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Cancer immunotherapy toxicities: A case report and review of the literature

Toxicité de l'immunothérapie anticancéreuse: Étude de cas clinique et revue de la littérature

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“It is through experience that men acquire science and art.”

Aristotle (384–322 B.C.E.), Metaphysics, book 1 [1.981a]

“C'est par l'expérience que la science et l'art font leur progrès chez les hommes.”

Aristote (384-322 av. J.-C.), Métaphysique, livre 1 [1.981a]

Summary

Introduction: Immunotherapy using checkpoint inhibitors has revolutionized the treatment of cancer, including melanoma by significantly increasing survival rates and disease control. However, despite their specific mechanism of action, checkpoint inhibitors can have specific immune-related adverse events, including rare but severe neurological toxicity.

Aim and methods: The objective of this work was to publish as 1st author a case report on an extraordinary clinical case presenting with specific immune checkpoint inhibitor related adverse events. I first perform a concise literature review on cancer immunotherapy and its toxicities, with special emphasis on immune checkpoint inhibitors. After careful review of the literature I collected, analyzed and interpreted all clinical data relevant for the publication and then wrote and revised the manuscript.

Results: We report a 44-year-old man diagnosed with stage IIIB melanoma who developed metastatic disease (pulmonary and brain metastases) and was treated with stereotactic radiosurgery and nivolumab immunotherapy. He developed asymptomatic multifocal diffuse white matter lesions consistent with active central nervous system demyelination seen on brain MRI. One month after cessation of the immunotherapy, spontaneous regression of the demyelinating lesions was observed, suggesting a nivolumab-related toxicity.

Discussion and conclusion: We report the first case of a melanoma patient with an asymptomatic and spontaneously reversible central nervous system demyelination following nivolumab immunotherapy. This case highlights the need for better recognition of such atypical and rare neurological toxicities which could be mistaken for progressive brain metastases. Early recognition and appropriate management are crucial to reduce severity and duration of these toxicities, especially for patients with less favorable evolution. This case report has been recently published in the *Journal of ImmunoTherapy of Cancer* (Pillonel et al. J Immunother Cancer. 2019 Dec 2;7(1):336).

Keywords: cancer immunotherapy, immune checkpoint inhibitors, immune related adverse events, nivolumab, neurological toxicities, CNS demyelination, metastatic melanoma

Traduction du résumé

Introduction: L'immunothérapie anticancéreuse avec les inhibiteurs de point de contrôle immunitaire *(Immune checkpoint inhibitors)* a révolutionné le traitement du cancer, dont le mélanome, en améliorant considérablement la survie des patients et le contrôle de la maladie. Cependant, malgré leur mécanisme d'action spécifique, les inhibiteurs de point de contrôle peuvent être à l'origine d'effets secondaires dysimmunitaires pouvant notamment entraîner dans de rares cas une toxicité neurologique grave.

Objectif et méthodologie: L'objectif de ce travail était de publier en tant que 1er auteur une étude d'un cas clinique extraordinaire présentant des effets indésirables spécifiques liés aux inhibiteurs de point de contrôle immunitaire. J'ai d'abord effectué une analyse bibliographique concise sur l'immunothérapie anticancéreuse basé sur les inhibiteurs de point de contrôle et des toxicités qui en résultent. Après un examen minutieux de la littérature, j'ai collecté, analysé et interprété toutes les données cliniques pertinentes pour la publication du cas et ensuite rédigé et révisé le manuscrit.

Résultats : Nous rapportons le cas d'un homme de 44 ans diagnostiqué avec un mélanome de stade IIIB qui a développé une maladie métastatique (métastases pulmonaires et cérébrales) et a été traité par radiochirurgie stéréotaxique et immunothérapie avec nivolumab. Il a développé des lésions asymptomatiques multifocales diffuses de la substance blanche correspondant à une démyélinisation active du système nerveux central observée à l'IRM du cerveau. Un mois après l'arrêt de l'immunothérapie, une régression spontanée des lésions démyélinisantes a été observée, suggérant une toxicité liée au nivolumab.

Discussion et conclusion: Nous rapportons le premier cas d'un patient atteint d'un mélanome avec une démyélinisation du système nerveux central asymptomatique et spontanément réversible suite à l'immunothérapie avec nivolumab. Ce cas souligne la nécessité de mieux reconnaître ces toxicités neurologiques atypiques et rares qui pourraient être confondues avec une progression des métastases cérébrales. Une reconnaissance précoce ainsi qu'une prise en charge appropriée sont cruciales pour réduire la gravité et la durée de ces toxicités, en particulier pour les patients dont l'évolution est moins favorable. Ce cas clinique a été récemment publié dans le *Journal of ImmunoTherapy of Cancer* (Pillonel et al. J Immunother Cancer. 2019 Dec 2;7(1):336).

Mots-clés: immunothérapie anticancéreuse, inhibiteurs de point de contrôle immunitaire, effets secondaires dysimmunitaires, nivolumab, toxicité neurologique, démyélinisation du SNC, mélanome métastatique

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2. Abbreviations

CAR	Chimeric antigen receptor
CHUV	Centre hospitalier universitaire vaudois
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
FDA	US Food and drug administration
FDG	18F-fluorodeoxyglucose
ICPis	Immune checkpoint inhibitors
irAEs	Immune-related adverse events
MRI	Magnetic resonance imaging
PD-1	Programmed death protein 1
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
SRS	Stereotactic radiosurgery
TCR	T cell receptor

3. Introduction

3.1. Cancer immunotherapy

Immunotherapy is an approach to antineoplastic therapy that manipulate the immune response against cancer. A series of ground-breaking discoveries since the middle of the last century in immunity and cancer research contributed to the breakthrough of cancer immunotherapy (1). In 2018, James P. Allison and Tasuku Honjo were awarded with the Nobel prize for physiology or medicine for the discovery of cancer therapy by inhibition of negative immune regulation (checkpoint inhibitors) (2). The field of cancer immunotherapy continues to rapidly evolve and has established itself as "fifth pillar" of cancer therapy, alongside surgery, chemotherapy, radiotherapy, and other targeted therapies. Cancer immunotherapy approaches include immune checkpoint inhibitors (ICPis) (3), adoptive cell therapy (4,5), as well as cancer vaccines, cytokine therapy, oncolytic viruses, agonists of innate immune receptors and many more (6–8). These therapies demonstrated durable clinical responses in many cancer types and have revolutionized the treatment of cancer (9). For the purpose of this work, this review will mainly focus on ICPis.

3.1.1. Checkpoint inhibitors

Immune checkpoint inhibitors (ICPis) are therapeutic monoclonal antibodies that target several regulatory molecules on T cells, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death protein 1 (PD-1) and its ligand, programmed death-ligand 1 (PD-L1) (10). CTLA-4 downregulates IL-2 production and T-cell proliferation in the early phase of the immune response, predominantly in lymph nodes, whereas PD-1 signaling inhibits previously activated T cells in peripheral tissues (11). CTLA-4 and PD-1 signaling pathways are tightly controlled to maintain self-tolerance; however, cancer cells can take advantage of these immune checkpoint molecules which inhibit T cell activation and thereby evade the immune system (10,12–14). Thus, ICPis activate the immune system by inhibiting these molecules and thereby boost T cell activation against cancer.

The most used checkpoint inhibitor agents in clinic are ipilimumab and tremelimumab (anti-CTLA-4), nivolumab, pembrolizumab and cemiplimab (anti-PD-1) as well as atezolizumab, durvalumab and avelumab (PD-L1). These ICPis demonstrated clinical efficacy and were shown to induce durable remission in different cancer types, which lead to their approvals by the Food and Drug Administration (FDA) for multiple oncological indications (9,15). Currently, ICPis have FDA approvals for different cancer types: melanoma (16–19), lung cancer (small cell and non–small cell) (20–22), renal cell carcinoma (23), urothelial carcinoma (24), Hodgkin's lymphoma (25), hepatocellular carcinoma (26), advanced gastric cancer (27), head and neck squamous cell carcinoma (28), tumors with microsatellite instability or mismatch repair defects (29,30) and others (10). Response rates range from 15-60%, being higher in melanoma and microsatellite instability-high tumors (31). Comprehensive reviews on immune checkpoint blockade with their mechanisms and implications have been published (3,11,32–35).

3.1.2. Cellular immunotherapy

An alternative and prominent approach for immunotherapy based cancer treatment is adoptive cell therapy (5). This therapy based on autologous tumor reactive T cells takes advantage of tumor-infiltrating lymphocytes (TILs), which are isolated and then expanded ex vivo before reinfusion into the patient. Adoptive T cell therapy is often combined with chemotherapy, high-dose IL-2, and ICPIs and was shown to induce durable and complete tumor regressions in some melanoma patients (5,8). Another type of adoptive cellular therapy is T cell therapy with T cell receptors (TCR) that may be affinity-enhanced. This therapy is based on T cells that have been modified to express TCRs that recognize antigen presented on tumor cells. Encouraging clinical responses were observed in patients with advanced myeloma treated with TCR–engineered T cells (36). Chimeric antigen receptor (CAR) T cell therapy has further extended the successful application of adoptive cell therapy for cancer treatment (37). CAR T cells are autologous T cells that have been genetically engineered to express a cell surface receptor that may bind tumor cells directly, independent of MHC presentation. When reinfused, these CAR T cells are directly cytotoxic to tumor cells bearing the tumor specific antigen.

CD19-specific CAR T cells are designed and currently used to treat B cell leukemias and lymphomas with striking success. However, CD19 CAR T cells were shown to cause specific and potentially life-threatening toxicities in hematologic malignancies, including cytokine release syndrome and neurologic events (9,38,39) and their application in solid tumors has been limited thus far (40–43).

3.2. Cancer immunotherapy toxicities

Although cancer immunotherapies have revolutionized cancer treatment by delivering durable clinical responses in some patients, it has also resulted in the rise of new treatment-specific toxicities (10), which are distinct from toxicities observed with other cancer treatments. Adverse events vary depending on the type of immunotherapy, based on their distinct mechanism of action (44). For the purpose of this work, this review will focus exclusively on the immune-related adverse events (irAEs) of checkpoint inhibitors.

3.2.1. Immune-related adverse events

Immune modulation resulting from checkpoint inhibition leads to a reduction of self-tolerance, causing a range of inflammatory side effects (irAEs) that resemble autoimmunity (35). The overall incidence of all-grade irAEs has been reported in up to 72% of patients receiving anti-CTLA-4 (ipilimumab) (45). Severe irAEs (grade ≥3) have been reported with an overall incidence of 15-42% with anti-CTLA-4 agents and less frequently with anti-PD-1 (5-10%) or anti-PD-L1 (1-7%) agents (46). Higher frequencies were observed in case of combination therapy with different ICPis (47,48). Onset of irAEs usually occurs early after treatment initiation within the first few weeks to months, but can also occur much later, even after discontinuation of the treatment (10).

3.2.2. Toxicities of immune checkpoint inhibitors

Immune-related toxicities of ICPis can in principle involve almost any organ system, with most common sites being skin, gastrointestinal tract, endocrine system, lung, musculoskeletal and nervous system. Commonly encountered adverse events are reviewed by organ system in the following section.

Cutaneous toxicities are often the first irAEs to appear and are the most frequently reported side effects in patients treated with ICPis, occurring in up to 50% of cases (49). The most commonly reported dermatologic toxicities are rash, pruritis and vitiligo (50,51). However, severe and life-threatening skin toxicities have been reported such as toxic epidermal necrolysis, which are more common with combinations of ICPis (52,53).

Gastrointestinal toxicities, such as diarrhea or colitis, are the second most common complications of ICPis therapy after dermatologic side effects. Similar to skin toxicities, colitis occurs more frequently with anti-CTLA-4 compared to anti-PD-1 therapy and most frequently with the combination of both ICPis treatments (54) (55). Inflammation can occur in any part of the gastrointestinal tract, with symptoms ranging from mild to severe, including intestinal perforation or death (56). Gastrointestinal toxicities typically occur 6 to 7 weeks after treatment initiation (57).

Endocrine toxicities are commonly encountered adverse events affecting patients with ICPis treatment. The most common endocrinological irAEs reported were thyroiditis and hypophysitis (58). Thyroid dysfunction (hypothyroidism or hyperthyroidism), primary adrenal insufficiency and insulin-dependent diabetes mellitus have also been widely reported with ICPis (59–61). Although severe symptoms may occur, patients can be easily treated with exogenous administration of the missing hormone (62).

Pulmonary irAEs from ICPis have been described, including pneumonitis, the most frequently reported pulmonary toxicity (52) and rarely sarcoidosis or pleural effusions (63,64). Pneumonitis occurs much more frequently with anti-PD-1 compared to anti-CTLA-4 treatment (63) and is more frequent under dual therapy (65). While rare, ICPis-related pneumonitis is potentially life-threatening, with an associated mortality of 1%–2% (63). The onset of pneumonitis is variable and may occur

several weeks after initiating therapy (52,65). Exclusion of common differential diagnoses of non-ICPis causes of pneumonitis is essential (53).

Rheumatological irAEs have been reported at a low prevalence of approximately 5%, which however is thought to be underestimated due to erratic reporting and the lack of defined characterization (66). The most common rheumatologic irAEs are inflammatory arthrititis and myopathy. Other rare rheumatologic irAEs have been reported, including myositis, vasculitis, polymyalgia rheumatica, connective tissue diseases, or flare-up of a pre-existing rheumatic disease (52,67). Myopathy is the most severe rheumatological adverse event, which often requires permanent discontinuation of ICPis therapy and can be potentially life threatening in those who develop myocarditis (66).

Neurological toxicities are rare, with an overall incidence of less than 1% of patients treated with ICPis (68). Neurologic irAEs can vary depending on the class of immunotherapy used (69). They are mostly low grade toxicities, with a higher incidence of severe adverse events associated with anti–CTLA-4 compared to anti–PD-1 inhibitors (68,70). Patients may present with a variety of neurological disorders that can potentially affect any aspect of the central or peripheral nervous system. Diagnoses may include peripheral neuropathies, Guillain-Barré syndrome, myositis, myasthenia gravis and rare central nervous system toxicities such as immune-mediated encephalitis, vasculitis, aseptic meningitis or multiple sclerosis (52,68,69,71–73). Neurologic irAEs require ruling out other differential diagnoses, including progressive oncologic disease or infectious causes, as well as prompt disease-specific management (74).

Several other ICPis induced irAEs, although not extensively covered in this review, are of clinical importance and require diagnostic awareness and vigilance from the treating oncologists. For instance, liver toxicity occurs frequently in patients treated with ICPis (75) and may present as hepatitis with hepatocellular injury and elevation of liver enzymes (61). Renal toxicity may also rarely occur in patients treated with ICPis. The most commonly reported renal irAE is acute interstitial nephritis, but other pathologies such as minimal change disease or lupus-like nephritis have been reported (76,77). Cardiac toxicity is another possible rare irAE resulting from checkpoint blockade and may present in the form of myocarditis, pericarditis, or cardiomyopathy (52,78,79).

Cardiovascular toxicity of ICPis are associated with a considerable morbidity and mortality and need permanent treatment discontinuation at all grades (53). Ophthalmologic toxicity is another rare irAE of ICPis, which have been described in few case reports (80). Furthermore, rare haematological irAEs have also been reported, including immune thrombocytopenic purpura, hemolytic anemia, aplastic anaemia and acquired haemophilia (81–84).

3.2.3. Proposed mechanisms of checkpoint inhibitor toxicities

The precise pathophysiological mechanisms for immune-related toxicity have not been fully uncovered and are still under investigation. However, various mechanisms have been proposed to explain the development of irAEs. ICPis-related toxicity is thought to represent bystander effects from the immune system activation against cancer — which is the basis of their mode of action (61) — resulting in auto-inflammatory reactions against host-cells, mediated by T-cell, antibody and cytokine responses (10,31,85). Studies suggest that irAEs may be induced by disinhibited T cells which target antigens that are shared by tumor and normal tissue, inducing both toxicity and response (31). In addition to antigenic resemblance, other mechanisms underlying ICPis-induced autoimmunity have been proposed, including exacerbation of pre-existing inflammation, genetic predisposition or other host-related factors such as for instance the composition of the host microbiome (35,86). Incidence and severity of irAEs depends on the distinct mechanism of action of ICPis, treatment dose and certain combinations of ICPis agents (10,86). For example, anti-CTLA-4 agents were found to trigger regulatory T cell dysfunction and affect T cell priming in draining lymph nodes, whereas anti-PD-1 antibodies were found to trigger regulatory T cell dysfunction and production of pathological auto-antibodies (61). Interestingly, the irAEs from anti-CTLA-4 therapy (ipilimumab), when compared to anti-PD-1/PD-L-1 agents, are generally more common, more severe, and are dose related. In addition, as exemplified above, combination of CTLA-4 and PD-1 blockade have been shown to increases toxicity, but was also shown to improve treatment efficacity (10,35,86).

Several predictive clinical and molecular biomarkers have been described to identify patients who will respond to ICPis. These biomarkers include PD-L1 expression levels in the tumor microenvironment,

tumor mutational burden, microsatellite instability (87–91), or irAEs onset (31). Several studies investigated the potential link between irAEs and ICPis treatment efficacy, but conflicting data exist on whether the occurrence of toxicity may be associated with improved response rates (9,10). But, some specific adverse events, like rash and vitiligo were shown to be associated with a better overall survival benefit in patients with metastatic melanoma treated with ICPis (86,92). However, the occurrence of irAEs is not required to obtain a treatment benefit (10).

3.2.4. Guidelines for management of immune-related adverse events

To date, no prospective studies are available to guide clinical management of irAEs of cancer immunotherapies. Multi-disciplinary consensus management guidelines from the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and the Society for Immunotherapy of Cancer (SITC) have been published and provide up-to-date recommendations for monitoring, diagnosis, and treatment of irAEs (52,53,93–95). Management of irAEs depends on the severity of the toxicity and is based on treatment discontinuation, steroids or further immune-modulating agents, with additional symptomatic measures (96,97). The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 5) are used to grade severity of toxicity (98). The criteria categorize toxicities into following groups: asymptomatic/mild (grade 1), moderate (grade 2), severe (grade 3), and life-threatening (grade 4). In general, guidelines recommend to temporarily suspend ICPis treatment if grade 2 (but not grade 1) toxicity occurs, to suspend treatment and initiate high-dose systemic corticosteroids upon grade 3 toxicity, and in case of grade 4 toxicity to permanently discontinue the treatment and/or hospitalize the patient.

4. Aim and Methods

The objective of this master thesis in medicine was to study a clinical case of unexpected ICPis-related toxicity and to publish this case report as 1st author in a peer reviewed journal. I was expected to work in an independent manner and had access to the clinical data necessary for my case report. I was directly supervised by Dr Veronica Aedo Lopez (Cheffe de clinique) and under the direction of my tutor Prof Peters Solange (Cheffe de service) at the department of Medical Oncology of the CHUV. I first performed, using the PubMed database, a careful literature review on ICPis toxicities, including physio-pathological mechanisms and broad spectrum of applications (see Introduction chapter), to put this clinical case in the context of the current knowledge in the field of cancer immunotherapy. I then reviewed the literature specific to neurological toxicities of ICPis relevant for the case report. Subsequently, I extracted the patient data from the electronic patient record systems of the CHUV (Soarian, Archimed, PACS-web) and studied all clinical data relevant for the publication. I worked with a specialist in neuroradiology, Dr Vincent Dunet (Médecin associé), who performed radiological data analysis of the case (CT, MRI and PET data). I interacted with several other distinguished experts at the CHUV in the field of Oncology (Prof Olivier Michielin, Médecin chef and Dr Gregoire Berthod, Médecin agréé), Neuro-oncology (Dr Andreas Hottinger, Médecin associé), and Radiation Oncology (Dr Luis Schiappacasse, Médecin associé) to benefit from their respective expertise. I then analyzed and interpreted the patient case and wrote the manuscript. I used Adobe Illustrator® to generate the figures and Mendeley® reference manager to edit citations. After review of the manuscript by all co-authors, I took care of the submission, revised the manuscript and followed the editorial process until acceptance.

5. Results / Case Report

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CASE REPORT Open Access

Multiple nivolumab-induced CNS demyelination with spontaneous resolution in an asymptomatic metastatic melanoma patient

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Abstract

Background: Immune checkpoint inhibitors (ICPis) have revolutionised the treatment of melanoma by significantly increasing survival rates and disease control. However, ICPis can have specific immune-related adverse events, including rare but severe neurological toxicity.

Case presentation: We report a 44-year-old man diagnosed with stage IIIB melanoma who developed metastatic disease (pulmonary and brain metastases) and was treated with stereotactic radiosurgery and nivolumab immunotherapy. He developed asymptomatic multifocal diffuse white matter lesions consistent with active central nervous system demyelination seen on brain MRI. One month after cessation of the immunotherapy, spontaneous regression of the demyelinating lesions was observed, suggesting a nivolumab-related toxicity.

Conclusion: We report the first case of a melanoma patient with an asymptomatic and spontaneously reversible central nervous system demyelination following nivolumab immunotherapy. This case highlights the need for better recognition of such atypical and rare neurological toxicities which could be mistaken for progressive brain metastases. Early recognition and appropriate management are crucial to reduce severity and duration of these toxicities, especially for patients with less favourable evolution.

Keywords: Immune checkpoint inhibitors, Nivolumab, Immune related adverse events, Neurological toxicities, CNS demyelination, Metastatic melanoma

Background

Immune checkpoint inhibitors (ICPis), ipilimumab and nivolumab, are recombinant human monoclonal antibodies which target cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed death-1 (PD-1) receptor, respectively. By blocking these key immune suppressive molecules on T cell surface, they elicit a potent immune response against cancer cells that managed to hijack these natural inhibitory signals [1]. Ipilimumab and nivolumab provide significant clinical benefits in patients with advanced melanoma [2–9] and multiple other tumor types, leading to FDA-approval of ipilimumab in 2011 and nivolumab in 2014 [1]. However, immunotherapies may elicit imbalances in immunologic tolerance which can result in excessive unregulated immune response with inflammatory or autoimmune side effects [10]. Hence, despite significant clinical benefit, the use of ICPis is frequently associated with a large spectrum of immune-related adverse events (irAEs) [2–9, 11], including rare but severe (grade 3–4) neurological toxicities [12–14]. Patients may develop a variety of neurological disorders including transient peripheral neuropathies, Guillain-Barré syndrome, myositis, myasthenia gravis, or less frequently central nervous system (CNS) toxicity such as hypophysitis, immune encephalitis, vasculitis, aseptic meningitis and multiple sclerosis. These

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neurological irAEs are yet extensively reviewed [12–15]. However, there has been only few scarce reports of CNS demyelination in association with ICPIs. One case was reported after nivolumab [16] and one after ipilimumab [17], which were both severe and eventually fatal. One more case of CNS demyelination resulting in neurological symptoms was reported after pembrolizumab, another PD-1 inhibitor [18]. Here, we present the first case of a melanoma patient with asymptomatic and spontaneously reversible CNS demyelination following nivolumab immunotherapy.

Case presentation

A 44-year-old Caucasian man was diagnosed in March 2017 with a stage IIIB cutaneous nodular melanoma on the right forearm, with a tumor Breslow thickness of 3.43 mm, without ulceration (pT3a), one clinically detected tumor-involved axillary lymph node (pN1b), and no evidence of distant metastasis (cM0). He was treated with wide local excision, axillary lymph node dissection, and then with high-dose adjuvant ipilimumab monotherapy at 10 mg/kg i.v., according to EORTC 18071 protocol [7, 19]. Two days after the first ipilimumab infusion, he developed a persistent grade 2 colitis, which was corticosteroid-resistant, treated with infliximab, and that imposed termination of the treatment.

In September 2017, a follow-up computed tomography (CT) scan revealed pulmonary progression (one unique lesion) and wedge resection of segment 10 of the left inferior lobe was performed. The pathology confirmed metastatic melanoma, programmed death-ligand 1 (PD-L1) positive (60%) and wild-type *BRAF*. Three months later, subsequent imaging by CT scan and brain magnetic resonance imaging (MRI) revealed metastatic progression in lung with multiple lesions in the left superior and inferior lobe, hilar lymph nodes, and brain with one cerebellar and 4 millimetric contrast enhancing lesions in the frontal white matter. A CyberKnife (Accuray Incorporated, Sunnyvale, California) stereotactic radiosurgery (SRS) was administered 2 weeks later to the 5 cerebral lesions in one single fraction of 24 Gy and an immunotherapy anti-PD1 with nivolumab (3 mg/kg as monotherapy) was initiated. The decision to administer nivolumab as monotherapy was based on the very high PD-L1 positivity (60% of tumor cells), but also to minimize the risk of new irAEs, given his previous ipilimumab-induced corticosteroid-resistant colitis, and knowing that combination of ipilimumab and nivolumab result in more complications [3, 12, 13].

Two weeks after the first nivolumab infusion the patient presented with asthenia, headache, and apraxia of the upper right limb with impaired coordination of the right hand, and later developed a grade 1 erythematous maculopapular rash. A brain MRI showed multiple new metastatic brain lesions in the cerebellum, the left frontoparietal cortex, and the brain stem. The lesions were all complicated by perilesional oedema, for which he was administered dexamethasone (1 mg i.d. for 7 days and 5.25 mg tapered over 14 days). There was no evidence of infection and thyroid function studies were normal. Within 1 week, he presented at the hospital after a generalized epileptic seizure with clonic movements of the right-hand side of his body. Electroencephalogram (EEG) recording, performed after the seizure, was considered normal despite the presence of a discreet left temporal slowing. MRI revealed no changes in the known brain metastases and no evidence of ischemic or haemorrhagic events. He was hospitalized and an antiepileptic treatment was introduced (Levetiracetam 500 mg bid) which prevented a recurrence of the seizures. In January 2018, CyberKnife SRS was administered to treat 7 new small metastasis (24 Gy in one fraction) and 3 large ones (35 Gy in five fractions) (Fig. 1a).

In February 2018, the immunotherapy with nivolumab was resumed (3 mg/kg, every 2 weeks). Follow-up brain MRI in April 2018 showed early evidence of good response with decrease in size or disappearance of the multiple pre-existing lesions without any new metastasis (Fig. 2a). In June 2018, after 11 cycles of nivolumab, a routine follow-up brain MRI showed multiple new diffuse white matter lesions, consistent with active CNS demyelination with a patient that was completely asymptomatic (Fig. 2b). These lesions consisted of multiple, well-defined, ovoid, T2-hyperintense lesions with incomplete ring enhancement (i.e. open ring sign) after i.v contrast administration and hypovascularization on perfusion weighted imaging (Fig. 1b). In addition, there was no abnormal diffusion restriction on diffusion-weighted imaging (DWI) in these lesions. They were mainly located in the juxtacortical and periventricular white matter of the fronto-parietal lobes, respecting Dawson fingers distribution, classical of demyelinating lesions (Fig. 2b). In contrast, previously treated brain metastases were T2-hypointense with central necrosis and large perilesional oedema, had complete ring enhancement on post-contrast T1-weighted imaging and hypervascularization on perfusion weighted imaging (Fig. 1a). Hence, demyelinating lesions could radiologically clearly be distinguished from brain metastases. The patient was asymptomatic and there were no findings indicating an infection or progression of his melanoma. Systematic neurological examination did not reveal any cranial or peripheral nerve abnormalities and he showed no cognitive function impairment. The EEG was repeated and was found unchanged from previous exams. Cerebrospinal fluid (CSF) analysis showed clear appearance with normal glucose and lactate levels. Elevated white blood cells (14×10^6/l) and lymphocytes (13×10^6/

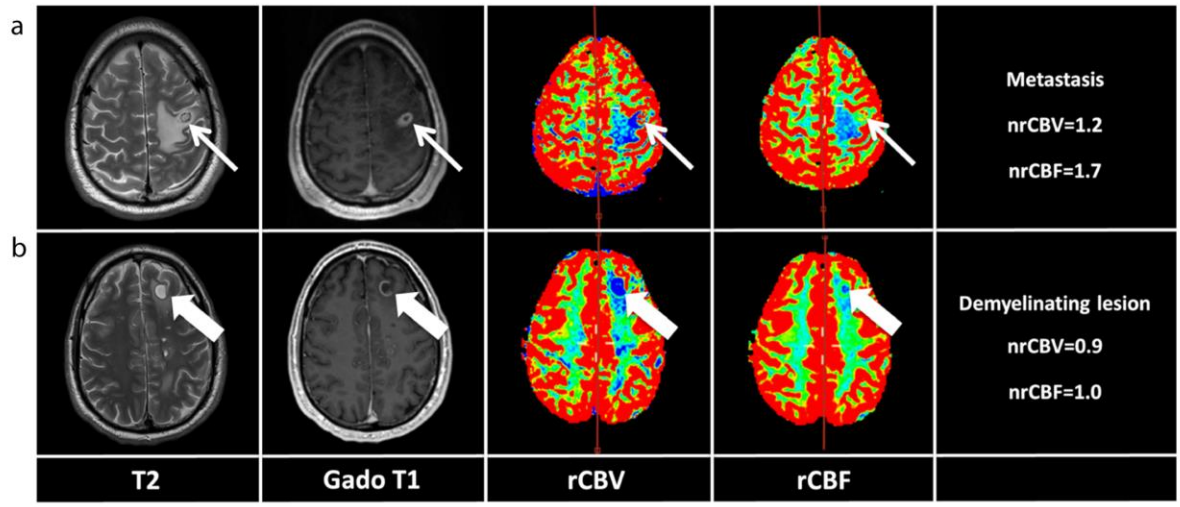

Fig. 1 Comparison of the appearance of metastasis and demyelinating lesion in this patient. **a** The patient was treated by stereotaxic radiotherapy in January 2018 for several brain metastases, the largest being located at the cortico-subcortical junction of the left precentral gyrus. The lesion appeared hypointense with central necrosis and large perilesional oedema on T2-weighted images, had complete ring enhancement on post-contrast T1-weighted images, and increased normalized cerebral blood volume (nrCBV = 1.2) and cerebral blood flow (nrCBF = 1.7) ratios on perfusion weighted images. **b** In June 2018, he developed several demyelinating lesions, the largest being located in the left superior frontal gyrus. Contrary to the brain metastasis, the lesion was juxtacortical, had little perilesional oedema, partial ring enhancement (i.e. open ring sign), and low nrCBV and nrCBF

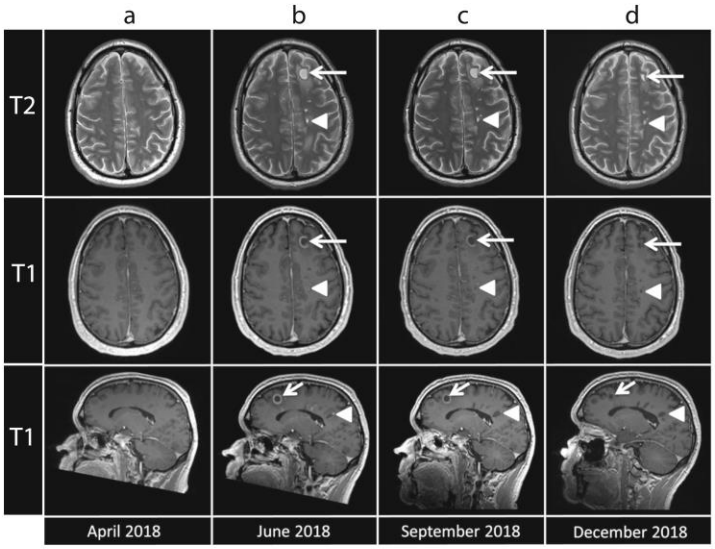

Fig. 2 Display of demyelinating lesions evolution over 6 months. Successive brain MRI are displayed on axial T2-weighted images (top row), axial (middle row) and sagittal (bottom row) T1-weighted images after i.v. infusion of gadolinium contrast media. **a** Baseline in April 2018 before CNS demyelination. **b** Demyelinating lesions were diagnosed in June 2018. The largest lesion was located in the juxtacortical white matter of the left superior frontal gyrus (arrows) while numerous small ovoid lesions (arrows' head) were located deep in the periventricular fronto-parietal white matter with a long axis perpendicular to the ventricle, corresponding to the typical "Dawson fingers" pattern. **c** After nivolumab discontinuation, lesions enhancement progressively decreased in September 2018. **d** The lesions disappeared in December 2018, leading to the characteristic "black hole" pattern on T1-weighted images

l) counts were found. Elevated protein level (594 mg/l, normal range: 150–450) and elevated albumin level (316 mg/l, normal range: 80–300) were observed. The CSF thus revealed a disrupted blood-brain barrier. Oligoclonal bands were absent, Immunoglobulins gamma (IgG) pattern and total IgG levels were normal in the CSF. Protein electrophoresis was normal, and serum autoantibody testing (anti-CNS, anti-LGT1, anti-CASPR2, anti-NMDA-R, anti-GluR1–2 AMPA) was negative. No tumor cell could be identified. Nivolumab immunotherapy was discontinued due to these demyelinating lesions. Since the patient was asymptomatic, it was decided not to give him any immunosuppressive treatment.

Strikingly, 1 month after cessation of nivolumab, the multiple demyelinating lesions spontaneously regressed (Fig. 2c), strongly suggesting an IrAEs of the immunotherapy, which was permanently discontinued. The patient has been followed by close monitoring for neurological symptoms and remained asymptomatic. Follow-up brain MRI every 3 months revealed complete resolution of these demyelinating lesions 6 months after initiation of nivolumab treatment (Fig. 2d and Fig. 3) along with stability in size and appearance of the prior identified cerebral metastases without new lesions. Tumor evaluation every 3 months by 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan did not reveal any hypermetabolic lesions and confirmed a complete systemic and cerebral response over 12 months after occurrence of his irAE.

Discussion and conclusions

Neurological complications of ICPis are rare, but often severe and may be life threatening, making its management challenging. This case study provides the first description of asymptomatic CNS demyelination after anti-PD1 blockade with nivolumab for metastatic melanoma with a spontaneous reversible course.

The patient reported here underwent an immunotherapy with nivolumab subsequent to adjuvant ipilimumab, which had to be discontinued after one dose of 10 mg/kg due to autoimmune colitis. Overall, the patient had been tolerating well the 11 cycles of nivolumab and was fully asymptomatic at the time of detection of lesions, radiologically compatible with CNS demyelinating lesions. Multiple juxta-cortical and periventricular white matter lesions with Dawson fingers distribution, open ring sign on post-contrast T1-weighted imaging and hypovascularization on perfusion weighted imaging were typical for demyelinating lesions.

Neurological adverse events of ICPis remain a complex diagnosis of exclusion [13]. In our case, all other differential diagnoses have been ruled out, including brain metastasis and leptomeningeal carcinomatosis for progressive oncologic disease, but also other demyelinating diseases of the CNS like multiple sclerosis as well as vascular, and infectious causes. The long interval of 12 months between the unique dose of ipilimumab and the occurrence of CNS demyelination argues against a role of this antibody. In previous case reports, the median time to onset of neurological irAEs following ICPis (mainly ipilimumab) was approximately 6 weeks (range: 1 to 74 weeks) and mostly occurs during the induction phase [20]. However, spontaneous regression of the radiological CNS lesions after nivolumab cessation strongly suggests a direct relationship between the two. Indeed, the onset and improvement of radiological

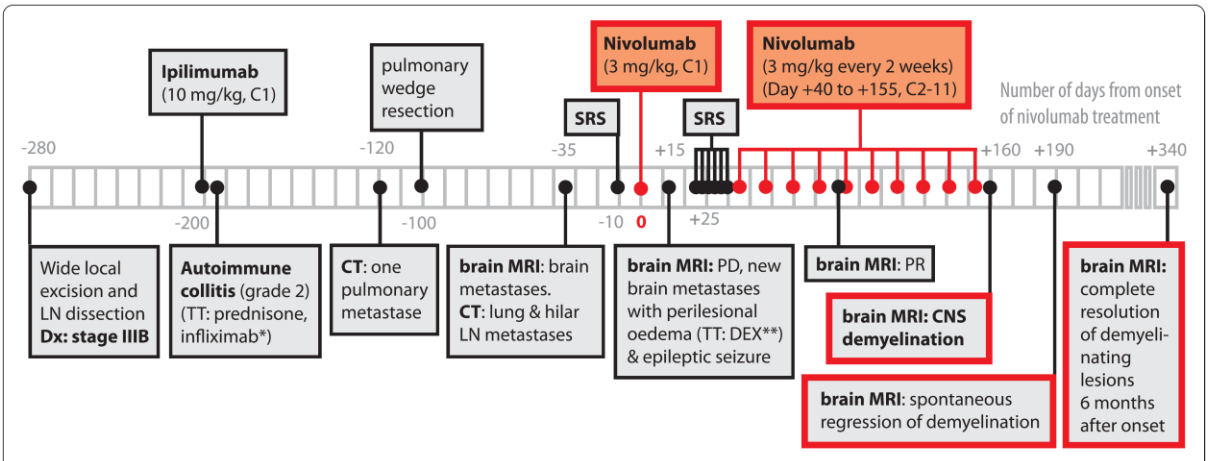

Fig. 3 Timeline of the patient's clinical, therapeutic, and radiological course. The 11 cycles of nivolumab administration and its related onset and resolution of CNS demyelinating lesions are highlighted in red. A time reference has been included, with Day 0 referring to the day of onset of nivolumab treatment. Abbreviations: LN: lymph node; C: cycle; SRS: stereotactic radiosurgery; Dx: diagnosis; TT: treatment; DEX: dexamethasone; PD: progressive disease; PR: partial response; MRI: magnetic resonance imaging; CT: computed tomography; CNS: central nervous system. *5 mg/kg; **1 mg i.d. for 7 days, and 5.25 mg tapered over 14 days

lesions correlates with the administration and discontinuation of nivolumab, respectively. This, along with the absence of any other possible etiology, indicates that CNS toxicity is most likely nivolumab-related. Considering the asymptomatic course, nivolumab immunotherapy was discontinued without administration of immunosuppression to avoid dampening of the antitumor activity. Remarkably, even without treatment all demyelinating lesions completely resolved 6 months after nivolumab discontinuation.

So far, CNS demyelination in association with ICPis treatment have not been reported in large cohorts of patients [21, 22], but only in few isolated cases [16–18]. Unlike in the case reported here, they were all severe, symptomatic and not spontaneously reversible. In addition, in two of these case reports, patients had either clinical or radiographic evidence of preexisting multiple sclerosis flares. Interestingly, PD1-blockade was previously shown to worsen demyelinating disease in animal models of multiple sclerosis [23, 24]. Moreover, a PD-1 gene polymorphism was found to be associated with disease progression in multiple sclerosis patients [25]. Taken together, these preclinical studies and the CNS demyelinating toxicity of PD-1 inhibitors observed in 3 case reports including this case [16, 18], suggest that the PD-1 pathway may play a regulatory role in the development of CNS demyelination.

This case report highlights the need for better recognition of atypical and rare neurological toxicities such as CNS demyelination under anti-PD1 treatment. It is essential to recognize such lesions as they may be mistaken for progressive brain metastases. Early recognition and appropriate management are crucial to reduce severity and duration of these toxicities, especially for patients with less favourable evolution [13, 15]. Atypical neurological irAEs like CNS demyelination may be more prevalent than expected and their real incidence has been possibly underestimated due to lack of recognition and/or underreporting, as these irAEs could be transient [12] and possibly asymptomatic like reported in this case. Of note, patients with active brain metastases were excluded from most pivotal clinical trials and hence, such rare asymptomatic CNS adverse events may have been missed in this particular setting. It is important, that oncologists, neurologists and radiologists are aware of such atypical and rare neurological toxicities, which are anticipated to rise given the increased use of ICPIs to treat melanoma and other malignancies. Further clinical trials are needed to evaluate the exact neurological safety profile and clarify the risk-benefit ratio of these ICPis in order to determine optimal management guidelines.

Abbreviations

CNS: Central nervous system; CSF: Cerebrospinal fluid; CT: Computed tomography; CTLA-4: Cytotoxic T-lymphocyte-associated antigen-4; FDA: Food and Drug Administration; FDG: 18F-fluorodeoxyglucose; ICPis: Immune checkpoint inhibitors; irAEs: Immune-related adverse events; MRI: Magnetic resonance imaging; PD-1: Programmed death-1; PET: Positron emission tomography; SRS: Stereotactic radiosurgery

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Authors' contributions

VP: analyzed and interpreted the patient case, wrote and edited the manuscript. VD: performed radiological data analysis and interpretation, provided the imaging figures and reviewed the manuscript. AFH: treated the patient, interpreted the case and reviewed the manuscript. BG: treated the patient, and reviewed the manuscript. LS: treated the patient, reviewed and confirmed the accuracy of the radiotherapy history. SP: interpreted the case and reviewed the manuscript. OM: treated the patient, interpreted the case and reviewed the manuscript. VLA: was the main treating physician, collected and interpreted the patient's data, and supervised this case report. All authors read and approved the final manuscript.

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Consent for publication

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Competing interests

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References

1. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov. 2018;8(9):1069–86.
2. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–23.
3. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob J, Cowey C, Lao C, et al. Combined Nivolumab and Ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373(1):23–34.
4. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320–30.

5. Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16(4):375–84.
6. Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol. 2014;32(10):1020–30.
7. Eggermont AMM, Chiarion-Sileni V, Grob J-J, Dummer R, Wolchok JD, Schmidt H, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2015;16(5):522–30.
8. Lebbe C, Weber JS, Maio M, Neyns B, Harmankaya K, Hamid O, et al. Survival follow-up and ipilimumab retreatment of patients with advanced melanoma who received ipilimumab in prior phase II studies. Ann Oncol Off J Eur Soc Med Oncol. 2014;25(11):2277–84.
9. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013;369(2):122–33.
10. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378(2):158–68.
11. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv119–42.
12. Liao B, Shroff S, Kamiya-Matsuoka C, Tummala S. Atypical neurological complications of ipilimumab therapy in patients with metastatic melanoma. Neuro-Oncology. 2014;16(4):589–93.
13. Perrinjaquet C, Desbaillets N, Hottinger AF. Neurotoxicity associated with cancer immunotherapy: immune checkpoint inhibitors and chimeric antigen receptor T-cell therapy. Curr Opin Neurol. 2019;32:500–10.
14. Larkin J, Chmielowski B, Lao CD, Hodi FS, Sharfman W, Weber J, et al. Neurologic serious adverse events associated with Nivolumab plus Ipilimumab or Nivolumab alone in advanced melanoma, including a case series of encephalitis. Oncologist. 2017;22(6):709–18.
15. Hottinger AF. Neurologic complications of immune checkpoint inhibitors. Curr Opin Neurol. 2016;29(6):806–12.
16. Maurice C, Schneider R, Kiehl T-R, Bavi P, Roehrl MHA, Mason WP, et al. Subacute CNS demyelination after treatment with Nivolumab for melanoma. Cancer Immunol Res. 2015;3(12):1299–302.
17. Cao Y, Nylander A, Ramanan S, Goods BA, Ponath G, Zabad R, et al. CNS demyelination and enhanced myelin-reactive responses after ipilimumab treatment. Neurology. 2016;86(16):1553–6.
18. Duraes J, Coutinho I, Mariano A, Geraldo A, Macario MC. Demyelinating disease of the central nervous system associated with Pembrolizumab treatment for metastatic melanoma. Mult Scler. 2019;25(7):1005–8.
19. Eggermont AMM, Chiarion-Sileni V, Grob J-J, Dummer R, Wolchok JD, Schmidt H, et al. Prolonged survival in stage III melanoma with Ipilimumab adjuvant therapy. N Engl J Med. 2016;375(19):1845–55.
20. Cuzzubbo S, Javeri F, Tissier M, Roumi A, Barlog C, Doridam J, et al. Neurological adverse events associated with immune checkpoint inhibitors: review of the literature. Eur J Cancer. 2017;73:1–8.
21. Johnson DB, Manouchehri A, Haugh AM, Quach HT, Balko JM, Lebrun-Vignes B, et al. Neurologic toxicity associated with immune checkpoint inhibitors: a pharmacovigilance study. J Immunother Cancer. 2019;7(1):134.
22. Malani R, Haggiagi A, Holder J, Shames Y, Briggs S, Callahan M, et al. Neurologic immune related adverse events (irAEs) in patients with metastatic solid tumors treated with immune checkpoint inhibitors: a single institution retrospective analysis (N6.001). Neurology. 2018;90(15 Supplement):N6.001.
23. Takizawa S, Kaneyama T, Tsugane S, Takeichi N, Yanagisawa S, Ichikawa M, et al. Role of the programmed Death-1 (PD-1) pathway in regulation of Theiler's murine encephalomyelitis virus-induced demyelinating disease. J Neuroimmunol. 2014;274(1–2):78–85.
24. Salama AD, Chitnis T, Imitola J, Ansari MJI, Akiba H, Tushima F, et al. Critical role of the programmed death-1 (PD-1) pathway in regulation of experimental autoimmune encephalomyelitis. J Exp Med. 2003;198(1):71–8.
25. Kroner A, Mehling M, Hemmer B, Rieckmann P, Toyka KV, Maurer M, et al. A PD-1 polymorphism is associated with disease progression in multiple sclerosis. Ann Neurol. 2005;58(1):50–7.

Publisher's Note

6. Discussion and Conclusion

6.1. Clinical case

This master thesis gave me the opportunity to explore the exciting field of checkpoint inhibitor-based cancer immunotherapy and its toxicities as well as to publish an unexpected clinical case of irAEs in a top oncology and immunology peer-reviewed journal. The case report presented here deserves to be published, since it provides the first description of asymptomatic CNS demyelination after anti-PD1 blockade with nivolumab for metastatic melanoma with a spontaneously reversible course. Thereby, this case study extends the few previous reports on immune-related neurological toxicity in the CNS upon immunotherapy with checkpoint inhibitors. So far, CNS demyelination in association with ICPis treatment have not been reported in large cohorts of patients (69,99), but only in few isolated cases (100–102), which were all severe, symptomatic and not spontaneously reversible as in the case described here. Furthermore, this work highlights the need for improved capture of atypical and rare neurological toxicities such as CNS demyelination under anti-PD1 treatment. It is important to recognize such lesions as they may be mistaken for progressive brain metastases. Atypical neurological irAEs like CNS demyelination may be more prevalent than expected and their real incidence has possibly been underestimated due to both lack of recognition and/or underreporting, as these irAEs can be transient (71) and possibly asymptomatic as in this case. Further studies will be required to evaluate the exact neurological safety profile and clarify the risk-benefit ratio of these ICPis in order to determine optimal management guidelines for such rare side-effects.

6.2. Future directions in onco-immunology

The field of cancer immunotherapy has rapidly evolved during the last decade and led to clinical benefit for patients with many different malignancies. The rapidly increasing number of indications for immunotherapy and the resulting increase in incidence of irAEs highlights the importance of early recognition and treatment of these unique toxicities, which is essential to minimize patient morbidity and mortality. Despite rapid advancements, the

precise pathophysiological mechanisms of immune-related toxicities have not been fully uncovered and are still under investigation. Numerous studies are ongoing to refine management, identify potential biomarkers of severity and susceptibility, and impact on anti-cancer efficacy. Furthermore, the identification of novel compounds targeting new immune pathways with increased potency and tumor selective distribution, as well as the increasing use of combination immunotherapy, will likely impact on the incidence and severity of irAEs (15).

7. References

1. Dobosz P, Dzieciątkowski T. The Intriguing History of Cancer Immunotherapy. Front Immunol. 2019;10:2965.
2. Altmann DM. A Nobel Prize-worthy pursuit: cancer immunology and harnessing immunity to tumour neoantigens. Vol. 155, Immunology. 2018. p. 283–4.
3. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012 Mar;12(4):252–64.
4. D'Aloia MM, Zizzari IG, Sacchetti B, Pierelli L, Alimandi M. CAR-T cells: the long and winding road to solid tumors. Cell Death Dis. 2018 Feb;9(3):282.
5. Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. Science. 2015 Apr;348(6230):62–8.
6. Chiang CL-L, Balint K, Coukos G, Kandalaft LE. Potential approaches for more successful dendritic cell-based immunotherapy. Expert Opin Biol Ther. 2015 Apr;15(4):569–82.
7. Ophir E, Bobisse S, Coukos G, Harari A, Kandalaft LE. Personalized approaches to active immunotherapy in cancer. Biochim Biophys Acta. 2016 Jan;1865(1):72–82.
8. Sanchez K, Page DB, Urba W. Immunotherapy Toxicities. Surg Oncol Clin N Am. 2019 Jul;28(3):387–401.
9. Kruger S, Ilmer M, Kobold S, Cadilha BL, Endres S, Ormanns S, et al. Advances in cancer immunotherapy 2019 - latest trends. J Exp Clin Cancer Res. 2019 Jun;38(1):268.
10. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. 2018 Jan;378(2):158–68.
11. Li X, Shao C, Shi Y, Han W. Lessons learned from the blockade of immune checkpoints in cancer immunotherapy. J Hematol Oncol. 2018 Feb;11(1):31.
12. Gajewski TF, Schreiber H, Fu Y-X. Innate and adaptive immune cells in the tumor microenvironment. Nat Immunol. 2013 Oct;14(10):1014–22.
13. Bhatia A, Kumar Y. Cellular and molecular mechanisms in cancer immune escape: a comprehensive review. Expert Rev Clin Immunol. 2014 Jan;10(1):41–62.
14. Vinay DS, Ryan EP, Pawelec G, Talib WH, Stagg J, Elkord E, et al. Immune evasion in cancer: Mechanistic basis and therapeutic strategies. Semin Cancer Biol. 2015 Dec;35 Suppl:S185–98.
15. Vanpouille-Box C, Lhuillier C, Bezu L, Aranda F, Yamazaki T, Kepp O, et al. Trial watch: Immune checkpoint blockers for cancer therapy. Oncoimmunology. 2017;6(11):e1373237.
16. Robert C, Long G V, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015 Jan;372(4):320–30.
17. Robert C, Schachter J, Long G V, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015 Jun;372(26):2521–32.
18. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010 Aug;363(8):711–23.
19. Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma

receiving nivolumab. J Clin Oncol. 2014 Apr;32(10):1020–30.

20. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016 Nov;375(19):1823–33.

21. Peters S, Reck M, Smit EF, Mok T, Hellmann MD. How to make the best use of immunotherapy as first-line treatment of advanced/metastatic non-small-cell lung cancer. Ann Oncol Off J Eur Soc Med Oncol. 2019 Jun;30(6):884–96.

22. Zimmermann S, Peters S, Owinokoko T, Gadgeel SM. Immune Checkpoint Inhibitors in the Management of Lung Cancer. Am Soc Clin Oncol Educ book Am Soc Clin Oncol Annu Meet. 2018 May;38:682–95.

23. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Nov;373(19):1803–13.

24. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee J-L, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017 Mar;376(11):1015–26.

25. Younes A, Santoro A, Shipp M, Zinzani PL, Timmerman JM, Ansell S, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. Lancet Oncol. 2016 Sep;17(9):1283–94.

26. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet (London, England). 2017 Jun;389(10088):2492–502.

27. Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, et al. Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. JAMA Oncol. 2018 May;4(5):e180013.

28. Ferris RL, Blumenschein GJ, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med. 2016 Nov;375(19):1856–67.

29. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017 Jul;357(6349):409–13.

30. Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz H-J, Morse MA, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol. 2017 Sep;18(9):1182–91.

31. Das S, Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. J Immunother cancer. 2019 Nov;7(1):306.

32. Miller JFAP, Sadelain M. The journey from discoveries in fundamental immunology to cancer immunotherapy. Cancer Cell. 2015 Apr;27(4):439–49.

33. Buchbinder EI, Desai A. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. Am J Clin Oncol. 2016 Feb;39(1):98–106.

34. Baumeister SH, Freeman GJ, Dranoff G, Sharpe AH. Coinhibitory Pathways in

Immunotherapy for Cancer. Annu Rev Immunol. 2016 May;34:539–73.

35. Urwyler P, Earnshaw I, Bermudez M, Perucha E, Wu W, Ryan S, et al. Mechanisms of checkpoint inhibition-induced adverse events. Clin Exp Immunol. 2020 Jan;

36. Rapoport AP, Stadtmauer EA, Binder-Scholl GK, Goloubeva O, Vogl DT, Lacey SF, et al. NY-ESO-1-specific TCR-engineered T cells mediate sustained antigen-specific antitumor effects in myeloma. Nat Med. 2015 Aug;21(8):914–21.

37. Singh AK, McGuirk JP. CAR T cells: continuation in a revolution of immunotherapy. Lancet Oncol. 2020 Mar;21(3):e168–78.

38. Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018 Jan;15(1):47–62.

39. Frey N, Porter D. Cytokine Release Syndrome with Chimeric Antigen Receptor T Cell Therapy. Biol blood marrow Transplant J Am Soc Blood Marrow Transplant. 2019 Apr;25(4):e123–7.

40. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018 Feb;378(5):439–48.

41. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019 Jan;20(1):31–42.

42. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019 Jan;380(1):45–56.

43. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017 Dec;377(26):2531–44.

44. Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. CA Cancer J Clin. 2020 Mar;70(2):86–104.

45. Bertrand A, Kostine M, Barnetche T, Truchetet M-E, Schaeverbeke T. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. BMC Med. 2015 Sep;13:211.

46. Davies M, Duffield EA. Safety of checkpoint inhibitors for cancer treatment: strategies for patient monitoring and management of immune-mediated adverse events. ImmunoTargets Ther. 2017;6:51–71.

47. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob J-J, Cowey CL, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2017 Oct;377(14):1345–56.

48. Shoushtari AN, Friedman CF, Navid-Azarbaijani P, Postow MA, Callahan MK, Momtaz P, et al. Measuring Toxic Effects and Time to Treatment Failure for Nivolumab Plus Ipilimumab in Melanoma. JAMA Oncol. 2018 Jan;4(1):98–101.

49. Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. Transl lung cancer Res. 2015 Oct;4(5):560–75.

50. Belum VR, Benhuri B, Postow MA, Hellmann MD, Lesokhin AM, Segal NH, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. Eur J Cancer. 2016 Jun;60:12–25.

51. Curry JL, Tetzlaff MT, Nagarajan P, Drucker C, Diab A, Hymes SR, et al. Diverse types of dermatologic toxicities from immune checkpoint blockade therapy. J Cutan Pathol. 2017 Feb;44(2):158–76.

52. Puzanov I, Diab A, Abdallah K, Bingham CO 3rd, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother cancer. 2017 Nov;5(1):95.

53. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol Off J Am Soc Clin Oncol. 2018 Jun;36(17):1714–68.

54. Geukes Foppen MH, Rozeman EA, van Wilpe S, Postma C, Snaebjornsson P, van Thienen J V, et al. Immune checkpoint inhibition-related colitis: symptoms, endoscopic features, histology and response to management. ESMO open. 2018;3(1):e000278.

55. Mantia CM, Buchbinder EI. Immunotherapy Toxicity. Hematol Oncol Clin North Am. 2019 Apr;33(2):275–90.

56. Reddy HG, Schneider BJ, Tai AW. Immune Checkpoint Inhibitor-Associated Colitis and Hepatitis. Clin Transl Gastroenterol. 2018 Sep;9(9):180.

57. Soularue E, Lepage P, Colombel JF, Coutzac C, Faleck D, Marthey L, et al. Enterocolitis due to immune checkpoint inhibitors: a systematic review. Gut. 2018 Nov;67(11):2056–67.

58. Ryder M, Callahan M, Postow MA, Wolchok J, Fagin JA. Endocrine-related adverse events following ipilimumab in patients with advanced melanoma: a comprehensive retrospective review from a single institution. Endocr Relat Cancer. 2014 Apr;21(2):371–81.

59. Byun DJ, Wolchok JD, Rosenberg LM, Girotra M. Cancer immunotherapy - immune checkpoint blockade and associated endocrinopathies. Nat Rev Endocrinol. 2017 Apr;13(4):195–207.

60. Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, et al. Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-analysis. JAMA Oncol. 2018 Feb;4(2):173–82.

61. Fessas P, Possamai LA, Clark J, Daniels E, Gudd C, Mullish BH, et al. Immunotoxicity from checkpoint inhibitor therapy: clinical features and underlying mechanisms. Immunology. 2020 Feb;159(2):167–77.

62. Darnell EP, Mooradian MJ, Baruch EN, Yilmaz M, Reynolds KL. Immune-Related Adverse Events (irAEs): Diagnosis, Management, and Clinical Pearls. Curr Oncol Rep. 2020 Mar;22(4):39.

63. Shannon VR. Pneumotoxicity associated with immune checkpoint inhibitor therapies. Curr Opin Pulm Med. 2017 Jul;23(4):305–16.

64. Suresh K, Psoter KJ, Voong KR, Shankar B, Forde PM, Ettinger DS, et al. Impact of Checkpoint Inhibitor Pneumonitis on Survival in NSCLC Patients Receiving Immune Checkpoint Immunotherapy. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. 2019 Mar;14(3):494–502.

65. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, et al. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. J Clin Oncol Off J Am Soc Clin Oncol. 2017 Mar;35(7):709–17.

66. Richter MD, Crowson C, Kottschade LA, Finnes HD, Markovic SN, Thanarajasingam U.

Rheumatic Syndromes Associated With Immune Checkpoint Inhibitors: A Single-Center Cohort of Sixty-One Patients. Arthritis Rheumatol (Hoboken, NJ). 2019 Mar;71(3):468–75.

67. Cappelli LC, Gutierrez AK, Bingham CO 3rd, Shah AA. Rheumatic and Musculoskeletal Immune-Related Adverse Events Due to Immune Checkpoint Inhibitors: A Systematic Review of the Literature. Arthritis Care Res (Hoboken). 2017 Nov;69(11):1751–63.

68. Larkin J, Chmielowski B, Lao CD, Hodi FS, Sharfman W, Weber J, et al. Neurologic Serious Adverse Events Associated with Nivolumab Plus Ipilimumab or Nivolumab Alone in Advanced Melanoma, Including a Case Series of Encephalitis. Oncologist. 2017 Jun;22(6):709–18.

69. Johnson DB, Manouchehri A, Haugh AM, Quach HT, Balko JM, Lebrun-Vignes B, et al. Neurologic toxicity associated with immune checkpoint inhibitors: a pharmacovigilance study. J Immunother cancer. 2019 May;7(1):134.

70. Cuzzubbo S, Javeri F, Tissier M, Roumi A, Barlog C, Doridam J, et al. Neurological adverse events associated with immune checkpoint inhibitors: Review of the literature. Eur J Cancer. 2017 Mar;73:1–8.

71. Liao B, Shroff S, Kamiya-Matsuoka C, Tummala S. Atypical neurological complications of ipilimumab therapy in patients with metastatic melanoma. Neuro Oncol. 2014 Apr;16(4):589–93.

72. Perrinjaquet C, Desbaillets N, Hottinger AF. Neurotoxicity associated with cancer immunotherapy: immune checkpoint inhibitors and chimeric antigen receptor T-cell therapy. Curr Opin Neurol. 2019 Mar;

73. Hottinger AF. Neurologic complications of immune checkpoint inhibitors. Curr Opin Neurol. 2016 Dec;29(6):806–12.

74. Zimmer L, Goldinger SM, Hofmann L, Loquai C, Ugurel S, Thomas I, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Cancer. 2016 Jun;60:210–25.

75. Cramer P, Bresalier RS. Gastrointestinal and Hepatic Complications of Immune Checkpoint Inhibitors. Curr Gastroenterol Rep. 2017 Jan;19(1):3.

76. Cortazar FB, Marrone KA, Troxell ML, Ralto KM, Hoenig MP, Brahmer JR, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. Kidney Int. 2016 Sep;90(3):638–47.

77. Wanchoo R, Karam S, Uppal NN, Barta VS, Deray G, Devoe C, et al. Adverse Renal Effects of Immune Checkpoint Inhibitors: A Narrative Review. Am J Nephrol. 2017;45(2):160–9.

78. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. N Engl J Med. 2016 Nov;375(18):1749–55.

79. Mahmood SS, Fradley MG, Cohen J V, Nohria A, Reynolds KL, Heinzerling LM, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. J Am Coll Cardiol. 2018 Apr;71(16):1755–64.

80. Antoun J, Titah C, Cochereau I. Ocular and orbital side-effects of checkpoint inhibitors: a review article. Curr Opin Oncol. 2016 Jul;28(4):288–94.

81. Meyers DE, Hill WF, Suo A, Jimenez-Zepeda V, Cheng T, Nixon NA. Aplastic anemia secondary to nivolumab and ipilimumab in a patient with metastatic melanoma: a case report. Vol. 7, Experimental hematology & oncology. 2018. p. 6.

82. Delyon J, Mateus C, Lambert T. Hemophilia A induced by ipilimumab. Vol. 365, The New

England journal of medicine. United States; 2011. p. 1747–8.

83. Davis EJ, Salem J-E, Young A, Green JR, Ferrell PB, Ancell KK, et al. Hematologic Complications of Immune Checkpoint Inhibitors. Oncologist. 2019 May;24(5):584–8.

84. Delanoy N, Michot J-M, Comont T, Kramkimel N, Lazarovici J, Dupont R, et al. Haematological immune-related adverse events induced by anti-PD-1 or anti-PD-L1 immunotherapy: a descriptive observational study. Lancet Haematol. 2019 Jan;6(1):e48–57.

85. Yoest JM. Clinical features, predictive correlates, and pathophysiology of immune-related adverse events in immune checkpoint inhibitor treatments in cancer: a short review. ImmunoTargets Ther. 2017;6:73–82.

86. Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in Resected and Unresectable Metastatic Melanoma: Characteristics of Immune-Related Adverse Events and Association with Outcomes. Clin cancer Res an Off J Am Assoc Cancer Res. 2016 Feb;22(4):886–94.

87. Gibney GT, Weiner LM, Atkins MB. Predictive biomarkers for checkpoint inhibitor-based immunotherapy. Lancet Oncol. 2016 Dec;17(12):e542–51.

88. Passiglia F, Bronte G, Bazan V, Natoli C, Rizzo S, Galvano A, et al. PD-L1 expression as predictive biomarker in patients with NSCLC: a pooled analysis. Oncotarget. 2016 Apr;7(15):19738–47.

89. Van Allen EM, Miao D, Schilling B, Shukla SA, Blank C, Zimmer L, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science. 2015 Oct;350(6257):207–11.

90. Danilova L, Wang H, Sunshine J, Kaunitz GJ, Cottrell TR, Xu H, et al. Association of PD-1/PD-L axis expression with cytolytic activity, mutational load, and prognosis in melanoma and other solid tumors. Proc Natl Acad Sci U S A. 2016 Nov;113(48):E7769–77.

91. Chan TA, Yarchoan M, Jaffee E, Swanton C, Quezada SA, Stenzinger A, et al. Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. Ann Oncol Off J Eur Soc Med Oncol. 2019 Jan;30(1):44–56.

92. Hua C, Boussemart L, Mateus C, Routier E, Boutros C, Cazenave H, et al. Association of Vitiligo With Tumor Response in Patients With Metastatic Melanoma Treated With Pembrolizumab. JAMA dermatology. 2016 Jan;152(1):45–51.

93. Thompson JA. New NCCN Guidelines: Recognition and Management of Immunotherapy-Related Toxicity. J Natl Compr Canc Netw. 2018 May;16(5S):594–6.

94. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. 2017 Jul;28(suppl_4):iv119–42.

95. Ernstoff MS, Puzanov I, Robert C, Diab A, Hersey P, Society for Immunotherapy of Cancer. SITC's guide to managing immunotherapy toxicity. Demos Medical Publishing; 2019.

96. Martins F, Sykiotis GP, Maillard M, Fraga M, Ribi C, Kuntzer T, et al. New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. Lancet Oncol. 2019 Jan;20(1):e54–64.

97. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019 Sep;16(9):563–80.

98. Common Terminology Criteria for Adverse Events (CTCAE) [Internet]. U.S. department of health and human services. National Cancer Institute; 2017. Available from:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Accessed April 19th 2020.

99. Malani R, Haggiagi A, Holder J, Shames Y, Briggs S, Callahan M, et al. Neurologic immune related adverse events (irAEs) in patients with metastatic solid tumors treated with immune checkpoint inhibitors: a single institution retrospective analysis (N6.001). Neurology [Internet]. 2018 Apr 10;90(15 Supplement):N6.001. Available from: http://n.neurology.org/content/90/15_Supplement/N6.001.abstract

100. Cao Y, Nylander A, Ramanan S, Goods BA, Ponath G, Zabad R, et al. CNS demyelination and enhanced myelin-reactive responses after ipilimumab treatment. Neurology. 2016 Apr;86(16):1553–6.

101. Maurice C, Schneider R, Kiehl T-R, Bavi P, Roehrl MHA, Mason WP, et al. Subacute CNS Demyelination after Treatment with Nivolumab for Melanoma. Cancer Immunol Res. 2015 Dec;3(12):1299–302.

102. Duraes J, Coutinho I, Mariano A, Geraldo A, Macario MC. Demyelinating disease of the central nervous system associated with Pembrolizumab treatment for metastatic melanoma. Mult Scler. 2019 Jun;25(7):1005–8.