Case Report

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Nivolumab Plus SOX as First-Line Treatment Achieved Partial Response in Micro-Satellite Stable Metastatic Hepatoid Adenocarcinoma of Stoma: A Case Report

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Keywords:

Hepatoid adenocarcinoma, Gastric cancer, Immunotherapy, AFP, PD-1

Abbreviations:

MSI: microsatellite instability; MSS: micro-satellite stable; MSI-H: microsatellite instability highly; TMB: tumor mutation burden; CPS: combined positive score; PR: partial response; CR: complete response; PD: progressive disease; N.D: no description.

1. Abstract

1.1. Background: Hepatoid Adenocarcinoma of the Stomach (HAS) is a unique and rare subtype of gastric cancer with poor prognosis and hepatocellular carcinoma-like features. However, the standard therapies are still in the development stage.

1.2. Case report: Here, we present a 61-year-old male patient with Micro-Satellite Stable (MSS) metastatic HAS who had a tumor mutation burden of 10.65 mut/Mb. As first-line treatment, the patient received a PD-1 inhibitor in combination with chemotherapy (nivolumab plus S-1 and oxaliplatin) and sustained an 8-month progression-free survival. The second-line treatment, durvalumab (a PD-L1 inhibitor) combined albumin-bound paclitaxel and capecitabine for four cycles resulted in disease progression. Surprisingly, the serum Alpha-Fetal Protein (AFP) level did not alter over time while the tumor became larger or smaller. Additionally, we reviewed some hepatoid adenocarcinoma in other organs that had been treated with immune checkpoint inhibitors.

1.3. Conclusion: PD-1 inhibitor in combination with chemotherapy could be an alternative for metastatic HAS, especially for patients diagnosed as highly micro-satellite instable, and PD-L1 inhibitor did not recommend to the following therapy.

2. Introduction

Hepatoid Adenocarcinoma of the Stomach (HAS) is special and rare subtype of gastric cancer, which mimics hepatocellular-carcinoma-like morphology. It accounts for 0.38–1.6% of all gastric cancers, and it is prone to liver and lymph node metastasis with a poor prognosis [1]. Although the treatment approaches mainly reference to guideline of common gastric cancers, no standard therapies for HAS are recommended. Traditionally, platinum-based chemotherapy is judged as an optional first-line systemic regimen for metastatic HAS, but the effect is not satisfactory, more effective treatment needs to be explored. Nowadays, Immune Checkpoint Inhibitors (ICI) including PD-L1 inhibitors and PD-1 inhibitors have made remarkable success in cancer therapy. To the best of our knowledge, it's the first report about effectiveness of PD-1 inhibitors plus chemotherapy as first-line treatment followed by PD-L1 inhibitors plus chemotherapy as second-line treatment for metastatic HAS. Here, we present a case of a HAS patient who has been maintained a partial response to nivolumab plus SOX for 8 months and discuss the effect of immunotherapy for this kind of cancer by reviewing related literature.

3. Case Report

A 61-year-old male complained of elevated serum Alpha-Fetal Pro-

tein (AFP) when annual physical check-up and was admitted to the gastroenterology department of Beijing friendship hospital in October 2020. He had no history of hepatitis and other associated symptom. The physical examination revealed no problem. The laboratory investigation showed negative hepatitis B virus, and normal carbohydrate antigen 19 9. The serum Alpha-Fetal Protein (AFP) and Carcinoembryonic Antigen (CEA) was elevated to 933.57 ng/ml and 6.39 ng/ml respectively. Enhanced Magnetic Resonance Imaging (MRI) of liver or enhanced abdominal Computed Tomography (CT) scans ruled out liver lesions. But the MRI revealed that a nodule measuring 3.9cm×1.5cm was above the head of pancreas (Figure 1). Moreover, CT scan detected diffuse thickening of gastric antrum (Figure 1). Then a gastroduodenoscopy underwent for further diagnosis and biopsy. The endoscopy indicated gastric antral cancer, and the Borrmann classification was type III (Figure 1). Pathological examination of the biopsy found that the gastric adenocarcinoma was composed of large cells, with large nucleus, eosinophilic cytoplasm, and few hyaline balls (Figure 2). Immunohistochemistry (IHC) staining of the biopsy showed positive for SALL4, AFP, GPC3, CK and CEA, Ki-67 >80% (Figure 2). Thus, the primary diagnosis, HAS, was established.

The patient underwent a laparoscopic exploration. Unluckily, the tumor had invaded into gastric wall and hepatoduodenal ligament, even it had spread to all of peritoneum. And metastatic lymph nodes of NO.7 and NO.8 and NO.9 were gathered together. We removed an omental nodule for pathological examination and closed abdominal wall. The result of histological exam of omental nodule was consistent with that of biopsy of gastric antrum. Tumor was confirmed as primary HAS, stage IV. TNM staging: cT4aN2M1.

In order to find a more efficient therapeutic strategy, targeted NGS test of 808 cancer-related genes was applied to the fresh tumor samples (Table 1). A TP53 gene exon7 p. G245D mutation was revealed at a mutant allele frequency 18.24%. ERBB2 gene expression was negative. This patient did not harbor high tumor mutation burden (TMB) (10.65 mut/Mb). Tumor Micro-Satellite Instability (MSI) status was stable (MSS). The tumor showed tumor cell PD-L1 expression less than 1% (Table 1). Despite the disappointing biomarkers, we still recommended a PD-1 inhibitor combined with chemotherapy to this patient. The patient received 200mg of nivolumab plus SOX every 3 weeks (intravenous oxaliplatin 200 mg and nivolumab 200mg on day 1, oral S-1 40 mg twice daily from day 1 to 14) for 6 cycles from November 2020 to April 2021. The first evaluation after 3 cycles by CT showed a partial response on the lymph node (the maximum diameter of the nodule over the pancreas decreased from 3.9 cm to 2.8 cm) (Figure 3) and AFP declined sharply from 933.57 ng/mL to 54.43 ng/mL (Figure 4). Although AFP increased to 434.2 ng/mL gradually, but the nodule did not grow. The main adverse events were grade 1 of leukopenia and grade 2 of thrombocytopenia, which appeared at the last cycle. A maintenance therapy by S-1 and nivolumab was administrated from April 2021 to July 2021. However, the AFP level increased to 1875.11 ng/mL and CT scan confirmed Progressive Disease (PD) with appearance of a new metastasis on liver after 4 cycles. During this stage, CEA has dropped to normal range at the beginning until PD (Figure 4). A second line treatment, durvalumab (a PD-L1 inhibitor) in combination with albumin-bound paclitaxel and capecitabine, was carried out and led to a novel decrease of AFP levels (1492.49 ng/ml). Unfortunately, the tumor turned PD 3 months later. scheduled an abdominal CT showed progression at the lymph node, especially at the liver. By the time, symptomatology was significant for decreased appetite and weakness. Patient therapy after 4 cycles of PD-L1 and chemotherapy had been switched to 3rd line treatment with RC48-ADC, a HER2-targeting antibody–drug conjugate. Patient's symptomatology didn't change the worse. To date, the patient's the progress-free survival time (PFS) of first-line treatment and the Overall Survival time (OS) were 8 months and 14 months respectively, with an ECOG performance status of 1.

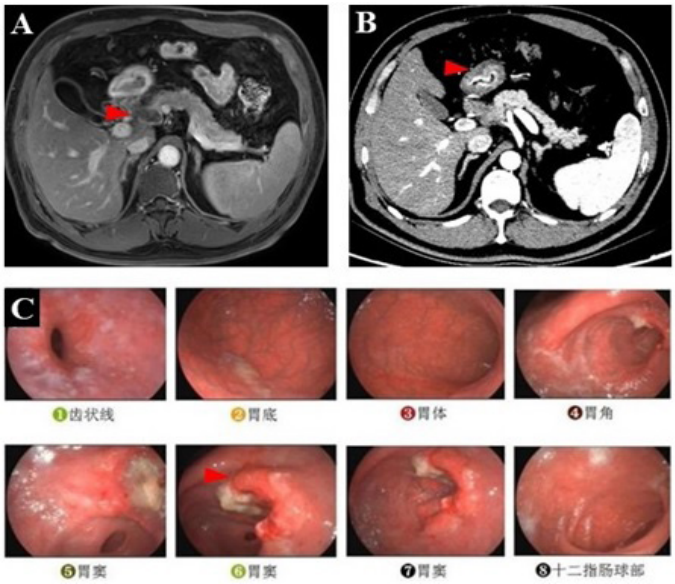

Figure 1: Imaging before laparoscopic exploration. (A) MRI showed a nodule measuring 3.9cm×1.5cm was above the head of pancreas. (B) CT detected diffuse thickening of gastric antrum. (C) Gastroduodenoscopy indicated gastric antral cancer, and the Borrmann classification was type III.

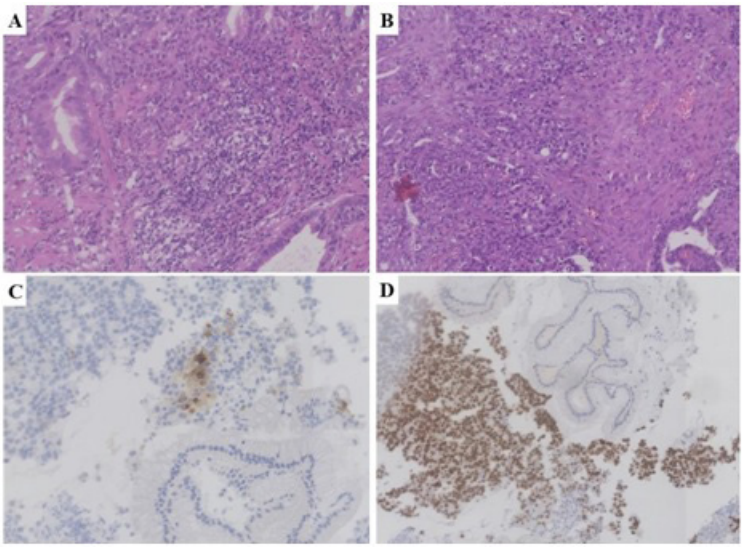

Figure 2: H&E and IHC staining of gastric antrum and omental nodule. (A) and (B) showed that the morphologic features mimicked hepatocellular carcinoma in gastric antrum and omental nodule, separately. (C) and (D) indicated positive for AFP and SALL4 of omental nodule biopsy by IHC respectively.

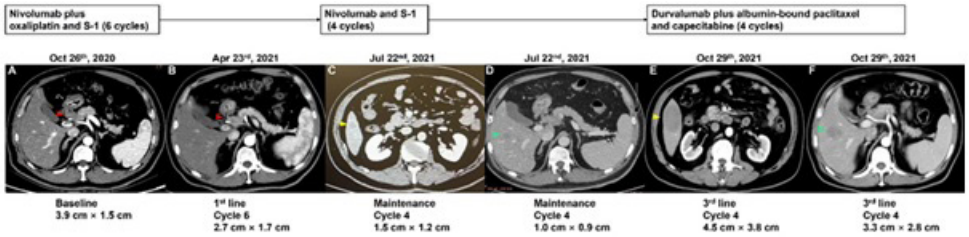

Figure 3: CT scans of metastasis at different stages during treatment. (A) showed the baseline of tumor before treatment. (B) manifested the change of nodule after 6-cycles nivolumab plus SOX. (C) to (D) manifested two new metastases on liver (marked by green arrow and yellow arrow) after 4-cycles of maintenance therapy, nivolumab and S-1. (E) to (F) manifested the enlarged liver metastases after 4-cycles durvalumab in combination with albumin-bound paclitaxel and capecitabine.

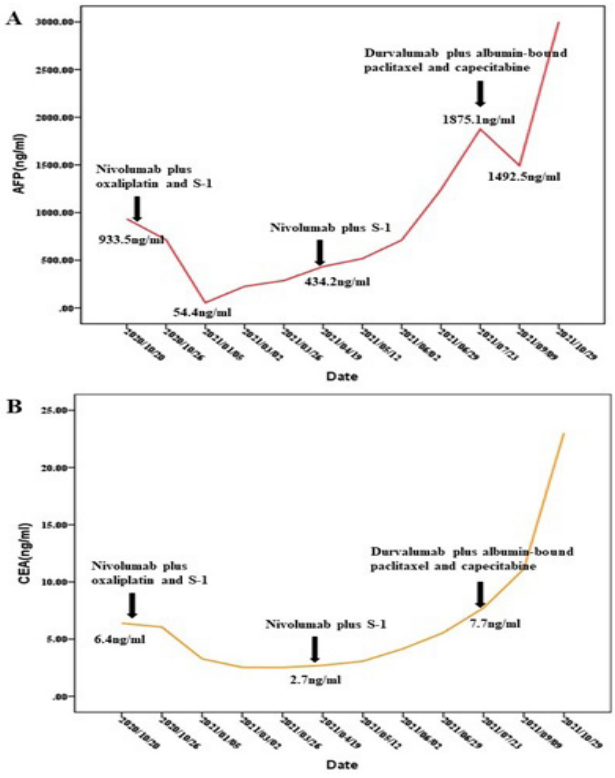

Figure 4: The line charts of changing trend of serum AFP (A) and CEA (B) at different stages during treatment.

Table 1: NGS and immunohistochemistry staining of PD-L1 expression in Fresh Tumor Tissue

	Variation	Nucleotide Change	Mutant allele frequency
TP53	p.G245D	c.734G>A	18.24%
TSC2	p.L1080X	c.3239T>G	3%
MSI	MSS		
TPS	< 1%		
TMB	10.65 mut/Mb		

Note: The expression of PD-L1 was evaluated by TPS.

Abbreviations: NGS, Next-generation sequencing; MSI, microsatellite instability; MSS, micro-satellite stable; TPS, tumor Proportion Score; TMB, tumor mutation burden.

Table 2: All Cases of Hepatoid Adenocarcinoma Treated with Immunotherapy

Autor, Publication Year	Age(year)	Gender	Tumor location	Metastasis	MSI	TMB (mut/Mb)	PD-L1 expression	Treatment	Line	The best response
Lagos, G. G, 2020[10]	54	male	lung	pleura, lymph nodes	N.D	20	＜5%	carboplatin, paclitaxel, pembrolizumab	first	PR
Zou, M, 2019[16]	28	male	peritoneum and omentum	N.D	N.D	58	＜1%	immunotherapy	later	N.D
Chen L, 2020[11]	65	male	lung	bone	MSS	8	≥1%	docetaxel plus sintilimab	later	PR
Basse, V, 2018[12]	43	N.D	lung	mediastinum, cerebrum, adrenal gland, and bone	MSI-H	N.D	negative	durvalumab	third	PR
Zhuansun, Y, 2021[13]	61	male	lung	right parathyroid lymph node	N.D	N.D	N.D	chemotherapy and anti-PD-1 antibody	first	N.D
Tonyali, O, 2020[15]	62	female	lung	N.D	N.D	N.D	N.D	nivolumab	second	N.D
El Khoury, 2019[14]	59	male	lung	mediastinum, adrenal gland,	N.D	N.D	≥50%	pembrolizumab plus cisplatin–etoposide	first	PR
Li, W, 2020[8]										
No.13	age <=60y (n=1), age>60y (n=6)	male	gastroesophageal junction(n=1), stomach(n=6)	liver (n=6), none (n=1)	MSS	N.D	CPS=1	nivolumab plus chemotherapy	first	PR
No.14		male				N.D	CPS=＜1			PR
No.15		male				N.D	CPS=1			CR
No.16		male				N.D	CPS=1			PR
No.17		male				N.D	CPS=1			PR
No.18		male				N.D	CPS=1			PR
No.20		male				N.D	CPS=10			PD

4. Discussion

Most previous studies have reported that patients with HAS have an unfavorable prognosis and a low 3-year survival rate. The reported survival for patients with unresectable HAS has generally been 3 to 14 months treated with chemotherapy [1]. PD-L1 expression, TMB and statue of MSI are biomarker to predict response of immunotherapy. REGONIVO trial and REGOMUNE trial [2, 3] manifested that a minority of patients with no positive biomarker could obtain disease control even response from immunotherapy. ATTRACTION-4 [4] and CheckMate 649 study [5] both showed that nivolumab plus chemotherapy were superior to chemotherapy alone as first-line treatment in all enrolled patients with metastatic gastric cancer. Additionally, some studies [6, 7] provided evidence that PD-L1 inhibitors can prolong PFS in lung adenocarcinoma with TP53 or/ and KRAS mutation. Therefore, our patient was first treated with nivolumab plus sox despite the TMB was as not high as 15 mut/Mb and other biomarkers were negative. We observed a partial response on imaging evaluation after first 3 cycles, but the tumor kept stable status until 3 cycles of maintenance therapy off. The patient's PFS time reached 8 months. Tianshu Liu's study [8] showed that the chemotherapy alone obviously inferior to immunotherapy plus chemotherapy (ORR 21.4% vs 85.7%, mPFS 4.3m vs 22.0m) in MSS advanced AFP-producing gastric cancer/HAS. In this study, 6 of 7 patients had positive PD-L1 in immunotherapy group, while only 4 of 14 patients had positive PD-L1 in chemotherapy group. It may could explain the significant difference of outcomes between two groups. Interestingly, one patient with strong positive PD-L1 exhibited hyper-progressive disease, and it is noted that one patient harbored negative PD-L1 had achieved PR for 6 months in Wei Li's study [8]. Our case also had a relatively longer PFS. It suggests that a few of PD-L1-negative patients could benefit from the combination of PD-1 antibody and chemotherapy. The success of this treatment strategy may result from the ability of chemotherapy-induced live injured cells promoting function of dendritic cell mediated T cell antitumor responses, which assists with ICIs to improve immune

response [9]. In review of some hepatoid adenocarcinoma cases occurred at other organ including lung [10-15] and peritoneum and omentum [16], every one of them had at least one of biomarkers representing significant shrinkage of tumor treated by immunotherapy (Table 2). It indicates that traditional immune biomarker can predict effect of ICIs on hepatoid adenocarcinoma despite which organ it originates from. Nevertheless, application of this treatment strategy on patients with no positive biomarker needs more validation.

What confused us about our case is that the patient's serum AFP level was increasing during first-line treatment when the target tumor was in stable status, and the transient decrease of AFP level occurred at beginning of second-line treatment, but the tumor was confirmed as progress disease finally. Only one case found elevated AFP with no evidence of progress on PET-CT, most case reports agreed that AFP serum level is useful for response evaluation [10-14]. While it's hard to judge whether the tumor progressed or not depending on only changed AFP when there is no evidence of imaging. In addition, the CEA also changed over time when tumor altered, which indicated that this tumor marker can be a reference of evaluation.

Inhibitors of PD-1 or PD-L1 are used to break the interaction between PD-1 and PD-L1 in tumor microenvironment, through which to avoid tumor immune escape. There were two cases [17, 18] reports reported patients who experienced a complete response treated with anti-PD-L1 antibody following disease progression of PD-1 inhibitor. Whereas a small retrospective study [19] found that this strategy had only limited benefit for non-small cell lung cancer. PD-1 and PD-L1 inhibitors are thought to be equally effective, but they indeed have some different mechanism. PD-1 inhibitors work by blocking the interaction of PD-1 with PD-L1 and PD-L2, which regulate T cell activation negatively. PD-L1 inhibitors prevent PD-L1 from binding to its receptors, PD-1 and CD80. CD80, a co-stimulatory receptor, which may also play a role in regulating negatively memory and effector T cells. Overexpression of CD-80 has been proposed as one of the causes for PD-1 inhibitor resistance [20]. And PD-L1 reduced the incidence of interstitial pneumonia. To prolong our patient's survival and explore more effective treatment, we tried this strategy but failed finally, which symbolled the primary resistance to these agents. The anti-angiogenesis targeting VEGFR-2 may also be the next option for this patient. Individual cases treated with apatinib [8] or ramucirumab monotherapy [21] after failure of chemotherapy showed significant clinical response, even the patient [8] suffered HRD mentioned above still had benefited from apatinib. Hence, there are some potential alternations for our patient in next stage. We hope that he could live longer with a better quality of life.

5. Conclusion

In summary, we described a metastatic MSS HAS patient treated with nivolumab plus SOX following maintenance with nivolumab plus S-1 as first-line treatment achieved PFS of 8 months, which provides a potential treatment for this kind of patients with slightly side effect.

6. Acknowledgment

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