Case Report

Tislelizumab for treatment of a pediatric patient with primary mediastinal choriocarcinoma: a case report

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Background: Primary mediastinal choriocarcinoma (PCC) is a rare, highly vascular invasive, and prognostically unfavorable malignant tumor. When occurring outside the gonads, primary choriocarcinoma is commonly found in midline locations such as the mediastinum or retroperitoneum. Currently, there is no standardized treatment strategy for PCC. In the case reported herein, we employed tislelizumab and chemotherapy in the treatment of a patient with PCC, and as in March 2024, the patient remained survive.

Case Description: A 15-year-old boy who presented with symptoms of fever and cough for a year. Chest computed tomography (CT) scan showed a relatively large soft tissue shadow in the right upper anterior mediastinum, measuring approximately 5.4 cm × 3.8 cm. The patient's soft tissue exhibited unclear demarcation from surrounding mediastinal structures and was accompanied by lung metastasis. The patient underwent a fine needle aspiration biopsy for a mediastinal mass, and the pathology results indicated a germ cell tumor with solid malignant components in the mediastinum, along with pulmonary metastasis of the solid malignancy. The patient's serum levels of beta-human chorionic gonadotropin (β-HCG) were elevated at 125,554 mIU/mL (normal range: <5 mIU/mL), and alpha-fetoprotein (AFP) was 75.8 ng/mL (normal range, 0.605–7 ng/mL). The patient's cranial magnetic resonance imaging (MRI) plain scan indicated multiple scattered abnormal signals in both cerebral hemispheres. Subsequently, the patient was transferred to Children's Hospital of Nanjing Medical University for his further treatment. During the treatment period, we employed various therapeutic approaches, including chemotherapy, radiotherapy and tislelizumab therapy. After five cycles of tislelizumab treatment, the patient's symptoms of cerebral edema significantly improved, β-HCG levels decreased. Brain MRI of the patient revealed multiple abnormal signals within the skull, with some lesions showing reduction in size and significant improvement in the surrounding edema zones. The clinical symptoms of the patient improved and he achieved partial remission (PR). At the moment, the patient is living with the disease.

Conclusions: The effectiveness of chemotherapy for PCC is limited. Tislelizumab may potentially serve as salvage treatment options for PCC.

Keywords: Primary mediastinal choriocarcinoma (PCC); tislelizumab; programmed cell death protein 1 inhibitor (PD-1 inhibitor); case report

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Introduction

Primary mediastinal choriocarcinoma (PCC), also known as non-gestational choriocarcinoma, is the rarest form of extragonadal germ cell tumor. The most common primary tumor location is the mediastinum followed by the retroperitoneum and the brain (1). At present, there is no standard treatment protocol for PCC. According to the 2021 edition of the 'Diagnosis and Treatment Guidelines for Gestational Trophoblastic Diseases', the recommended treatment principle for choriocarcinoma primarily involves chemotherapy, supplemented by surgical and radiotherapeutic interventions (2). The preferred chemotherapy regimen for high-risk gestational trophoblastic neoplasia (GTN) is the EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine) regimen or a combination chemotherapy regimen primarily based on 5-fluorouracil (5-FU)/fluorouracil (FU-DR) such as FAEV (5-FU/fluoropyrimidine drugs, actinomycin D, etoposide, and vincristine) (3). Patients with drug resistance and relapse may consider targeted therapy and programmed cell death protein 1 (PD-1)/programmed death ligand-1 (PD-L1) monoclonal antibodies either alone or in combination with chemotherapy (2,3). The indication for discontinuing chemotherapy is after normalization of blood beta-human chorionic gonadotropin (β-hCG), followed by consolidation chemotherapy for 3–4 cycles. Immune checkpoint inhibitors are a class of monoclonal antibody drugs that block immune checkpoints on immune cells. Currently, the commonly used immune checkpoint inhibitors include PD-1 and PD-L1 (4). Research has found high expression of PD-L1 in recurrent gestational trophoblastic cells. Hirokazu Iso *et al.* reported that treatment with combination of chemotherapy, nivolumab, and ipilimumab may be a promising option for advanced primary choriocarcinoma (5). Hongyan Cheng *et al.* reported the activity and safety of camrelizumab (PD-1 inhibitor) plus apatinib (Vascular endothelial growth factor receptor inhibitor) in patients with high-risk chemorefractory or relapsed GTN (6). Young Sok Ji *et al.* analyzed the features of primary choriocarcinoma observed in male patients treated at the Samsung Medical Center between 1996 and 2020. They believed PD-1/PD-L1 blockade therapy can be a salvage treatment for chemotherapy-resistant male PCC patients (7). Tislelizumab, a PD-1 inhibitor, may be effective in male PCC patients who are insensitive to chemotherapy, serving as a salvage therapy. We present this case in accordance with the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-124/rc).

Highlight box

Key findings

- We present a noteworthy case of primary mediastinal choriocarcinoma (PCC) treated with tislelizumab. This case highlights the potential of tislelizumab as a viable immunotherapy option for pediatric choriocarcinoma.

What is known and what is new?

- PCC is a rare and aggressive tumor in children, typically treated with conventional chemotherapy and surgery.
- Our case suggests tislelizumab as a potential new treatment avenue for pediatric choriocarcinoma, these findings highlighting the need for further clinical trials and research in this area.

What is the implication, and what should change now?

- Our case report suggests that tislelizumab can be a viable treatment option for children with PCC, potentially offering better outcomes compared to traditional therapies.

Case presentation

In April 2022, the patient visited the Affiliated People's Hospital of Ningbo University due to fever and cough. Computed tomography (CT) scan of the thorax showed a 5.4 cm × 3.8 cm mass in the upper right anterior mediastinum. The thorax showed uneven density, with enhanced imaging revealing peripheral ring enhancement. The boundary with surrounding mediastinal structures was indistinct. A preliminary diagnosis suggests a mediastinal tumor with lung metastasis. Subsequently, the patient underwent a mediastinal mass fine needle aspiration biopsy. Postoperative pathology revealed that the biopsy tissue lesion corresponded to a malignant epithelial tumor. Considering the patient's medical history and immunohistochemistry, it was suspected to be a germ cell tumor of the mediastinum with solid malignant components, including pulmonary metastasis of the solid malignant components. The immunohistochemical staining showed that: tumor cells TTF-1 (–), CK7 (+), CK5/6 (–), P40* (–), CD5 (–), Ki-67 (90%+), CD117* (–), TdT (–), P63* (minority+),34βE12 (+), SALL4 (+), PLAP (weakly +), AFP (–), NUT (–), CK (+), CD34 (–), CD99 (+), CDX2 (–). The patient's blood β-HCG level was 125,554 mIU/mL, and AFP was 75.8 ng/mL. Combining the medical history with immunohistochemistry results, the patient was diagnosed with PCC. The patient's parents were healthy, denying consanguineous marriage, and there was no family history of hereditary metabolic

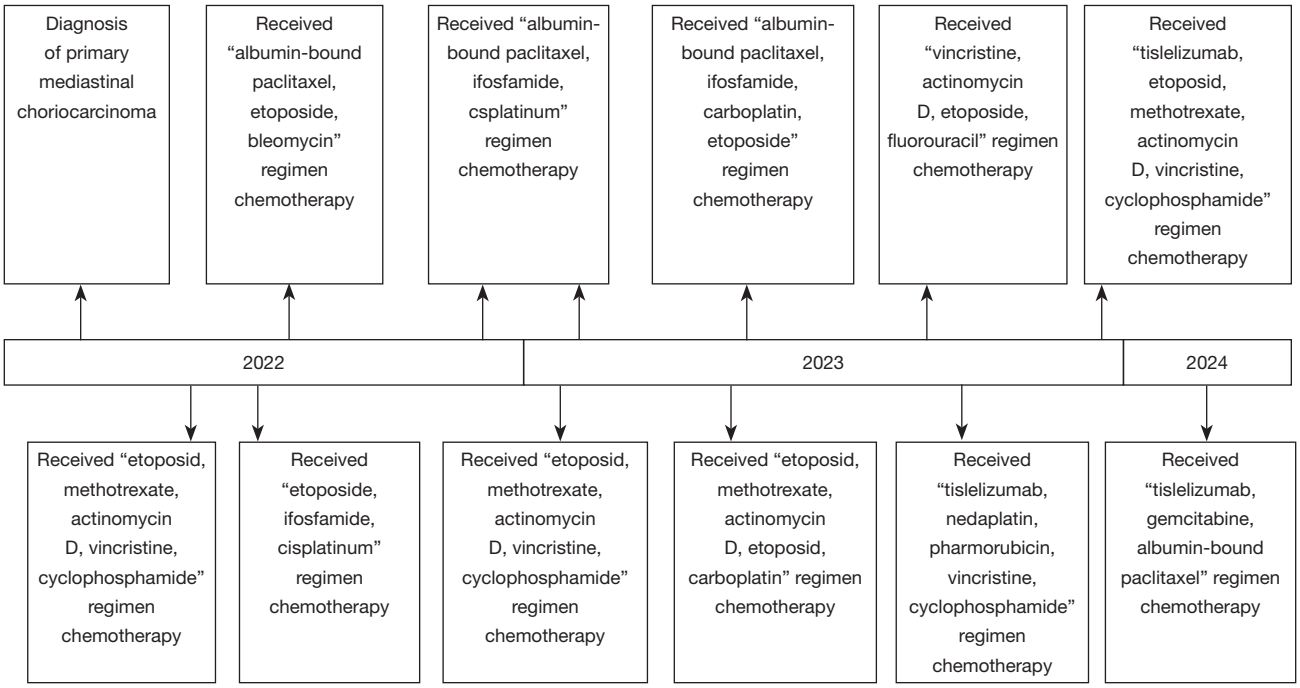

Figure 1 Chemotherapy regimen for the patient since diagnosis.

diseases or infectious diseases. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the parents of the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

The patient accepted five cycles of chemotherapy (the BEP regimen consists of bleomycin, etoposide, cisplatin) at the local hospital. Then, the patient was transferred to our hospital for the future treatment. Magnetic resonance imaging (MRI) demonstrated metastases in both lungs, the right kidney, frontal lobe, parietal lobe, liver, and spleen. After admission to our hospital, the patient was immediately treated with the EMA/CO regimen (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine); the TIP regimen (paclitaxel, ifosfamide, cisplatin); the ICE regimen (ifosfamide, carboplatin, etoposide); and FAEV (vincristine, actinomycin D, etoposide, 5-FU) (*Figure 1*). Chemotherapy for PCC was prone to drug resistance, with a very poor prognosis. According to literature, patients with gestational trophoblastic disease who are multidrug-resistant may choose to use PD-1/PD-L1 antibodies alone or in combination with chemotherapy (8-10). By combining PD-1/PD-L1 antibodies with chemotherapy, synergistic effects may be achieved, potentially amplifying anti-tumor activity and improving therapeutic outcomes. Therefore, even though the patient's PD-L1 is in a low expression state, we still used a combination of tislelizumab and chemotherapy.

On September 2, 2023, the patient started treatment with tislelizumab at a dose of 200mg, administered once every 3 weeks, in combination with chemotherapy. After five cycles of treatment, the patient's serum β-HCG decreased to 61.57 mIU/mL, butrose again. All serum β-HCG test results are shown in the *Figure 2*. The patient's chest CT showed a reduction in lung metastatic lesions, and cranial MRI revealed multiple abnormal signals within the skull, with some lesions showing reduction in size and significant improvement in surrounding edema zones (*Figure 3*). Clinical symptoms of the patient were improved, and partial remission (PR) was achieved during this period. During the treatment period, the patient did not experience intolerable adverse reactions. When the patient's β-hCG level rised again, we considered the disease may be progressing. Then, radiotherapy was added for the patient at this time. The patient will continue to receive tislelizumab and chemotherapy. The patient has survived for 23 months since the diagnosis of PCC. The latest chest CT

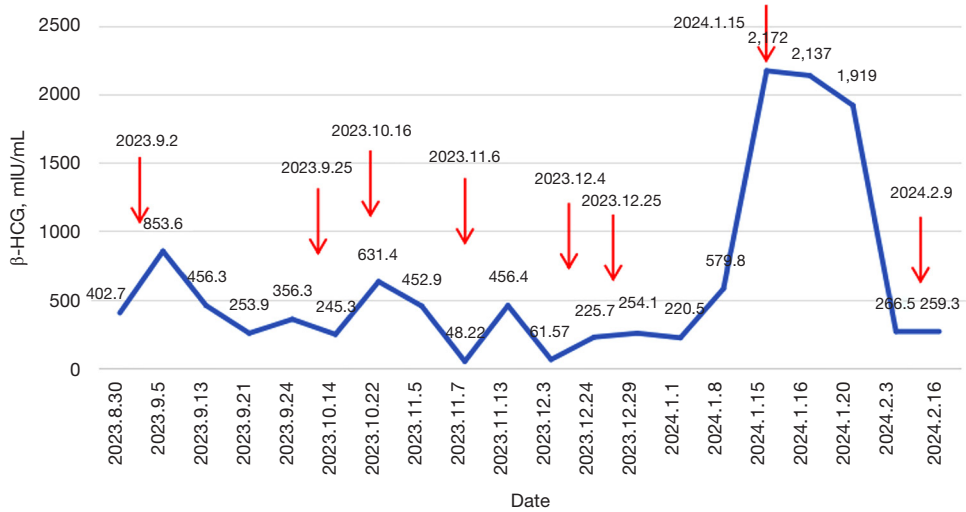

Figure 2 β-HCG trend from the admission to the hospital, with red arrows indicating treatment with tislelizumab. β-HCG, beta-human chorionic gonadotropin.

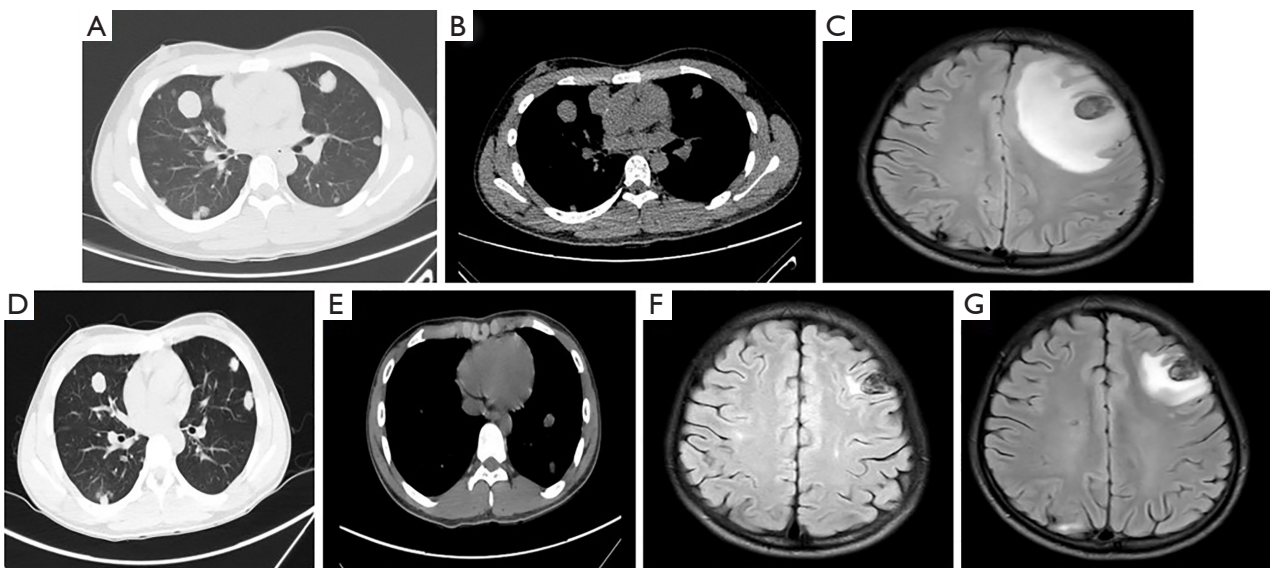

Figure 3 CT/MRI scans evaluate the progression of disease. (A,B) CT scan of the thorax reveals an enlarged anterior mediastinal mass and multiple metastatic lung nodules after the several cycles of chemotherapy. (C) MRI shows brain edema and lesions after chemotherapy. (D,E) Both mediastinal and pulmonary lesions are partially reduced after four cycles of tislelizumab. (F) MRI shows brain edema and lesions after four cycles of tislelizumab. (G) MRI shows brain edema and lesions after six cycles of tislelizumab. CT, computed tomography; MRI, magnetic resonance imaging.

scan shows that the mass in the upper right mediastinum has reduced in size compared to four months ago. The patient is still alive currently.

Discussion

PCC is the rarest form of extragonadal germ cell tumor. The clinical presentation symptoms are atypical and mainly include chest pain, cough, fatigue, hemoptysis, and shortness of breath. Early metastasis is common, with the lungs being the most common site of metastasis (11).

PCC comprises of mononuclear cytotrophoblasts and multinucleated syncytiotrophoblasts, which generate human chorionic gonadotropin (12). Laboratory tests often reveal a significant elevation in β-hCG. Therefore, treatment response can be evaluated by monitoring the patient's serum β-HCG levels. According to the International Germ Cell Cancer Collaborative Group guidelines, patients with HCG levels above 50,000 U/L would be considered to have a poor prognosis (13). The initial serum levels of β-HCG in the patient of this case report were extremely high, suggesting a potentially poor prognosis.

According to reports, many patients die within a short period. The majority of patients pass away within a brief timeframe, with overall survival ranging from 20 days to 115 months (14). Yokoi *et al.* reported that the average survival time for males with primary choriocarcinoma is only 7.7 months (15). The patient herein experienced multiple relapses during the treatment process and showed insensitivity to chemotherapy, with a significant increase in β-HCG levels compared to before. PD-1/PD-L1 inhibitors are recommended for the treatment of choriocarcinoma (16). Immune checkpoints are molecules in the human immune system that play a protective role, acting as brakes to prevent inflammation damage caused by excessive activation of T cells, among other functions. Immune checkpoint inhibitors are a class of monoclonal antibody drugs that block immune checkpoints on immune cells. Tislelizumab is a humanized recombinant PD-1 monoclonal antibody that binds to PD-1, blocking its interaction with PD-L1 and PD-L2, thereby releasing the immune response inhibition mediated by the PD-1 pathway.

Tislelizumab has been approved for use in classical Hodgkin lymphoma, urothelial carcinoma, non-small cell lung cancer, high levels of tumor microsatellite instability (MSI-High), among others. Han *et al.* reported that one male with primary neck choriocarcinoma achieved remission after pembrolizumab combined with chemotherapy (17). Effective remission was achieved in female patients with choriocarcinoma resistant to chemotherapy after treatment with pembrolizumab (18). Weiyu Pan *et al.* reported a case of a 19-year-old male patient with primary thoracic choriocarcinoma and pulmonary metastases treated with pembrolizumab (200 mg fixed dose) and paclitaxel for one cycle, followed by the EMA/CO regimen for another cycle (11). Although the mediastinal mass shrank after two cycles of treatment, the patient's condition progressed rapidly, resulting in treatment failure. Chantel Cacciotti *et al.* reported a pineal choriocarcinoma showed a durable response to ipilimumab and nivolumab (19). In our case, the patient received a combination chemotherapy regimen of tislelizumab. The patient's condition has been relatively stable, and radiation therapy has been initiated, which is currently effective for the patient. So far, the treatment of PCC remains a challenge, and the effectiveness of immunotherapy is still unclear. This case demonstrates that the PCC patient achieved disease stability through the use of tislelizumab. The combination of tislelizumab with chemotherapy may be an effective treatment modality.

However, whether early adoption of PD1/PD-L1 inhibitors can further enhance treatment efficacy for refractory/recurrent choriocarcinoma patients warrants further investigation in clinical practice.

Conclusions

In conclusion, PCC is a rare malignancy unrelated to pregnancy, with a higher incidence in males (20). If a patient is diagnosed with PCC and concurrently presents with elevated β-HCG levels, treatment with PD-1/PD-L1 inhibitors may be considered when the patient is insensitive to chemotherapy regimens during the treatment process. Tislelizumab could serve as an important novel approach for the management of PCC with high expression of PD-L1.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-124/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-124/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the parents of the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Qiu J, Jia S, Li G. Incidence and prognosis factors of extragonadal choriocarcinoma in males: a population-based study. Cancer Manag Res 2018;10:4565-73.
2. Chinese Anti-Cancer Association Gynecologic Oncology Professional Committee, Guidelines for the Diagnosis and Treatment of Gestational Trophoblastic Disease. Chinese Journal of Cancer 2021;31:520-32.
3. Fan D, Xiang Y, Yin R, et al. Gestational Trophoblastic Tumor. Chinese Guidelines for Integrated Cancer Diagnosis and Treatment 2022:1729-68.
4. Lei Q, Wang D, Sun K, et al. Resistance Mechanisms of Anti-PD1/PDL1 Therapy in Solid Tumors. Front Cell Dev Biol 2020;8:672.
5. Iso H, Hisakane K, Terashi N, et al. A remarkable response to combination chemotherapy with nivolumab and ipilimumab in a patient with primary pulmonary choriocarcinoma: a case report. Transl Cancer Res 2023;12:2212-8.
6. Cheng H, Zong L, Kong Y, et al. Camrelizumab plus apatinib in patients with high-risk chemorefractory or relapsed gestational trophoblastic neoplasia (CAP 01): a single-arm, open-label, phase 2 trial. Lancet Oncol 2021;22:1609-17.
7. Ji YS, Park SH. Clinical Experience of Male Primary Choriocarcinoma at the Samsung Medical Center. Cancer Res Treat 2021;53:874-80.
8. Woods JK, Lidov HG, Ligon KL, et al. PD-L1 and PD-1 expression in pediatric central nervous system germ cell tumors. Mod Pathol 2022;35:1770-4.
9. Zhang X, Ding B, Chen L, et al. Primary pulmonary choriocarcinoma in male: report a case with genetic testing and review of the literature. Transl Cancer Res 2022;11:1844-9.
10. Ghorani E, Kaur B, Fisher RA, et al. Pembrolizumab is effective for drug-resistant gestational trophoblastic neoplasia. Lancet 2017;390:2343-5.
11. Pan W, Hou J. Pembrolizumab for treatment of a male with primary mediastinal choriocarcinoma: a case report. Transl Cancer Res 2022;11:3416-20.
12. Cheung AN, Zhang HJ, Xue WC, et al. Pathogenesis of choriocarcinoma: clinical, genetic and stem cell perspectives. Future Oncol 2009;5:217-31.
13. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol 1997;15:594-603.
14. Qiu Z, Wu Y, Wang Y, et al. Male primary mediastinal choriocarcinoma with diffuse metastases: A case report. Medicine (Baltimore) 2019;98:e16411.
15. Yokoi K, Tanaka N, Furukawa K, et al. Male choriocarcinoma with metastasis to the jejunum: a case report and review of the literature. J Nippon Med Sch 2008;75:116-21.
16. Cheng H, Zong L, Yu S, et al. Expression of the immune targets in tumor-infiltrating immunocytes of gestational trophoblastic neoplasia. Pathol Oncol Res 2023;29:1610918.
17. Han C, Zhou Y, Ma JA, et al. A promising treatment

option for refractory male primary choriocarcinoma: report of two cases. Transl Cancer Res 2020;9:3054-60.
18. Huang M, Pinto A, Castillo RP, et al. Complete Serologic Response to Pembrolizumab in a Woman With Chemoresistant Metastatic Choriocarcinoma. J Clin Oncol 2017;35:3172-4.
19. Cacciotti C, Choi J, Alexandrescu S, et al. Immune checkpoint inhibition for pediatric patients with recurrent/refractory CNS tumors: a single institution experience. J Neurooncol 2020;149:113-22.
20. Wang H, Chen X, Zhang R. Primary mediastinal choriocarcinoma in an 18-year-old male with pulmonary and brain metastasis: A case report. Clin Respir J 2023;17:1082-7.

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