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Case Report

Giant Cell Temporal Arteritis Followed by Severe Encephalopathy Induced by Immunotherapy in a Patient with Metastatic Renal Cell Carcinoma Achieving Durable Partial Response: A Case Report

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Keywords
Giant cell arteritis · Encephalopathy · Immunotherapy · Immune-related adverse events · Immune-related adverse effects · Renal cell carcinoma · Nivolumab

Abstract
Introduction: Combined immuno-oncology (IO) regimens are the cornerstone of the current front-line systemic therapy for metastatic renal cell carcinoma (mRCC). Despite the fact that combined IO regimens show high efficacy, they are often accompanied by a wide spectrum of immune-related adverse effects (irAEs). ***Case Presentation:*** We describe a case of rare irAEs manifested as giant cell temporal arteritis (GCA) followed by severe encephalopathy occurring after continuing immunotherapy in a 66-year-old man with mRCC receiving a combination of ipilimumab and nivolumab in the first line of systemic therapy. GCA occurred 4 months after the initiation of IO and responded promptly to the low-dose prednisone therapy. Four months after the continuation of nivolumab maintenance, the patient was hospitalized due to severe irAE encephalopathy which presented as psycho-behavioral abnormalities and progressive cognitive decline. He was treated with high-dose methylprednisolone which led to complete resolution of

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the symptoms and IO was permanently discontinued. The patient achieved a durable partial response. ***Conclusion:*** Both GCA and the subsequent encephalopathy in our patient responded well to the corticosteroid therapy, leading to the complete resolution of the symptoms and the patient achieved a durable partial response. Although the risk of severe neurologic irAEs affecting the central nervous system induced by IO re-administration, following previous discontinuation due to irAE, is not well-defined because of their rarity, this case highlights the need for caution, particularly in cases with a history of previous irAE-associated GCA.

Introduction

Immuno-oncology (IO) therapies, particularly immune checkpoint inhibitors targeting the programmed cell death protein-1 (PD-1)/ligand-1 (PD-L1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathway have revolutionized the systemic treatment of metastatic renal cell carcinoma (mRCC) in recent years. Combined IO regimens based on immune checkpoint inhibitors are the cornerstone of the current front-line systemic therapy for mRCC. However, alongside their effectiveness, IO regimens come with a wide spectrum of immune-related adverse effects (irAEs). They are caused by over-activation of the immune system and can affect various tissues or organs, most commonly the skin, gastrointestinal tract, liver, and endocrine system [1, 2]. The combination of an anti-CTLA-4 antibody, ipilimumab, and anti-PD-1 antibody, nivolumab, represents an IO regimen widely used for the first-line therapy of mRCC. In the phase III randomized trial, CheckMate 214, irAEs of any grade were reported in 93% of patients, and grade 3–4 irAEs were reported in 46% of patients receiving nivolumab plus ipilimumab, respectively. Particularly, high-dose corticosteroids were required in 35% of patients due to irAEs [3]. The type and intensity of irAEs are always highly individual and cannot be predicted. Notably, combination IO regimens are associated with more severe irAEs as compared to monotherapy [4].

We describe a case of rare irAEs manifested as giant cell temporal arteritis (GCA) followed by severe encephalopathy in a patient with metastatic clear cell renal cell carcinoma. These irAEs occurred after the continuation of immunotherapy with a combination of ipilimumab and nivolumab as the first line of systemic therapy, resulting in a durable partial response.

Case Presentation

In April 2021, a 66-year-old man underwent left-side radical nephrectomy with adrenalectomy for clear cell renal cell carcinoma with sarcomatoid dedifferentiation, pT1b cN0 cM0, clinical stage I, grade 4. A local recurrence and metastatic spread with multiple lung metastases occurred in December 2021. According to the IMDC prognostic system, the patient was classified with intermediate risk (with one risk factor represented by less than 1 year from the time of diagnosis to systemic therapy). The first-line systemic therapy with a combination of nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) applied every 3 weeks was initiated in December 2021. Initially, the therapy was tolerated well, the patient was administered four cycles of combination IO without any side effects and the CT in March 2022 showed partial regression. After that, the treatment was continued with nivolumab maintenance monotherapy (240 mg) administered every 2 weeks. In April 2022 the patient

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complained of headache with a peak in the right temple area. Laboratory tests showed an increase in C-reactive protein (CRP) and erythrocyte sedimentation rate (FW). For the clinical suspicion of temporal arteritis, a temporal artery biopsy was performed, and the diagnosis of giant cell arteritis was confirmed (Fig. 1). Because of the mild symptoms without vision loss, oral prednisone (10 mg/day) therapy was initiated and nivolumab therapy was discontinued. The effect of the low-dose corticosteroid therapy was promptly leading to complete resolution of the symptoms after less than 2 weeks; subsequently, prednisone was continued for 6 weeks with gradual dose reduction until discontinuation. From May 2022 nivolumab maintenance therapy was continued. In September 2022, the patient was hospitalized for severe psycho-behavioral abnormalities including paranoid delusion of being killed by his wife and progressive cognitive decline. The CT scan revealed durable partial remission of the primary tumor and lung metastases. A brain CT followed by an MRI did not show any signs of brain metastases or other pathology. Laboratory tests including blood count, liver and renal function tests, sonogram, CRP, and thyroidal hormones did not show any significant abnormalities. The case was discussed with a psychiatrist who did not recommend any specific psychiatric medication. Suspecting irAE encephalopathy, the patient was administered a high-dose intravenous methylprednisolone therapy (2 mg/kg/day), which had a good effect and led to complete resolution of the symptoms within 5 days. Subsequently, oral prednisone (initially 50 mg/day) was continued and gradually tapered off over 4 months until complete discontinuation. The immunotherapy was permanently discontinued, and the follow-up was further monitored. As of March 2024, the patient is still in good physical and mental condition, without any residual neurologic deficit, and the CT scan shows durable partial remission of the metastatic tumor mass and complete remission of pulmonary metastases (Fig. 2).

Discussion

GCA, also known as temporal arteritis, is an autoimmune vasculitis that affects medium and large arteries, particularly those in the head and scalp, occurring either alone or associated with polymyalgia rheumatica [5]. It is characterized by granulomatous inflammation of the triple-layered vessel wall that may result in vessel obstruction, wall disruption, and aneurysmal formation. The granulomatous infiltrates are mainly formed by T lymphocytes, mostly CD4+ T lymphocytes, and macrophages, while in about 50% of cases, typical multinucleated giant cells are present. Although GCA is a rare type of irAE, there have been several reports of its occurrence in cancer patients receiving systemic therapies based on IO [6–8]. We describe a case of isolated GCA (without polymyalgia rheumatica or any other autoimmune disorder) occurring after administration of combined IO therapy consisting of four cycles of ipilimumab and nivolumab initially, followed by maintenance nivolumab monotherapy in a patient with mRCC. The symptoms, including headache with a peak in the right temple area, occurred 4 months after the initiation of immunotherapy, which is consistent with the literature, where the common duration between the initiation of IO and manifestation of various irAE-associated vasculitis (not specifically GCA) has been reported to be 3–4 months, although cases of delayed onset have also been reported [9, 10]. The diagnosis was based on clinical symptomatology and elevation of inflammation laboratory parameters (CRP, FW); subsequently, the GCA was confirmed by biopsy. Currently, there are no formal guidelines for the treatment of irAE-associated GCA, due to its rare incidence. Delaying or discontinuation of IO should be considered and the use of corticosteroids is suggested according to the recommendations for the management of GCA [11]. In our patient, we opted for low-dose corticosteroid therapy with oral prednisone, which had a very good clinical effect leading to an early resolution of symptoms, while the immunotherapy was discontinued. Since our patient exhibited only mild symptoms of GCA and

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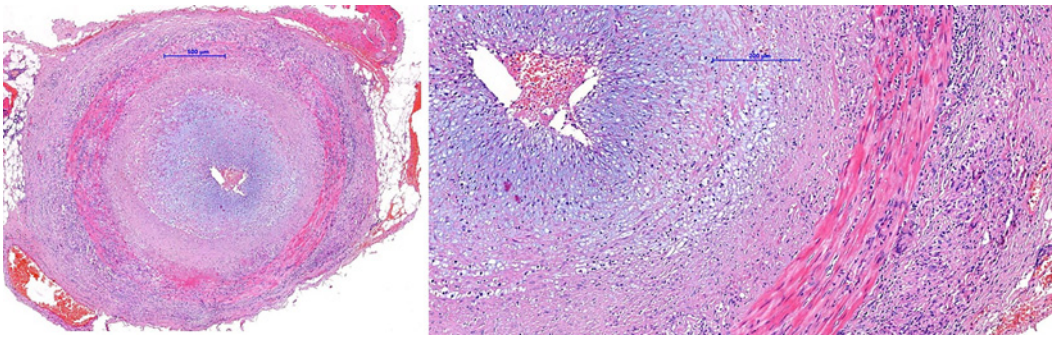

Fig. 1. Temporal artery biopsy showing remodeling of the arterial wall with marked narrowing of the lumina and irregular luminal contours conditioned by changes in the subendothelial connective tissue (tunica intima) with indistinct lamina elastica interna. A transmural round cell inflammatory infiltrate is present. The presence of giant multinucleated cells is noted in the tunica media and externa.

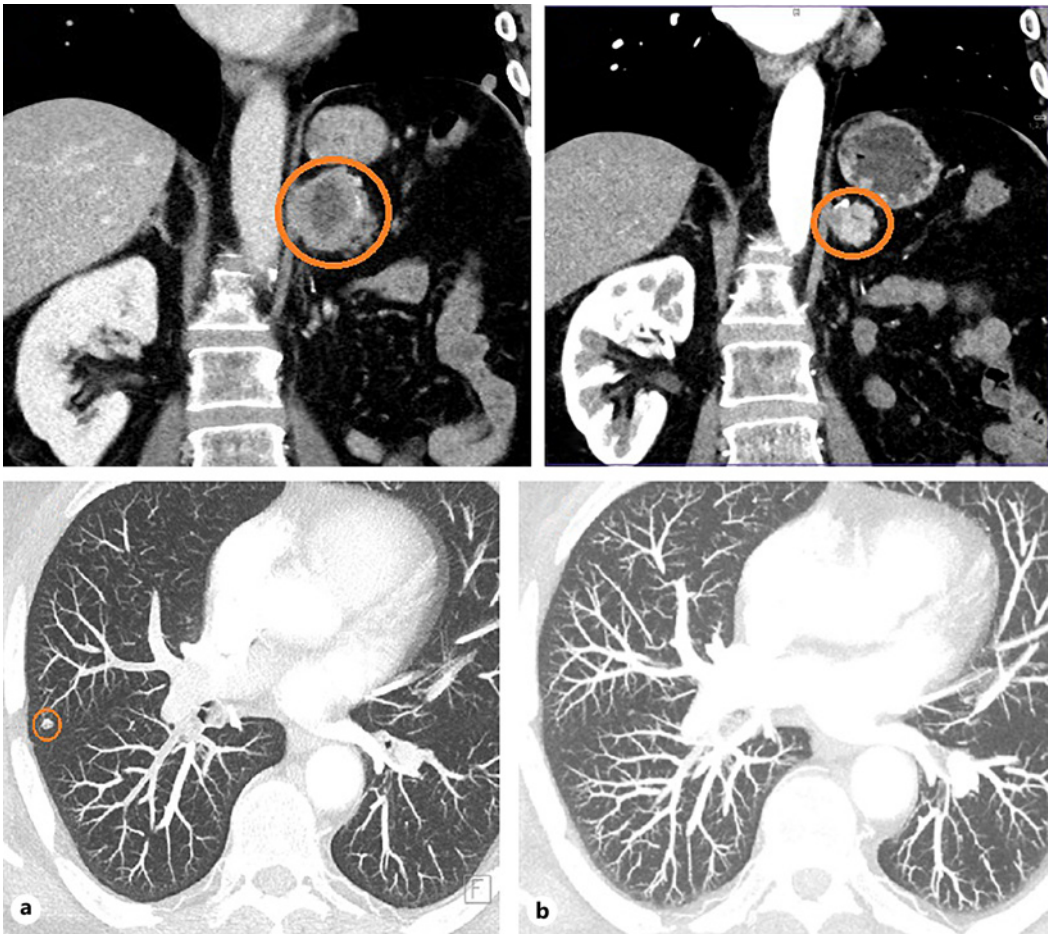

Fig. 2. Baseline CT taken in December 2021 (**a**) and control CT taken in March 2024 (**b**) showing durable partial regression of the metastatic tumor mass and complete regression of lung metastases.

responded rapidly to low-dose corticosteroid therapy and the follow-up CT scan indicated partial regression, we decided to continue with maintenance treatment using nivolumab. Four months later another irAE occurred in form of severe encephalopathy, manifested with psycho-behavioral abnormalities, including paranoid delusion and progressive cognitive decline. The condition required hospitalization and treatment with high-dose methylprednisolone, which was very effective, leading to the complete resolution of the symptoms with no residual psycho-behavioral abnormalities or neurologic deficits. Neurological irAEs affecting the central nervous system are rare. Notably, there is very limited data on the occurrence of encephalopathies in cancer patients treated with IO-based therapies. However, they are often of a high grade and potentially fatal. Thus, their early recognition and appropriate treatment are extremely important due to their wide differential diagnosis and potential severity [12, 13]. According to our best knowledge, a case of severe encephalopathy induced by re-administration of nivolumab after discontinuation for previous irAE-associated GCA has not been reported in the literature before. Although the immunotherapy was complicated by the described irAEs, our patient achieved a durable partial response that had lasted for more than 2 years at the time of publication. The positive associations between irAEs and the oncological outcome of cancer patients treated with IO have recently been debated. However, the prognostic role of rheumatic irAEs including GCA is unclear [14]. Similarly to our findings, Khan et al. [8] have recently reported a case of a patient with mRCC complicated with GCA following immunotherapy, who achieved a good partial response. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000540660).

Conclusion

We report a case of mRCC patient treated with a front-line combination IO regimen. This treatment was complicated by rare irAEs in the form of GCA and, subsequently, severe encephalopathy, which manifested with psycho-behavioral abnormalities and cognitive decline after the continuation of nivolumab. Both GCA and following encephalopathy responded well to corticosteroid therapy, leading to the complete resolution of symptoms. Although the risk of severe neurologic irAEs affecting the central nervous system induced by IO re-administration after a previous discontinuation due to another type of irAE is not defined because of their rarity, this case underscores the need for caution, particularly in patients with a history of previous irAE-associated GCA. Finally, the importance of reporting rare cases of severe irAEs should be emphasized as these events are likely underreported in clinical trials.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

O.F. received honoraria from Novartis, Janssen, Merck, and Pfizer for consultations and lectures unrelated to this project. J.F. has received honoraria from Astra Zeneca, Roche, and Novartis for consultations and lectures unrelated to this project. M.H. received honoraria from

Merck Sharp and Dohme for consultations and lectures unrelated to this project. M.T., K.P., J.B., P.S., and D.Š. declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

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Author Contributions

Study concept, design, drafting of the manuscript, and obtaining funding: O.F. Acquisition of data and critical revision of the manuscript for important intellectual content: O.F., M.T., K.P., J.B., P.S., D.S., M.H., and J.F. Analysis and interpretation of data; statistical analysis; administrative, technical, or material support; and supervision: none.

Data Availability Statement

The data that support the findings of this case report are not publicly available due to their containing information that could compromise the privacy of the patient but are available from the corresponding author (O.F.) upon reasonable request.

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