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CASE REPORT

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Pseudoprogression during treatment with pembrolizumab followed by rechallenge with chemotherapy in metastatic colorectal cancer: A case report

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Abstract

Disease progression during immunotherapy in colorectal cancer does not always indicate treatment failure. A case argues that carcinoembryonic antigen (CEA) may serve as an early marker to distinguish between pseudoprogression and real progression. Presentation of results from reintroduction of chemotherapy after progression on immunotherapy that suggest increased efficiency.

KEYWORDS

carcinoembryonic antigen, colorectal cancer, immunotherapy, pseudoprogression, reintroducing chemotherapy

1 | INTRODUCTION

Colorectal cancer (CRC) is the third most common solid malignancy in western countries.[1] Around half of patients develop metastatic CRC (mCRC). Median overall survival of patients with mCRC has increased after the introduction of chemotherapy (5-fluorouracil combined with oxaliplatin or irinotecan or both) and the targeting of the vascular endothelial growth factor and epidermal growth factor receptor systems.[2] The recent introduction of immunotherapy has added a new layer of treatment opportunities for the minority of patients with mismatch repair deficient tumors (dMMR).[3]

The mismatch repair (MMR) system corrects errors that occur spontaneously during DNA replication. In dMMR tumors, DNA errors accumulate causing microsatellite length mutations, microsatellite instability (MSI),[4] and truncated peptides with potential immune activation.[5] Tumors with dMMR are rather common in localized colon cancer, approximately 15%, and these patients have an overall better stage-adjusted survival and may respond differently to 5-fluorouracil-based chemotherapy.[6,7] The presence of tumors with a dMMR system in the metastatic setting is consequently less common, typically 4%-5%.[8]

The high degree of "genetic noise" characteristic for dMMR tumors gives the theoretical basis for effect from immunotherapy. Pembrolizumab is a humanized antibody targeting the programmed cell death 1 (PD-1) receptor on the lymphocytes. In 2017, it was approved for solid tumors harboring MSI.[9] Pembrolizumab, along with other immune modulating drugs, is currently being investigated in multiple different settings in mCRC. The introduction of immunotherapy has also challenged our traditional way of interpreting treatment response.

Pseudoprogression is a phenomenon describing apparent progression on treatment followed by tumor regression. Pseudoprogression has been observed in patients treated with

immunotherapy in various tumor types but the frequency and role of pseudoprogression in colon cancer, during immunotherapy, are largely unknown.[10,11]

2 | CASE PRESENTATION

A middle-aged man diagnosed with mCRC and synchronous renal cell carcinoma. A low-risk malignant melanoma was surgically removed from his back approximately one year before the diagnosis.

The patient was referred to the hospital because of difficulties in swallowing and with symptoms of anemia. A gastroscopy showed esophageal candidiasis. A computed tomography (CT) scan demonstrated a tumor in the colon ascendens, a synchronous tumor in the left kidney, and a solitary lever metastasis of 10 cm in addition to several nonspecific lung nodules. A biopsy from the primary tumor confirmed adenocarcinoma, staged T4N2M1 at a multidisciplinary team (MDT) conference. Mutation analysis revealed a *BRAF* mutation (Val600Glu) and immunohistochemistry loss of MLH1 and PMS2 protein expression. Additional analyses revealed methylation of the *MLH1* promoter together with no familial history of bowel cancer in this case was considered sporadic.

The liver metastasis was deemed potentially resectable, and it was decided to treat the patient with neoadjuvant chemotherapy. Four cycles of folinic acid, 5-fluorouracil and oxaliplatin (FOLFOX), and bevacizumab resulted in stable disease (SD). An additional biopsy from the left kidney revealed a renal cell carcinoma. After a further four cycles of FOLFOX and bevacizumab, CT scans showed regression in the liver and a liver biopsy confirmed adenocarcinoma from colorectal origin. The patient underwent right hemicolectomy with radical removal of the tumor in the colon after a total of nine cycles of FOLFOX + bevacizumab. A hemihepatectomy was planned, but the patient was deemed nonresectable due to the occurrence of peritoneal carcinomatoses and growth of, and new liver metastases.

The overall treatment strategy changed to a palliative focus and the patient received four cycles of FOLFIRI resulting in disease progression. After five cycles of capecitabine and bevacizumab, a CT scan again confirmed disease progression with growth of the peritoneal carcinomatoses. Pembrolizumab was then initiated after individual approval by the National Board of Health. The patient was hospitalized after only two days with fever and clinical symptoms of infection and abdominal pain. Performance status (PS) was now rapidly declining and the patient was totally confined to the bed and with limited ability to carry out self-care during the following week (PS = 3). Progression of the peritoneal carcinomatoses was suspected, threatening to perforate the skin. Pseudoprogression was later documented by a CT scan after three cycles of pembrolizumab demonstrating progression of peritoneal carcinomatoses (primarily nontarget lesions) and multiple new lung metastases (Figure 1). Clinically, in contrast, PS was now improving to PS = 1 and CEA was dropping and we decided to continue treatment despite progressive disease (PD) as defined by RECIST1.1. Performance status normalized and the patient received an overall of 21 cycles of pembrolizumab (15 months) before PD was confirmed, again, and this time backed up by increasing CEA (Figure 2).

As the patient was unaffected, PS = 0, it was decided to reintroduce FOLFIRI. This has so far resulted in stable disease, and treatment is currently ongoing on its seventh month (Figure 2).

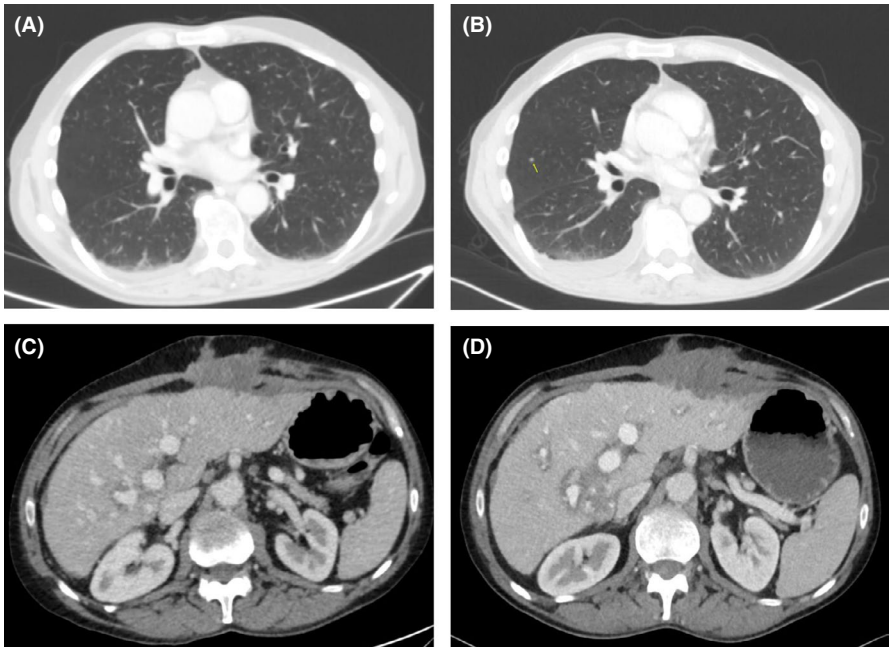

FIGURE 1 Computer tomography scans of the thorax and abdomen before ignition of pembrolizumab (A + C) and at the first evaluation after two months of treatment (B + D). One of the new lung metastasis is identified by the small arrow (B). The longest diameter of the peritoneal carcinomatoses locus demonstrated increased from 6.2 cm at baseline (C) to 8.0 cm at the first evaluation (D)

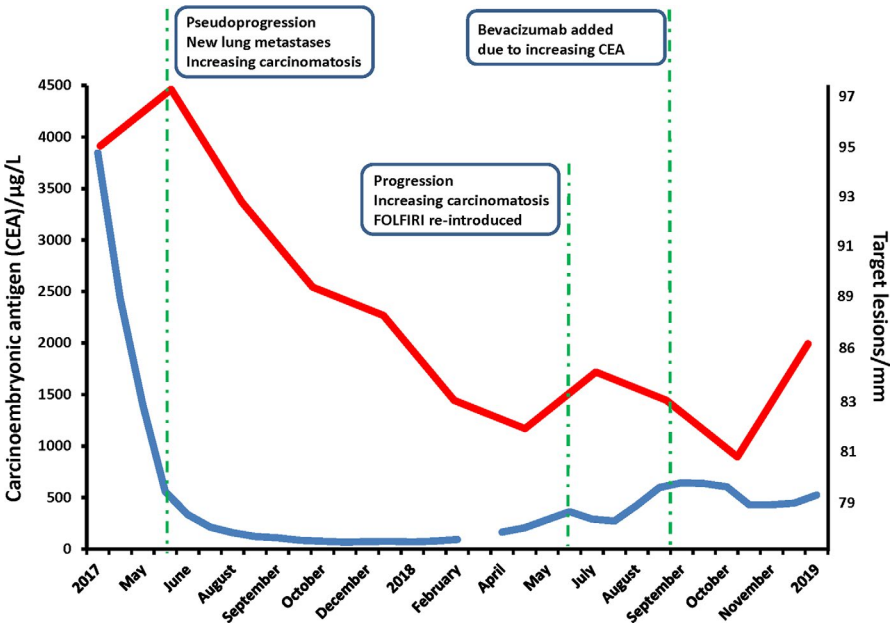

FIGURE 2 Changes in carcinoembryonic antigen (CEA, blue line) and total target lesion dimension (red line, according to RECIST 1.1) from initiation of pembrolizumab in March 2017 to progression in June 2018 and the following reintroducing of folinic acid, fluorouracil, and irinotecan (FOLFIRI). CEA was not measured in the sample drawn in March 2018

3 | DISCUSSION

Pseudoprogression is a rather new concept in clinical oncology. The growth of existing lesions (carcinomatoses) and the appearance of new metastases (multiple lung metastases) combined with clinical improvement of the patient let us to suspect pseudoprogression in this case. The phenomenon primarily reported for patients with malignant melanoma, lung cancer, and urothelial cancers is reported with a frequency of <10%.[10] The incidence in mCRC is unknown, and we only encountered one case report published in 2017.[11] The new lung metastases detected in the present case were actually confirmed on the following CT scan after an additional nine weeks of treatment but they did not increase in size. The decision to continue treatment after initial radiologic progression should, naturally, be supported by clinical benefit to the patient. Predisposing factors of pseudoprogression are still largely unknown but the combination of a high disease proliferation rate combined with slower cancer cell elimination may increase the likelihood. This case with a *BRAF*-mutated dMMR mCRC treated with pembrolizumab may resemble such a combination.

Relying on pseudoprogression, pose a new challenge, for example, risk of continuing a treatment that may not benefit the patient. This concern is real since most progressions are real progressions. The fear of terminating effective treatments, because of pseudoprogression, led to the introduction of several immune-related response evaluation criteria (irRC, irRECIST, iRECIST) requiring confirmation of tumor progression after an additional four weeks. Hyperprogression during immunotherapy has made it even more important to discriminate between these two outcomes as early as possible. Based on this case, we propose CEA as an early marker. A rapid decline was identified early during the pseudoprogression phase followed by an increase when true progression was confirmed. Chae et al proposed that lactate dehydrogenase (LDH) may serve as a marker for discrimination. However, LDH increased during the initial tumor progression in their study. In this case, LDH remained within the normal range throughout the treatment. Recent reports have proposed quantification of circulating tumor DNA as a way to discriminate; however, in the setting of mCRC, the role of this strategy is largely unknown.[12,13] One may also argue that a routine assessment of CEA is less laborious and easier to interpret.

How to proceed after progression on immunotherapy in a patient with mCRC and unaffected PS? The answer may be obvious in patients treated with immunotherapy upfront but less obvious in patients that receives immunotherapy as a last line of treatment. The present case illustrates the last scenario and was furthermore complicated by persisting neuropathy from previous oxaliplatin exposure and a *BRAF*-mutated disease. Reintroducing FOLFIRI thus seemed to be the only real option although PD was detected after only two months of treatment when the patient was first exposed. We hoped that the influence by pembrolizumab on the immune system might have altered the response to subsequent chemotherapy. The reintroduction led to a decrease in CEA, and the first CT evaluation after two months confirmed a SD with minor shrinkage of target and nontarget lesions. Due to an increase in CEA after three months of treatment with FOLFIRI, we decided to add Bevacizumab, although progression was not

documented and even though the disease had also progressed on a bevacizumab containing regimen previosly. This strategy has now kept the disease stable for more than seven months after cessation of pembrolizumab. CEA is still stable, and the patient is doing well with no limitations (PS = 0). Increased efficiency of standard chemotherapy has been reported following immunotherapy in patients with lung cancer[14] and malignant melanoma[15] but we are not aware of any previous reports regarding patients with mCRC.

This rather unique observation adds speculations to the optimal handling of patients with mCRC and dMMR. Should we use all standard chemotherapy regimens first, then immunotherapy, and then rechallenge with standard chemotherapy again? We are planning to offer ipilimumab + nivolumab once the disease progresses again, to explore the potential benefit of a second intervention with immunotherapy.

4 | CONCLUSIONS

Treatment beyond progression in patients with mCRC receiving immunotherapy may be indicated in patients with clinical benefit, and CEA may aid in discriminating pseudoprogression from real progression. Furthermore, immunotherapy may revert earlier resistance to chemotherapy and reintroduction of chemotherapy can be an option.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

NDT: identified the special learning points and conceived the idea for the case report, responsible for collection and assembly of data, drafted the primary manuscript, discussed the results, commented, and approved the final version of the manuscript. CR: identified the special learning points and conceived the idea for the case report, discussed the results, commented, and approved the final version of the manuscript. LHJ: identified the special learning points and conceived the idea for the case report, discussed the results, commented, and approved the final version of the manuscript. TFH: identified the special learning points and conceived the idea for the case report, responsible for collection and assembly of data, drafted the primary manuscript, discussed the results, commented, and approved the final version of the manuscript.

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