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Anti-PD-1 Vasculitis of the central nervous system or radionecrosis?

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Abstract

Commentary on « Cerebral vasculitis mimicking intracranial metastatic progression of lung cancer during PD-1 blockade » by Läubli H et al., J Immunother Cancer. 2017;5:46.
The authors diagnosed a cerebral tumor-like lymphocytic vasculitis associated with anti-endothelial cell auto-antibodies secondary to anti-PD-1 therapy, treated by surgical resection and corticosteroids. We thought that this diagnosis should be discussed for at least two reasons. First, etiological explorations were not sufficient. Second, the diagnostic of radionecrosis should also be discussed.

Keywords: Cerebral vasculitis, Immunotherapy, Radionecrosis

Main text

In the June edition of Journal for ImmunoTherapy of Cancer, Läubli H et al. analyzed an interesting case report concerning a 53-year old man with stage IV non-squamous cell lung cancer with primary cerebral metastasis who developed an inflammatory tumor-like disease of the brain after anti PD-1 antibody treatment [1].

Primarily, the patient was treated with one fraction of 20 Gy stereotactic radiotherapy on the right parieto-temporal lesion and received four cycles of chemotherapy with cisplatin and pemetrexed. Two months later, he received nivolumab infusions, an anti PD-1 monoclonal antibody, as second line treatment for progressive disease. He rapidly developed focal neurological symptoms which seemed to be related to a new parieto-temporal lesion, suspected to be disease progression. Other lesions remained stable and he did not develop extra-neurological symptoms.

The parieto-temporal lesion was surgically removed and pathological analysis clearly eliminated a metastatic focus. The authors concluded a diagnosis of cerebral vasculitis, also called Angiitis of the Central Nervous System (ACNS). Indeed, histopathology seems to confirm necrotizing encephalitis associated with a perivascular infiltrate of T-cells. Although the patient had no preexisting auto-immune diseases, serum analysis revealed pre-existing anti-nuclear auto-antibody, anti-SSA/Ro and anti SSB/La antibodies. Moreover, at the time of the diagnosis of ACNS, serum anti-endothelial cells antibodies were observed, which prompted the authors to confirm this diagnosis.

ACNS is a rare and severe inflammatory disease of small leptomeningeal and parenchymal blood vessels of the brain, which could be caused by several neurologic insults such as malignancy, infection, ionizing radiation, and auto-immune disease [2]. Its main clinical manifestations are headache, focal neurological deficits, or seizures. Although tumor-like behavior is a well-known presentation of ACNS, they are more frequently observed as multifocal lesions of supratentorial cerebral ischemic infarctions, associated with hemorrhagic manifestations (parenchymal, subarachnoid or both) and leptomeningeal involvement in Magnetic Resonance Imaging (MRI) [3]. Pathological analysis of ACNS could show granulomatous, lymphocytic and/or necrotizing vasculitis [4]. The main lesions are perivascular, and extend through the vascular wall. Importantly, large and medium vessel involvement must be confirmed by cerebral conventional or magnetic resonance angiography. There are no specific auto-antibodies which permit confirmation of the diagnosis of ACNS.

In summary, the authors diagnosed a cerebral tumor-like lymphocytic vasculitis associated with anti-endothelial cell auto-antibodies secondary to anti-PD-1 therapy, treated by

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surgical resection and corticosteroids. We thought that this diagnosis should be discussed for at least two reasons.

First, if the patient had really developed cerebral vasculitis because of nivolumab, etiological explorations were not sufficient. The patient should have had a cerebral angiography, the gold standard in visualizing large or medium vessel arteritis to support diagnosis of ACNS, especially since there were no multifocal lesions, no signs of ischemic infarctions, no punctiform and linear enhancement, and no meningeal enhancement on the contrast-enhanced T1-weighted imaging. Further, no T2*-weighted or vascular sequences (TOF or Tricks) were performed to look for leptomeningeal hemorrhage or large vessel abnormalities. Moreover, although he did not develop systemic manifestations, a cryoglobulinemia associated vasculitis could be suspected by lymphocytic and necrotizing small vessels arteritis and presence of anti-nuclear, anti SSA and anti SSB antibodies [5]. Other systemic vasculitis should be eliminated, such as anti neutrophil cytoplasmic antibody (ANCA) associated vasculitis [6]. These points are important because primary and secondary angiitis of the central nervous system are severe diseases which should be treated with immunosuppressive drugs such as cyclophosphamide, mycophenolate mofetil or rituximab, and not only with surgical resection and corticosteroids [7]. The favorable outcome without any immunosuppressive treatment is also a strong argument against a primary or secondary cerebral vasculitis.

Second, the diagnostic of radionecrosis should also be discussed. Radionecrosis is the most common delayed complication of stereotactic radiotherapy in the treatment of brain metastases. Using the single high fraction dose radiotherapy used in this patient, radionecrosis occurs in about 10% of treated lesions, from 6 months to several years after treatment [8, 9]. Here, the timeline, the MRI findings, the response to corticotherapy and the localization of the new parieto-temporal lesion in the formerly irradiated area are all highly suggestive of radionecrosis. The imaging provided shows a nodular enhancement which is compatible with progression, but also with radionecrosis, corresponding to a leakage of gadolinium through the blood-brain barrier. A MR perfusion weighted imaging would then have shown changes in blood-brain barrier permeability and no increased relative cerebral blood volume (rCBV) [10]. Moreover, necrotizing and perivascular lymphocytic infiltrates found in the tissues are also compatible with this diagnosis, as shown in several pathological studies of radionecrosis [11]. The widely accepted pathophysiological hypothesis of radionecrosis is that direct primary injury to the blood vessels causes the brain parenchymal injury as secondary damage.

It is essential to note that the presence or development of auto anti-antibodies or anti-endothelial cell antibodies development do not confirm an auto-immune disease [12]. Clinical and/or radiological criteria are mandatory. In this case report in particular, the presence of anti-endothelial cell antibodies could be related to the radionecrosis leading to endothelial aggression. The specificity of anti-endothelial cell antibodies is not given and these antibodies could have targeted various antigens. Furthermore, it has been reported that patients who receive immunotherapy after stereotactic radiotherapy may have an increased rate of radionecrosis [13, 14].

For all these reasons, we think that "cerebral vasculitis" should not have been a definitive diagnosis for this patient. This very interesting case report highlights the need to establish strong collaborative networks between oncologists, radiotherapists, radiologists, organ specialists, internists and clinical immunologists. We do believe that the etiology of such rare events should be discussed and confronted in order to avoid misleading conclusions regarding the safety of immune checkpoint inhibitors and radiotherapy. Such combinations are currently the focus of more than 150 trials [15]. One should stress the absence of a straightforward randomized trial comparing stereotactic radiotherapy to stereotactic radiotherapy plus immunotherapy. It remains difficult to conclude the safety of the combination over irradiation alone which is known to give rise to 50% radionecrosis depending on the volume and dose-fractionation patterns [16]. It should however to be noted that a recent review of a large cohort of 85 patients receiving brain-directed radiation and anti-PD-1 did not report any radionecrosis, but favorable outcomes with prolonged survival [17].

Conclusions from limited size series always carry intrinsically their limits. For example, recent controversies related to the safety of BRAF inhibitors combined to brain radiotherapy with expediting adverse events have been solved by large enough series of data which eventually failed to confirm initial safety concerns [18]. Clinicians must disseminate toxicity data early on whenever possible. However, extreme caution should be standard to avoid the confusion between small and larger series of patients.

Abbreviations

ACNS: Angiitis of the Central Nervous System; ANCA: Anti neutrophil cytoplasmic antibody; MRI: Magnetic Resonance Imaging; PD-1: Programmed cell death 1; rCBV: Relative cerebral blood volume

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