Case Report

Maintenance Therapy with Pembrolizumab after Platinum-Doublet Chemotherapy Leading to Hyperprogression in a Patient with Metastatic Bladder Cancer

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ABSTRACT

The anti-programmed cell death receptor 1 (anti-PD-1) immunotherapy has been recommended in several treatment scenarios of metastatic urothelial cancer (UC), including as a maintenance therapy after first-line chemotherapy. However, the PD-1 inhibitor accelerates tumor growth occasionally, causing hyperprogressive disease (HPD). We presented here a case of HPD in a 43-year-old male Chinese patient with bladder UC, metastasizing to liver and bone, and harboring amplification of *Murine Double Minute gene 2*, *cyclin-dependent kinase 4*, *fibroblast growth factor receptor substrate 2*, *ERBB3*, and *Enhancer of Zeste Homolog 2*. After achieving partial remission with the traditional platinum doublet chemotherapy, he sought PD-1 inhibitor (pembrolizumab) for maintenance therapy in another hospital. After 3 doses of pembrolizumab in <2 months, his liver metastasis dramatically increased both in size and number. Liver biopsy confirmed genuine progression. He died from liver failure 6 months later. This case alerted us about HPD again in the scenario of maintenance therapy, enhanced the importance of selecting appropriate patients.

Key words: Bladder urothelial cancer, hyperprogressive disease, immunotherapy, maintenance therapy, *murine double minute gene 2*

Introduction

The anti-programmed cell death receptor 1 (anti-PD-1) or anti-PD-1 ligand 1 (anti-PD-L1) immunotherapy is a preferred second-line regimen for advanced urothelial cancer (UC) and is recommended as a first-line regimen for platinum ineligible patients with high PD-L1 expression.[1] Recently, avelumab, a PD-L1 inhibitor, was used as a maintenance therapy for patients whose disease did not progress after the first-line platinum-doublet chemotherapy and it produced survival benefits successfully.[2] However, immunotherapy has been occasionally reported to accelerate the tumor growth rate (TGR) to more than twofold, causing hyperprogressive disease (HPD) in up to 11.9% of UC patients, which is unignorable.[3] Great obstacles exist in identifying these unfortunate patients in advance. In the wish of stimulating an

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inspiration, we present a case that an anti-PD-1 monotherapy was initiated during the remission after the traditional chemotherapy, and the patient suffered from HPD.

Case Report

A 43 year-old male Chinese patient, a restaurant owner, presented himself in a local hospital with intermittent gross hematuria for a week and was diagnosed with muscle-invasive bladder UC by cystoscopy and biopsy in May 2016. He had been healthy before and denied any family history of cancer or genetic diseases. Despite two suspicious lesions in his liver, he received radical cystectomy and pelvic lymph node dissection at the department of urology in our hospital in June 2016. The operation revealed a high-grade UC [Figure 1a] with invasion into his prostate stromal and bilateral seminal vesicles, and metastasis to his obturator lymph nodes, which was categorized as a T4aN1M0 Stage IIIA disease (American Joint Committee on Cancer staging system for Bladder 8th Edition). He did not comply well with an adjuvant chemotherapy and only finished three cycles of a gemcitabine/cisplatin (GP) regimen irregularly (exact dose unavailable), in the local hospital. He stopped treatment in October 2016, with no regular follow-up.

Then, the patient showed up at our department in March 2017, suffering from lumbosacral pain and mild claudication. The physical examination identified a percussion pain on his sacral bone. We gave him a thorough examination with computed tomography (CT) that showed multiple liver metastases [Figure 2a-c], including those two suspicious lesions discovered before surgery which were moderately enlarged, and several bone metastases (lumbosacral vertebrae and pubis). These findings indicated a disease relapse with extensive distant metastases. His disease-free survival (DFS) was 9 months. The immunohistochemistry result of PD-L1 expression with the SP142 antibody was negative (TC 0% and IC 0%) [Figure 1b]. The next-generation sequencing (3D Medicines Inc., Shanghai, China) results were as follows: moderate tumor mutation burden (TMB) (10.48 mutations/megabase, ranking at 30% according to the companies' database), stable microsatellite, and copy number variation (CNV)/amplification of several genes including the *Murine Double Minute gene 2 (MDM2)* (CNV 6), *cyclin-dependent kinase 4 (CDK4)* (CNV 7), *fibroblast growth factor receptor substrate 2* (*FRS2*) (CNV 11), *ERBB3* (CNV 8), and *Enhancer of Zeste Homolog 2* (CNV 5).

The patient might have developed resistance to the GP regimen considering his DFS (9 months). Therefore, we moved on to a second-line treatment. The anti-PD-1/PD-L1 therapy was not commercially available in the mainland in

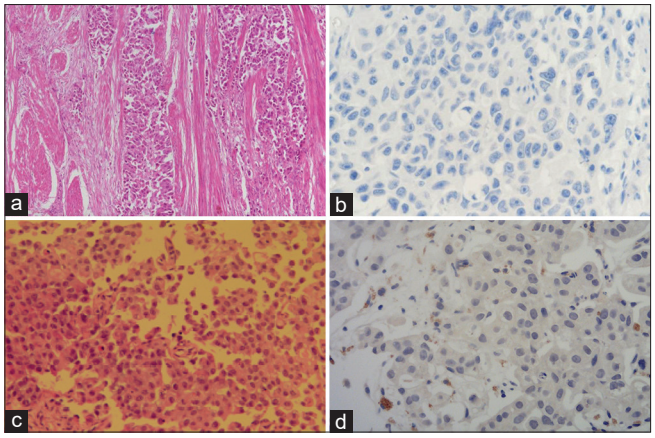

Figure 1: Pathological findings of bladder tumor and liver metastasis biopsy. a: bladder, H&E staining, 100 × b: bladder programmed cell death ligand 1 {PD-L1}, immunohistochemistry {IHC} SP142, 400 ×; c: liver, H&E staining, 100 ×; d: liver, PD-L1 IHC 22C3, 400 ×.

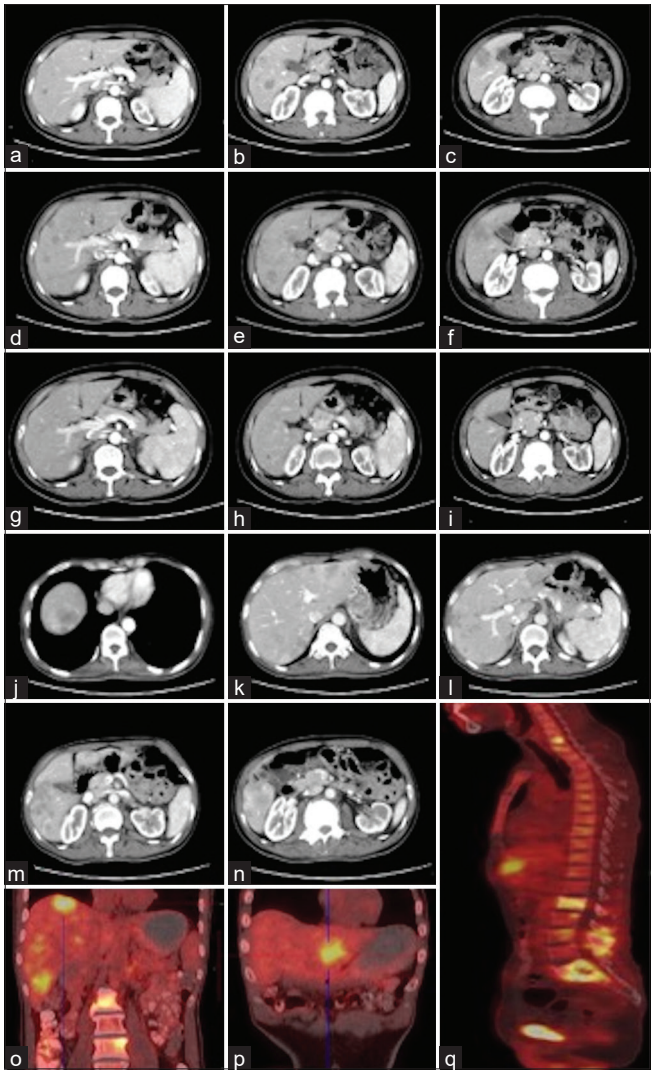

Figure 2: Computed Tomography (CT) and positron-emission tomography (PET) of liver metastasis and bone metastasis. (a-c), CT before Doc/Bev therapy, (d-f), CT before gemcitabine/cisplatin regimen re-challenge; (g-i,) CT before pembrolizumab treatment; (j-n,) CT after pembrolizumab; (o-p), PET after pembrolizumab; (q), PET after pembrolizumab

2017, and we gave him docetaxel (75 mg/m^2 body surface area (BSA) on day 1) and bevacizumab (7.5 mg/kg body weight on day 1) once every 3 weeks beginning from May 2017. However, the disease progressed after two cycles (about 7 weeks later) with mildly enlarged target liver metastases and several new ones [Figure 2d-f], and with no obvious change in the symptoms. Then, we re-challenged him with a full-dose GP chemotherapy (gemcitabine 1000 mg/m^2 BSA on days 1 and 8, cisplatin 70 mg/m^2 BSA on day 1, every 3 weeks) for up to six cycles, with his good compliance; and we obtained a partial response in him, surprisingly [Figure 2g-i], with only Grade 2 myelosuppression. Then, we administered radiotherapy against the lumbosacral metastasis to further alleviate his pain. All these treatments were completed in December 2017, and the patient's performance status (PS) Eastern Cooperative Oncology Group (ECOG) was 0, with no pain, by then.

The patient sought an anti-PD-1 immunotherapy in Hong Kong during the remission period and started pembrolizumab (200 mg every 3 weeks) in January 2018. This could be regarded as a maintenance therapy. After 3 doses of pembrolizumab (about 7 weeks later), he came back to us in severe fatigue and nausea, with rapidly deteriorating lumbosacral pain, claudication, and tenderness in the lumbosacral region, and his PS ECOG became 1. However, he showed no signs of rash, fever, hypothyroidism, impaired liver or renal functions, or other adverse effects of immunotherapy. CT scanning showed dramatically enlarged target lesions as well as a great many new or reappeared lesions in his liver [Figure 2j-n]. These liver lesions were hypermetabolic on positron-emission tomography [Figure 2o-p], and new bone metastasis in the cervical vertebra was observed [Figure 2q]. To perform differential diagnosis between authentic progression and pseudoprogression in the patient, we did a liver biopsy. The pathology result was that cancer cells occupied >90% of the tissue, with few immune cells infiltration and no signs of necrosis or edema [Figure 1c]. The PD-L1 expression of liver metastasis was TC 0% and IC 3% (22C3 antibody) [Figure 1d]. These results met most of the criteria of HPD, with the time to treatment failure (TTF) being <2 months, and the tumor burden increase being over 50%, but there was no ideal reference period to calculate tumor growth kinetics (TGK).

Thereafter, the patient tried a salvage chemotherapy for four cycles of a pemetrexed/carboplatin regimen (exact dose intensity unavailable) in his local hospital, and his wife told us that his disease kept progressing, without available CT images. He died of liver failure with ascites about 6 months after the diagnosis of HPD in October 2018. The timeline of his disease is shown in Figure 3.

Discussion

The phenomenon of HPD has become a concern in the era of immunotherapy, but its diagnostic criteria keep evolving with a core concept of accelerated (greater than twofold) TGK. Some investigators have tried different ways to calculate the TGR or supplemented extra conditions, such as tumor burden increase, TTF, and the number of new metastases.[3,4] Although there was no ideal "reference period" for accurate calculation of the TGR, the period of the unsuccessful second-line treatment with docetaxel and bevacizumab could be taken as an alternative. According to the exponential growth model,[5] the TGRs of the two target liver metastases during the "reference period" and the immune checkpoint inhibitor (ICI) treatment were 19.31% and 177.78%, respectively, demonstrating a ninefold acceleration. Therefore, this case met most of the criteria of HPD, including tumor TTF <2 months, tumor burden increase >50%; and it was confirmed pathologically.

On the other hand, the maintenance therapy with PD-1/PD-L1 inhibitors has been investigated in advanced UC. Compared with placebo, avelumab, a PD-L1 inhibitor, improved the overall survival (OS) and progression-free survival (PFS), when administered after the first-line platinum-doublet chemotherapy in patients with unresectable, locally advanced or metastatic bladder cancer (JAVELIN Bladder 100 study).[2] Pembrolizumab, another PD-1 inhibitor, also demonstrated a longer PFS, compared with placebo in a Phase II trial.[6] In the present case, the patient's "maintenance therapy" with pembrolizumab was not a strictly defined one because it was initiated after the third-line chemotherapy of platinum-doublet regimen re-challenge. However, we valued the similarity of the timing that the disease was under control with a relatively low tumor burden. However, his disastrous outcome called for special concern, that is, to whom should we apply this strategy, and to whom could we avoid doing harm? The subgroup analysis of the JAVELIN Bladder 100 study indicated that patients with negative PD-L1 expression and visceral metastasis, especially liver metastasis, could not benefit from maintenance therapy.[1] Moreover, liver metastasis has been reported as a predictive marker of HPD across studies.[7] An anti-PD-1 monotherapy might still be able to wake up the liver metastases, even though they were under perfect control by previous treatment and under low tumor burden. There were some other clinical markers relating to HPD, such as high level of lactate dehydrogenase (LDH).[7] However, the LDH level of this patient remained normal throughout the course of his disease.

Predictive biomarkers for ICIs, either positive or negative ones, remain a hot area for investigation. Besides the clinical predictors mentioned above, molecular predictors such as high-level PD-L1 expression and TMB, as well as microsatellite instability, have received consensus on their

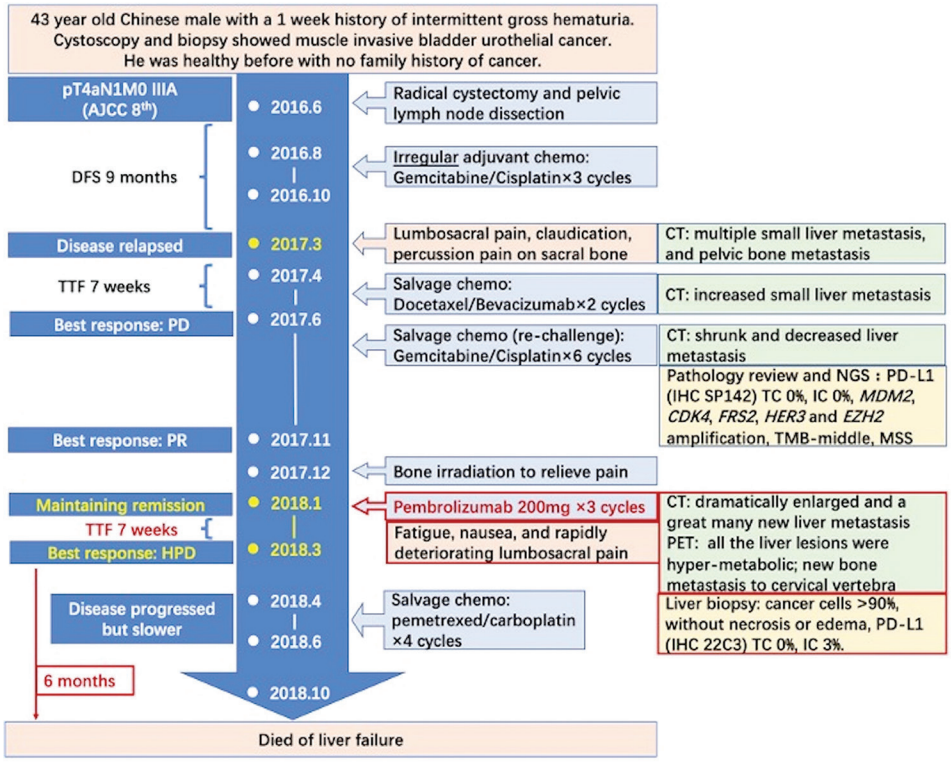

Figure 3: Timeline of the interventions and outcomes. AJCC: American Joint Committee on Cancer staging system, DFS: Disease-free survival, TTF: Time to treatment failure, PD: Progressive disease, PR: Partial remission, HPD: Hyperprogressive disease, CT: Computed tomography, PET: Positron-emission tomography, IHC: Immunohistochemistry, NGS: Next-generation sequencing, PD-L1: Programmed cell death ligand 1, *MDM2*: *Murine double minute gene 2*, *CDK4*: *Cell cycle-dependent kinase 4*, HER3: Human epidermal growth factor receptor 3, *FRS2*: *Fibroblast growth factor receptor substrate 2*, *EZH2*: *Enhancer of Zeste Homolog 2*

ability of predicting benefit from ICIs treatment in many cancer types. However, opinions on negative predictive biomarkers remain divided, especially those associated with HPD, such as *MDM2* amplification, which this patient harbored.[8,9] In a pan-cancer analysis, patients with *MDM2* or its homolog *MDM4* amplification responded poorly to ICIs with shorter OS, compared with those without the amplification.[10] Still, there has been, by now, neither clinical evidence nor molecular mechanism sufficient enough to establish a causal relationship between *MDM2* amplification and HPD, with only eight cases published involving bladder cancer (two cases), lung cancer (three cases), esophagogastric junction adenocarcinoma, breast cancer, endometrial stromal sarcoma, and melanoma.[8,11-14] A hypothesis of the underlying mechanism has been proposed that the expression of the amplified *MDM2* gene might be further augmented by the interferon (IFN) regulatory factor-8, a transcription factor upregulated by IFN-gamma (IFN-γ) through JAK/STAT signaling in tumor cells.[15] The *MDM2* might impair the patient's response to the ICI treatment by influencing the function of P53, and its inhibitor APG-115 was able to enhance the antitumor activity of anti-PD-1 agents by remodeling the tumor microenvironment, including repolarizing macrophages to the anti-tumor M1 phenotype, activating T cells, and upregulating PD-L1 expression on tumor cells.[15] What's more, co-altered genes with *MDM2* amplification might also play critical roles in resistance to the anti-PD-1 immunotherapy or HPD. It was reported that up to 99% of cancers with *MDM2* amplification had co-altered genes, involving the cell cycle (68.5%), tyrosine kinase (37.9%), *PI3K* pathway (25.4%), TP53 pathway (24.9%), and MAPK pathway (23.6%).[11] The patient in this report had co-amplification of *CDK4*, one of the key drivers of the cell cycle, and *FRS2*, which could transduce signals from the fibroblast growth factor to the downstream *MAPK* pathway.[16] Both *CDK4* and *FRS2* resided close to *MDM2* on chromosome 12q15.

Re-biopsy should also be emphasized not only for differential diagnosis from pseudoprogression but also for exploration of the underlying mechanisms of resistance to ICIs or HPD. The immune cell signatures of the post-ICIs treatment samples were more immunosuppressive than those before treatment.[17] Furthermore, pro-tumorigenic immune cells were discovered in HPD specimens, such as specific M2-like tumor-associated macrophages that were reprogrammed by their crystallizable fragment receptors binding with the Fc domain of PD-1 antibodies, and the proliferation and suppressive functions of regulatory T-cells (Tregs) got enhanced.[18,19] Comparison of mutations

and transcriptomes between pre- and post-ICIs treatments also gave hints of HPD mechanisms, including more deleterious somatic mutations (*TSC2* and *VHL* mutations), upregulation of oncogenic pathways (*IGF-1*, *ERK/MAPK*, *PI3K/AKT*, and *TGF-β*), and downexpression of the antigen processing genes in the HLA family.[17] It was a pity that the tissue obtained from the liver metastasis in our case was not enough for further investigations.

To our knowledge, it was the earliest report of HPD in the setting of switch maintenance with anti-PD-1 monotherapy in patients whose disease has been controlled. And once more, the case enhances the importance of patient selection for ICIs treatment, calling for further investigation into potential clinical and molecular predictors, such as PD-L1 expression, liver metastasis, and *MDM2* amplification.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal patient identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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