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Pseudoprogression on treatment with immune-checkpoint inhibitors in patients with gastrointestinal malignancies: Case series and short literature review

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A B S T R A C T

Gastrointestinal cancers are very common cancers with colorectal being the fourth most common type, gastric the sixth, and esophageal the tenth. Although recent advances have been made in management including incorporation of antiangiogenic, anti-EGFR, and anti-HER2 directed therapies, overall their prognosis remains poor. Anti-PD-1 therapy with nivolumab and pembrolizumab are licensed for advanced chemorefractory gastroesophageal cancer and many other checkpoint inhibitor therapies are being assessed alone and in combination in these diseases. One of the challenges posed in assessing response to immunotherapy treatment is the phenomenon of pseudoprogression. This phenomenon, which is well described in patients with malignant melanoma is most frequently described as a size increase of contrast enhancing lesions or appearance of new lesions that stabilize or reduce in size with time. Most other solid tumors have a low incidence of pseudoprogression although cases have been reported for lung, head, and neck cancer and a range of gliomas. Herein we present 6 cases of patients with gastrointestinal cancers who were treated with anti-PD1 (programmed cell death) and anti-PD-L1 (programmed cell death ligand-1) antibodies, and experience pseudoprogression.

Introduction

Among gastrointestinal malignancies, colorectal and gastric cancer represents respectively the fourth and the sixth most common cancer and the fourth and the fifth leading cause of cancer-

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related death.[1] Immune checkpoint blockade has been licensed to treat melanoma, nonsmall cell lung cancer, urothelial cancer, renal cell carcinoma, and most recently gastroesophageal cancer. In colorectal cancer, with the exception of microsatellite unstable cancers, immunotherapy has been less successful and combination approaches are warranted.[2] Active clinical trial programs currently investigate single agent and combination studies for both gastroesophageal and colorectal cancers.[3]

The imaging manifestations of tumor response to immunotherapy may appear quite distinct from what is currently observed with classical cytotoxic anticancer treatments. According to conventional RECIST 1.1 criteria, tumor size reduction implies a favorable response to cytotoxic therapy and correlates well with clinical outcome.[4] The use of RECIST 1.1 to evaluate the efficacy of immunotherapies is challenging given the different mechanism of action of these agents. In patients treated with immuno-oncology therapy, if evidence of tumor growth or the appearance of new lesions on follow-up imaging studies is demonstrated, these imaging findings do not necessary reflect treatment failure but they may represent "pseudoprogression," and clinically stable patients should be allowed to continue treatment until the next imaging assessment.[5] Such transient tumor enlargement or the appearance of new lesions may be followed by a delayed response, which consists of tumor shrinkage or long-term tumor stability and which ultimately indicates successful treatment.

In this case series, we present 5 cases of pseudoprogression amongst 83 patients treated for advanced inoperable gastric or colorectal cancers whilst enrolled in clinical trials at our institution. All 6 patients were treated with immunotherapy, given as single agent or in combination with conventional cytotoxic or targeted drugs.

Case presentation

Case 1

A 55-year-old woman was diagnosed with HER2 negative, poorly differentiated adenocarcinoma of the gastric antrum. At initial staging, the tumor was considered potentially operable. Preoperative chemotherapy was initiated with 3 cycles of epirubicin, cisplatin, capecitabine (ECX). At re-staging prior to surgery, the PET-CT revealed distant metastases with new supraclavicular and paratracheal lymphadenopathies. The patient was then treated with 6 cycles of docetaxel chemotherapy for 4.5 months until disease progression. She was referred to our center and anticancer therapy with an anti PD-1 monoclonal antibody in combination with an anti-VEGFR2 antibody was commenced. After 2 cycles (8 weeks) of treatment the first CT scan revealed stable appearances of the target lesions but new nodal groups involvement in keeping with disease progression according to RECIST 1.1. The patient continued on treatment and according to immune-response criteria, a re-assessment CT study was performed 4 weeks later which demonstrated stable disease (irRECIST unconfirmed progressive disease followed by stable disease – iuPD followed by iSD). The following CT studies demonstrated partial response with over 30% shrinkage from baseline of the target lesions (immune partial response – iPR). The patient achieved the best response after 14 months from treatment initiation with 50% reduction of the target lesions.

Case 2

A 64 year-old man was diagnosed with HER2 negative metastatic adenocarcinoma of the gastroesophageal junction with nodal metastases. He was referred to our center and palliative chemotherapy with ECX in combination with anti-MET antibody and/or placebo was started. After 2 cycles of combination therapy, he continued 4 cycles of ECX chemotherapy and at the end of treatment stability of the disease was achieved at imaging. On progression 4 months later, second line chemotherapy with weekly paclitaxel was commenced, which was discontinued after 5 cycles due to disease progression. On a clinical trial an anti-PD-1 antibody in combination

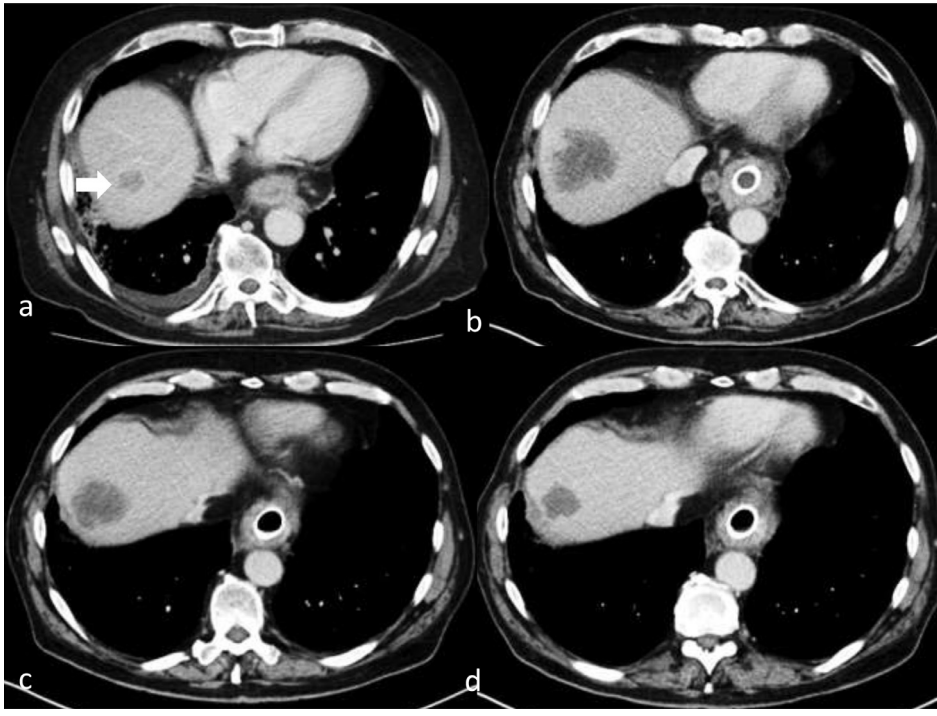

Fig. 1. Case 3: Contrast-enhanced CT images acquired at baseline (a), at 8 weeks (b), at 4-week follow-up after disease progression (c) and at 6 months (d). At 8-weeks follow-up the hepatic metastasis in segment VIII (arrow) had increased in size (+55%) and new lesions had appeared within the liver in keeping with disease progression. The 4-week CT follow-up showed favorable response of the liver metastases suggesting pseudoprogression." At 6-months ongoing response was again observed.

with an anti-VEGFR-2 antibody inhibitor was commenced. The patient's on study first imaging assessment revealed the presence of new liver metastases (iuPD). He continued treatment and disease stability was observed at imaging for a total of 8 months (immune stable disease – iSD).

Case 3

A 54-year-old man was referred with a diagnosis of HER2 negative metastatic gastric adenocarcinoma with liver metastases. First line treatment with an anti-PD-1 antibody in combination with an anti-VEGFR2 antibody inhibitor was commenced. On completion of 2 cycles the first assessment CT revealed evidence of new liver metastases (iuPD). The patient continued on treatment and according to the immune-response criteria the re-assessment CT was repeated 4 weeks later and demonstrated stable disease (iSD). The patient remained well and continued on treatment for 8 months (Fig 1).

Case 4

A 64-year-old man was diagnosed with HER2 negative poorly differentiated metastatic gastroesophageal adenocarcinoma with nodal metastases. He embarked on ECX chemotherapy which was poorly tolerated and completed 5 cycles before disease progression with new liver metastases. An anti-PD-1 antibody was administered as single agent in the second line setting.

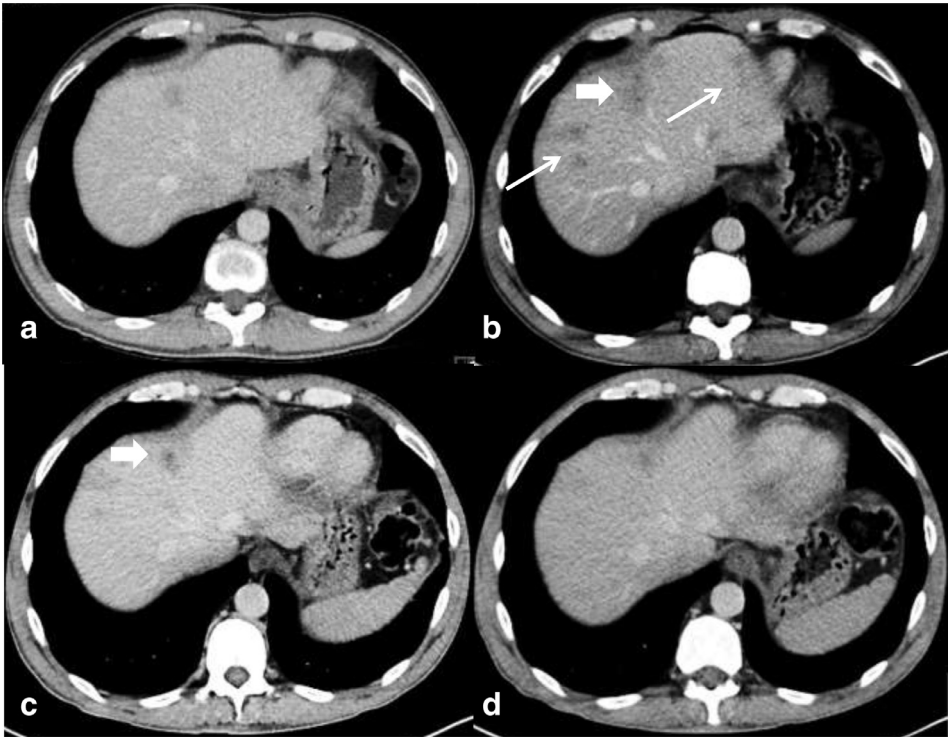

Fig. 2. Case 4: Contrast-enhanced CT images acquired at baseline (a), at 8-weeks (b), at 4-week follow-up after disease progression (c) and at 9 months (d). At 2-months follow-up the hepatic metastasis in the dome (arrow) had increased in size (+37%) compared with the baseline in keeping with disease progression. At 4-week follow-up the hepatic metastasis showed size decrease which suggested "pseudoprogression." At 9-months CT follow-up further response to treatment was observed.

After 2 cycles, the follow-up CT study detected new liver metastases (iuPD). The patient continued on treatment and according to the irRECIST guidelines the re-assessment CT study was repeated 4 weeks later and demonstrated stable disease (iSD). Currently the patient derives ongoing benefit from immunotherapy as his target lesions have shrunk by 23% with complete resolution of the new metastatic liver lesions (Fig 2).

Case 5

A 61-year-old man was diagnosed with HER2 negative poorly differentiated adenocarcinoma of the gastroesophageal junction with liver, nodal, and bilateral adrenal metastases. He completed 6 cycles of cisplatin and capecitabine chemotherapy to excellent response and entered a maintenance clinical trial receiving an anti-PD-L1 antibody. The first CT scan assessment after 2 months of treatment revealed progressive disease with new carinal, pretracheal, and retroperitoneal lymphadenopathy (iuPD). The patient continued on treatment and according to the immune-response criteria a re-assessment CT scan was performed 4 weeks later revealing stable appearances (iSD). The patient continues on treatment.

Case 6

A 31-year-old lady with microsatellite stable (MSS) KRAS mutated adenocarcinoma of the lower rectum was treated with preoperative chemoradiation (capecitabine) and abdominal

perineal resection. A postoperative CT showed the appearance of bilateral metastatic lung nodules which were treated with 6 cycles of capecitabine and oxaliplatin chemotherapy followed by surgical resection and radiofrequency ablation. After 10 weeks, the lung metastases relapsed and the patient was treated with aflibercept in combination with FOLFIRI chemotherapy (for 12 cycles plus a subsequent further 10 cycles as re-challenge). Second line FOLFOX chemotherapy was then undertaken for 4 cycles. She was then treated in the context of a Phase 1 clinical trial with oral PI3K inhibitor for 20 months which was discontinued due to toxicity. However, her disease remained stable for the following 6 months. At progression, an anti-PD-L1 antibody in combination with a MEK inhibitor was started. The first CT scans on study demonstrated stable disease (iSD). After 6 months of treatment on study, CT revealed progressive disease of target lesions, stable disease of the nontarget lesions and no new lesions. She continued treatment as per trial protocol and the following re-assessment CT study demonstrated size decrease of the target lesions, stable disease of the nontarget lesions, and no evidence of new lesions. The patient has ongoing treatment benefit after 15 months.

Discussion

Pseudoprogression was first described in melanoma patients treated with a monoclonal antibody blocking CTLA-4.[6] This consists of an initial increase in tumor burden either due to increased tumor size and/or to the appearance of new lesions which is followed either stable disease or response, but no further progression. Immune cells tumor infiltration associated with edema appears to be responsible for these imaging findings, ie increased tumor burden and appearance of focal lesion initially undetectable. These new patterns of response observed at imaging during immunotherapies and directly related to their mechanism of action have made clear that conventional imaging response criteria such as RECIST 1.1 appear inadequate to capture these features and that there was an unmet need for new imaging criteria. Therefore, the Immune-related Response Criteria were developed based on the results from clinical trials in advanced melanoma patients treated with Ipilimumab and more recently these criteria have been updated with the immune-RECIST criteria.[5,7,8] These “modified RECIST” criteria require imaging re-assessment of the disease status at not less than 4 weeks from the detection of the disease progression, to differentiate between true progression and pseudoprogression, which are responsible for different therapeutic decisions and clinical outcomes.

The frequency of pseudoprogression during immunotherapy has been previously reported for melanoma patients and accounts for 10% or less of cases of progression.[5,9-11] For other malignant solid tumors, the frequency remains unclear: less than 2% has been reported for bladder, renal, lung and head and neck cancers treated with anti-PD-1 and PD-L1 antibodies.[11,12] Recently, a case of pseudoprogression has been reported by Chae et al[13] in a patient with metastatic colorectal cancer treated with combined therapy of PD-L1 inhibitor and OX40 antagonist in the setting of a clinical trial. To our knowledge, this is the only published report of immunotherapy-induced pseudoprogression in GI cancers. Thus, the present case series may provide an interesting contribution to better delineate the frequency of this relatively uncommon tumor response in GI cancers and also to try to identify eventual predisposing factors and to understand possible developmental patterns. Considering the high costs of these therapies, early guidance as to whether a patient might benefit has not only a potential financial impact, but also a medical advantage to change therapy sooner or to continue the ongoing treatment.

Several trials investigating various combinations of immune modulating drugs have been published to date. However, very few of them used the immune-related response criteria and only a small cohort of patients with gastric cancer has been reported.[14-26] In our series 5 out of 83 (6%) patients with GI malignancies treated with immune modulating agent, experienced pseudoprogression at imaging which is similar to what is seen in other tumor types such as melanoma.

All our patients were assessed according to immune-related response criteria.[5,7,8] The patients were all clinically well at the first presentation of disease progression while on treatment

Table 1
Patient characteristics.

Gastric cancer						
Case No	Age at diagnosis	HER2 status	No of prior lines of treatment	PD1/PDL1 antibody	Combination/ Single agent	Duration of treatment
1	55F	HER2 negative	2	PD1	PD1Ab + VEGFR2 Ab	18 months
2	64M	HER2 negative	2	PD1	PD1Ab + VEGFR2 Ab	8 months
3	54M	HER2 negative	0	PD1	PD1Ab + VEGFR2 Ab	7 months
4	64M	HER2 negative	1	PD1	PD1 Ab single agent	11 months
5	61M	HER2 negative	1	PD1	PD L1 Ab single agent	Ongoing (7 months to date)
Colorectal cancer						
Case No	Age at diagnosis	KRAS status/ MMR status	No of prior lines of treatment	PD1/PDL1 antibody	Combination/ Single agent	Duration of treatment
6	31F	KRAS MT - MSS	3	PDL1	PDL1 Ab + MEK inh	Ongoing (15 months to date)

Patient characteristics: three patients with HER2 negative gastric or gastroesophageal junction cancer treated with PD1 antibody in combination with a VEGFR2 antibody. The patient with colorectal cancer had microsatellite stable disease. Ab, antibody; MSS, microsatellite stable; MT, mutant; WT, wild type.

with immunotherapy, prompting the clinicians to continue treatment and rescan as per trials protocols. In our series, the patients had common characteristics as shown in Table 1. All patients were diagnosed with gastric or gastroesophageal junction cancer and were all HER2 negative, while the patient with colorectal cancer had MSS disease. It is acknowledged in general that patients with MSS colorectal cancers are not responsive to immunotherapy.[2] The addition of other agents as observed in our colorectal patient might contribute to the development of an immunogenic tumor microenvironment, suggesting that combination treatment leads to synergistic response to immune-modulating treatments. Three out of five patients with gastric or gastroesophageal junction cancers were on treatment combinations with VEGF inhibitors, which as previously described in melanoma encourage synergistic effects in combination with immune-checkpoint blockade. However this could reflect the numbers of patients treated with this combination at our institution rather than any specific association between anti-VEGFR2 therapy and pseudoprogression.[27] These 3 patients were treated in the same clinical trial in different cohorts depending on prior lines of treatment.[28] We observed that in these small groups of patients with gastric and gastroesophageal cancer pseudoprogression was detected on the first CT assessment scan after therapy initiation, while in the colorectal cancer patient the pseudoprogression pattern was observed after 6 months of treatment initiation. There is no clear explanation to this observed tumor behavior vs potential different tumor behavior in other tumor types and this could be something that could be investigated in larger patient numbers.

Further and larger studies, validation cohorts, translational research are warranted to identify imaging tools (eg functional CT/MR) which might serve to identify predictive biomarkers of tumor response to immunotherapy, including immunotherapy-related phenomena such as pseudoprogression or hyperprogression. This research should be integrated with work on blood-based biomarkers in order to provide an integrated understanding of response to facilitate the best patient outcomes, to determine whether pseudoprogression is a surrogate for clinical benefit and increased survival and to further elucidate the complex dynamics of tumor interactions with the immune system.

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