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Regression of a melanoma brain metastasis that had appeared after immune checkpoint inhibitor discontinuation: a hypothesis-generating case

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ABSTRACT

We present the case of a 50-year-old woman previously treated with nivolumab-ipilimumab combination therapy for a metastatic melanoma. Despite premature discontinuation of these immune checkpoint inhibitors (ICIs) after 2 cycles due to severe immune-related hepatitis, the patient achieved a complete response. Nine months later, brain magnetic resonance imaging (MRI) showed progression of a single cerebral lesion, and the patient was referred for stereotactic radiosurgery. Unexpectedly, the brain MRI acquired one month later as part of radiosurgery planning showed a spontaneous regression of this lesion, allowing for radiosurgery cancellation. Follow-up imaging showed a sustained response, although the patient did not receive any other oncological treatment. We discuss here the potential immune mechanisms involved in this unusual course and the importance of better understanding the behaviour of tumours in the era of ICIs.

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Introduction

Immune checkpoint inhibitors (ICIs) have significantly improved the prognosis of metastatic melanoma (MM). Indeed, the combination of anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed cell death (PD-1) antibodies in MM has led to prolonged overall survival, reaching up to 52% at five years [1,2]. Immune-related adverse events (ir-AEs) are auto-immune reactions that are frequently induced by ICIs. These ir-AEs can be severe (i.e. leading to treatment discontinuation in approximately 30% of cases) and are difficult to predict [1,2]. Several studies have also highlighted the association between ir-AEs occurrence and the efficacy of ICIs, as both phenomena are associated with T cell activation [3,4].

Case presentation

A 50-year-old woman with no prior relevant medical history presented with headache and bradypsychia and was diagnosed with a right frontal brain lesion. Surgical resection was performed, and histology showed a metastasis from a *BRAF V600E*-mutated melanoma of unknown primary location. Staging with 18-fluorodeoxyglucose Positron Emission Tomography (FDG PET) revealed two other secondary lesions (one in the right lung and one in the left rectus abdominus muscle). Adjuvant radiotherapy to the resection cavity was delivered, and systemic treatment with dabrafenib and trametinib was started. Two months after treatment initiation, FDG PET showed disease progression with multiple new lesions in muscles and lymph nodes, and brain magnetic resonance imaging (MRI) demonstrated multiple brain metastases (Figure 2(a)). Second-line treatment with dual ICIs (nivolumab and ipilimumab) was started but had to be interrupted after two cycles due to Common Terminology Classification for Adverse Events (CTCAE) grade 3 hepatitis. The patient was treated with high dose intravenous methylprednisolone (maximal dose of 2 mg/kg/day for 5.5 weeks), oral mycophenolate mofetil (maximal dose of 4 g/day), and oral ciclosporin (maximal dose of 200 mg/day for 3.5 weeks), with complete resolution of the hepatitis (Figure 1).

Two months after ICIs discontinuation, while still on immunosuppressive treatment (methylprednisolone 64 mg/day, mycophenolate mofetil 4 g/day, and ciclosporin 200 mg/day), FDG PET imaging showed complete metabolic response of extra-cerebral metastases according to the iRECIST criteria, and brain MRI showed partial response (PR) based on RECIST 1.1 criteria, with a residual 2.5 mm lesion in the right parietal lobe (Figure 2(b)) [5,6]. Immunosuppression was then tapered off after two months, and no ICIs were restarted.

Four months after ICI arrest and one month after discontinuation of immunosuppressive agents, FDG PET showed a sustained complete response while the

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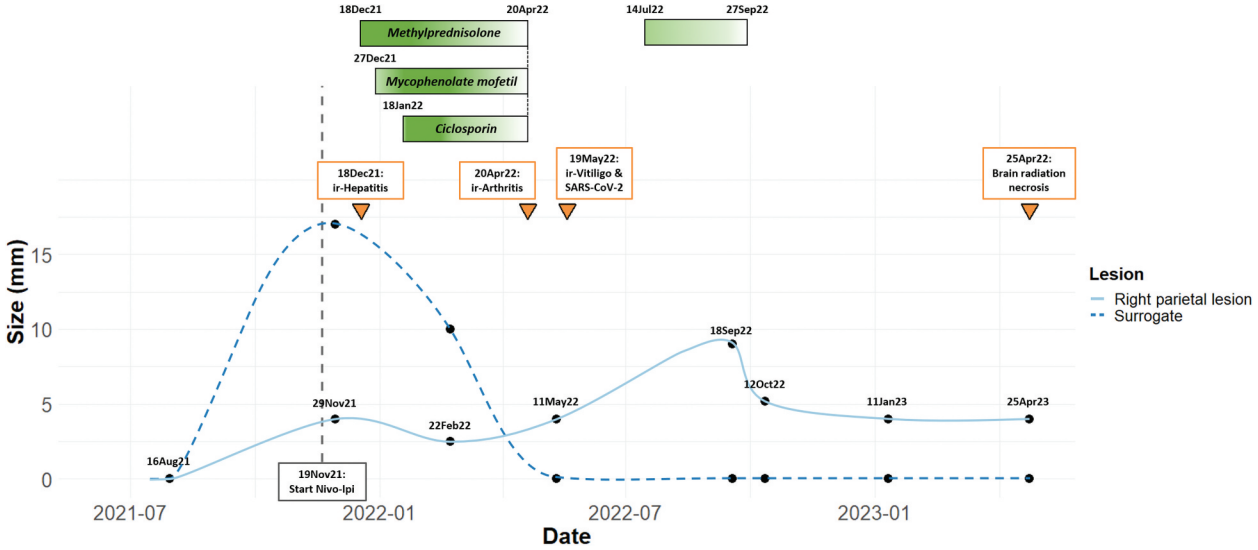

Figure 1. Overview of the oncological history of the patient. The change in the diameter of the right parietal lesion was compared to that of another brain metastasis, which was chosen as a 'surrogate' of the systemic disease evolution. After an initial reduction in size, the right parietal lesion underwent a progression followed by a spontaneous regression. The black dots represent the different times when a brain MRI was performed (intermediate size values were interpolated). The dashed grey line corresponds to the initiation date of nivolumab-ipilimumab therapy, which was discontinued after two cycles.

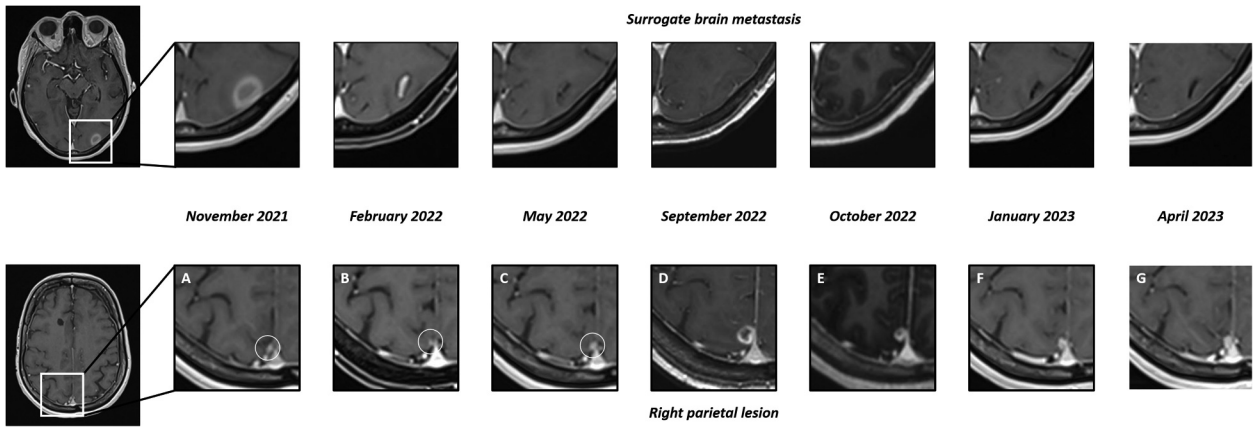

Figure 2. MRI showing a brain metastasis selected as a surrogate of the systemic disease and the right parietal lesion. A complete response was reached in all other brain and systemic lesions at the time of the third MRI (9 months after ICI discontinuation), as demonstrated by the evolution of the surrogate brain lesion.

right parietal brain lesion modestly increased to 4 mm (Figure 2(c)), allowing for close radiological follow-up. The patient subsequently presented with sequential symptoms likely to be immune-mediated. First, arthralgia, probably due to immune-related arthritis (negative serologic tests), appeared gradually. Four weeks later, she presented a mildly symptomatic SARS-CoV-2 infection (proven by real-time reverse transcriptase polymerase chain reaction), rapidly followed by vitiligo lesions of the neck and arms (Figure 1). Arthritis progressively worsened, and low-dose methylprednisolone (8 mg/day) was started but only resulted in a slight improvement of the symptoms despite a 2-month course (Figure 1).

Nine months after ICI discontinuation, at the end of this second steroid therapy, a new brain MRI showed that the right parietal brain lesion had increased to 9 mm (Figure 2(d)), and radiosurgery was proposed. Surprisingly, the MRI scan performed one month later as part of radiosurgery treatment planning showed that the lesion size had spontaneously decreased to 5 mm (Figure 2(e)). Radiosurgery was cancelled, and the patient underwent close follow-up. Control MRI scans performed 3 months (Figure 2(f)) and 6 months (Figure 2(g)) later (i.e. 17 months after ICIs discontinuation) showed further regression of the lesion to 4 mm (Figures 1 and 2(f)). Last brain MRI also showed a new contrast-enhancing lesion in the right genu of the corpus callosum. This lesion is located within the field of the adjuvant radiotherapy delivered previously to the right frontal surgical cavity. Additional methionine PET imaging did not show increased uptake at the level of this lesion, which is therefore most compatible with radiation necrosis. Noteworthy, ICIs could also be

associated with a higher risk of radiological necrosis although this remains controversial [7–9]. FDG PET performed at the same timepoints showed continuous complete remission.

Discussion

ICI drastically improved the outcome of MM patients. The emergence of ir-AE in these patients is likely associated with a better prognosis [3,4]. This is illustrated in the present patient, who showed sustained response for 17 months despite the early interruption of ICIs due to ir-AEs. The unusual feature presented here is the growth of a single brain metastasis several months after ICI discontinuation, followed by its spontaneous regression.

The initial growth of this brain lesion could be explained by surviving tumour clones (i.e. due to heterogeneous intratumoral sensitivity to ICIs), which were able to proliferate after ICI discontinuation [10]. The subsequent regression could be explained by several hypotheses, highlighting the link between the immune system of the patient and the tumour: (1) host antitumor immune response; (2) cross-reactivity with SARS-CoV2; (3) immunosuppressive treatment; (4) pseudo-progression; and (5) alternative etiologies mimicking brain metastasis.

First, tumour proliferation is associated with a high tumour mutational burden and increased neoantigen synthesis. Tumoral neoantigen release is also increased in growing brain tumours as well as immune cells migration, due to disruption of the blood-brain barrier [11–13]. As a result of the growth of the cerebral lesion, the host immune system, which was previously exposed to ICIs, could have been re-stimulated, leading to an antitumoral effect.

Second, an intercurrent immune-stimulating event (i.e. the patient experienced a SARS-CoV2 infection) could have led to 'cross-reactivity' of the immune system. Antigens generating an immune response during this event could share some similarities with tumoral cells and increase the immune response against the tumour. This immune reaction could have taken some time to overcome tumoral proliferation, explaining why the tumour size peaked a few weeks after the infection before the apparent spontaneous regression. This hypothesis is consistent with reported cases of spontaneous tumour response following SARS-CoV-2 infection, reflecting cross-reactivity of pathogen-specific T cells with tumour neoantigens and natural killer cell activation [14,15].

Third, the lesion growth could be due to the immunosuppressive treatments initiated to treat the ir-AEs, thereby counteracting the effect of ICIs. Indeed, regression of the lesion occurred rapidly after discontinuation of steroids and persisted thereafter, suggesting that the recovery of the immune system could be the primary mechanism involved. There are two arguments against this hypothesis. First, all initial lesions regressed despite the initial administration of high-dose immunosuppressive agents. This is consistent with other reports showing that immunosuppressive drugs initiated for ir-AEs do not impact the outcomes of patients [16,17]. Second, the steroid dose used during the second immunosuppression was much lower than the dose used during the first immunosuppression and did not exceed 8 mg/day, which is the accepted threshold that does not impact ICIs outcomes [16,17].

Fourth, the increase in lesion size could be related to pseudo-progression rather than oncological progression. If we consider that the visible brain lesion could have been a remnant of metastasis populated with inflammatory cells, we can hypothesise that the accumulation of pro-inflammatory episodes such as ir-AE (arthritis and vitiligo) and COVID infection could have triggered an inflammatory reaction in this lesion.

Fifth, the increased use of ICIs has led to the identification of uncommon neurologic adverse events, which may display MRI features similar to those of metastatic progression [18]. Other malignant (lymphoma, glioma, etc.) and non-malignant etiologies (abscess, tuberculosis, multiple sclerosis, etc.) can mimic brain metastases on MRI but they are not compatible with the spontaneous regression observed in our patient [19].

This case reflects the current difficulties in understanding precisely the outcome of some metastatic lesions following ICI treatment. A limitation of the present report is the lack of histological documentation of the right parietal lesion, which does not allow us to formally prove its malignant nature. This malignant nature is assumed based on radiologic interpretation. Although not specific, the annular enhancement and the disproportionate peripheral vasogenic oedema of the right parietal lesion on MRI are typical of a metastasis and do not support the hypothesis of a non-malignant origin [20]. Also, the right parietal lesion appeared at the time of systemic and brain progression, suggesting its metastatic origin. In the absence of tissue samples, multi-modality imaging could be of great value in orienting the diagnosis of tumoral progression (Table 1) [20–26]. However, routine imaging is not perfectly accurate for resolving all diagnostic uncertainties, and recent informatics technologies have been developed to guide the clinician. These innovations include radiomics analysis, which can help to distinguish tumour progression and pseudo-progression of brain metastases in ICIs-treated melanoma [27]. Furthermore, currently emerging artificial-intelligence models could be of great interest for the radiographic assessment of complex immunological phenomena observed in patients treated with immunotherapy. Integration of non-imaging

Table 1. Imaging findings of brain lesions in patients treated with immune checkpoint inhibitors[21–24].

Imaging modality	Tumour progression	Immune infiltrate	Brain necrosis
Contrast-enhanced CT	Annular/nodular enhancement with peripheric edema	-	Annular enhancement with peripheric edema
T1W MRI	Hypointense	Hypointense	Hypointense
Post contrast T1W- MRI	Annular/nodular enhancement	Variable enhancement	Annular enhancement
T2W/FLAIR MRI	Hyperintese	Hyperintense	Hyperintese
Perfusion MRI	↑ rCBV	-	↓ rCBV
AA-PET	↑ uptake	↑ uptake	↓ uptake
MR spectroscopy	↑ choline, ↓ N-acetylaspartate	-	↑ lipid-lactate peak, ↓ other metabolites

AA-PET: Amino-acid positron emission tomography, ADC: apparent diffusion coefficient, CT: Computed tomography, MRI: Magnetic resonance imaging, rCBV: Cerebral blood volume ratio, T1/2W: T1/2-weighted.

analysis is also promising. The detection of cell-free tumour DNA in cerebrospinal fluid could be used as a liquid biopsy to confirm the malignant nature of a brain lesion, while cerebrospinal fluid enrichment in clonal T-cell and/or autoimmune IgG antibodies would suggest neurologic ir-AEs [18,28]. Plasma cell-free tumour DNA has been found in low amounts in patients with brain metastases, but blood analysis with autoimmune antibody detection could also help to distinguish between a malignant progression and a neurologic immune reaction [18,29–31]. Another limitation of this report is that the exact moment when this lesion reached its maximum size is unknown as a result of the usual 3- to 4-month interval between MRI check-ups.

Conclusion

We discuss the case of a patient with metastatic melanoma whose clinical course was atypical. Nine months after the last oncological therapy, a brain metastasis began to grow and then spontaneously disappeared without any oncological treatment. We describe potential scenarios including host antitumor immune response, cross-reactivity, immunosuppressive treatment, pseudo-progression, and alternative etiologies. This case emphasises the strong link between cancer and the immune system and underscores the many remaining questions in this field.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Ethical statement

The subject has provided informed consent for the publication of the data that have been presented here.

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