



## Case report

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

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## 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,  $\beta$ hCG 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; Ghorani 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

**Abbreviations:** NGC, Non-gestational choriocarcinoma; GC, gestational choriocarcinoma; ICI, immune checkpoint inhibitor; TPS, tumor proportion score; CPS, combined positive score; EMA/CO, methotrexate, etoposide, actinomycin-D, cyclophosphamide and vincristine; TC/TE, paclitaxel/cisplatin alternating with paclitaxel/etoposide; 5FU, 5-fluorouracil; FOLFOX, leucovorin (folinic acid), fluorouracil, oxaliplatin;  $\beta$ hCG, beta-human chorionic gonadotropin.

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<https://doi.org/10.1016/j.gore.2022.100923>

Received 8 November 2021; Received in revised form 16 December 2021; Accepted 3 January 2022

Available online 17 January 2022

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quadrant pain, and a  $\beta$ hCG 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 choriocarcinoma 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 association with gestation. Although  $\beta$ hCG 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,  $\beta$ hCG 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 # SPEC1, 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 choriocarcinoma was non-gestational. Accordingly, when the  $\beta$ hCG 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 score and potentially premature termination of pembrolizumab provided rationale for resuming ICI therapy. However, given the uncertainty about pembrolizumab efficacy in NGC and a desire to avoid delaying systemic therapy, pembrolizumab was given concurrently with radiation. An initial decline in  $\beta$ hCG (-42%; from 30,193 to 17,513 IU/L) was encouraging but by the third dose of pembrolizumab,  $\beta$ hCG rose sharply by 814% (from 17,513 to 160,074 IU/L) and treatment was discontinued. Of note, the  $\beta$ hCG assay (BHCG 61718, <https://www.mayocliniclabs.com/test-catalog/overview/61718>) is designed specifically for tumor monitoring to detect both intact hCG and free  $\beta$ hCG, resulting in greater sensitivity in detecting hCG-producing tumors. A CT scan showed profound progression of disease in the liver, outside of the

radiation field, and an unexpected appearance of innumerable new pulmonary metastases (Fig. 2). The patient was admitted to the hospital to begin chemotherapy with paclitaxel and ifosfamide (TIP without cisplatin) but died from disease-related complications, including respiratory failure, before a second cycle could be given.

### 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  $\beta$ 2-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

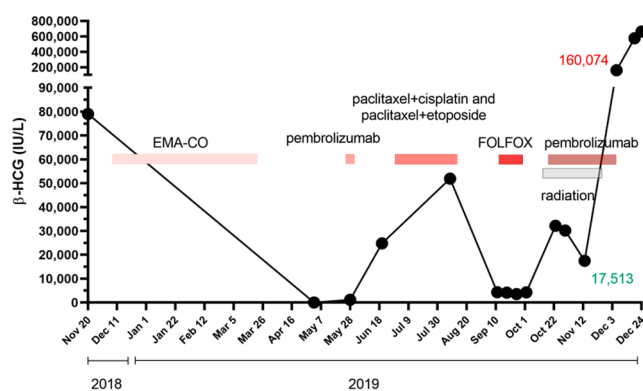


Fig. 1. Treatment timeline and tumor marker levels. EMA-CO (methotrexate, etoposide, actinomycin-D, cyclophosphamide and vincristine). FOLFOX (5FU, leucovorin, oxaliplatin).

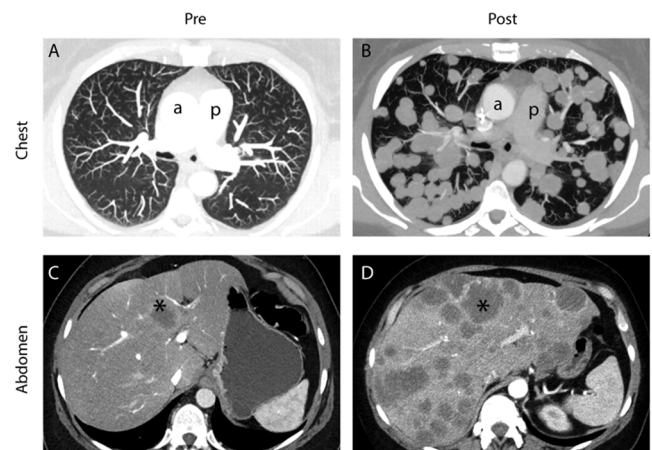


Fig. 2. CT scans before and after pembrolizumab therapy. (A) No lung lesions were present at baseline, prior to pembrolizumab but (B) innumerable metastases were visible by the end of treatment. Similarly, (C) a solitary liver lesion (\*) progressed to (D) innumerable metastases but only the baseline lesion is identified with \*. Aorta (a) and pulmonary artery (p) are identified for orientation.

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 proteasome degradation (Hafner 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; Jelinic 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 abdominal pain and 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. **S. 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.

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