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Use of a PD-1 checkpoint inhibitor in a patient with ultra-high-risk gestational trophoblastic neoplasia and gastrointestinal metastases

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ABSTRACT

Gestational trophoblastic neoplasia (GTN) are rare diseases that are typically chemo-responsive. While the majority of patients are cured with chemotherapy alone, a small portion of cases are fatal due to chemotherapy resistance. Risk factors for treatment failure are liver and brain metastases, extensive disease, and chemo-refractory disease. Gastrointestinal (GI) metastases are extremely rare and indicate a poor prognosis. Treatment with immunotherapy has been studied and included in treatment guidelines for high-risk and chemotherapy-resistant GTN. This case reports on the early use of programmed cell death protein 1 (PD-1) inhibitor in combination with systemic chemotherapy in a patient with ultra-high risk GTN with GI metastases.

1. Introduction

Gestational trophoblastic neoplasia (GTN) describes a group of diseases that arise from abnormal placental trophoblast cell proliferation. GTN is typically very responsive to chemotherapy, but up to 5 % of cases are fatal due to chemotherapy resistance (Ngan et al., 2021). The International Federation of Gynecology and Obstetrics (FIGO) staging system and the World Health Organization (WHO) prognostic score guide treatment of GTN. High risk GTN, defined as those with a WHO score of 7 or higher or stage IV disease, is treated with multi-agent chemotherapy (FIGO Oncology Committee, 2002). For those with ultra-high risk disease, including a WHO score of 12 or higher or those with liver, brain, or extensive metastases, treatment often begins with induction chemotherapy to avoid complications associated with rapid tumor collapse. In this subset of patients, induction chemotherapy has been found to reduce early deaths, but late mortality due to relapse or treatment-resistant tumors still occurs (Ngan et al., 2021).

In cases of refractory disease, salvage therapy has traditionally consisted of platinum based regimens and tumor resection; however, more recent data supports the use of checkpoint inhibitor immunotherapy for high-risk chemotherapy-resistant disease (Baas et al., 2024). The NCCN clinical practice guidelines also support the use of PD-1/PD-L1 inhibitors as an option for chemotherapy-resistant and high-risk refractory disease (Abu-Rustum et al., 2023). The use of PD-1/PD-L1 checkpoint inhibitors in low risk disease or as a component of first line therapy in high-risk disease is not well established.

We describe the case of a patient with ultra-high risk GTN presenting with a GI bleed secondary to intestinal metastases who was successfully treated with multi-agent chemotherapy in combination with early use of a PD-1 checkpoint inhibitor.

2. Case summary

The patient is a 23-year-old G1P1 who initially presented at 10 weeks postpartum to an outside hospital for acute blood loss anemia secondary to a GI bleed. At 7 weeks postpartum, she had a positive urine pregnancy test. At 9 weeks postpartum, the patient developed rectal bleeding, which quickly progressed to an episode of large volume, bright red blood per rectum with several episodes of syncope. At initial presentation to the emergency room, she was hypotensive with a hemoglobin of 3.6 g/dL and a human chorionic gonadotropin (hCG) level of 43,000 mIU/mL. She was resuscitated with 8 units of packed red blood cells, 4 units of fresh frozen plasma, and 1 unit of platelets. A transvaginal ultrasound showed a thickened, cystic endometrium without a gestational sac. CT angiography of the abdomen and pelvis showed wall enhancement of a loop of jejunum concerning for angiodysplasia or other vascular

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neoplasm (Fig. 1). She was evaluated by interventional radiology for possible embolization, but there was no active site of bleeding at the time. She underwent an upper endoscopy to assess for active GI bleeding but none was identified. She did not undergo a colonoscopy at the outside hospital. She was transferred to a tertiary medical center with plans for further GI workup to identify the source of bleeding.

Upon transfer, she was admitted to the medical intensive care unit and gynecologic oncology was consulted. Her hCG on admission was 37,000 mIU/mL. CT scan of the chest, abdomen, and pelvis demonstrated 8 pulmonary nodules and multiple liver lesions, the largest of which measured 3.1 cm. MRI of the brain was unremarkable. Based on hCG and imaging findings, she was diagnosed with FIGO stage IV GTN, presumed to be choriocarcinoma. We recommended against any endoscopic diagnostic procedure given the hemorrhage risk associated with biopsy and disruption of these metastases. Her WHO score was 13. Given the extent of her disease with liver and presumed intestinal metastases, she was deemed very high risk for hemorrhage and was given inpatient low dose induction EP (etoposide 100 mg/m^2 IV and cisplatin 20 mg/m^2 IV days 1 and 2 every 7 days for 2 cycles) with plan to follow with EMA/EP (etoposide, methotrexate, actinomycin-D/etoposide, cisplatin).

On cycle 1 day 2 of induction chemotherapy, hCG was 75,000 mIU/mL. She remained inpatient due to continued GI bleeding and received additional 8 units pRBC over the course of her hospitalization. On cycle 2, day 1 of induction chemotherapy, hCG rose to 173,000 mIU/mL. The patient was counseled that in the setting of ultra-high-risk disease, as well as several risk factors for treatment failure and severe morbidity/mortality associated with treatment failure due the location of intestinal disease, the addition of pembrolizumab to the treatment regimen was recommended starting with cycle 2 of induction chemotherapy. She was counseled that an aggressive treatment approach was recommended given her young age and healthy status at baseline in combination with the ultra-high-risk nature of her disease.

After 2 cycles of induction chemotherapy, hCG began decreasing, and she was started on standard EMA/EP therapy in combination with pembrolizumab every 3 weeks. After three cycles of EMA/EP and two cycles of pembrolizumab, hCG normalized. Complete serologic response was achieved 56 days after initial presentation (Fig. 2). She received an additional 3 cycles of EMA (EP discontinued due to acute kidney injury) (Table 1). The acute kidney injury was likely due to cisplatin, and the patient's creatinine normalized after cessation of cisplatin. At the time of this report, patient has approximately 4 months of serologic remission, and she remains without evidence of disease.

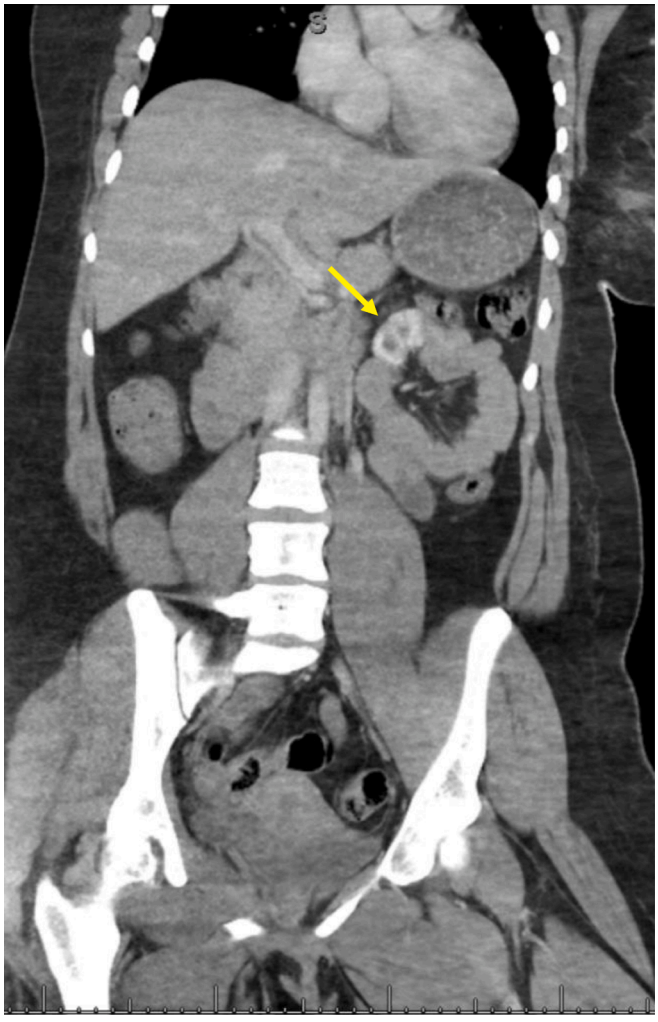

Fig. 1. Image from CT angiography. Image from CT angiography showing wall enhancement of a loop of jejunum (yellow arrow) concerning for angiodysplasia or other vascular neoplasm.

3. Discussion

Although GTN is rare, approximately one in 40,000 pregnancies are affected. With chemotherapy, over 90 % of patients with GTN are cured (Lurain, 2010). Survival rates are halved for patients with widespread metastases involving the liver, making this a marker of poor prognosis (Seckl et al., 2010). GI metastases in general are present in less than 5 % of cases, and even fewer cases are affected by intestinal metastases specifically, which most often accompany liver metastases and thus portend a poor prognosis (Wang et al., 2022; Mangili et al., 2014). GI metastases are associated with extensive disease, high morbidity, and high mortality. We are aware of only 31 cases of gestational choriocarcinoma with intestinal metastases having been reported in the English literature (Wang et al., 2022). Presenting symptom of GI bleeding, as in the case presented here, is even more rare.

Expression of PD-L1 has been identified in placental tissue, including almost all forms of GTN, regardless of chemoresistance (Bolze et al., 2017). Current evidence supports the use of PD-1/PD-L1 inhibitors in chemo-resistant and relapsed GTN (Ghorani et al., 2017; Paspalj et al., 2021; Wang et al., 2023; Niimi et al., 2023; Goldfarb et al., 2020). Several cases have reported on patients with GTN refractory to multiagent therapy achieving complete response with pembrolizumab, a PD-1 inhibitor, alone (Ghorani et al., 2017; Paspalj et al., 2021; Goldfarb et al., 2020).

In addition to well-tolerated adverse effects, a synergistic effect of immunotherapy combined with chemotherapy in this population has been found in cohort and case studies. Niimi et al. describe a case of a patient who was diagnosed with low risk GTN (WHO 6) that was refractory to single and multiagent chemotherapy. Following hysterectomy and additional multiagent chemotherapy, she still did not achieve remission. She then received 10 cycles of pembrolizumab followed by additional chemotherapy and achieved remission (Niimi et al., 2023). In a retrospective study of 66 cases, Wang et al. found that for patients with chemotherapy-resistant or relapsed GTN, the combination of PD-1/PDL-1 inhibitor with systemic therapy had a significantly higher complete response rate and progression free time compared to anti-PD-1 therapy alone (Wang et al., 2023). Phase I and II trials have been completed and are ongoing using a PD-L1 inhibitor alone and in combination with chemotherapy for GTN (Mangili et al., 2022).

This case study demonstrates a high therapeutic response with early use of a PD-1 inhibitor in combination with systemic therapy in a patient with high risk GTN and active bleeding. By achieving a complete serologic response only 49 days after starting treatment for ultra-high-risk GTN, this case demonstrates the potential for the early use of PD-1/PD-L1 inhibitors plus chemotherapy in the treatment of high-risk GTN, potentially decreasing the number of cycles of chemotherapy and associated toxicity, as well as decreasing the rate of chemoresistance.

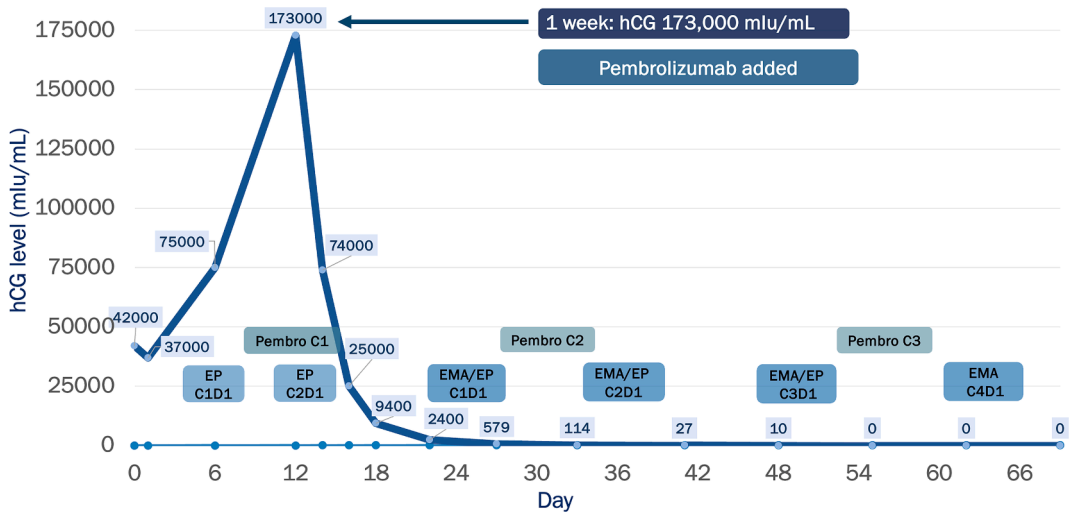

Fig. 2. hCG value during treatment. Graphical representation of hCG value from initial presentation (day 0) through first four cycles of systemic therapy. The hCG value was negative (<5 mIU/mL per our lab standard) after 2 cycles of low dose induction EP, 2 cycles of pembrolizumab, and 3 cycles of EMA/EP.

Table 1
Chemotherapy regimen. Two cycles of induction chemotherapy were given. Pembrolizumab was given every 21 days. Three cycles of EMA/EP were given, followed by three cycles of EMA alone due to acute kidney injury.

Induction: etoposide 100 mg/m^2, cisplatin 20 mg/m^2 on days 1 and 2, weekly x 2 cycles
Pembrolizumab 200 mg IV q21d, first dose given C2D1 induction chemotherapy
Consolidation: EMA-EP q14d (Day 1: etoposide 100 mg/m^2; methotrexate 300 mg/m^2; dactinomycin 0.5 mg; Day 2: etoposide 100 mg/m^2, dactinomycin 0.5 mg; Day 8, etoposide 100 mg/m^2, cisplatin 60 mg/m^2)

Considering the tolerability of immunotherapy, this case supports the continued investigation of PD-1/PD-L1 inhibitor use as a component of first-line treatment of high risk GTN.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

Amalia Brawley, MD – literature review, wrote report, figure design, edited report.
Casey Moffitt, MD – literature review, figure design, edited report.
Shaina Bruce, MD – edited report.
Caitlin Farabaugh, MD – edited report.
Edward Podczaski, MD – edited report.
Joel Sorosky, MD – edited report.

CRediT authorship contribution statement

Amalia Brawley: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Casey Moffitt:** Writing – review & editing, Visualization. **Shaina Feldman Bruce:** Writing – review & editing, Conceptualization. **Caitlin Stashwick Farabaugh:** Writing – review & editing, Conceptualization. **Edward Podczaski:** Writing – review & editing. **Joel Sorosky:** Writing – review & editing, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abu-Rustum, N.R., Yashar, C.M., Arend, R., et al., 2023. NCCN Guidelines Index Table of Contents Discussion. Published online 2023.
Baas, I., Westermann, A., You, B., Bolze, P., Seckl, M., Ghorani, E., 2024. Immunotherapy for gestational trophoblastic neoplasia: a new paradigm. Gynecol. Obstet. Invest. 89 (3), 230–238. https://doi.org/10.1159/000533972.
Bolze, P., Patrier, S., Massardier, J., et al., 2017. PD-L1 expression in premalignant and malignant trophoblasts from gestational trophoblastic diseases is ubiquitous and independent of clinical outcomes. Int. J. Gynecol. Cancer 27 (3), 554–561. https://doi.org/10.1097/IGC.0000000000000892.
FIGO Oncology Committee, 2002. FIGO staging for gestational trophoblastic neoplasia 2000. Int. J. Gynaecol. Obstet. 77 (3), 285–287. https://doi.org/10.1016/s0020-7292(02)00063-2.
Ghorani, E., Kaur, B., Fisher, R., et al., 2017. Pembrolizumab is effective for drug-resistant gestational trophoblastic neoplasia. Lancet 390 (10110), 2343–2345. https://doi.org/10.1016/S0140-6736(17)32894-5.
Goldfarb, J., Dinoi, G., Mariani, A., Langstraat, C., 2020. A case of multi-agent drug resistant choriocarcinoma treated with Pembrolizumab. Gynecol. Oncol. Rep. 32 (100574). https://doi.org/10.1016/j.gore.2020.100574.
Lurain, J.R., 2010. Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. Am. J. Obstet. Gynecol. 203 (6), 531–539. https://doi.org/10.1016/j.ajog.2010.06.073.
Mangili, G., Lorusso, D., Brown, J., et al., 2014. Trophoblastic disease review for diagnosis and management: a joint report from the International Society for the Study of Trophoblastic Disease, European Organisation for the Treatment of Trophoblastic Disease, and the Gynecologic Cancer InterGroup. Int. J. Gynecol. Cancer Off. J. Int. Gynecol. Cancer Soc. 24 (9 Suppl. 3), S109–S116. https://doi.org/10.1097/IGC.0000000000000294.
Mangili, G., Sabetta, G., Cioffi, R., et al., 2022. Current evidence on immunotherapy for gestational trophoblastic neoplasia (GTN). Cancers 14 (11), 2782. https://doi.org/10.3390/cancers14112782.
Ngan, H., Seckl, M., Berkowitz, R., et al., 2021. Diagnosis and management of gestational trophoblastic disease: 2021 update. Int. J. Gynaecol. Obstet. 155, 86–93. https://doi.org/10.1002/ijgo.13877.
Niimi, K., Yamamoto, E., Oda, Y., et al., 2023. A case of complete remission of intractable gestational choriocarcinoma with subsequent chemotherapy after pembrolizumab. Taiwan. J. Obstet. Gynecol. 62 (5), 745–748. https://doi.org/10.1016/j.tjog.2023.07.019.
Paspalj, V., Polterauer, S., Poetsch, N., Reinthaller, A., Grimm, C., Bartl, T., 2021. Long-term survival in multiresistant metastatic choriocarcinoma after pembrolizumab treatment: a case report. Gynecol. Oncol. Rep. 37 (100817). https://doi.org/10.1016/j.gore.2021.100817.

Seckl, M.J., Sebire, N.J., Berkowitz, R.S., 2010. Gestational trophoblastic disease. Lancet Lond. Engl. 376 (9742), 717–729. https://doi.org/10.1016/S0140-6736(10)60280-2.

Wang, X., Cang, W., Liu, X., et al., 2023. Anti-PD-1 therapy plus chemotherapy versus anti-PD-1 therapy alone in patients with high-risk chemorefractory or relapsed gestational trophoblastic neoplasia: a multicenter, retrospective study. EClinicalMedicine. 59 (101974). https://doi.org/10.1016/j.eclinm.2023.101974.

Wang, Y., Wang, Z., Zhu, X., et al., 2022. Intestinal metastasis from choriocarcinoma: a case series and literature review. World J. Surg. Oncol. 20 (1), 173. https://doi.org/10.1186/s12957-022-02623-0.