Journal of Cancer Research and Practice

journal homepage: www.ejcrp.org

Case Report

Durable Response of Immune Checkpoint Inhibitor for a Patient with Advanced Gastric Adenosquamous Carcinoma

Cheng-Lun Lai[1]*, Ming-Huang Chen[2,3]

[1]Division of Hematology/Medical Oncology, Department of Medicine, Taichung Veterans General Hospital, Taichung, Taiwan
[2]Department of Oncology, Center of Immuno-Oncology, Taipei Veterans General Hospital, Taipei, Taiwan
[3]School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

Abstract

Gastric adenosquamous carcinoma (GASC) is an extremely rare malignancy of the stomach. It is generally diagnosed at an advanced stage and is associated with a poor prognosis. Notably, the standard treatments for GASC remain undetermined because of the condition's rarity. In this report, we present a patient diagnosed with advanced GASC with positive predictive biomarkers for immune checkpoint inhibitors (ICIs), who achieved a durable response through nivolumab monotherapy. We also review and discuss the management of GASC and possible roles of ICIs in gastric cancers.

Keywords: Combined positive score, gastric adenosquamous carcinoma, immune checkpoint inhibitor, microsatellite instability, tumor mutation burden

Introduction

Among primary gastric malignancies, gastric adenocarcinoma (GAC) is the most common pathologic type, whereas gastric adenosquamous carcinoma (GASC) is extremely rare, accounting for <1% of cases.[1] The diagnosis of GASC is based on the coexistence of adenocarcinoma and squamous cell carcinoma components within the same tumor.[2] Because GASC is rare, most relevant literature is in the form of case reports or series, involving small patient numbers, and therefore, standard treatments have not been established. In these studies, GASC presented at an advanced initial stage and with a poorer prognosis than GAC.[3] In this study, we present a patient with advanced GASC with positive predictive biomarkers for immune checkpoint inhibitors (ICIs), who underwent nivolumab monotherapy with a durable response.

Submitted: 21-Feb-2022 **Revised:** 20-Jun-2022
Accepted: 05-Jul-2022 **Published:** 06-Dec-2022

Access this article online

Quick Response Code:

Website: www.ejcrp.org

DOI: 10.4103/2311-3006.362634

Case Report

In March 2020, we examined a 71-year-old male complaining of intermittent epigastric pain and tarry stool that had lasted for approximately 2 months. The patient also reported

Address for correspondence: Dr. Cheng-Lun Lai, Division of Hematology/Medical Oncology, Department of Medicine, Taichung Veterans General Hospital, 1650 Taiwan Boulevard Sect. 4, Taichung, Taiwan 407219.
E-mail: leader20030@hotmail.com

How to cite this article: Lai CL, Chen MH. Durable response of immune checkpoint inhibitor for a patient with advanced gastric adenosquamous carcinoma. J Cancer Res Pract 2022;9:145-8.

experiencing indigestion, decreased appetite, and abdominal distension for approximately 1 year. The patient had no underlying comorbidities and the initial laboratory data revealed microcytic anemia (hemoglobin 5.6 g/dL; normal range: 14–18 g/dL, mean corpuscular volume 78.7/fL; normal range: 80.0–100.0/fL) without liver and kidney impairment. The physical examination was not remarkable except for conjunctival pallor.

Duodenoscopy revealed a large ulcerated mass in the gastric antrum of the lesser curvature [Figure 1]. Endoscopic biopsy of the ulcerated lesion was arranged, and the pathology revealed poorly differentiated GASC [Figure 2a and b]. The tumor cells with squamous differentiation were immunoreactive for p40, whereas the adenocarcinoma components were positive for hepatocyte nuclear factor 4 alpha antibodies [Figure 2c]. Additional immunohistochemistry (IHC) demonstrated the loss of human MutL homolog 1 and postmeiotic segregation increased 2 and increased programmed death-ligand 1 (PD-L1) expression (combined positive score [CPS]: 10%, Dako 22C3 IHC assay, Dako, Carpinteria, CA) [Figure 2d] but was negative for synaptophysin, human epidermal growth factor receptor-2 (HER-2), and v-raf murine sarcoma viral oncogene homolog B1 V600E. Using a commercially available gene sequencing panel (ACTOnco, ACT Genomics, Taipei, Taiwan), the tumor mutational burden (TMB) was 28.6 mutations per megabase (muts/Mb). Contrast-enhanced computed tomography (CT) of the abdomen revealed irregular wall thickening at the gastric antrum, measuring approximately 7 cm and involving the posterior wall and lesser curvature and multiple regional metastatic lymphadenopathies [Figure 3a]. The patient underwent exploratory laparotomy on April 7, 2020. However, because of tumor invasion of the esophagus, liver, duodenum, mesocolon, and retroperitoneal space, tumor excision was not performed. The final stage identified was cT4bN3M0, Stage IVA, according to the American Joint Committee on Cancer (Eighth Edition) Cancer Staging Manual (2017).

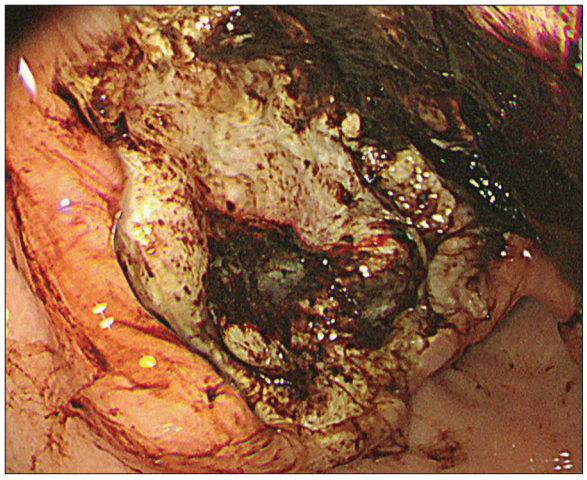

Figure 1: Large ulcerated mass in the gastric antrum of the lesser curvature revealed through duodenoscopy

Due to the patient's age and unresectable disease, the patient received local radiotherapy over the gross tumor with a total of 50.40 Gy in 28 fractions from April 22, 2020, to May 29, 2020. The patient declined systemic chemotherapy due to old age and concern of side effects. Because the patient had positive predictive biomarkers for ICIs (CPS = 10%, TMB-H and microsatellite instability-high [MSI-H]), nivolumab (2 mg/kg) has been prescribed every 2 weeks since April 25, 2020. After four cycles of nivolumab, at July 1, 2020, abdominal CT scan showed regression in the tumor [Figure 3b]. At April 21, 2021, abdominal CT scans still revealed a stationary condition [Figure 3c]. A progression-free survival (PFS) of 12 months was achieved. The carcinoembryonic antigen levels did not exceed 5 ng/mL and the anemia condition was improved without red blood cell transfusion dependence during the following periods. No immune-related adverse events have been identified during the ICI treatment period.

Discussion

GASC is a rare gastric malignancy and is generally diagnosed at an advanced stage. It has been reported to have a poorer prognosis than GAC.[1,3] Due to its rarity, no standard treatment for primary GASC has been established. The current National Comprehensive Cancer Network (NCCN) guidelines for gastric cancer focus on GAC rather than on GASC.[4] Radical surgical resection remains the curative management option for local GASC. No standard neoadjuvant or adjuvant therapeutic approaches have been established, but adjuvant chemotherapy and/or radiotherapy may improve the patient's survival.[5]

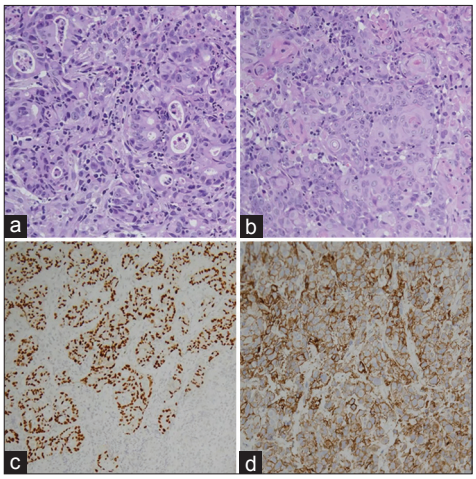

Figure 2: Pathohistological findings of the gastric tumor biopsy. The tumor was composed of nests of hyperchromatic and pleomorphic neoplastic cells in solid and glandular patterns. (a) Component of adenocarcinoma. (b) Component of squamous cell carcinoma. (c) The component of adenocarcinoma showed HNF4α expression by immunohistochemistry. (d) Increased PD-L1 expression by immunohistochemistry. HNF4 α: Hepatocyte nuclear factor 4 alpha, PD-L1: Programmed death-ligand 1

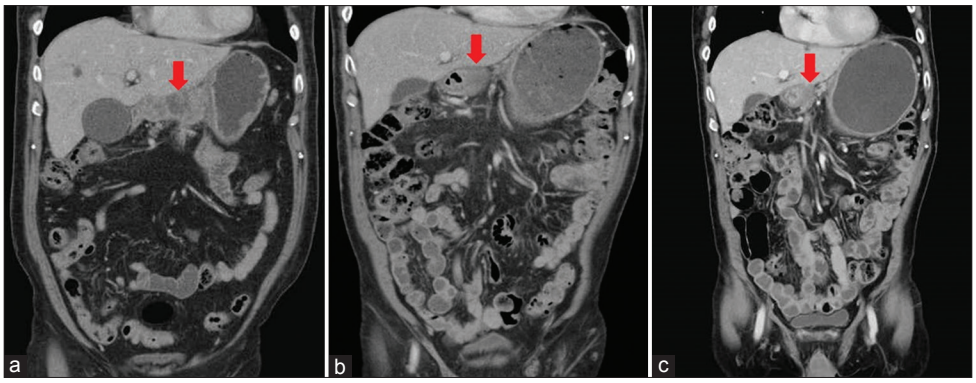

Figure 3: (a) Coronary image of an abdominal CT scan from April 2020 revealing an irregular wall thickening at the gastric antrum. (b) Coronary image of an abdominal CT scan from July 2020 revealing a regressive change in the irregular wall thickening at the gastric antrum. (c) Coronary image of an abdominal CT scan from April 2021 revealing a stable condition in the irregular wall thickening at the gastric antrum. CT: Computed tomography

Because the squamous carcinoma component in GASC is sensitive to radiotherapy, radiotherapy can be considered for palliative care and symptom relief.[5,6] In other studies, most patients with GASC have received the same chemotherapy regimen as for GAC.[5,7-10] Based on the NCCN guidelines, the preferred first-line chemotherapy regimens for locally advanced or metastatic GAC involve fluoropyrimidine combined with a platinum agent. The addition of trastuzumab is recommended for HER2-positive metastatic disease.[4]

In recent years, ICIs have demonstrated their efficacy in many types of solid malignancies. ICIs, including pembrolizumab and nivolumab, are regarded as a novel treatment strategy for gastric, esophageal, and gastroesophageal cancers under different treatment settings. The CheckMate 649 trial revealed that first-line nivolumab combined with chemotherapy has survival benefits for patients with advanced gastric, gastroesophageal, or esophageal adenocarcinoma.[11] Nivolumab also prolonged survival in patients with heavily pretreated advanced gastric or gastroesophageal junction adenocarcinoma in the ATTRACTION-2 trial.[12]

The role of PD-L1 expression as a predictive biomarker for ICIs in gastric cancer remains undetermined. In the KEYNOTE-061 and KEYNOTE-062 trials, pembrolizumab was revealed to be noninferior to chemotherapy in patients with advanced gastric cancer with PD-L1 CPS ≥1. However, in a *post hoc* analysis, pembrolizumab was more effective in patients with PD-L1 CPS ≥10.[12] According to these trials, CPS ≥10 is a potential predictive biomarker for ICIs in gastric cancers.

ICIs are considered more effective in malignancies with DNA mismatch repair (dMMR), MSI-H, and TMB-H.[13,14] In the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 trials, pembrolizumab was proved to be more effective than chemotherapy in patients with MSI-H gastric cancer.[12] In the KEYNOTE-158 trial, pembrolizumab monotherapy demonstrated an overall response rate of 45.8% (95% confidence interval [CI]: 25.6–67.2) and median PFS of 11.0 months (95% CI: 2.1–not reached) in patients with advanced and previously treated MSI-H and dMMR gastric cancer. In addition, TMB-H (≥10 mut/Mb) status could have a strong response to pembrolizumab monotherapy. Objective responses were observed in 29% of patients in the TMB-H group compared with 6% of patients in the non-TMB-H group.[15]

In this patient, a combination of radiotherapy and ICIs is effective for both local and systemic disease control. The impact of radiotherapy on ICIs is still unclear, but the local effect of radiation may change the tumor microenvironment and possibly increase the immune response are supposed.[16,17] Besides, the example of our patients also shows that with appropriate supportive care, the strategy of coadministration of radiotherapy and ICI may not increase additional immune-related adverse events.

Although several clinical trials have demonstrated that ICIs can provide clinical benefits for GAC, and different clinical trials have proposed their own predictive biomarkers, the efficacy of ICI in rare GASC patients is still uncertain, and the predictive biomarkers are inconclusive. However, our case used several predictive biomarkers commonly used in gastrointestinal tumors,[18] and we did see a durable response with nivolumab as a monotherapy strategy.

In conclusion, we presented a patient with GASC with predictive biomarkers for ICIs (including IHC stain results, TMB level, and MSI status) who achieved a durable response through nivolumab monotherapy. Our results indicate that ICIs can be an effective treatment for GASC when predictive biomarkers are present.

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Ming-Huang Chen, an editorial board member at *Journal of Cancer Research and Practice*, had no role in the peer review

process of or decision to publish this article. The other author declared no conflicts of interest in writing this paper.

References

1. Chen YY, Li AF, Huang KH, Lan YT, Chen MH, Chao Y, *et al.* Adenosquamous carcinoma of the stomach and review of the literature. Pathol Oncol Res 2015;21:547-51.
2. Bae HI, Seo AN. Early gastric adenosquamous carcinoma resected using endoscopic submucosal dissection. Case Rep Gastroenterol 2019;13:165-72.
3. Ge Y, Lin L, Ma X, Luo D, Shi L, Jiang M, *et al.* Adenosquamous carcinoma of the stomach: A population-based study from the SEER database. J Cancer 2019;10:5705-13.
4. Gastric Cancer (Version 2.2022). Available from: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. [Last accessed on 2022 Jan 11].
5. Chen H, Shen C, Yin R, Yin Y, Chen J, Han L, *et al.* Clinicopathological characteristics, diagnosis, treatment, and outcomes of primary gastric adenosquamous carcinoma. World J Surg Oncol 2015;13:136.
6. Feng F, Zheng G, Qi J, Xu G, Wang F, Wang Q, *et al.* Clinicopathological features and prognosis of gastric adenosquamous carcinoma. Sci Rep 2017;7:4597.
7. Ebi M, Shimura T, Yamada S, Hirata Y, Tsukamoto H, Okamoto Y, *et al.* A patient with gastric adenosquamous carcinoma with intraperitoneal free cancer cells who remained recurrence-free with postoperative S-1 chemotherapy. Intern Med 2012;51:3125-9.
8. Saito S, Hosoya Y, Morishima K, Ui T, Haruta H, Kurashina K, *et al.* A clinicopathological and immunohistochemical study of gastric cancer with squamous cell carcinoma components: A clinically aggressive tumor. J Dig Dis 2012;13:407-13.
9. Kadowaki S, Yatabe Y, Nitta S, Ito Y, Muro K. Durable response of human epidermal growth factor receptor-2-positive gastric adenosquamous carcinoma to trastuzumab-based chemotherapy. Case Rep Oncol 2014;7:210-6.
10. Tohma T, Yamamoto Y, Seki Y, Takaishi S, Sakuma Y, Funami Y, *et al.* Weekly paclitaxel therapy is effective for gastric adenosquamous carcinoma: A case report. Hepatogastroenterology 2009;56:568-70.
11. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, *et al.* First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): A randomised, open-label, phase 3 trial. Lancet 2021;398:27-40.
12. Kono K, Nakajima S, Mimura K. Current status of immune checkpoint inhibitors for gastric cancer. Gastric Cancer 2020;23:565-78.
13. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, *et al.* PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-20.
14. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. N Engl J Med 2017;377:2500-1.
15. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, *et al.* Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: Results from the phase II KEYNOTE-158 study. J Clin Oncol 2020;38:1-10.
16. Williamson CW, Sherer MV, Zamarin D, Sharabi AB, Dyer BA, Mell LK, *et al.* Immunotherapy and radiation therapy sequencing: State of the data on timing, efficacy, and safety. Cancer 2021;127:1553-67.
17. Lee Y, Auh SL, Wang Y, Burnette B, Wang Y, Meng Y, *et al.* Therapeutic effects of ablative radiation on local tumor require CD8+T cells: Changing strategies for cancer treatment. Blood 2009;114:589-95.
18. Li M, Kaili D, Shi L. Biomarkers for response to immune checkpoint inhibitors in gastrointestinal cancers. World J Gastrointest Oncol 2022;14:19-37.