
7 Dec 2018	Blood routine: WBC: 3.88 × 10 ⁹ /L, PLT: 158 × 10 ⁹ /L, Hb: 73 g/L, UA: 476 μ mol/L, ALT: 53 U/L, GLOB: 19 g/L, EMA/CO protocol was finished
14 Dec 2018	Blood routine: WBC: 9.25 × 10 ⁹ /L, PLT: 380 × 10 ⁹ /L, Hb: 75 g/L, UA: 455 μ mol/L, PA: 194 mg/L, ALT: 62 U/L, GLOB: 19 g/L, β -hCG: 10.16 mIU, TIBC: 33.5 μ mol/L, TF: 940.68 μ mol/L GOP protocol was started. gemcitabine (1.3 mg/m ² , IV drip d1) Taxol (120 mg/m ² , IV drip d1) Oxaliplatin (220 mg/m ² , IV drip d1)
18 Dec 2018	Blood routine: WBC: 2.88 × 10 ⁹ /L, PLT: 284 × 10 ⁹ /L, Hb: 77 g/L, UA: 606 μ mol/L, ALT: 58 U/L, AST: 48 U/L, GLOB: 20.7 g/L, LDH: 726 U/L. We injected recombinant human granulocyte colony-stimulating factor (G-CSF) and the suppression was alleviated. WBC was 13.36 × 10 ⁹ /L

(Continued on following page)

Table 1 (continued)

Date	Event
22 Dec 2018	The sixth cycle of chemotherapy was finished
5 Jan 2019	The seventh cycle of chemotherapy and immunotherapy started and protocol was changed to EMA/CO + opdivo Opdivo (180 mg/m ² , IV drip d0) Etoposide (170 mg/m ² , IV drip d1-2) Methotrexate (170 mg/m ² , IV drip) actinomycinD (0.5 mg/m ² , IV drip d1-2) cytotoxin (1,000 mg/m ² , IV drip d8) vincristine (1.7 mg/m ² , IV drip d8)
27 Jan 2017	Blood routine: WBC: 6.69 × 10 ⁹ /L, PLT: 259 × 10 ⁹ /L, Hb: 94 g/L, UA: 625 μmol/L, ALT: 87 U/L, AST: 43 U/L, β-HCG: 40.6 mIU.
28 Jan 2019	The second cycle of chemotherapy combined immunotherapy Opdivo (180 mg/m ² , IV drip d0) Etoposide (170 mg/m ² , IV drip d1-2) Methotrexate (170 mg/m ² , IV drip) actinomycinD (0.6 mg/m ² , IV drip d1; 0.4 mg/m ² , IV drip d2) cytotoxin (1,000 mg/m ² , IV drip d8) vincristine (1.7 mg/m ² , IV drip d8)
13 Feb 2019	EMA/CO Etoposide (170 mg/m ² , IV drip d1-2) Methotrexate (170 mg/m ² , IV drip) actinomycinD (0.6 mg/m ² , IV drip d1; 0.4 mg/m ² , IV drip d2) cytotoxin (1,000 mg/m ² , IV drip d8) vincristine (1.7 mg/m ² , IV drip d8)
26 Feb 2019	Blood routine: WBC: 3.34 × 10 ⁹ /L, PLT: 162 × 10 ⁹ /L, Hb: 71 g/L, ALT: 91 U/L, AST: 27U/L β-HCG: 73.34 mIU
27 Feb 2019	The third cycle of chemotherapy combined immunotherapy Opdivo (180 mg/m ² , IV drip d0) Etoposide (170 mg/m ² , IV drip d1-2) Methotrexate (170 mg/m ² , IV drip) actinomycinD (0.6 mg/m ² , IV drip d1; 0.4 mg/m ² , IV drip d2) cytotoxin (1,000 mg/m ² , IV drip d8) vincristine (1.7 mg/m ² , IV drip d8)
13 Mar 2019	Sintilimab 200 mg IV drip
26 Mar 2019	Blood routine: WBC: 13.30 × 10 ⁹ /L, Hb: 90 g/L, UA: 628 μmol/L, ALT: 87 U/L, β-HCG: 75.46 mIU
27 Mar 2019	Sintilimab 200 mg IV drip Etoposide (100 mg/m ² , IV drip d1-2) Methotrexate (100 mg/m ² , IV drip) actinomycinD (0.6 mg/m ² , IV drip d1; 0.4 mg/m ² , IV drip d2) cytotoxin (680 mg/m ² , IV drip d8) vincristine (1.0 mg/m ² , IV drip d8)
9 Apr 2019	Blood routine: WBC: 6.49 × 10 ⁹ /L, Hb: 89 g/L, PLT: 170 × 10 ⁹ /L, UA: 484 μmol/L, β-HCG: 127.05 mIU
10 Apr 2019	Opdivo (180 mg/m ² , IV drip d0) Etoposide (160 mg/m ² , IV drip d1-2) Methotrexate (160 mg/m ² , IV drip) actinomycinD (0.5 mg/m ² , IV drip d1; 0.5 mg/m ² , IV drip d2) cytotoxin (800 mg/m ² , IV drip d8) vincristine (1.7 mg/m ² , IV drip d8)
23 Apr 2019	Blood routine: WBC: 2.77 × 10 ⁹ /L, Hb: 70 g/L, PLT: 107 × 10 ⁹ /L, UA: 484 μmol/L, β-HCG: 45.73 mIU
24 Apr 2019	Opdivo+ EMA/CO
16 May 2019	Cytotoxin (800 mg/m ² , IV drip d8)
28 Jun 2019	Experienced a sudden death during hospitalization for hematopoietic stem cell transplantation

PET-CT, positron emission tomography-computed tomography.

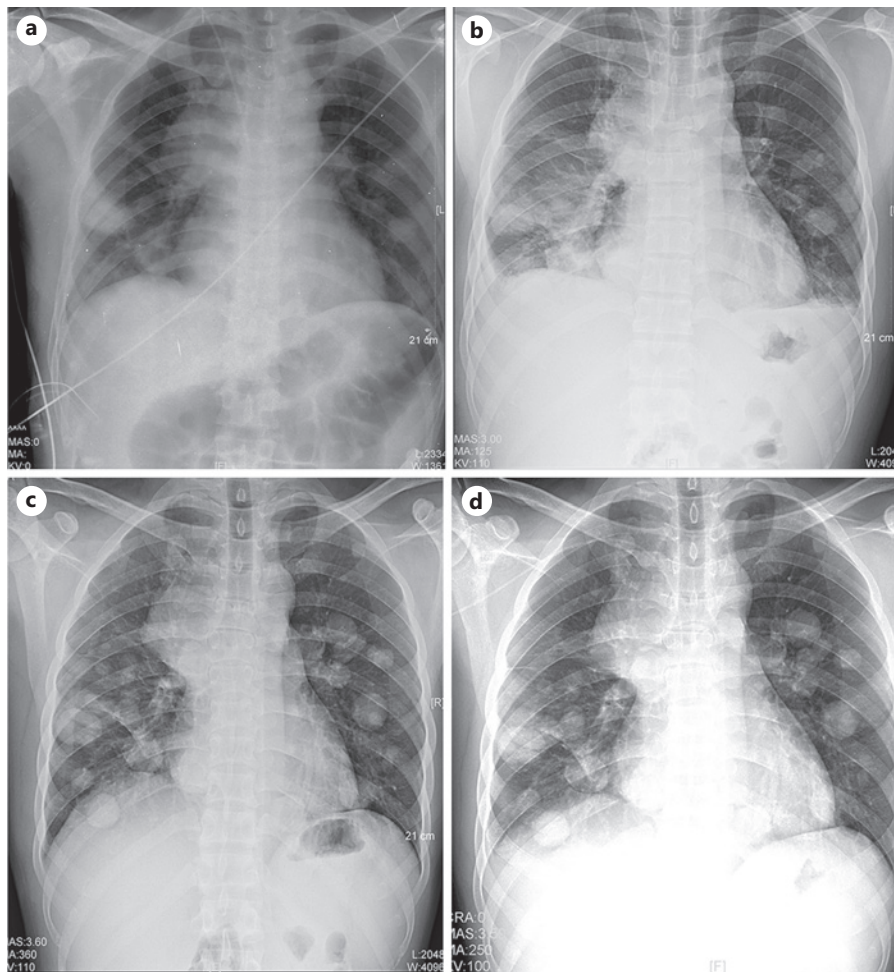


Fig. 3. X-ray scan of the lung. **a** 25 August 2018: There were nodules both right lung and left lung. **b** 28 August 2018: The number of nodules increased and the sizes became bigger. **c** 13 September 2018: During the first cycle of chemotherapy, some of the metastatic bilateral pulmonary nodules began to shrink, while others became larger and there were also new nodules appeared. **d** 18 September 2018: After the first cycle of chemotherapy, metastatic nodules didn't change much compared to 5 days before.

most common primary tumor location is mediastinum, followed by the retroperitoneum and the brain [6]. In some researches, it is said that primary tumor location is associated with ages, to be more precise, primary mediastinum choriocarcinoma presents more commonly in young patients while choriocarcinoma of parenchymal organs tends to affect older patients. There is also an interesting finding that extragonadal germ cell tumors occur more frequently in the Korean population than in western countries, so that genetic and dietary factors may possibly be explanations for the difference [7]. An investigation based on 97 patients with male choriocarcinoma revealed that the median overall survival time was 7.7 months and the 6-month mortality rate was 45.4% [8]. Some case reports also indicate that biochemical remission may not be associated with clinical remission in male mediastinal choriocarcinoma [9].

In this case, the patient was 29, at an age which choriocarcinoma is highly developed, and presented gynecomastia so that it was easy to consider about some diseases associated with increased estrogen or decreased androgen, such as choriocarcinoma, hyperthyroidism, liver disease, adrenal neoplasms, and ectopic production of β -HCG by lung, kidney, and liver cancer.

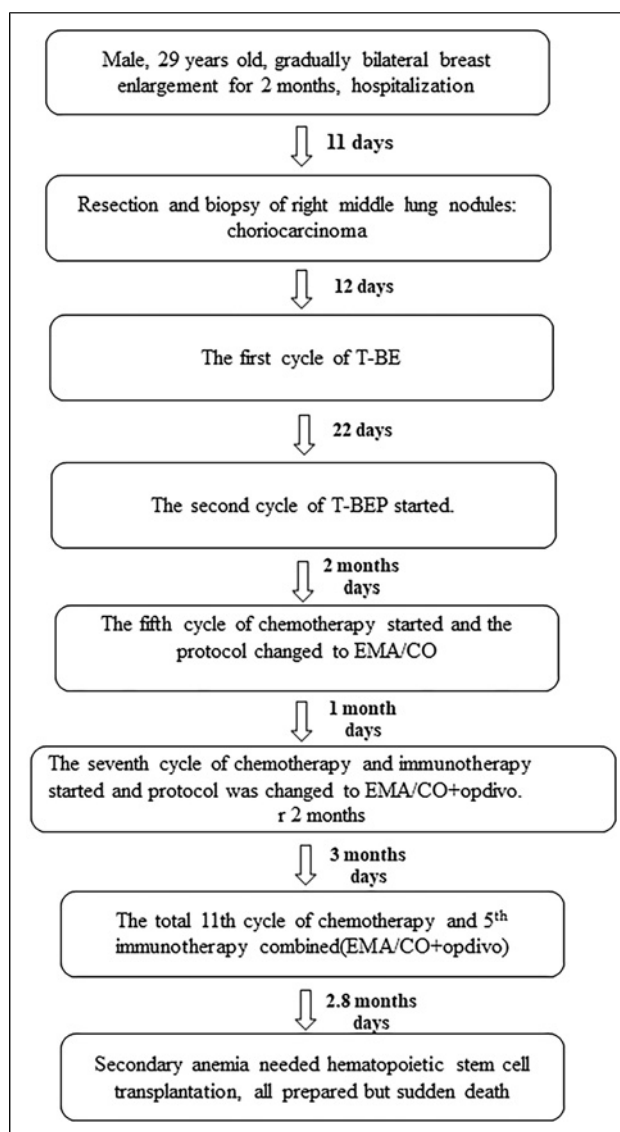


Fig. 4. Clinical course of treatment.

Exposure to some drugs such as estrogen and anabolic steroids can also contribute to gynecomastia. As a consequence, serum β -HCG was examined and found abnormal increasing which was considered a predominant diagnosis of choriocarcinoma and meanwhile, testicles were examined, nothing abnormal found. Pathological and immunostaining results confirmed the diagnoses.

However, majority of extragonadal choriocarcinoma patients present no symptoms of fatigue, weight loss, and so on, which are not characteristic and often fail to notice. In some cases, patients present cough, dyspnea, and chest pain, owing to the hematogenous dissemination to lung. These symptoms are usually not distinct and may lead to misdiagnosis of lung cancer or other diseases. That's the reason why a majority of patients' prognosis with extragonadal choriocarcinoma appears to be poor.

There is no standard treatment for primary choriocarcinoma of anterior mediastinum now, and surgery, chemotherapy, and radiotherapy are traditional treatments. Different tumor locations tend to have different treatments, brain tumor patients are more prone to receive beam radiation, and mediastinum tumor patients are less likely to receive surgery.

However, some study surprisingly finds that beam radiation or surgery could not prolong survival time [4]. Surgery is usually not the first-line treatment for mediastinum choriocarcinoma due to distant metastasis and surgical difficulties. But it has to be performed under emergent circumstances such as superior vein cava syndrome, dysphagia, hemothorax, and so on [10]. Chemotherapy is generally considered as the primary initial treatment [11], though sometimes it may not work well and there are no standard protocols. Numerous studies had tried various chemotherapy regimens, such as methotrexate/actinomycin/chlorambucil and 5-fluorouracil/leucovorin/oxaliplatin, but these were shown to be unsuccessful in this disease [12, 13].

According to the cases reported early, nongestational choriocarcinoma was more insensitive to chemotherapy, so we decided to use the first-line treatment: BEP, and added Taxol to enhance the treatment effect. Because of the side effect of myelosuppression, we prophylactically injected recombinant human G-CSF and also informed the patient and family members of possibility of infertility. The patient and family members refused to do sperm cryopreservation. In this case, patient received four cycles of T-BEP scheme at first, we could find that the level of β -HCG decreased sharply at first two cycles, but since the third cycle, the level of β -HCG did not change and remained above the normal which indicated chemotherapy resistance. CT demonstrated there was still cancer residual, so the scheme changed to EMA/CO for one cycle and β -HCG didn't drop, then the scheme was changed to GOP scheme for one cycle and then changed back to EMA/CO again. The β -HCG was still above the normal, which indicated insensitive to chemotherapy. The patient was tested PD-L1 80–90% positive so that in the circumstance, we tried immunotherapy and opdivo was used. The patient has been treated for 6 months, although there is still cancer residual, he is in fine condition: his liver function and renal function were generally good despite a low level of globulin and increase of uric acid sometimes and blood routine were tested after every cycle. Despite adding immunotherapy, the results of treatment were still not good.

Conclusion

This case inspire us to think of the possibility of choriocarcinoma when a man presents gynecomastia or lung metastatic symptoms and, the treatment outcomes for choriocarcinoma in men are usually poor; introducing Opdivo to the classic chemotherapy regimen for choriocarcinoma might not improve final treatment outcomes. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000533476>).

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Statement of Ethics

Ethical approval is not required for this study in accordance with local guidelines. Written informed consent was obtained from the patient's mother for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Funding was not required; hence, funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

Dong Liu and Yuebo Yang were responsible for the design of the study and interpretation of the data. Qingjian Ye and Minjuan Ye were responsible for the data acquisition, selection and analysis, and clinical interpretation of the data. Dong Liu involved in the drafting of the report. Yuebo Yang and Dong Liu have read, revised, and approved the final manuscript. All authors read and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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