Journal of Cancer Research and Practice

journal homepage: www.ejcrp.org

Case Report

Hyperprogressive Disease after Nivolumab in a Patient with Microsatellite Instability-High Ampullary Cancer

Yi-Hsuan Lai[1], Shih-Hung Yang[2,3*]

[1]Division of Hematology and Oncology, Department of Internal Medicine, Taipei City Hospital, Renai Branch, Taipei, Taiwan
[2]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan
[3]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

Abstract

Ampullary cancer is a rare type of cancer with a limited choice of systemic therapy. Anti-programmed death-1 monoclonal antibodies have shown promising clinical benefits in multiple types of cancer, especially in tumors with microsatellite instability-high (MSI-H)/defective DNA mismatch repair and high tumor mutation burden. We report a case of a 61-year-old woman with MSI-H ampullary cancer who initially had slow progression without chemotherapy after recurrence. She experienced hyperprogressive disease with a dramatic deterioration of liver metastases following a short duration of nivolumab treatment.

Keywords: Ampullary cancer, hyperprogressive disease, microsatellite instability, nivolumab

Introduction

Ampullary cancer, a rare type of cancer and a heterogeneous entity is characterized by both intestinal and pancreatobiliary malignancies but an in-between prognosis.[1,2] The prognosis of ampullary cancer is much better than pancreatic cancer, and more than 50% of patients present with resectable disease and a 5-year survival rate of more than 50%.[2,3] However, adjuvant or neoadjuvant therapy plays a limited role in improving overall survival (OS) in patients with resectable disease.[4,5] In addition, the OS of patients with recurrent or advanced disease is poor, and the current choice of palliative chemotherapy is limited to gemcitabine-based chemotherapy.[6,7]

Immune checkpoint inhibitors, such as monoclonal antibodies (mAbs) targeting cytotoxic T-lymphocyte-associated antigen-4 and programmed death-1 (PD-1) and its ligand (PD-L1) have become an important component of standard therapy for various types of cancer.[8] These novel agents induce durable disease control by restoring an effective antitumor T-cell response.[8] However, only a fraction of patients obtain clinical benefits from these agents.[8] The predictive biomarkers for a response to immune checkpoint inhibitors remain inconsistent among different types of cancer. There is accumulating evidence that the clinical benefits of these agents are greater in tumors bearing high mutational burden (TMB).[9,10] In addition, the amounts of tumor-associated neoantigens and

Received: 29-Jul-2018 **Revised**: 18-Sep-2018 **Accepted:** 25-Sep-2018

Access this article online

Quick Response Code:

Website: www.ejcrp.org

DOI: 10.4103/JCRP.JCRP_9_18

Address for correspondence: Dr. Shih-Hung Yang, Department of Oncology, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 10002, Taiwan.
E-mail: b4401064@gmail.com

How to cite this article: Lai YH, Yang SH. Hyperprogressive disease after nivolumab in a patient with microsatellite instability-high ampullary cancer. J Cancer Res Pract 2019;6:50-4.

elicited anti-tumor T-cells have been reported to be higher in tumors with high TMB,[9-12] such as various cancer types with microsatellite instability-high (MSI-H) or deficient DNA mismatch repair (dMMR).[10] This is reflected by the tissue/site agnostic indication of pembrolizumab, a humanized IgG4 mAb against PD-1, approved by the US Food and Drug Administration for advanced solid tumors with MSI-H or dMMR.[13] Promising responses have also been observed in some patients with MSI-H or dMMR ampullary cancer or cholangiocarcinoma.[13]

Not all patients respond to immune checkpoint inhibitors, even those with high TMB.[8,13] In addition, distinct response patterns mimicking true progression, known as pseudoprogression and hyperprogressive disease (HPD), have been observed with these novel agents. Pseudoprogression is transient enlargement of tumors or the appearance of new lesions with a subsequent reduction in tumor burden, whereas HPD is true disease progression which exceeds the rate of tumor growth before treatment with immune checkpoint inhibitors.[14] How best to discriminate between these entities in daily clinical practice is challenging.

Nivolumab, a fully human IgG4 anti-PD-1 mAb, is approved for various cancer types,[8] including MSI-H or dMMR metastatic colorectal cancer.[15] Herein, we report a patient with MSI-H ampullary cancer who experienced HPD following nivolumab treatment.

Case Report

A 61-year-old woman presented with intermittent epigastric pain for 3 months. She also had tea-colored urine and weight loss of 6 kg in 4 months. She was admitted to the National Taiwan University Hospital, where abdominal magnetic resonance imaging revealed a focal ill-defined high-signal change at the pancreatic head with main pancreatic duct dilatation and a hepatic nodule. Endoscopic retrograde cholangiopancreatography revealed an ulcerative mass at the papilla of Vater. The pathology report of a biopsy was adenocarcinoma. Whipple procedure and atypical hepatectomy were performed in August 2016, and the surgical pathology revealed a moderately differentiated adenocarcinoma arising from the ampulla of Vater with local invasion into the pancreas, common bile duct and duodenal wall, and distant metastasis to the liver. Postoperative chemotherapy with S-1 was administered from October 2016 to January 2017. However, local recurrence with peritoneal metastases was identified in abdominal computed tomography (CT) in April 2017. Neither lung nor liver metastasis was identified [Figures 1a, 2a-c]. She chose palliative care due to malnutrition and chronic diarrhea unresponsive to pancreatic enzyme supplement. Malignant ascites had developed gradually since November 2017. A CT scan revealed the progression of the local recurrence with peritoneal metastases, ascites and a small liver metastasis [Figure 2d-f]. A tiny lung metastasis was also identified [Figure 1b]. She was in a chronic wasting

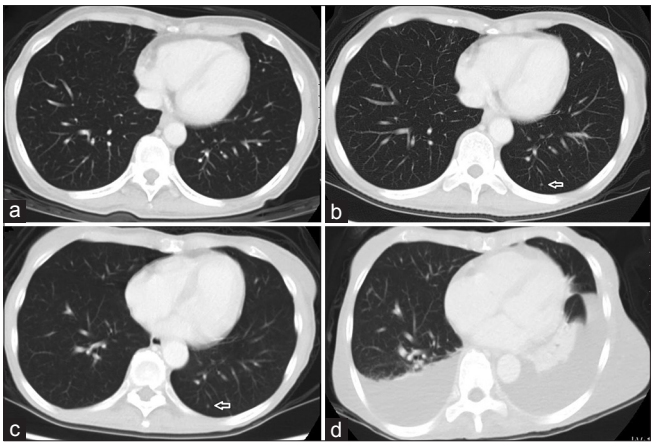

Figure 1: Computed tomography showing (a) no lung metastasis 12 months before nivolumab treatment; (b) a small lung metastasis (arrow) 6 months before nivolumab treatment; (c) a stable lung metastasis (arrow) before nivolumab treatment; (d) massive pleural effusion 3 weeks following the second dose of nivolumab

status, and pain control, oral diuretic therapy, and intermittent paracentesis were given without palliative chemotherapy. A CT scan in April 2018 revealed stable lung metastasis [Figure 1c] and slow disease progression of liver and peritoneal metastases [Figure 2g-i]. She requested immunotherapy with nivolumab after discussion. Meanwhile, the genetic test (Promega MSI Analysis System) reported MSI-H at all of the mononucleotide and pentanucleotide repeat markers. Two doses of nivolumab (2.5 mg/kg) were administered in May and June 2018. Intra-abdominal infections occurred immediately after both doses of nivolumab, and she was treated with antibiotics. Nevertheless, a CT scan performed 3 weeks following the second dose of nivolumab revealed massive pleural effusion [Figure 1d] and rapid progression of the liver metastases [Figure 2j-l]. In addition, the level of carbohydrate antigen 19-9 (CA 19-9) was elevated from 449.3 U/mL to 1297.1 U/mL before and after nivolumab therapy, respectively. Her clinical condition rapidly deteriorated, and she died from *Pseudomonas aeruginosa* bacteremia 4 weeks after the second dose of nivolumab therapy.

Discussion

In recent years, immune checkpoint inhibitors have become widely available, and physicians face great challenges in adequately managing the adverse events and evaluating the tumor response of these novel agents. How best to select patients who may potentially benefit from these agents is also challenging among different types of cancer and investigations are still ongoing. For example, the evaluation of PD-L1 expression with an immunohistochemistry (IHC) assay before the application of pembrolizumab in non-small cell lung cancer has become a widely accepted standard.[16]

The expression of PD-L1 has also been evaluated in ampullary cancer and extrahepatic cholangiocarcinoma.[17,18] With a cutoff point of 5% neoplastic cells as positive staining, 7

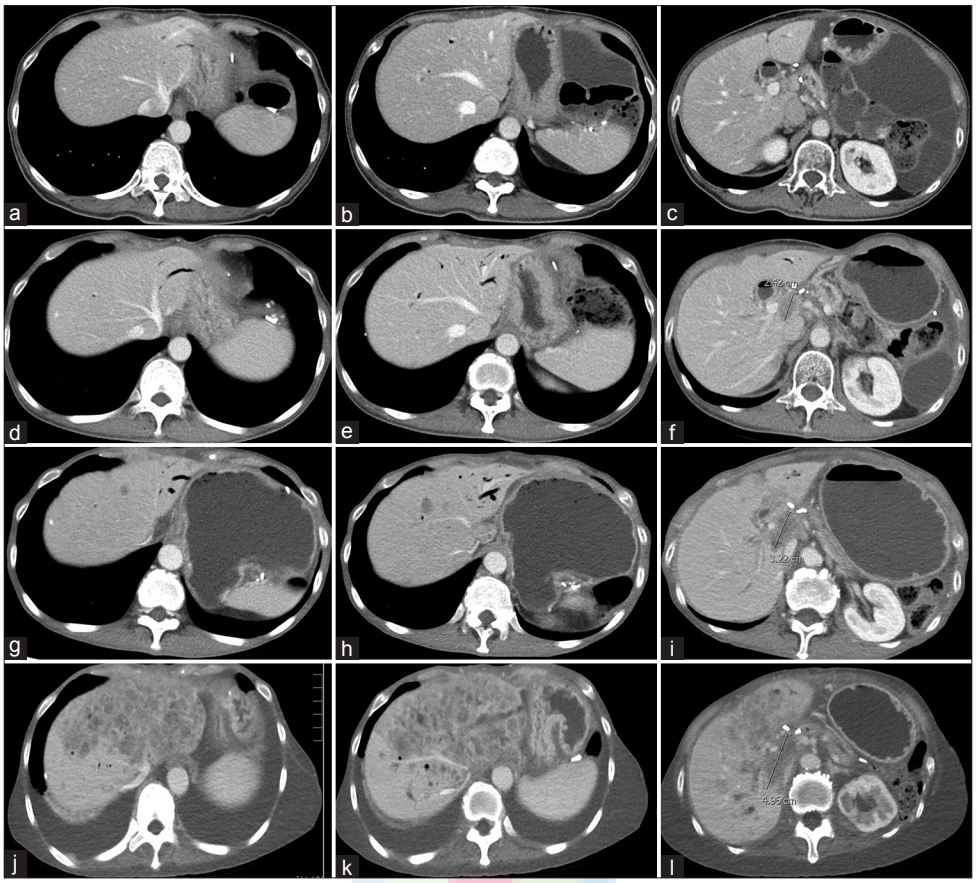

Figure 2: Computed tomography showing (a-c) intrahepatic duct dilatation without liver metastases 12 months before nivolumab treatment; (d-f) a small liver metastasis at the liver hilum (2.42 cm in diameter) 6 months before nivolumab treatment; (g-i) a larger liver tumor at the liver hilum (3.22 cm in diameter) with a few small new liver metastases before nivolumab treatment; (j-l) an even larger liver tumor at the liver hilum (4.96 cm in diameter) and dramatic progression in liver metastases 3 weeks following the second dose of nivolumab

of 26 (26.9%) patients with ampullary cancer had PD-L1 expression.[17] Two of the four patients with dMMR had a strong PD-L1 staining of the neoplastic epithelium.[17] The rate of PD-L1 expression was lower (8/69, 11.6%) in another study of extrahepatic cholangiocarcinoma evaluated with a semi-quantitative score incorporating both percentage and intensity of staining.[18] Although PD-L1 expression was of no prognostic significance, the combination of PD-L1 expression in tumor cells and low intratumoral infiltration of CD3+ T cells was associated with a poor prognosis.[18] In the biliary cohort of the KEYNOTE-028 study, 37 of 89 (42%) patients with biliary tract cancer had PD-L1-positive tumors.[19] However, ampullary cancer was excluded from this study.[19] Different methods of staining and interpretation and the various locations of tumors may partially explain the wide variation in PD-L1 expression.[17-19]

Only a small fraction of biliary tract cancer is responsive to anti-PD-1 mAb. In the KEYNOTE-028 study, the response rate and disease control rate of pembrolizumab were 17% and 34%, respectively.[19] Although the expression of PD-L1 was not evaluated in our patient, a prior study demonstrated strong PD-L1 staining in 2 of 4 patients with dMMR ampullary cancer.[17] Moreover, Le *et al*. reported that 2 of 4 patients with dMMR ampullary cancer had disease control under pembrolizumab therapy.[13] In contrast, an enormous increase in metastases within the liver and a concomitant increase in CA 19-9 after a short duration of nivolumab treatment was observed in our patient. Pseudoprogression, a rare clinical entity, was not considered in our patient. A patient's general condition usually improves after this phenomenon.[14] However, in contrast to the slowly deteriorating condition of our patient without treatment for 1 year after recurrence, her condition rapidly worsened after nivolumab treatment.

Immune checkpoint inhibitors may be deleterious through accelerating the disease in a subset of patients. However, the prevalence, mechanisms, and predictive factors for HPD remain unclear. In a study of 218 patients treated with anti-PD-1 or anti-PD-L1 mAb, 9% (12/131) of the patients had HPD and were associated with older age.[20] Genomic markers associated with HPD have also been evaluated.[21] Among 155 patients with multiple types of cancer treated with various types of immunotherapy, 4 of 6 patients with murine double minute 2 (MDM2) family amplification experienced HPD.[21] Notably, the IHC expression of MDM2 was identified in 35 of 47 (75%) patients with ampullary cancer.[22] Although the prevalence of

MDM2 amplification is unknown in ampullary cancer, 2 of the 4 patients with MSI-H intrahepatic cholangiocarcinoma had a positive IHC expression for MDM2.[23] However, the mechanism underlying MDM2 and HPD remains elucidated. The IHC expression and amplification of MDM2 were not evaluated in our patient.

The natural course of disease progression in ampullary cancer following the failure of any anti-cancer treatment, namely nivolumab in our patient, cannot be totally excluded. The use of nivolumab in this fragile patient with cancer cachexia and compromised immune system may potentially have obscured the benefits. Furthermore, the intra-abdominal infection that occurred following the nivolumab therapy may also have played a role in promoting tumor progression and metastases in our patient. In addition, a recent study demonstrated that the interaction between inflamed neutrophils and tumor cells promoted the spread of tumor cells.[24]

There is currently no global consensus on the definition of HPD. One retrospective study used tumor growth rate (TGR) to estimate the increase in tumor volume over time, and HPD was defined as at least a 2-fold increase in the TGR.[20] In our patient, the prenivolumab TGR from December 2017 to April 2018 [Figure 2f and i] was 9.7%, while the postnivolumab TGR from April to June 2018 [Figure 2i and l] was 32.5%. Therefore, our patient had HPD by definition with a 3.6-fold increase in the TGR. Another study defined HPD as time-to-treatment failure (TTF) of shorter than 2 months with >50% increase in tumor load and more than a 2-fold increase in progression pace according to immune-related response criteria.[21,25] Our patient also met these criteria, with a TTF of 2 months and >5-fold increase in tumor load and progression pace.

Conclusion

The definition and underlying mechanism of HPD remains to be elucidated. It is important to identify any clinical symptoms and signs of HPD as early as possible. Tumors with MSI-H or dMMR do not guarantee a response to immune checkpoint inhibitors. The predictive factors of HPD should be identified in this era of cancer immunotherapy to preclude patients who may be harmed by immune checkpoint inhibitor treatment.

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Reid MD, Balci S, Ohike N, Xue Y, Kim GE, Tajiri T, *et al.* Ampullary carcinoma is often of mixed or hybrid histologic type: An analysis of reproducibility and clinical relevance of classification as pancreatobiliary versus intestinal in 232 cases. Mod Pathol 2016;29:1575-85.
2. Williams JL, Chan CK, Toste PA, Elliott IA, Vasquez CR, Sunjaya DB, *et al.* Association of histopathologic phenotype of periampullary adenocarcinomas with survival. JAMA Surg 2017;152:82-8.
3. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, *et al.* Adjuvant chemotherapy with gemcitabine vs. observation in patients undergoing curative-intent resection of pancreatic cancer: A randomized controlled trial. JAMA 2007;297:267-77.
4. Neoptolemos JP, Moore MJ, Cox TF, Valle JW, Palmer DH, McDonald AC, *et al.* Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs. observation on survival in patients with resected periampullary adenocarcinoma: The ESPAC-3 periampullary cancer randomized trial. JAMA 2012;308:147-56.
5. Cloyd JM, Wang H, Overman M, Zhao J, Denbo J, Prakash L, *et al.* Influence of preoperative therapy on short- and long-term outcomes of patients with adenocarcinoma of the ampulla of vater. Ann Surg Oncol 2017;24:2031-9.
6. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, *et al*. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273-81.
7. Morizane C, Okusaka T, Mizusawa J, Katayama H, Ueno M, Ikeda M, *et al*. Randomized phase III study of gemcitabine plus S-1 combination therapy versus gemcitabine plus cisplatin combination therapy in advanced biliary tract cancer: A Japan Clinical Oncology Group study (JCOG1113, FUGA-BT). J Clin Oncol 2018;36 (suppl 4):205.
8. Lee A, Sun S, Sandler A, Hoang T. Recent progress in therapeutic antibodies for cancer immunotherapy. Curr Opin Chem Biol 2018;44:56-65.
9. Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, *et al.* Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014;371:2189-99.
10. 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.
11. McGranahan N, Furness AJ, Rosenthal R, Ramskov S, Lyngaa R, Saini SK, *et al.* Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science 2016;351:1463-9.
12. Turajlic S, Litchfield K, Xu H, Rosenthal R, McGranahan N, Reading JL, *et al.* Insertion-and-deletion-derived tumour-specific neoantigens and the immunogenic phenotype: A pan-cancer analysis. Lancet Oncol 2017;18:1009-21.
13. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, *et al.* Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-13.
14. Wang Q, Gao J, Wu X. Pseudoprogression and hyperprogression after checkpoint blockade. Int Immunopharmacol 2018;58:125-35.
15. Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz HJ, Morse MA, *et al.* Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): An open-label, multicentre, phase 2 study. Lancet Oncol 2017;18:1182-91.
16. Roach C, Zhang N, Corigliano E, Jansson M, Toland G, Ponto G, *et al.* Development of a companion diagnostic PD-L1 immunohistochemistry assay for pembrolizumab therapy in non-small-cell lung cancer. Appl Immunohistochem Mol Morphol 2016;24:392-7.
17. Saraggi D, Galuppini F, Remo A, Urso ED, Bacchin D, Salmaso R, *et al.* PD-L1 overexpression in ampulla of vater carcinoma and its pre-invasive lesions. Histopathology 2017;71:470-4.
18. Walter D, Herrmann E, Schnitzbauer AA, Zeuzem S, Hansmann ML, Peveling-Oberhag J, *et al.* PD-L1 expression in extrahepatic cholangiocarcinoma. Histopathology 2017;71:383-92.
19. Bang YJ, Doi T, de Braud F, Piha-Paul S, Hollebecque A, Abdul Razak AR, *et al.* Safety and efficacy of pembrolizumab (MK-3475) in patients (pts) with advanced biliary tract cancer: Interim results of KEYNOTE-028. Eur J Cancer 2015;51 Suppl 3:S112.
20. Champiat S, Dercle L, Ammari S, Massard C, Hollebecque A,

Postel-Vinay S, *et al.* Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. Clin Cancer Res 2017;23:1920-8.
21. Kato S, Goodman A, Walavalkar V, Barkauskas DA, Sharabi A, Kurzrock R, *et al.* Hyperprogressors after immunotherapy: Analysis of genomic alterations associated with accelerated growth rate. Clin Cancer Res 2017;23:4242-50.
22. Perysinakis I, Minaidou E, Mantas D, Sotiropoulos GC, Leontara V, Tsipras H, *et al.* Differentiation and prognostic markers in ampullary cancer: Role of p53, MDM2, CDX2, mucins and cytokeratins. Pathol Res Pract 2016;212:1039-47.
23. Momoi H, Itoh T, Nozaki Y, Arima Y, Okabe H, Satoh S, *et al.* Microsatellite instability and alternative genetic pathway in intrahepatic cholangiocarcinoma. J Hepatol 2001;35:235-44.
24. Chen MB, Hajal C, Benjamin DC, Yu C, Azizgolshani H, Hynes RO, *et al.* Inflamed neutrophils sequestered at entrapped tumor cells via chemotactic confinement promote tumor cell extravasation. Proc Natl Acad Sci U S A 2018;115:7022-7.
25. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, *et al.* Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. Clin Cancer Res 2009;15:7412-20.