Case report

Non-gestational choriocarcinoma with hyperprogression on pembrolizumab: A case report and review of the literature

Nazanin Yeganeh Kazemi a, Carrie Langstraat b, S. John Weroha c,⁎

a Medical Scientist Training Program, Mayo Clinic Alix School of Medicine, Rochester, MN 55905, USA
b Gynecologic Surgery, Mayo Clinic Rochester, Rochester, MN, USA
c Department of Medical Oncology, Mayo Clinic, Mayo Clinic Rochester, MN 55905, USA

ARTICLE INFO

Keywords:
Hyperprogression
Non gestational choriocarcinoma
Immunotherapy
Pembrolizumab
CHEK2
TP53

ABSTRACT

Non-gestational choriocarcinoma is a rare and aggressive germ cell tumor. Here we present the case of a post-menopausal 49-year-old woman who presented with metastatic disease and initially achieved a complete radiographic and biomarker response with seven cycles of EMA-CO chemotherapy. Upon recurrence, she received two separate courses of chemotherapy, initially with paclitaxel/cisplatin/etoposide and later FOLFOX. Tumor analysis revealed 22% PD-L1 positivity (tumor proportion score) and she was treated with pembrolizumab. However, βhCG levels rose abruptly and uncharacteristically through all three cycles of anti-PD1 therapy. The patient developed dyspnea on exertion, cough, and right flank pain. CT imaging demonstrated marked progression of liver metastases and innumerable new pulmonary metastases and the patient died 10 weeks after starting pembrolizumab. Here we describe the clinical presentation and management of this patient, along with analysis of molecular aberrations which could potentially explain hyperprogression in response to pembrolizumab.

1. Introduction

Non-gestational choriocarcinoma (NGC) is an exceedingly rare and aggressive germ cell tumor of the ovary. NGC is distinguished from gestational choriocarcinoma (GC) by the lack of paternal DNA by polymorphism analysis (Fisher et al., 1992; Wu et al., 2018). The distinction between gestational and non-gestational disease is important because it determines the optimal management and influences prognosis. For instance, systemic therapy for high-risk GC typically includes a methotrexate-based regimen such as EMA/CO (methotrexate, etoposide, actinomycin-D, cyclophosphamide and vincristine) but the rarity of NGC makes it difficult for clinicians to make evidence-based treatment recommendations and likely contributes to worse prognosis (Mello et al., 2017). Although >80% of GCs are PD-L1 positive (Bolze et al., 2017; Veras et al., 2017; Lu et al., 2019) and case reports provide anecdotal support for PD-L1/PD1 immune checkpoint inhibitors (Clair et al., 2020; Goldfarb et al., 2020; Paspalj et al., 2021; Ghoreian et al., 2017), similar data are not currently available for NGC. This case report describes the clinical course of a patient with NGC who rapidly progressed on pembrolizumab despite PD-L1 positivity and reviews the current literature regarding hyperprogression as a response pattern to immune checkpoint inhibitor (ICI) therapy.

Hyperprogression on an ICI is an unexpected increase in the tumor growth rate after checkpoint blockade therapy, surpassing the projected trajectory without therapy (Champiat et al., 2018). Although a single definition of hyperprogression is lacking, several characteristics have been used in other studies describing this pattern of response: time-to-treatment failure <2 months, >50% increase in tumor burden compared with pre-immunotherapy imaging, and >2-fold increase in progression pace (Kato et al., 2017; Park et al., 2021).

2. Case report

A 49-year old, G2P2 woman with a past medical history of asthma, pulmonary edema, and hyperlipidemia but no history of molar pregnancy presented with high-grade fevers, persistent cough, right upper
quadrant pain, and a βhCG level of 79,000 IU/L (reference <7). A CT scan demonstrated multiple large liver and scattered small lung metastases, but no pelvic masses. A liver biopsy revealed chorionicarcoma with 22% PD-L1 positivity by immunohistochemistry. Because it is unknown whether a tumor proportion score (TPS) or combined positive score (CPS) should be used for NGC and no thresholds for positivity have been clinically validated, any staining was considered positive. In this case, a TPS was reported. Prior to consultation and management at our institution, she was treated elsewhere with chemotherapy typically reserved for GC with seven cycles of EMA-CO (Fig. 1) despite the lack of 38 association with gestation. Although βhCG normalized after two cycles of EMA-CO and subsequent PET/CT imaging revealed a complete response after the final seventh cycle, hepatic metastases were detected only two months later by PET/CT. Given the PD-L1 staining, she was treated with pembrolizumab but prior to cycle two, βhCG levels rose substantially (from 26.7 to 24,778 IU/L) and treatment was discontinued due to a concern that immunotherapy may have a delayed onset of efficacy and instead, traditional cytotoxic chemotherapy might provide better disease control. The next course of treatment was paclitaxel/cisplatin alternating with paclitaxel/etoposide (TC/TE) but acute kidney injury developed after two cycles, requiring a treatment delay for renal recovery and a subsequent change in the treatment regimen to a 5-fluorouracil (5FU) regimen, FOLFOX, since 5FU is listed by NCCN for treatment of GC. As the patient was being treated with FOLFOX, a consultation at our institution led to additional testing of the tumor to clarify its origin. PCR-based panel testing (test ID # SPECI, Mayo Clinic Laboratories, Rochester, MN) of highly variable DNA markers in the patient’s germline DNA (peripheral blood) and archived tumor specimens revealed a complete match, indicating the absence of paternal DNA and confirming that the chorionicarcoma was non-gestational. Accordingly, when the βhCG began to rise after only two cycles of FOLFOX, alternative options were considered. At this time, the only visible disease was a symptomatic intrahepatic mass, so a localized approach was taken with radiation (5000 cGy in 25 fractions). Although ICI efficacy data are lacking for NGC, the high PD-L1 tumor proportion visible disease was a symptomatic intrahepatic mass, so a localized 38 treatment was considered positive. In this case, a TPS was reported. Prior to consultation and management at our institution, she was treated elsewhere with chemotherapy typically reserved for GC with seven cycles of EMA-CO (Fig. 1) despite the lack of association with gestation. Although βhCG normalized after two cycles of EMA-CO and subsequent PET/CT imaging revealed a complete response after the final seventh cycle, hepatic metastases were detected only two months later by PET/CT. Given the PD-L1 staining, she was treated with pembrolizumab but prior to cycle two, βhCG levels rose substantially (from 26.7 to 24,778 IU/L) and treatment was discontinued due to a concern that immunotherapy may have a delayed onset of efficacy and instead, traditional cytotoxic chemotherapy might provide better disease control. The next course of treatment was paclitaxel/cisplatin alternating with paclitaxel/etoposide (TC/TE) but acute kidney injury developed after two cycles, requiring a treatment delay for renal recovery and a subsequent change in the treatment regimen to a 5-fluorouracil (5FU) regimen, FOLFOX, since 5FU is listed by NCCN for treatment of GC. As the patient was being treated with FOLFOX, a consultation at our institution led to additional testing of the tumor to clarify its origin. PCR-based panel testing (test ID # SPECI, Mayo Clinic Laboratories, Rochester, MN) of highly variable DNA markers in the patient’s germline DNA (peripheral blood) and archived tumor specimens revealed a complete match, indicating the absence of paternal DNA and confirming that the chorionicarcoma was non-gestational. Accordingly, when the βhCG began to rise after only two cycles of FOLFOX, alternative options were considered. At this time, the only visible disease was a symptomatic intrahepatic mass, so a localized approach was taken with radiation (5000 cGy in 25 fractions). Although ICI efficacy data are lacking for NGC, the high PD-L1 tumor proportion visible disease was a symptomatic intrahepatic mass, so a localized

3. Genetic analysis for hyperprogression-associated mutations

To determine whether underlying somatic mutations may have contributed to hyperprogression in this patient, autopsy specimens of a lung metastasis were analyzed using the Tempus xT panel of 648 genes. No mutations were found in previously-reported hyperprogression-associated genes: MDM2/MDM4 (Kato et al., 2017), EGFR (Kato et al., 2017), JAK/STAT (Zaretsky et al., 2016), MHC and β2-microglobulin (Zaretsky et al., 2016; Sade-Feldman et al., 2017; Kamada et al., 2019; Lo Russo et al., 2019). However, a loss-of-function splice region variant in CHEK2 (c.444–1G>A) and a frameshift mutation in TP53 (p.V73fs) was detected. Additionally, copy number loss was detected for SMARCA4. The tumor exhibited a moderate mutation burden (5.8 million/megabase) and microsatellite stability.

4. Discussion

This case underscores the importance of clinical, pathologic, and molecular characterization of cancers to guide treatment decisions. The initial management of this patient focused on chemotherapy that is typically reserved for gestational trophoblastic neoplasms. Although EMA-CO resulted in a complete radiographic and biochemical response, the recurrence-free interval was disappointingly short. Whether TC/TE or other cisplatin-based chemotherapies would have provided durable responses is unknown since the acute renal failure complicated treatment options. While there is no clinical efficacy data supporting pembrolizumab in NGC, this patient’s tumor demonstrated measurable PD-L1 positivity, prompting immune check point blockade therapy. However, pembrolizumab was associated with substantial tumor growth and rapid disease progression in under 2 months, which is consistent with hyperprogression. While the genetic analysis did not identify previously-described individual putative drivers of immune-evasion which could contribute to hyperprogression, it is possible that mutations in both CHEK2 and TP53 created a tumor microenvironment which was conducive to hyperprogression.

The combination of genetic aberrations found in this NGC may have

![Fig. 1. Treatment timeline and tumor marker levels. EMA-CO (methotrexate, etoposide, actinomycin-D, cyclophosphamide and vincristine). FOLFOX (SFU, leucovorin, oxaliplatin).](image_url)

![Fig. 2. CT scans before and after pembrolizumab therapy. (A) No lung lesions were present at baseline, prior to pembrolizumab but (B) innumerable metastases were visible by the end of treatment. Similarly, (C) a solitary liver lesion (*) progressed to (D) innumerable metastases but only the baseline lesion is identified with *. Aorta (a) and pulmonary artery (p) are identified for orientation.](image_url)
contributed to hyperprogression. CHEK2 (checkpoint kinase 2, also known as RAD53) is a serine/threonine kinase and tumor suppressor which is necessary for proper DNA damage response. Phosphorylation and activation of CHEK2 is induced by DNA damage and stalling of the replication fork. Activated CHEK2 inhibits CDC2C phosphatase, which stabilizes p53 (the gene product of TP53) resulting in cell cycle arrest at G1. Mutations in CHEK2 have been associated with Li-Fraumeni syndrome and genetic predisposition to sarcomas, breast, and brain tumors (Stolarova et al., 2020). TP53 is the quintessential tumor suppressor gene which is also found to be mutated in Li-Fraumeni syndrome and a majority of spontaneous tumors, with an important role in the induction of cell cycle arrest in response to a variety of insults including DNA damage (Olivier et al., 2010). Importantly, the loss of CHEK2 and TP53 may phenocopy MDM2/MDM4 amplification since MDM2/MDM4 protein typically negatively regulates p53 protein by directly blocking the p53 trans-activating domain and promotes ubiquitination, thus inhibiting p53 activity and targeting it for proteosome degradation (Haimer et al., 2019). Relevant to the case presented herein, MDM2/MDM4 amplification has previously been associated with hyperprogression after immunotherapy (Kato et al., 2017). For instance, in 155 stage IV cancer patients who received immunotherapy, MDM2/MDM4 amplification was present in all six patients with time-to-treatment failure <2 months.

The third genetic aberration, copy number loss of SMARCA4, may not have contributed to hyperprogression. BRG1 (the gene product of SMARCA4) is a SWI/SNF family protein which contains both ATPase and helicase domains to regulate gene transcription through alteration of chromatin structure. Germline and somatic mutations in SMARCA4 are characteristic of the small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) and inactivation/deficiencies in SMARCA4 have also been described in undifferentiated uterine and thoracic sarcomas (Witkowski et al., 2014; Nambirajan and Jain, 2021; Connor et al., 2020). Contrary to the patient presented herein, case reports indicate that thoracic sarcomas, small cell lung carcinomas, and SCCOHT with BRG1 deficiency exhibit increased sensitivity to ICI treatment (Naito et al., 2019; Takada et al., 2019; Jelincic et al., 2018). The copy number loss in our patient clearly did not confer sensitivity to pembrolizumab.

Few examples of hyperprogression after immunotherapy exist in gynecologic oncology. However, since endometrial and cervical cancers have FDA indications for pembrolizumab (Makker et al., 2020; Chung et al., 2019; Marabelle et al., 2020), more cases of hyperprogression may be reported in the future and new genes may be implicated in this process. For instance, in a case of squamous cell cervical carcinoma, rapid radiologic progression was observed in the setting of an AKT1 E17K mutation, despite PD-L1 expression and mutations in MSH2, MSH6 and PMS2 (Xu et al., 2019). During treatment, there was an increase in the amount of circulating tumor DNA and circulating tumor cells associated with an increasing tumor volume and new pulmonary metastases. It was determined that the patient had hyperprogressive disease after pembrolizumab treatment according to previously described criteria including time to treatment failure <2 months, >50% increase in tumor burden compared to pretreatment imaging, and >2-fold increase in tumor growth rate. In a second case, hyperprogression after ICI therapy was observed in a 65-year-old woman with an MDM2-mutated endometrial stromal sarcoma (Kato et al., 2017). She had increased liver metastases while on targeted therapy which prompted a switch to nivolumab combined with stereotactic body radiation therapy (SBRT). This was followed by development of new palpable masses. CT imaging 6 weeks after starting nivolumab showed rapid progression of liver metastasis with new abdominal masses indicating a 242% increase from pre-immunotherapy. This progression was associated with an increase in tumor marker (CA125) levels from 33 to 1,040 U/mL. Pseudoprogression was ruled out using tumor biopsy which did not reveal lymphocyte infiltration or tumor necrosis. A third report of hyperprogression in a gynecologic malignancy was captured in a retrospective analysis of 89 patients with platinum-resistant epithelial ovarian cancer treated with immune checkpoint blockade (Boland et al., 2019). Half exhibited early disease progression and 9% died within the first 12 weeks of therapy due to rapid disease progression but it is unclear whether the rate of progression reflected the natural history of their diseases or whether immunotherapy influenced an unexpected acceleration of tumor growth.

5. Conclusion

Here we describe a case of NGC which was initially managed with chemotherapy and exhibited hyperprogression on pembrolizumab. ICI therapy in this patient resulted in rapid metastatic growth and overwhelming tumor burden. Our molecular analysis failed to demonstrate mutations in genes previously described in hyperprogression but did reveal mutations in CHEK2 and TP53 which may phenocopy MDM2/4 amplification. Additional studies are needed to determine how mutations in different tumor types interact to induce resistance and hyperprogression to ICI.

Informed consent

The Mayo Clinic Institutional Review Board (IRB) provided a waiver of consent to conduct post-mortem tumor sequencing under protocol # 20-001935.

CRediT authorship contribution statement

Nazanin Yeganeh Kazemi: Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Supervision. Carrie Langstraat: Conceptualization, Methodology, Writing – original draft.

5. John Weroha: Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Supervision, Project administration, Funding acquisition.

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

Boland, J.L., et al., 2019. Early disease progression and treatment discontinuation in patients with advanced ovarian cancer receiving immune checkpoint blockade. Gynecol. Oncol. 152 (2), 251–256.
Bolze, P.-A., 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.
Champiat, S., et al., 2018. Hyperprogressive disease: Recognizing a novel pattern to improve patient management. Nat. Rev. Clin. Oncol. 15 (12), 748–762.
Chung, H.C., et al., 2019. Efficacy and safety of Pembrolizumab in previously treated advanced cervical cancer: Results from the phase II KEYNOTE-158 study. J. Clin. Oncol. 37 (17), 1470–1478.
Clair, K.H., Gallegos, N., Bristow, R.E., 2020. Successful treatment of metastatic refractory gestational chorio carcinoma with pembrolizumab: A case for immune checkpoint salvage therapy in trophoblastic tumors. Gynecol. Oncol. Rep. 34, 100625.
Connor, Y.D., et al., 2020. Germline mutations of SMARCA4 in small cell carcinoma of the ovary, hypercalcemic type and in SMARCA4-deficient undifferentiated uterine sarcoma: Clinical features of a single family and comparison of large cohorts. Gynecol. Oncol. 157 (1), 106–114.
Fisher, R.A., et al., 1992. Gestational and nongestational trophoblastic tumors distinguished by DNA analysis. Cancer 69 (3), 839–845.
Ghorani, E., et al., 2017. Pembrolizumab is effective for drug-resistant gestational trophoblastic neoplasia. Lancet 390 (10110), 2343–2345.
Goldfarb, J.A., et al., 2020. A case of multi-agent drug resistant choriocarcinoma treated with Pembrolizumab. Gynecol. Oncol. Rep. 32, 100574.
Hafner, A., et al., 2019. The multiple mechanisms that regulate p53 activity and cell fate. Nat. Rev. Mol. Cell Biol. 20 (4), 199–210.
Jelincic, P., et al., 2018. Immune-active microenvironment in small cell carcinoma of the ovary, hypercalcemic type: Rationale for immune checkpoint blockade. J. Natl. Cancer Inst. 110 (7), 787–790.
Kamada, T., et al., 2019. PD-1(+) regulatory T cells amplified by PD-1 blockade promote hyperprogression of cancer. Proc. Natl. Acad. Sci. U. S. A. 116 (20), 9999–10008.

Kato, S., et al., 2017. Hyperprogressors after immunotherapy: Analysis of genomic alterations associated with accelerated growth rate. Clin. Cancer Res. 23 (15), 4242–4250.

Lo Russo, G., et al., 2019. Antibody-Fc/FcR interaction on macrophages as a mechanism for hyperprogressive disease in non-small cell Lung cancer subsequent to PD-1/PD-L1 blockade. Clin. Cancer Res. 25 (3), 989–999.

Lu, B., et al., 2019. Analysis of PD-L1 expression in trophoblastic tissues and tumors. Hum. Pathol. 84, 202–212.

Makker, V., et al., 2020. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. J. Clin. Oncol. 38 (26), 2981–2992.

Marabelle, A., et al., 2020. Efficacy of Pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J. Clin. Oncol. 38 (1), 1–10.

Mello, J.B., et al., 2017. Genomic profile in gestational and non-gestational choriocarcinomas. Placenta 50, 8–15.

Naito, T., et al., 2019. Successful treatment with nivolumab for SMARCA4-deficient non-small cell lung carcinoma with a high tumor mutation burden: A case report. Thorac. Cancer 10 (5), 1285–1288.

Nambirajan, A., Jain, D., 2021. Recent updates in thoracic SMARCA4-deficient undifferentiated tumor. Semin. Diagn. Pathol. 38 (5), 83–89.

Olivier, M., Hollstein, M., Hainaut, P., 2010. TP53 mutations in human cancers: Origins, consequences, and clinical use. Cold Spring Harb. Perspect. Biol. 2 (1), a001008.

Park, H.J., et al., 2021. Definition, incidence, and challenges for assessment of hyperprogressive disease during cancer treatment with immune checkpoint inhibitors: A systematic review and meta-analysis. JAMA Netw. Open 4 (3), e211136.

Paspalj, V., et al., 2021. Long-term survival in multiresistant metastatic choriocarcinoma after pembrolizumab treatment: A case report. Gynecol. Oncol. Rep. 37, 100817.

Sade-Feldman, M., et al., 2017. Resistance to checkpoint blockade therapy through inactivation of antigen presentation. Nat. Commun. 8 (1), 1136.

Stolarova, L., et al., 2020. CHEK2 germline variants in cancer predisposition: Stalemate rather than checkmate. Cells 9 (12), 2675. https://doi.org/10.3390/cells9122675.

Veras, E., et al., 2017. PD-L1 expression in human placentas and gestational trophoblastic diseases. Int. J. Gynecol. Pathol. 36 (2), 146–153.

Witkowski, L., et al., 2014. Germline and somatic SMARCA4 mutations characterize small cell carcinoma of the ovary, hypercalcemic type. Nat. Genet 46 (5), 438–443.

Wu, C.-J., et al., 2018. Short tandem repeat analysis for confirmation of uterine non-gestational choriocarcinoma in a postmenopausal Taiwanese woman. Medicine (Baltimore) 97 (8), e9899.

Xu, Z., et al., 2019. Hyperprogressive disease in cervical small cell carcinoma treated by immune checkpoint inhibitor. Onco Targets Ther. 12, 8873–8877.

Zaretsky, J.M., et al., 2016. Mutations associated with acquired resistance to PD-1 blockade in Melanoma. N. Engl. J. Med. 375 (9), 819–829.