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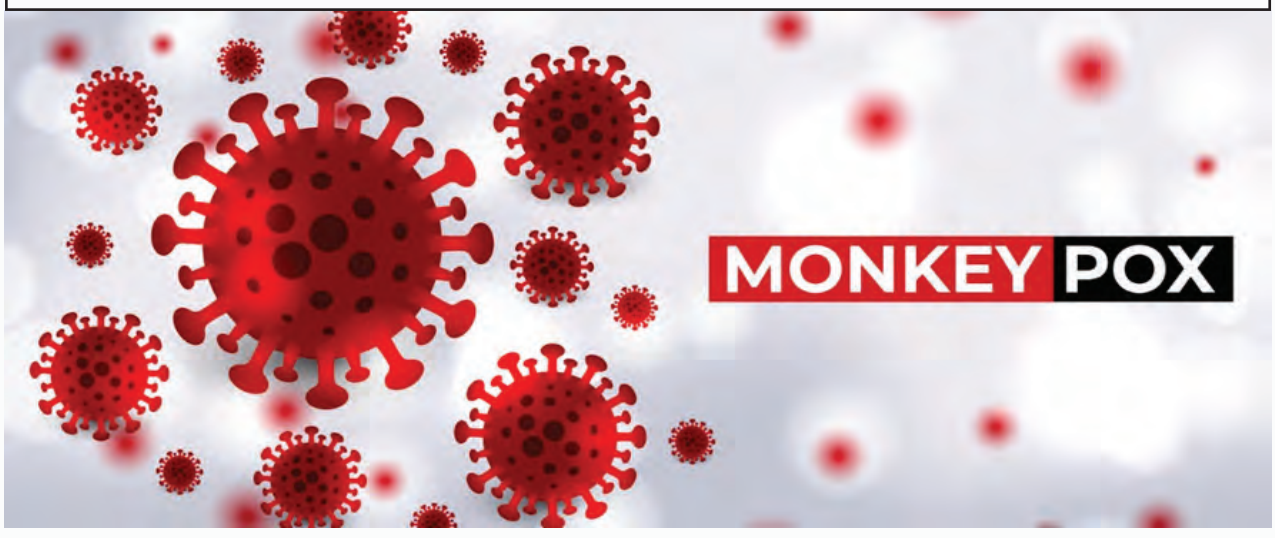


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October 27-28, 2024

STATE OF KUWAIT



The Official Journal of the Gulf Federation For Cancer Control

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Case Report

Pembrolizumab in the Management of Chemorefractory Gestational Choriocarcinoma: Report of Two Cases.

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Abstract

Background: Treatment of gestational trophoblastic disease (GTD) with chemotherapy is a success story for medical oncology; a combination of chemosensitive disease with a sensitive tumour marker makes GTD an eminently curable disease. However, 0·5–5·0% of women with this cancer continue to die as a result of multidrug resistance. PD–L1 is strongly expressed in these tumours, making them a target for immune therapy with immune checkpoint inhibitors such as pembrolizumab.

Case Presentation: We present two challenging cases of gestational choriocarcinomas, resistant to multiple interventions including multiple lines of chemotherapy, surgery and radiation, who are in long term remission after pembrolizumab immunotherapy.

Discussion and Conclusion: Immunotherapy is a potent weapon in the treatment of GTD and should be considered earlier option as it has the potential to alter the natural history of refractory choriocarcinoma with possible cure.

Keywords: Gestational trophoblastic disease, choriocarcinoma, chemo–refractory, immunotherapy, pembrolizumab.

Introduction

Overgrowth of placental tissue following a gestational event (abortion or pregnancy) result in a spectrum of disease collectively called gestational trophoblastic disease (GTD); these range from the benign hydatidiform mole (partial or complete) to the and placental site trophoblastic tumour/epitheloid trophoblastic tumour (PSTT/ETT); the malignant versions are termed gestational trophoblastic neoplasia (GTN). The chemosensitivity of the tumour coupled with a very sensitive biomarker (beta human chorionic gonadotropin, B–HCG) makes them an eminently curable disease[1,2]. However, a small percentage develops chemoresistance and results in the death of about 0.5 to 5% of such cases. Recently, the treatment of cancers has been revolutionized by introduction of immunotherapy, and several case reports have appeared about the efficacy of immune check point inhibitors (ICI) in this chemoresistant subset. We present two cases of chemoresistant gestational choriocarcinomas that were treated in our center with the ICI, pembrolizumab resulting in long disease–free survival (DFS). To the best of our knowledge, these are the first cases to be reported from the Gulf region.

Case Presentation

Case Number 1:

The first patient, an Omani lady aged 34 years, mother of 3 children, was diagnosed in August 2018 with choriocarcinoma. Her WHO risk score was 9, and she had lung and bone metastasis. Her initial B–HCG was 6280624 IU/L. She was treated with EMA–CO regimen, with partial response, followed by second line treatment with paclitaxel–etoposide alternating with paclitaxel–cisplatin (TE/TP) regimen, again with partial response. She also underwent total abdominal hysterectomy with bilateral salpingo–oopherectomy (TAH/BSO) in June 2020 as a PET scan showed disease confined to pelvis. Imaging and serological assessment post–surgery showed residual disease, with a rising BHCG. She was planned for high dose chemotherapy with autologous stem cell transplant (AuSCT) in a specialized center but due to

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the ongoing COVID pandemic, it was delayed. Based on encouraging case reports, pembrolizumab was started in July 2020. There was rapid serological response with B–HCG normalizing in September 2020 after 3 cycles. She completed a total of 9 doses of pembrolizumab by January 2021. PET scan in August 2022 showed post–operative fibrotic changes in pelvis with a stable right upper lobe nodule. B HCG was normal (< 2 IU/L) at the last follow up in December 2023; she is now alive and well with 3 years DFS. (Figure 1)

Case Number 2:

The second patient was again an Omani lady, aged 33 years, a known case of sickle cell disease, and was diagnosed as a case of gestational choriocarcinoma, initially graded as low risk disease in 2014 and treated with single agent methotrexate. She went into remission but then relapsed with high–risk metastatic disease in 2017. She progressed on 3 lines of chemotherapy with EMA–CO, TP/TE and EMA/EP regimens and an AuSCT was done in Aug 2019. Her BHCG continued to be marginally elevated. Residual pelvic disease as shown in PET scan was resected in July 2020. MRI pelvis done September 2020 showed local disease recurrence. PET scan in October 2020 showed progression of the right pelvic disease with interval progression of left superior mediastinal lymph nodes. Beta HCG was high at 90001854 IU/L. She underwent RT to mediastinum and pelvis 45 Gy/25 fractions from 19/11/20 to 23/12/20. She had transient BHCG response, but it again rose to 1526 IU/L in April 2021; PET scan done in the same month showed local disease recurrence with a new pulmonary lesion. She underwent left parenchymal sparing metastectomy in June 2021. Histopathology confirmed choriocarcinoma, the resected lymph nodes were negative for malignancy. Follow up PET scan in July 2021 noted surgical changes in the left lung, with metabolic progression in mediastinal lymph nodes and the soft tissue thickening/mass in the right pelvic wall with associated encasement of the distal right ureter with obstructive hydronephrosis. BHCG July 2021 was 5417 IU/L. She also had recurrent attacks of pain due to her underlying sickle cell disease. In view of disease progression post multiple lines of chemotherapy, surgery and radiotherapy, she was started on pembrolizumab in August 2021. BHCG level normalized after 4 cycles in October 2021 and has remained normal since. PET scan, last done June 2022 showed no evidence of FDG avid local disease recurrence, with further interval size and metabolic regression in right pelvic wall mass. She continued on pembrolizumab until December 2022 for a total of 17 cycles. She is currently on follow up with DFS of 27 months. (Figure 2)

Discussion and Conclusion

Treatment of GTD is one of the remarkable success stories of medical oncology. This spectrum of diseases is characterized by extreme chemosensitivity (initially shown by Li et al in 1956 with single agent methotrexate) [3] and a sensitive tumour marker in BHCG. Patients undergo surgical evacuation and chemotherapy is used if BHCG remains elevated. Standard guidelines exist for indications for treatment, risk scoring, and the type of chemotherapy regimen to be used based on risk score[4,5]

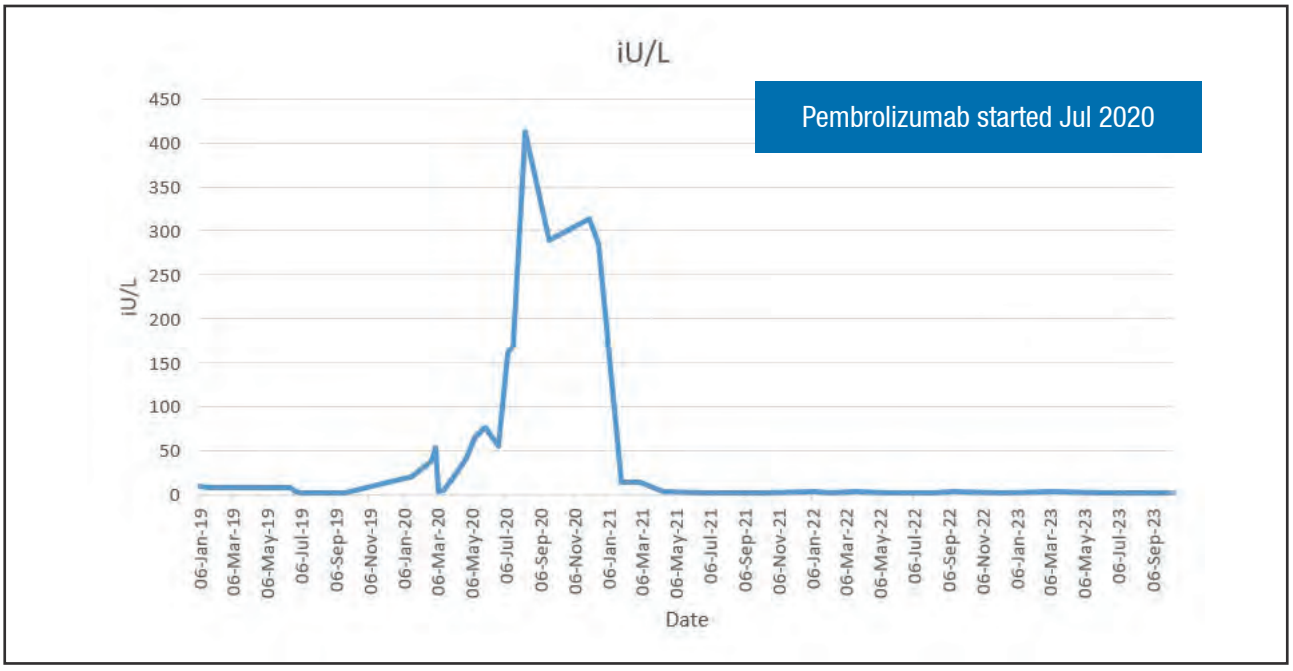


Figure 1

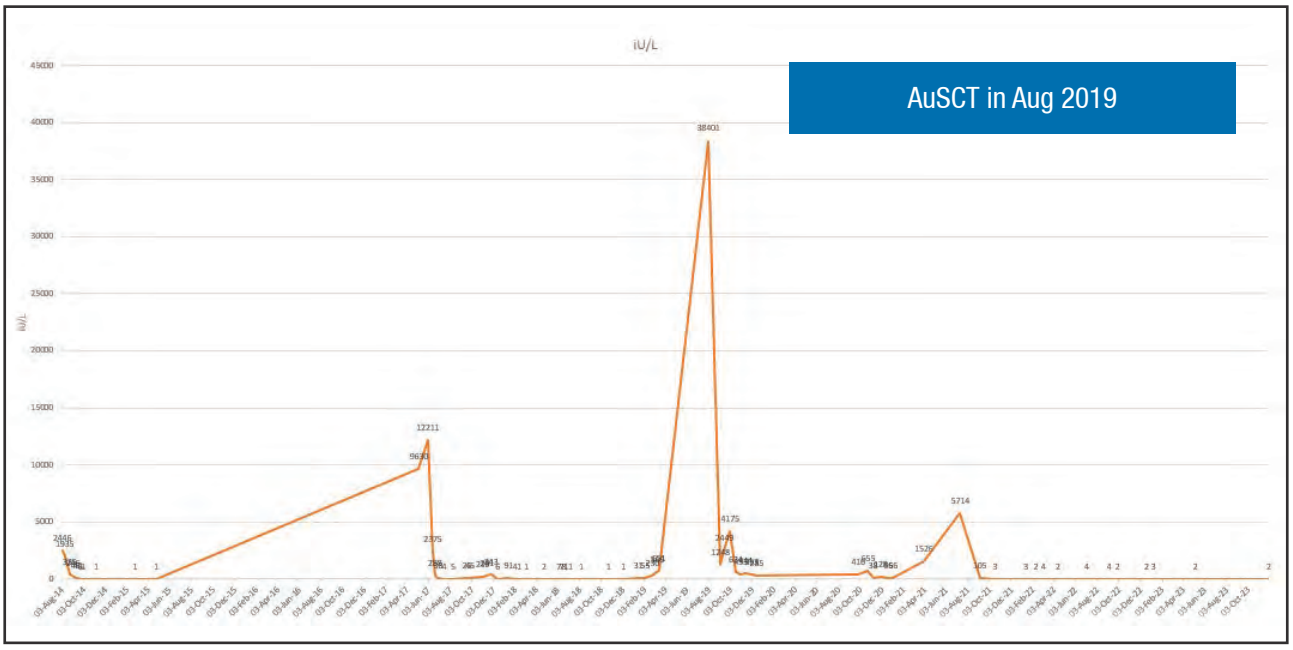


Figure 2

though these may vary depending on institutional protocols. Unfortunately, about 0.5 to 5% of patients develop drug resistance and succumb to their disease.

Most of the low risk and about 80% of the high risk will respond to combination chemotherapy, and about 20% will need salvage chemotherapy. Up to 80% of the latter will be cured with third line standard and/or high dose chemotherapy. Salvage regimens include single agent paclitaxel, alternating TE/PE regimen, gemcitabine with carboplatin, etc. High dose chemotherapy with regimens such as ICE (ifosfamide, carboplatin and etoposide) followed by stem cell transplant can rescue a small percentage; one series reported long term survival in 13 of 32 transplanted patients (41%)[6]. A PET scan can reveal oligometastatic disease and such patients can be subjected to surgery[7] or radiation[8] with curative intent. Targeted therapy has not been successful so far in GTN due to lack of druggable mutations. Thus, though more than 95% of patients can be cured, a small percentage eventually succumb to their disease for want of effective treatment, a tragedy as these are young women of reproductive age group.

Immune checkpoint inhibitors (ICI) are an exciting new group of drugs that have revolutionized treatment of heretofore hard to treat cancers. Essentially, ICIs are monoclonal antibodies directed against the surface antigens, either PD–1 or PDL–1; the interactions between these two antigens expressed on cancer cells and cytotoxic T–lymphocytes (CTLs) prevent destruction of cancer cells by the immune system. By preventing such interaction with these antibodies, CTLs are activated to recognize and destroy cancer cells. Examples of well–established anti–PD1 ICIs are pembrolizumab and nivolumab, while examples of anti–PDL1 ICIs are avelumab, atezolizumab and durvalumab.

In a landmark letter to The Lancet in 2017, Ghorani et al reported 4 patients of chemo–refractory GTN treated in UK and Sweden with pembrolizumab, with complete remission in 3 of them; these patients had high expression of PDL–1 with dense tumoral infiltration with lymphocytes[9]. A recent review by the same author[10] collected 133 cases treated with ICIs, 118 of them high risk, of which 77 were cured by the use of ICIs, such as pembrolizumab, avelumab, or camrelizumab. Camrelizumab is of Chinese origin and is not readily available outside the country. The efficacy of avelumab appears to be limited as suggested by the poor results of Arm B of the French TROPHIMMUN study[11]. However, it showed better outcomes in low–risk disease resistant to single agent methotrexate in Arm A of the same study[12]. Thus, pembrolizumab appears to be more effective than other ICIs; indeed, there is a case report of pembrolizumab being used to successfully salvage a patient resistant to avelumab[13]. Retreatment with pembrolizumab is also an option in patients who relapse after initial complete remission to the drug[14].

The National Comprehensive Cancer Network (NCCN) guidelines have been updated recently to include pembrolizumab, nivolumab and avelumab as “useful under certain circumstances” (Additional agents/ regimens shown to have some activity in treating multiagent chemotherapy–resistant GTN)[15]. However, other guidelines (such as of American Society of Clinical Oncology or European Society of Medical Oncology) are yet to be updated.

We are reporting two cases of refractory gestational choriocarcinomas treated with pembrolizumab in Oman (Table 1). Both had rapid response to single agent immunotherapy with normalization of BHCG, with minimal toxicity and long term DFS. The exact duration of treatment after normalization of BHCG is not known. Indeed, the appropriate dosage of immunotherapy agents is a matter of controversy; there are suggestions that lower doses may be effective, resulting in huge cost savings which is vital for less developed countries[16]. We did not do PDL–1 testing in either of these patients before starting treatment and this may not be required as its expression appears fairly ubiquitous[17].

Although PD–L1 expression is common in testicular germ cell tumours, their response to immunotherapy has been uniformly poor, and two Phase II trials were negative[18,19]. There is also a case report of hyperprogression in a case of non–gestational (ovarian) choriocarcinoma; hence caution is suggested in other cancers[20].

GTD is an eminently curable disease condition; however, a small percentage can become chemoresistant and result in the death of the patient. Recent advances in immunotherapy have provided an exciting option for potential cure in such patients. We present our positive experience in two patients of gestational choriocarcinoma with long–term disease–free survival. Gynecologists and medical oncologists need to be aware about the use of checkpoint inhibitors such as anti–PDL1 pembrolizumab in the treatment of refractory GTN to enable more patients to receive appropriate therapy. The undeniably excellent responses and long term DFS seems to obviate the need for randomized trials to confirm efficacy, but further investigations are needed to define appropriate dosages and schedules. Longer follow–ups are also indicated to clarify the impact of these drugs on fertility and future pregnancies.

Funding and Conflict of Interest

We declare that we have received no funding for management of the case or preparation of manuscript.

We further declare that we have no conflict of interests related to this article.

Ethical Standards: Both the reported patients have given written consent for publication of their case details.

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Patient No	Age	Lines of chemo	AuSCT	Surgery	RT	Response to pembro @cycle	Total cycles
1	34	2	No	Yes	No	3	9
2	33	3	Yes	Yes	Yes	4	17

Table 1

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