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Hyper- or Pseudoprogression? A Case Report of MSI-High Metastatic Colorectal Cancer

Schuler A[1], Omlin A[1], Husarik DB[2], Denecke B[1] and Rothermundt C[1]*

[1]*Department of Medical Oncology and Haematology, Cantonal Hospital St. Gallen, Switzerland*

[2]*Department of Radiology and Nuclear Medicine, Cantonal Hospital St. Gallen, Switzerland*

Abstract

About 4% to 8% of patients with metastatic Colorectal Cancer (CRC) harbor deficient Mismatch Repair proteins (dMMR) and/or high Microsatellite Instability (MSI-H). We present the case of a patient with somatic dMMR (loss of MLH1 and PMS2), MSI-H and BRAF V-600E mutated metastatic right-sided colon cancer treated with an Immune Checkpoint Inhibitor (ICI), who had radiological signs of Hyperprogressive Disease (HPD) with also an increase in tumour marker levels, followed by a Complete Remission (CR).

Keywords: Colorectal cancer; Hyperprogression; Immune checkpoint inhibitor therapy; Microsatellite instability; Pseudoprogression

Introduction

In patients with MSI-H CRC, Immune Checkpoint Inhibitor (ICI) therapy can be an effective treatment option [1,2]. New patterns of tumour response have been seen on ICI treatment. The concept of HPD is based on a faster than expected tumour growth on ICI compared to the rate of progression on standard chemotherapy. HPD was reported in 4% to 29% of patients treated with immunotherapy [3]. It can be hard to distinguish HPD from pseudoprogression, which is a rare condition also occurring in patients treated with ICI. After an initial radiologic evaluable progressive disease, a late tumour response occurs [3,4]. The rate of pseudoprogression is ≤ 10% of patients, independent of tumour type [3].

Case Presentation

The patient was initially diagnosed with stage IIIC (pT3, pN2b (8/22), cM0) disease, treated with a right hemicolectomy and received adjuvant chemotherapy with capecitabine and oxaliplatin (XELOX). Due to sensory neuropathy, oxaliplatin was stopped after 4 cycles. Adjuvant treatment was completed for total duration of 6 months with capecitabine monotherapy until September 2018. At the end of adjuvant chemotherapy, a PET-CT showed new development of peritoneal carcinomatosis and hepatic metastases (Figure 1). A first line PD-1-inhibitor therapy with pembrolizumab was initiated in the light of MSI-H metastatic CRC. After three doses of pembrolizumab, an early PET-CT scan was initiated due to clinical signs of disease progression with beginning bowel obstruction. At this time the tumour marker Carcinoembryonic Antigen (CEA) had increased from 8.42 µg/l (at start of pembrolizumab) to 52.9 µg/l. The PET-CT showed metabolic and morphologic progression of peritoneal carcinomatosis, in contrast to metabolic regression but morphologic progression of hepatic metastases. At the time, we interpreted the combination of clinical findings, imaging and increasing tumour marker levels, as signs of rapid tumour progression and started a second line palliative therapy with 5-Fluoruracil, Leucovorin and Irinotecan (FOLFIRI). Treatment was stopped after two courses due to patient wish. The PET-CT after treatment stop showed minor metabolic and morphologic residuals of the peritoneal carcinomatosis and no evidence of hepatic metastases, corresponding to a near Complete Remission (nCR). Tumour marker CEA had decreased to 3.25 µg/l and subsequently normalized. The latest PET-CT in April 2021 showed continued CR (Figure 1).

Discussion

A possible explanation for the rapid disease progression on the first restaging PET-CT after 3 pembrolizumab doses is HPD on ICI therapy. It has been shown that patients with HPD had a lower frequency of new lesions compared to patients with disease progression without HPD [5].

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Correspondence:
Alexandra Schuler, Department of Medical Oncology and Haematology, Cantonal Hospital St. Gallen, Rorschacherstrasse 95, 9007 St. Gallen, Switzerland, Tel: + 41 (0) 71 494 1111; E-mail: alexandra.schuler@kssg.ch

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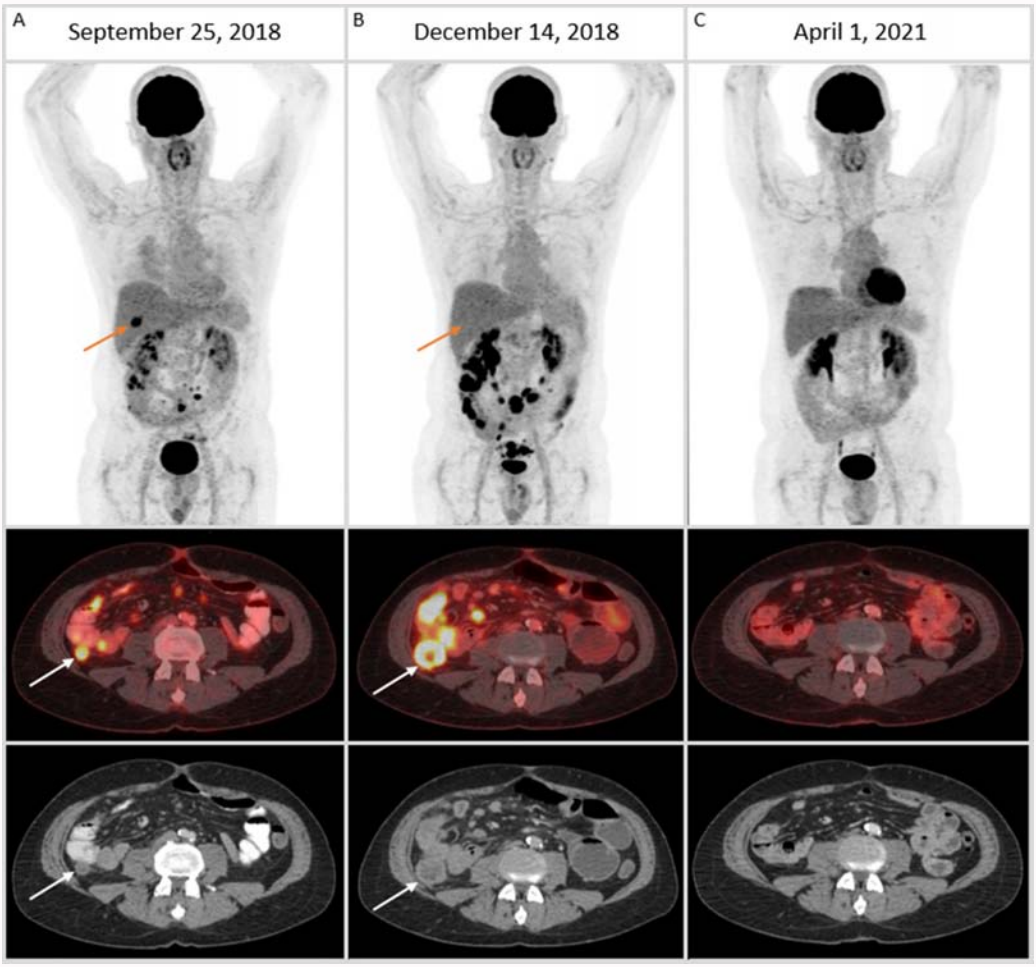

Figure 1: PET-CT demonstrating hyper- or pseudoprogression. The PET-CT at the end of adjuvant chemotherapy (Panel A) demonstrated hypermetabolic hepatic metastases (orange arrow on maximum intensity projection – top image) and one of several hypermetabolic peritoneal masses measuring 1.9 cm, SUVmax 7.1 (white arrow on PET-CT fusion – middle image and CT at same level – bottom image). After three doses of pembrolizumab and clinical signs of progression the PET-CT (Panel B) revealed metabolic and morphologic progression of peritoneal carcinomatosis with the reference mass measuring 3.9 cm, SUVmax 11.3 (white arrow on middle and bottom image) in contrast to metabolic regression of hepatic metastases (orange arrow on maximum intensity projection - top image). After two courses of a second line palliative therapy with FOLFIRI there was near complete remission with minor morphologic residuals in February 2019. The patient remained without hypermetabolic activity as demonstrated on the PET-CT in April 2021 (Panel C).

In our case, the patient had progression of peritoneal carcinomatosis on PET-CT. However, there was no clear evidence of new lesions. Another explanation for the rapid disease progression is an initial response to pembrolizumab in terms of pseudoprogression. The hypothesis is that pseudoprogression is associated with immune cells infiltrating in tumour tissue [3,4]. It remains unclear whether pseudoprogression is a result of natural tumour growth before response to ICI [3]. As our patient continues to be in CR, it seems plausible that pseudoprogression led to a durable response, which resolved in CR. The role of FOLFIRI remains unclear: Whether the chemotherapy induced a tumour response by itself or in combination with the previous immunotherapy. First line chemotherapy with FOLFIRI has a CR rate of about 5% [6]. Recently, the second interim analysis of the KEYNOTE-177 study was published. The open-label phase III trial enrolled 307 previously untreated patients with MSI-H/dMMR metastatic CRC. The patients were randomized 1:1 to first-line pembrolizumab for up to 2 years or investigator´s choice of FOLFIRI or modified FOLFOX6 (5-Fluorouracil, Leucovorin and Oxaliplatin) with or without bevacizumab or cetuximab. The median PFS was 16.5 months for the pembrolizumab group *vs.* 8.2 months for the chemotherapy group (Hazard Ratio [HR], 0.60; 95% CI, 0.45 to 0.80; P=0.0002), OS data are not available yet. Overall response rate was 43.8% for the pembrolizumab group *vs.* 33.1% in the chemotherapy group, with CR as best response in 11.1% *vs.* 3.9% of patients, respectively [7]. In an update of the CheckMate 142 trial, comparing the combination of nivolumab and low-dose ipilimumab with nivolumab monotherapy as first line treatment in patients with MSI-H/dMMR metastatic CRC, the combination treatment achieved an objective response rate of 64% by investigator assessment and a disease control rate of 84%. OS and PFS is not reached yet [8,9]. Final results from CheckMate 142 and KEYNOTE-177 are still pending, suggesting possibly durable responses in a subgroup of patients [7,8,10]. In our case, CEA levels increased during treatment with pembrolizumab, CEA levels dropped from 52.9 µg/l to 23.2 µg/l two weeks after starting FOLFIRI, and continued to decrease until normalization in March 2019 and continue to be in the normal range as of April 2021. The rising tumour marker CEA remains unclear. It has been demonstrated in a small group of patients with dMMR/MSI-H CRC that the degree of CEA decline after one dose of pembrolizumab was predictive of PFS and OS, the CEA response occurred prior to radiographic confirmation of disease control (range, 10 to 35 weeks) [2].

Conclusion

We think that the clinical course and ongoing response in our patient is more likely the result of PD1-inhibitor therapy with pembrolizumab and not of chemotherapy with FOLFIRI. This hypothesis is supported by higher CR rates in patients with metastatic MSI-H/dMMR CRC treated with PD1-inhibitor therapy and the unique patterns of response resulting from immunotherapy. We believe that the scenario described in our case is relevant and that physicians should be aware of the possibility of misleading early signs for disease progression. Importantly, ICI treatment should only be continued in case the patient is clinically well, because pseudoprogression generally is not very common. Distinction between pseudoprogression and HPD remains a challenge and we envision that data from large trials will help to further characterize these events.

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