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Rapid subcutaneous progression after immunotherapy in pretreated patients with metastatic carcinoma: two case reports

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Abstract

There is heterogeneity in cancer patients' responses to immune checkpoint inhibitors (ICIs), including hyperprogression, which is very rapid tumor progression following immunotherapy, and pseudoprogression, which is an initial increase followed by a decrease in tumor burden or in the number of tumor lesions. This heterogeneity complicates clinical decisions because either premature withdrawal of the treatment or prolonged ineffective treatment harms patients. We presented two patients treated with ICIs with heterogeneous responses. One patient had Merkel cell carcinoma in the right thigh, and the other had nasopharyngeal squamous carcinoma. The first patient was treated with sintilimab and the second with sintilimab combined with abraxane. In the first patient, subcutaneous lesions grew substantially after the first cycle of treatment with sintilimab. In the second patient, subcutaneous lesions grew gradually after the second cycle of treatment with sintilimab combined with abraxane. In both cases, biopsy examination confirmed that newly emerged lesions were metastases of the primary tumor. These two cases remind clinicians that when subcutaneous nodules appear after treatment with ICIs, pathological biopsy is needed to determine the nature—pseudoprogression or rapid progression—of the disease course.

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Introduction

Immune checkpoint inhibitors (ICIs), an effective treatment strategy in multiple solid tumor types, have revolutionized cancer therapy.[1] During treatment with ICIs, some patients experience an initial increase in the size of tumor lesions or the appearance of new lesions that show necrosis or inflammatory cell infiltration on biopsy pathological examination and which subsequently subside. This unconventional clinical response is recognized as pseudoprogression and could be misclassified as disease progression.[2] In addition to pseudoprogression, another response during checkpoint blockade, named tumor flare or hyperprogression (HPD), is characterized by dramatic progression that would outpace the expected rate of growth in the absence of ICIs, according to evidence primarily from prior imaging scans.[3,4] Patients with hyperprogression have a more deleterious time course than they might have had with other therapies, or even in the absence of therapy.[5] A study described by Champiat et al. reported that "hyper-progressive disease" was found in 9% of patients treated with ICIs.[4] Several approaches have been used to define hyperprogression, namely tumor growth rate (TGR), tumor growth kinetics (TGK), and time to treatment failure (TTF).[6] As immunotherapeutics, such as anti-programmed death (PD)-1/PD ligand (PD-L)1 agents, are widely available, clinicians face a great challenge in accurately evaluating hyperprogression during immunotherapy.[7]

Here, we presented two patients with metastatic carcinoma, one who developed rapid subcutaneous progression, and one who developed hyperprogression, after initiation of ICIs. This case report was written in accordance with the CARE guidelines.[8] Written consent for treatment and publication was obtained from both patients. Ethics approval was obtained from the Review Board of Beijing Fengtai You'anmen Hospital.

Case presentation

Rapid subcutaneous progression after receiving an ICI

A 73-year-old man, a smoker, was diagnosed with Merkel cell carcinoma of the right thigh in February 2019. He was treated with etoposide and cis-platinum until May 2019. Computed tomography (CT) demonstrated a good response in the primary lesion. However, new metastases developed in the lymph nodes in the abdomen and bilateral inguinal regions, and radiotherapy was performed in July 2019. One month later, the disease progressed, with a dramatic increase in the neuron-specific enolase (NSE) level from 13.63 μg/mL (at diagnosis) to 224.0 μg/mL. The NSE level is a valuable biomarker in Merkel cell carcinoma because the level can distinguish responders from non-responders during immunotherapy.[9] A cycle of irinotecan and cis-platinum was administrated after inducing grade 4 bone marrow suppression.

This cycle was followed by sintilimab at a dose of 200 mg q 21 days, in September 2019. Two days after the first cycle of sintilimab, new subcutaneous lesions appeared in the patient's right leg (Figure 1). Three weeks after the first cycle, the NSE level decreased to 203.9 μg/mL, and the subcutaneous lesions in the right leg grew substantially (Figure 1). Another cycle of sintilimab was administrated in October 2019, and the NSE decreased to 111.9 μg/mL 10 days later. The lymph nodes tumors in the abdomen and bilateral inguinal regions responded to the first cycle of sintilimab, decreasing from 12 cm × 2 cm to 6 cm × 1 cm in size (abdomen and right inguinal region) and from 2 cm × 1 cm to 1 cm × 1 cm (left inguinal region). However, the tumors in these regions progressed 1 month after the second cycle of sintilimab. Immunohistology (IHC) revealed the following: CAM5.2 (+), cluster of differentiation (CD)20 (−), CD21 (−), CD3 (−), cytokeratin (CK) (+), CK18 (+), human melanoma black (HMB)-45 (−), Ki-67 (95%), Melan-A (−), S-100 (−), CD56 (+), chromogranin A (CgA) (+), synaptophysin (Syn) (+), CD99 (−), and thyroid transcription factor (TTF)-1 (−). Pathological analysis of biopsy samples revealed that the subcutaneous nodules in the patient's right leg were not caused by pseudoprogression but were actually metastatic lesions from the primary tumor. Palliative treatment was provided after these findings. The patient died in November 2019 due to bacterial aspiration pneumonia.

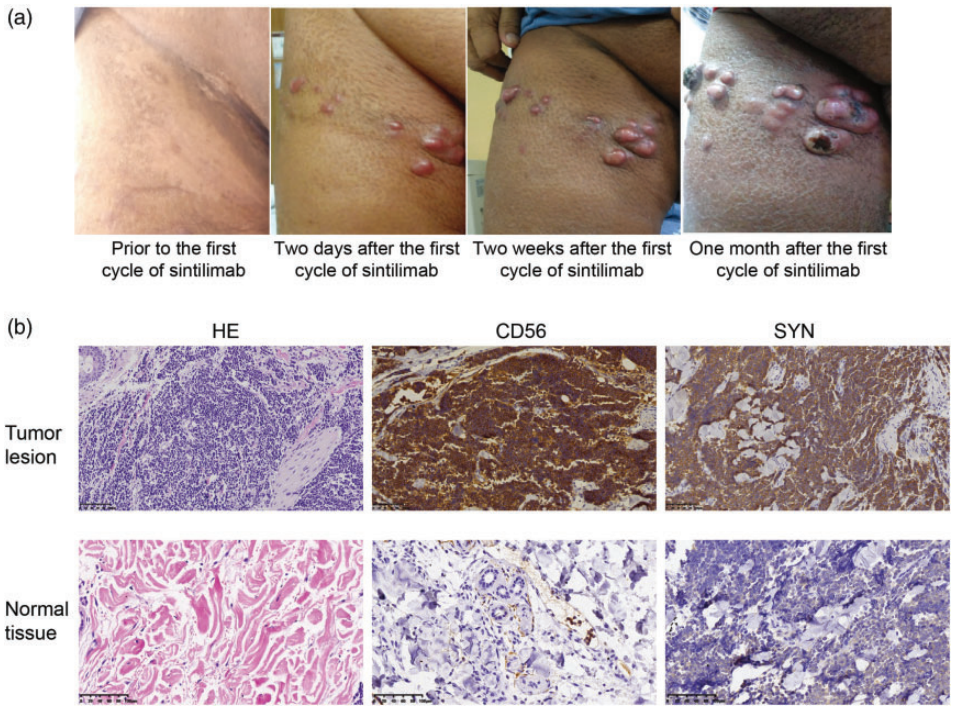

Figure 1. Hyperprogression after immunotherapy in a patient with Merkel cell carcinoma
(a) Hyperprogression indicated by subcutaneous metastatic lesions. (b) IHC (×20) staining of the subcutaneous metastatic lesions showed CD56 and SYN positivity. Normal tissue from the same patient was obtained and used as a negative control for IHC staining.
IHC, immunohistochemistry; CD, cluster of differentiation; SYN, synaptophysin; HE, hematoxylin and eosin.

Subcutaneous progression after receiving an ICI

A 51-year-old man with no family history of cancer was diagnosed with nasopharyngeal squamous carcinoma in January 2014. He received radiotherapy (70 Gy/35 fractions) until May 2014, and magnetic resonance imaging (MRI) demonstrated a good response in the primary lesion. However, in December 2018, the patient developed continuous pain in the oropharynx. MRI demonstrated a large enhancing mass in the oropharynx and laryngopharynx. He received four cycles of nimotuzumab combined with paclitaxel and cis-platinum until April 2019. The efficacy evaluation of this treatment was stable disease. Four months later, the disease progressed again. Targeted sequencing was performed and revealed a blood tumor mutational burden (TMB) of 17.75 mut/Mb. Two cycles of abraxane combined with sintilimab were administrated, and subcutaneous nodules subsequently appeared (Figure 2). The primary tumor responded to abraxane and sintilimab (Supplementary Figure 1). IHC of the biopsy tissue from the new subcutaneous nodules revealed the following: CK (+), CK5 (+), P40 (+), Ki67 (80%), desmin (Des) (−), myogenic determination gene (MyoD1) (−), myogenin (−), S-100 (−),

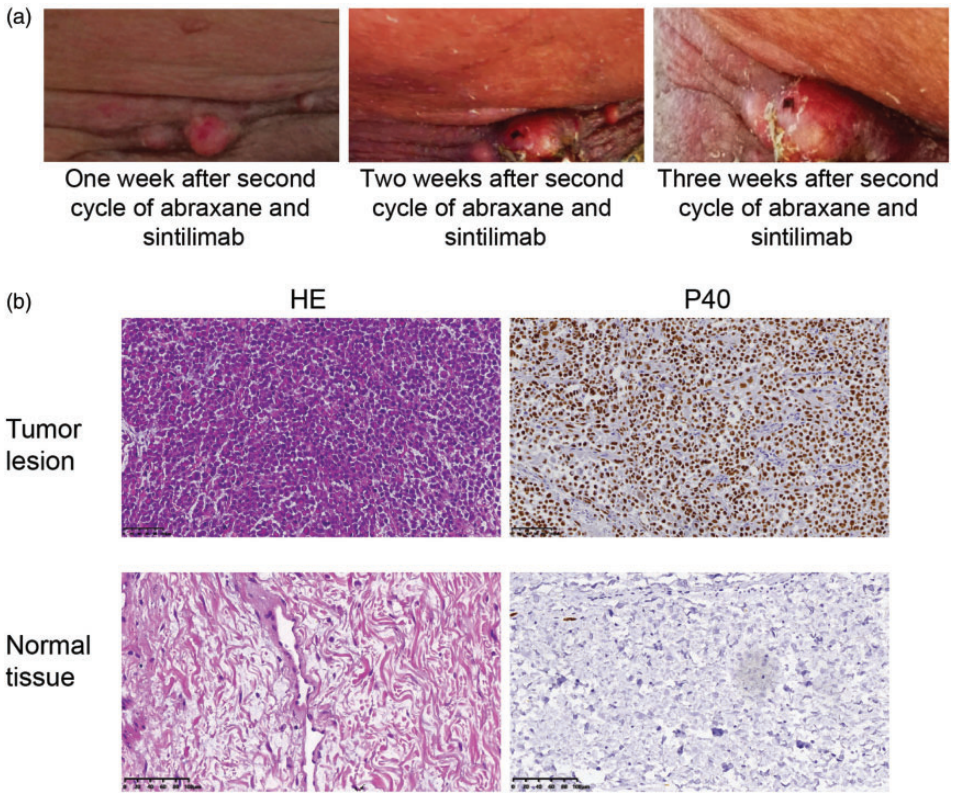

Figure 2. Hyperprogression after immunotherapy in a patient with nasopharyngeal squamous carcinoma (a) Hyperprogression indicated by subcutaneous metastatic lesions. (b) IHC (×20) staining of the subcutaneous metastatic lesions showed P40 positivity. Normal tissue from the same patient was obtained and used as a negative control for IHC staining.
IHC, immunohistochemistry; HE, hematoxylin and eosin.

Melan-A (−), and CD68 (−), indicating that the new subcutaneous nodules were metastases from the primary lesion. Palliative treatment was provided thereafter, and unfortunately, the patient died in January 2020 owing to exhaustion.

Discussion

ICIs, such as monoclonal antibodies targeting cytotoxic T-lymphocyte-associated antigen-4 and PD-1, are profoundly changing cancer patient management. To date, two PD-1 inhibitors (nivolumab and pembrolizumab) and three PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab) have been approved by the US Food and Drug Administration for various indications.[10–13] Sintilimab is another anti-PD-1 inhibitor that was approved by National Medical Products Administration (NMPA) for treating lymphoma and lung cancer and which has also been actively tested in other types of cancers.[14,15] Responses to ICIs appear to be heterogeneous. Pseudoprogression and hyperprogression present as similar initial responses to ICIs, yet they have different prognoses. However, the underlying mechanisms for the heterogeneity in response to ICIs remain largely unknown. Sarfaty et al. reported a case of subcutaneous pseudoprogression in lung squamous cell carcinoma that was treated with nivolumab previously.[16] The current report presented two advanced cancer cases with rapid progression after ICIs, emphasizing the importance of timely pathological biopsy to determine the nature of newly-developed masses and appropriate therapeutic strategies. Another concern we raised relates to the current definition of HPD. HPD is defined as tumors with a $\geq$two-fold increase in the experimental TGR compared with the reference TGR. Various HPD definitions have been proposed in addition to TGR,[17] namely TGK ratio,[18] early tumor burden increase and time to treatment failure,[19] and increased ratio of measurable lesions.[20] However, the implementation of these assessments is challenging, clinically, as the calculation of TGR and TGK ratio requires intensive measurements and multiple time point calculations.[7,21] A consensus statement and easy-to-use HPD criteria would greatly benefit cancer patients with tumor growth acceleration during immunotherapy. In conclusion, our case report shows the importance of pathological biopsy and standardization of HPD criteria for patients receiving immunotherapy.

Declaration of conflicting interest

Ruoying Yu is an employee of Nanjing Geneseeq Technology Inc. The remaining authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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