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Case Report

Giant cell arteritis and therapeutic response: a dual facet of immunotherapy in metastatic clear cell renal carcinoma

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Abstract

Immune checkpoint inhibitors have emerged as a promising cancer treatment, allowing significant and long-term therapeutic responses. Nivolumab, an anti-programmed cell death protein-1, is one of the molecules of this therapeutic class with known and manageable side effects. Giant cell arteritis is a rare immune-related adverse event most often manifested by headaches poorly released by common antalgics and can result in visual loss. We report its occurrence in an 80-year-old patient on maintenance nivolumab for metastatic clear cell renal carcinoma. Prompt diagnosis and initiation of glucocorticoid therapy led to symptom improvement and visual recovery.

Keywords: giant cell arteritis; nivolumab; immunotherapy; cancer; renal; side effect

Introduction

In recent years, immunotherapy has provided a new and practical pathway for cancer treatment, especially in advanced settings. Immunotherapy involves using substances that leverage the patient's immune system to counteract evasion mechanisms and improve its ability to destroy cancer cells. The most clinically effective way is targeting immune checkpoints CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) and PD-1/PDL-1 (program death 1/program death ligand), used by cancer cells to evade immune detection and elimination.

By promoting immune system activity, immune checkpoint inhibitors (ICI) can trigger a wide range of inflammatory side effects known as immune–related adverse events (irAEs), ranging from mild to life-threatening. They may warrant treatment withdrawal in 0.5%–13% of cases. Common irAEs include skin reactions, gastrointestinal disorders, endocrine system dysfunctions, hepatitis, and pneumonitis [1].

Cardiovascular disorders such as vasculitis are less often encountered [2]. Giant cell arteritis (GCA), also called temporal arteritis, is a type of vasculitis characterized by inflammation of arteries, especially cranial arteries.

We here report a rare case of GCA with an 80-year-old patient receiving Nivolumab for renal cell carcinoma.

Case scenario

An 80-year-old male patient, with a history of high blood pressure, was diagnosed with an advanced clear cell renal carcinoma with metastasis to the lung, mediastinal nodes, and pelvic bones. He also had a tumoral vena cava thrombus. The disease risk was intermediate based on the Heng score. He received a double ICI with anti-CTLA4 Ipilimumab and anti-PD1 Nivolumab. After 4 cycles, the disease was stable and nivolumab was kept in maintenance at 240 mg every three weeks.

After 6 cycles of Nivolumab, he presented a temporal headache that resolved spontaneously. A week after the eighth cycle, a recurrence of left frontal headache was observed without hyperesthesia, comb sign, and jaw claudication. There was no pain in the shoulder belt and cervical region. Temporal arteries were tender and sinuous. There also was a curtain effect on the left eye with a defect of the visual nasal field on the same eye. Fundoscopy showed an asymmetry of the optic disc, without prominent edema but the optic cup was not visualized in the left eye. Indocyanine green angiography showed choroidal delayed perfusion, evocative of GCA. C-reactive protein (CRP) was elevated at 46 mg/l (Normal <5 mg/l).

Further examination with PET-CT (Positron Emitting Tomography and Computed Tomography) did not find any argument for

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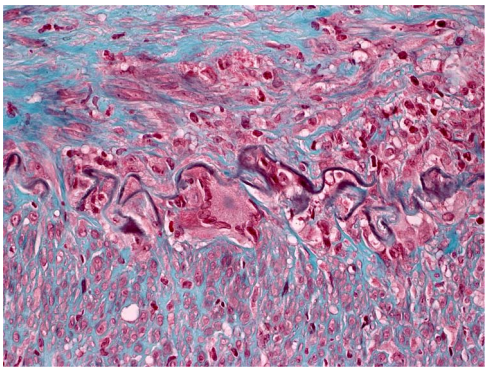

Figure 1. Histological image with trichrome masson staining × 400.

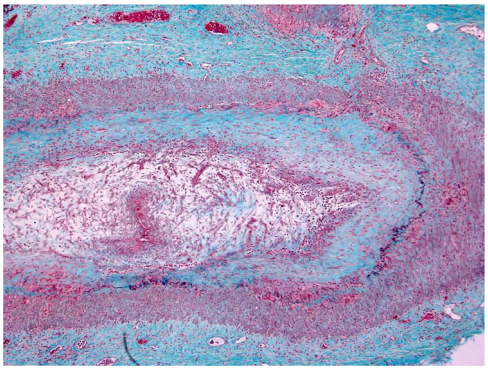

Figure 2. Histological image with trichrome masson staining × 50.

vasculitis of the large vessels. A biopsy of the left temporal artery confirmed giant cell arteritis (Figs. 1 and 2).

Nivolumab was discontinued and the patient received oral prednisone at 1 mg/kg/day, with a 5 mg reduction per month. All clinical manifestations were entirely regressed.

After 4 months of ICI discontinuation, the patient had a cancer progression while still on corticosteroid therapy. He then received cabozantinib with poor tolerance requiring dose regression and experienced further disease progression after 3 months. The patient is currently under third-line treatment with axitinib with no sign of progression after 3 months.

Discussion

GCA is a granulomatous vasculitis involving large and medium vessels, mainly the aorta and extracranial branches of the external carotid artery such as the temporal artery. Age is the main risk factor of GCA, as it rarely occurs before 50 years and has its peak incidence between 70 and 80 years [3].

A retrospective pharmacovigilance study revealed a noteworthy association between ICI treatment and vasculitis, specifically GCA, with the highest risk observed in the combination of anti-PD1/PDL1 and anti-CTLA4 antibodies [2].

Low expression and transcription of PD1 have been linked to various forms of vasculitis. It may be responsible for the infiltration of activated T-cells and high levels of inflammatory cytokines in the vasculature of affected arteries, as well as hyperplasia and neovessel formation in the intima. Mechanisms of the development of GCA in the setting of ICI use are not known, but they might reproduce in a similar environment [2, 4, 5].

The aforementioned inflammatory cytokines, especially interleukin 6, are correlated to the frequent and unspecific systemic signs of GCA. Low-grade fever is the most common along with anorexia and weight loss. Polymyalgia rheumatic is associated with around 40% of patients and is characterized by bilateral aching and stiffness of the neck, shoulder, and pelvic girdle [3].

Ischemic signs are more specific to GCA and depend on the vascular remodeling which can lead to stenosis or occlusion of affected arteries. Topography of the arterial involvement defines the type of ischemic manifestation. Due to the common involvement of the cranial artery, new onset headache is the most frequent sign. It is poorly released by common antalgics. Other cephalic signs include jaw claudication, scalp tenderness, and more rarely scalp or tongue necrosis. Patients can present with stroke in 7% of cases [3, 6].

The main concern with GCA is impairment and permanent loss of vision, resulting from ischemic optic neuropathy and occlusion of the ophthalmic artery and its branches [7]. Ophthalmic events can occur in 15%–20% of affected patients and are considered an emergency [2]. Transient visual loss can predict permanent visual loss, which is rarely reversible once established [7, 8]. Any ophthalmic sign needs to be addressed with prompt administration of glucocorticoids. Treatment may seldom improve an established visual loss but can prevent further deterioration [8].

Fortunately, in our case, symptoms improved after initiation of treatment and the patient recovered to full visual capacity.

Diagnosis of GCA is confirmed by temporal artery biopsy, which reveals granulomatous pan arteritis and the presence of inflammatory infiltrate within the media or intima [4]. However, a biopsy may not be performed before treatment initiation or can be falsely negative, mainly in extracranial large vessel involvement.

Retinal angiography is useful when ophthalmic symptoms are present like in our case. It shows a delay in choroidal vessel filling or the presence of non-vascularized choroidal areas [9].

Other imaging modalities have an interest in GCA diagnosis when large thoracic vessels like the aorta and subclavian arteries are concerned. These include magnetic resonance imaging (MRI), computed tomography (CT) with angiography, or PET-CT. When the disease is confined to the cranial like for our patient these procedures tend to be negative [9, 10].

The pathogenesis of GCA is not yet well understood. Case/control studies have reported the involvement of an environmental factor and in particular infectious by an increase in the DNA of certain bacteria or viruses in the temporal arteries of patients with GCA: cytomegalovirus, parvovirus B19, Herpes simplex virus, *Chlamydia pneumoniae* [11].

Varicella Zoster virus (VZV) is a neurotropic virus capable of replicating in arteries, particularly in the brain, and inducing vasculopathy [12].

An important role of the immune system has also been described through dendritic cells (DC), CD4 T lymphocytes, interleukins, and interferons via chemokines [13].

Programmed death-1 (PD-1) is a surface protein of activated T cells allowing its binding to PDL1 or L2 of dendritic cells. This binding induces apoptosis, anergy, and secretion of IL-10 by T cells. Lower expression of PD-L1 by vascular DC has been reported in patients with GCA, leading to sustained IL-17, IL-21, and IFN gamma-producing PD-1+ T cells [14].

The involvement of CTLA4 has also been reported in patients treated with Ipilumumab [15].

The pre-therapeutic assessment and evaluation under treatment didn't find any viral infectious cause and the involvement of other therapies. Pathological confirmation and pharmacovigilance made it possible to involve treatment with immunotherapy.

Management of GCA induced by ICI, like most irAEs is based on immunosuppressive agents. High doses of intravenous methylprednisolone should be considered in the first three days and then progressively reduced to target less than 5 mg/day. Depending on the severity of the irAEs, and the extent of immunosuppression required, ICI may have to be discontinued. However, the effectiveness of ICI has to be maintained as much as possible, as they can provide a long-lasting tumor response [16].

Conclusion

ICI can trigger GCA in cancer patients. Any new headache onset while on treatment, especially when associated with visual impairment, must alert the medical team and need to be addressed rapidly because of the risk of permanent visual loss.

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Authors' contribution

Acquisition and interpretation of data: AG, JM.
Drafting of the manuscript: AG, KH, JM, MF, RB.
Critical revision: HK, JM, MF, IE, RB.
All authors read and approved the final manuscript.

Conflict of interest

Authors declare no competing interests.

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Ethics approval

Not applicable.

Consent

Written informed consent from the patient for the publication of the manuscript and accompanying images is available.

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