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Combined chemotherapy and pembrolizumab salvages multi-chemotherapy agent and avelumab resistant choriocarcinoma: A case report

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A B S T R A C T

Introduction: Gestational trophoblastic neoplasia (GTN) including choriocarcinoma (CC) frequently requires multi-agent chemotherapy to achieve cure. In chemotherapy-resistant GTN, immunotherapy with the checkpoint inhibitors pembrolizumab, avelumab and camrelizumab are potential new treatment options previously described in small case series, phase 2 trials and case reports.

Case description: A 32-year-old woman was diagnosed with gestational choriocarcinoma (FIGO score 5). Prior administered therapy regimes included methotrexate, actinomycin-D followed by open hysterectomy with bilateral salpingectomy (histology without GTN) as well as multi-agent chemotherapy and avelumab single-agent. After detection of a suspicious pulmonary mass video- assisted thoracoscopic left lung segmentectomy was performed confirming CC. The patient experienced an intracerebral haemorrhage and was treated with an emergency decompressive craniotomy. The cerebrospinal fluid showed an increased ratio of hCG compared to serum. Therapy with combined escalated etoposide and cisplatin with pembrolizumab was commenced followed by maintenance pembrolizumab achieving a complete hCG response and negative PET CT.

Discussion: In the management of multi drug- resistant GTN, application of checkpoint inhibitor pembrolizumab is a new therapeutic strategy. In this heavily pre-treated patient incorporation of pembrolizumab resulted in complete long-term response in a patient who had also failed avelumab therapy.

1. Introduction

Gestational trophoblastic disease (GTD) is a group of benign to malignant disorders, the latter often referred to as gestational trophoblastic neoplasia (GTN). The malignant forms of GTD include post-hydatidiform molar GTN, choriocarcinoma (CC) and the very rare placental site and epithelioid trophoblastic tumours (PSTT/ETT). All forms of GTN can arise after any type of pregnancy. To determine the type of treatment required for all forms of GTN apart from PSTT/ETT, the FIGO scoring system is used to determine the risk of the tumour developing resistance to single agent chemotherapy. In low risk GTN (FIGO-score 0–6) single-agent intramuscular methotrexate with calcium folinic acid rescue (MTX/FA) or pulsed intravenous actinomycin-D is typically used. In the event of resistance or toxicity to one single agent, the alternative single agent therapy can be tried. Nevertheless, many select this option only if the hCG level is below a cut-off of 1,000 IU/L (Mangili et al., 2022). Even GTN with a FIGO-score 5–6 can be cured with one or two sequential single agents in 60% of cases. The remaining 40% will end up needing multi-agent chemotherapy (Mangili et al., 2022). First-line multi-agent chemotherapy for patients with high-risk profile (FIGO-score >6) is typically the EMA/CO scheme, including etoposide, methotrexate, actinomycin-D alternating weekly with cyclophosphamide and vincristine, showing remission rates of 70–91% (Mangili et al., 2022). Those failing EMA/CO can in most cases be salvaged with further combination-agent chemotherapies so overall survival for high risk is 96% (Savage et al., 2020). In low-risk and most high-risk disease treatment should be continued until hCG level returns to normal and then for further 6 consecutive weeks (Mangili et al., 2022).

In refractory cases other regimens like EP alternating with EMA, paclitaxel and etoposide/ cisplatin (TE/TP), etoposide, ifosfamide and cisplatin (VIP), bleomycin, etoposide and cisplatin (BEP), ifosfamide, carboplatin and etoposide (ICE) or gemcitabine-paclitaxel, ifosfamide and cisplatin (GEM-TIP) can be considered. Patients exposed to multi-

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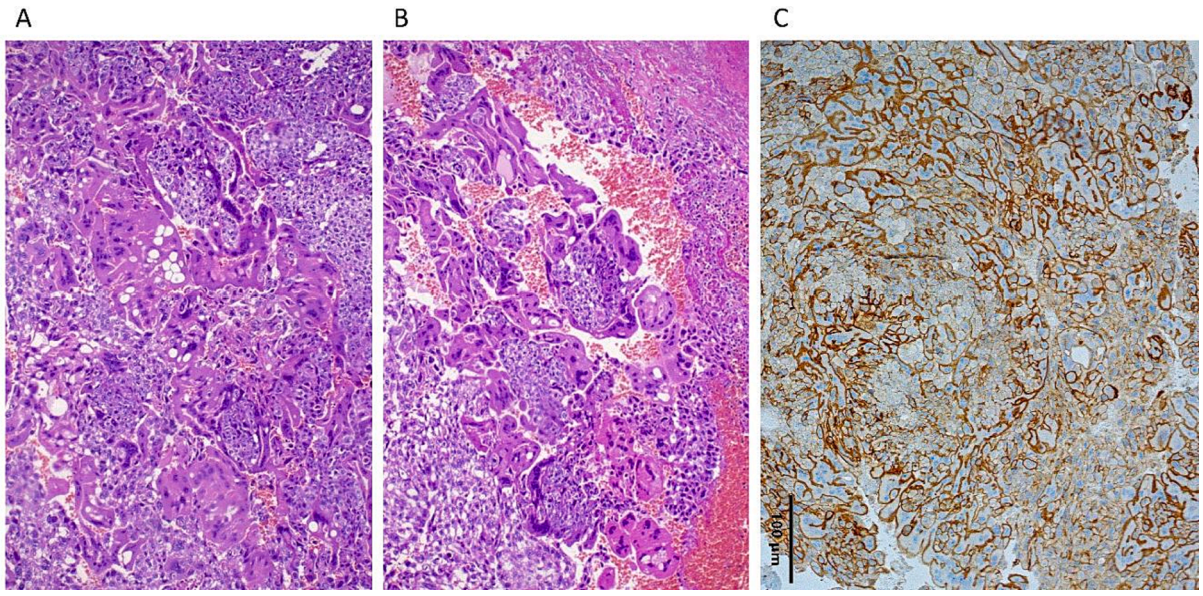

Fig. 1. Histology of the D&C confirming uterine choriocarcinoma (picture A and B). PDL1 immunohistochemical staining showed a 100% positivity (picture C). Courtesy G. Hofstetter, Department of Clinical Pathology, Medical University Vienna.

agent chemotherapy experience toxicities affecting quality of life and psychological health. In particular neurotoxicity has a negative influence in long time health-related quality of life. In addition to that, patients with FIGO score 13 or more are at higher risk of developing drug resistance (Mangili et al., 2022).

Placental tissue is characterised by high expression of programmed cell death ligand 1 (PD-L1) (Bolze et al., 2017). Therefore, immune checkpoint inhibitors (CPIs) might represent a promising treatment strategy in chemotherapy-resistant GTN. Data on immune CPIs in the management of GTN is very limited with small case series, non-randomised small phase 2 trials and case reports (Huang et al., 2017; Ghorani et al., 2017; Wong et al., 2022; Clair et al., 2020; Paspalj et al., 2021; Goldfarb et al., 2020). Nevertheless, the most recent international guidelines include immunotherapy as a possible therapeutic strategy for chemotherapy-resistant GTN. National Health Service England is supporting routine use as third line treatment, when clinical criteria are met including a high risk GTN that failed to respond to EMA/CO multi-agent chemotherapy and failed to second line treatment like EP alternating with EMA. (Tempfer and Horn, 2022; Abu-Rustum et al., 2019; Goldfarb et al., 2020; Urgent Clinical Commissioning Policy, 2021). Reports of Paspalj et al, Goldfarb et al, Huang et al, Ghorani et al and Clair et al indicate that patients with multi-drug relapsed disease can enter sustained remission with single agent pembrolizumab (Huang et al., 2017; Ghorani et al., 2017; Clair et al., 2020; Paspalj et al., 2021; Goldfarb et al., 2020). In general CPIs are well tolerated, adverse events like pneumonitis, dermatologic and mucosal toxicity and colitis are described, but in most cases they are reversible or manageable (Mangili et al., 2022).

To our knowledge no report has yet examined the possibility of combining chemotherapy with pembrolizumab although this has been described at international meetings.

Here, we present a case of a patient with widely metastatic CC that was heavily pre-treated with multiple lines of chemotherapy then failed single agent avelumab and achieved a complete response after combined chemotherapy with pembrolizumab remaining in remission for 14 months.

2. Case description

A 32-year-old woman (gravida 2, para 1, abortus 1) presented with abnormal uterine bleeding five months after undergoing an emergency caesarean section due to fetal distress at term. The patient had a copper intrauterine device (IUD) as contraception. A dilation and curettage (D&C) and removal of IUD was performed. Histological findings confirmed uterine CC (Fig. 1). A computed tomography (CT) scan showed an abnormal uterus and a suspected granuloma measuring 1,5mm in the left lower lung lobe not suspicious for malignancy. CT of the abdomen as well as cerebral magnetic resonance imaging (MRI) appeared inconspicuous for additional metastatic lesions. First measured serum hCG was 13,575 IU/L.

Table 1
The patients' results according to WHO-scoring system as used by FIGO.

Categories	Results	Score
Age	<40	0
Antecedent pregnancy	Term	2
Interval from index pregnancy, months	4- < 7	1
Pretreatment hCG mIU/ml	$>10^4$–10^5	2
Largest tumour size including uterus, cm	–	0
Site of metastases including uterus	–	0
Number of metastases identified	–	0
Previous failed chemotherapy	–	0

The patient scored 5 points on the WHO Prognostic Scoring System for GTN as adapted by FIGO (Table 1) and received four cycles of methotrexate intramuscular weekly (50 mg/m^{2}d1, d8, d15, q21) and hCG decreased to 0.2 IU/L (cut- off premenopausal: <1 IU/L).

57 weeks after the last cycle hCG began to rise again and it reached 568 IU/L. Re- staging CT scan showed no signs of malignancy. Five cycles Actinomycin-D therapy intravenous (1.25 mg/m^2) were administered. After initial hCG decrease to <0.1 IU/L it increased again after 9 weeks of therapy. An open hysterectomy with bilateral salpingectomy was undertaken to exclude possible transformation of her CC to PSTT/ETT. The final histology however was without GTN. Postoperative CT imaging two weeks later showed a new suspicious pulmonary mass in the left lower lobe not equivalent to the previously diagnosed granuloma.

HCG increased again in one week's time to 19.6 IU/L. Multi-agent chemotherapy with EMA/CO intravenous (day 1: etoposid 100 mg/m^2, methotrexate 300 mg/m^2, actinomycin-D 0.5 mg; day 2: etoposide 100 mg/m^2, actinomycin-D 0.5 mg; day 8: vincristine 1 mg/m^2, cyclophosphamide 600 mg/m^2) was started and four cycles administered. A

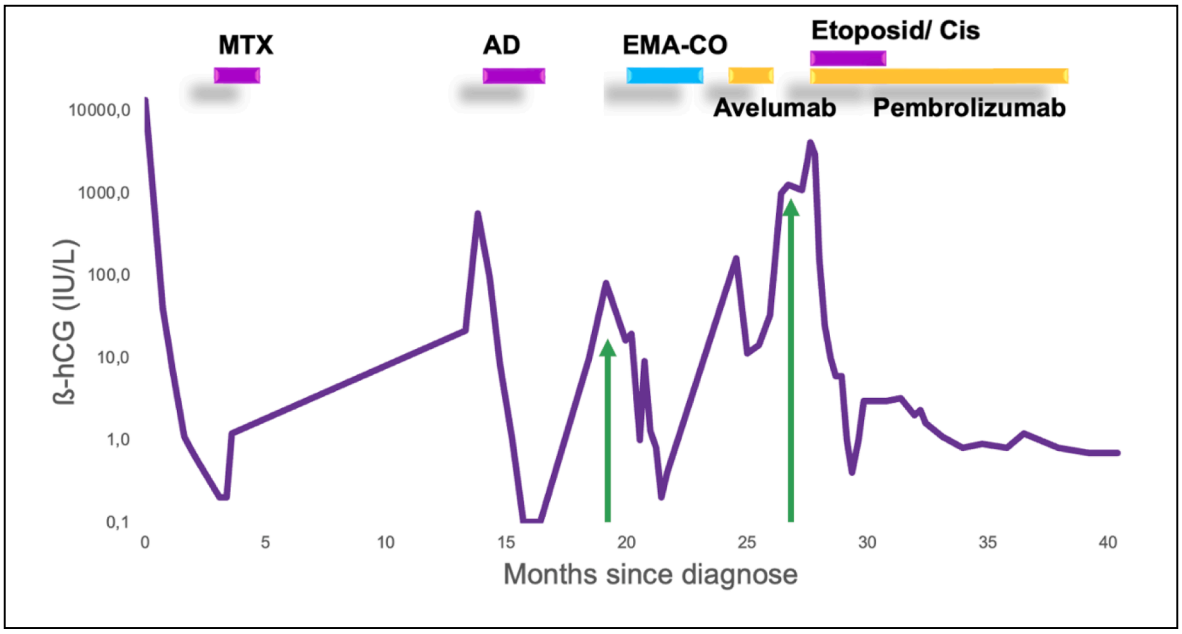

Fig. 2. Trend of serum hCG levels measured during treatment and maintenance periods. The coloured boxes represent treatment regimens (a) MTX = methotrexate, (b) AD = actinomycin-D, (c) EMA-CO = etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine, (d) Avelumab, (e) Etoposid/ Cis = escalated etoposide/ cisplatin combined with pembrolizumab, (f) Pembrolizumab maintenance. The left green arrow represents the open hysterectomy and bilateral salpingectomy whereas the right green arrow represents the partial lung segment resection.

cerebral MRI performed during treatment was without signs of malignancy.

EMA-CO resulted in a decrease of hCG, but whilst on treatment began to rise again to 160 IU/L (Fig. 2). A CT scan and MRI pelvis showed an unchanged pulmonary mass and no other new visible lesions. Off label immunotherapy with avelumab single- agent was initiated and three cycles were completed. After initial hCG decrease, it increased to 992 IU/L at the time point of the last avelumab administration (Fig. 2). An abdomen/ thorax CT showed an increase of the pulmonary mass.

Following a partial lung segment resection was indicated and a video- assisted thoracoscopic left lung segmentectomy was performed. Pathology confirmed metastatic CC. After surgery only a slight decrease in the hCG level was observed but the later was further rising to 2,598 IU/L shortly afterwards. Repeated staging was performed showing findings suspicious for multiple micro-vascular thrombosis or new cerebral metastases.

During this progression the patient experienced an intracerebral haemorrhage with an acute subdural hematoma and midline shift. A decompressive craniotomy was conducted and the patient was transferred to intensive care unit. Charing Cross Hospital in London was consulted for advice and due to the critical situation of the patient emergency administration of escalated etoposide/ cisplatin combined with pembrolizumab (etoposide 500 mg/m^2(q14), cisplatin 60 mg/m^2(q14), pembrolizumab 200 mg(q21)) was commenced. The intraoperative biopsies of the cerebral parenchyma were negative for malignancies, but hCG in the cerebrospinal fluid was 848 IU/L compared to 2,598 IU/L in serum which results in a ratio of 1:30 (normal ratio <1:60) (Athanassiou et al., 1983).

While the patient recovered after the subdural hematoma, eight cycles of escalated etoposide/ cisplatin and pembrolizumab were administered. An unsuspicious hCG at 0.4 IU/L (cut off premenopausal: <1 IU/L) was achieved after cycle three. A PET CT scan following treatment completion showed complete response. Since the hCG measurements showed stable low results although not being negative, a continuation of pembrolizumab intravenous (pembrolizumab 200 mg) as maintenance single-agent was established. After additional twelve cycles, the patients' hCG level was at 0.8 IU/ml (Fig. 2), the PET CT showed complete response and the ECOG status was at 2. The immunotherapy with pembrolizumab was discontinued and a monthly follow- up with hCG controls established. Remission off treatment has remained for 14 months and hCG measurements were negative.

3. Discussion

New treatment opportunities in chemotherapy-resistant GTN are CPIs (Mangili et al., 2022; Bolze et al., 2017). In our case, the CC showed 100% expression of PDL-1. The TROPHIMMUN trial cohort A is the first prospective study of avelumab in single-agent chemotherapy-resistant GTN. Avelumab is a programmed death ligand-1 (PD-L1) antibody and was examined in low risk GTN patients failing one single agent. In this setting it cured about 50% of patients with an acceptable safety profile (You et al., 2020). In the TROPHIMMUN trial cohort B avelumab was administered in patients with resistance to multi-agent chemotherapy but this arm of the trial was shut down earlier because of futility (You et al., 2023). A limitation of this study was the small population size of 15 (cohort A) und 7 patients (cohort B). In our case, the patient received three cycles of avelumab that led to an initial hCG decrease followed by progression of a pulmonary mass during treatment. A rise in hCG was associated indicating this was likely not pseudoprogression.

A promising CPI is pembrolizumab. This agent targets PD-1 directly on immune cells rather than one of its ligands like PD-L1 that is blocked by avelumab. There are several described case reports of successful pembrolizumab treatment in chemotherapy-resistant CC (Huang et al., 2017; Ghorani et al., 2017; Clair et al., 2020; Paspalj et al., 2021; Goldfarb et al., 2020). An ongoing small phase II trial (NCT04303884) examines the clinical efficacy of pembrolizumab in patients with chemotherapy- resistant GTN, which is important for development of new therapeutic strategies especially in multi-agent drug resistant CC.

To our knowledge our case is the first to report achievement of a complete response with chemotherapy plus pembrolizumab followed by pembrolizumab as maintenance single-agent therapy after being resistant to four lines prior systemic treatment, including immunotherapy with avelumab. A repeated exposure to immunotherapy might therefore be possible and previous resistance to one immune CPI does not preclude

response to another (Wong et al., 2022). We cannot exclude the possibility that avelumab combined with chemotherapy might result in a better response compared to avelumab single-agent. However, it is interesting that avelumab appears to be less effective as a single agent in multi-drug resistant GTN compared to single agent pembrolizumab on the limited available non-randomised data. Further exploration of combined pembrolizumab and chemotherapy is warranted. At the time point of writing this manuscript our patient remains disease free for 14 months.

4. Conclusion

In this patient, complete response and sustained remission could be achieved by incorporating the CPI pembrolizumab combined with escalated EP into the management of multi-drug and avelumab immunotherapy resistant GTN. Further prospective multicentre trials are needed to more fully determine the role of CPIs alone or in combination with other therapies as a new treatment opportunity in GTN.

Credit authorship contribution statement

M. Lehmann: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **H. Hosa:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Visualization. **T. Bartl:** Methodology, Visualization. **I. Tsibulak:** Writing – review & editing. **S. Polterauer:** Methodology, Writing – review & editing. **N. Pötsch:** Visualization. **M.J. Seckl:** Methodology, Writing – review & editing, Supervision. **C. Marth:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration.

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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