



Case Report

Acute Late-Onset Diffuse Encephalopathy Secondary to Target Therapies in Metastatic Melanoma

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Abstract

Immunotherapy and targeted therapies are both major drugs used for metastatic melanomas. Various severe adverse event are reported with both. Few cases of acute encephalopathy induced by targeted therapies are described, resolving after discontinuation, but it rarely occurs as a late adverse event. We report a severe acute late-onset diffuse encephalopathy induced by targeted therapy (BRAF and MEK inhibitors), not resolving after treatment discontinuation and immunosuppressive treatment.

Keywords: Adverse Event; Encephalopathy; Immunotherapy; Melanoma; Targeted Therapy

Case

A 49-year-old woman presented with a left ankle MM in Fitzpatrick III, SSM, Clark III, Breslow 1.4 mm diagnosed in September 2015, stage IB, AJCC8th. A regional node relapse occurred in August 2018, treated by surgery and adjuvant local radiation without additional systemic drug. Molecular testing revealed BRAFV600E mutation on tumoral node. Follow-up imaging (whole body PET/CT scan) in November 2019, showed metastasis (3 pulmonary nodes, and 2 lytic lesions on sacrum bone). Anti PD-1 (pembrolizumab 400mg/6w) was started and stopped after 3 cycles, due to diffuse visceral progression there was no brain lesion on magnetic resonance imaging (MRI). TT was initiated on April 2020 (BRAFi DABRAFENIB 150mg twice daily combined with MEKi TRAMETINIB 2mg once daily). Two months later, patient presented a non-infectious colitis, grade III, refractory to 1mg/kg daily oral corticosteroids. Colitis resolution occurred after TT discontinuation. Another BRAFi and MEKi combination was restarted (ENCORAFENIB 450 mg/d with BINIMETINIB 45mg/td) without any colitis, enabling a complete response. On

Introduction

Prognosis of metastatic melanoma has considerably changed with the development of immune checkpoint inhibitors (ICI) as anti-PD-1 and anti-CTLA-4 to become the gold standard of first line treatment. Targeted therapies (TT) as BRAF inhibitors (BRAFi) combined to MEK inhibitors (MEKi), [1] are also part of the therapeutic arsenal for BRAF-mutated melanomas. Severe grade III-IV adverse events are reported on both of therapies; immune-related adverse events (irAEs) may occur days, months, or years later [2]. Few cases of early acute posterior reversible encephalopathy syndrome (PRES) in metastatic melanoma [3,4], treated with TT are reported. We report an acute late-onset diffuse encephalopathy TT-induced, not resolving after treatment discontinuation in a CR-MM (metastatic melanoma with complete response).

August 2022, 19th (i.e., 600 days after TT initiation) the patient presented sudden aphasia, headache, nausea, and memory loss. TT was not interrupted. Brain MRI (Figure 1A and 1D) performed in emergency revealed new T2 hyper intensity in the cortical region of left frontal lobe with juxtacortical and periventricular white matter hyper intensities without enhancement; PET/CT confirmed persistent extra cerebral complete response. Cerebrospinal fluid (CSF) analyses performed on August 26th excluded infectious, carcinomatous meningitides, and paraneoplastic syndrome (onconeuronal and anti-neuropil antibodies were not detected neither in blood, nor in CSF). High doses of IV corticosteroids (1g/day) were initiated for 5 days, followed by 1mg/kg, oral, to treat acute encephalopathy, with clinical benefit. After 6 days, patient presented few residual losses of words only. TT was not discontinued, to maintain complete response. Control MRI performed on 02 September and 23 September (Figure 1B and 1E) showed extension of T2 lesions with edema despite corticosteroid treatment. PET/CT on 15 September confirmed extra cerebral complete response but showed left front-parietal hypo metabolism (Figure 2). Neurological status rapidly deteriorated. On 26th September, patient presented complete loss of contact with mutism, impossible oral intake, and muscular deficit of upper and lowers limbs. TT was discontinued, corticosteroids high dose were continued, but without clinical improvement. Another MRI performed after 5 half-life of discontinuation of the TT, on 05 October (Figure 1C and 1F) showed partial reduction of edema with worsening of leptomeningeal enhancement. Mitoxantrone (MTX) (12mg/m², 3 courses) was initiated on October 07th, with the rationale that it was the most effective immunosuppressive treatment given its cerebral effect, as lymphocytes may potentially be involved. We noticed an improvement of neurological status, with resumption of contact and movement of upper limbs the 09th of October. She died the 10th of October, due to pulmonary sepsis without any additional exploration to support the response to mitoxantrone.

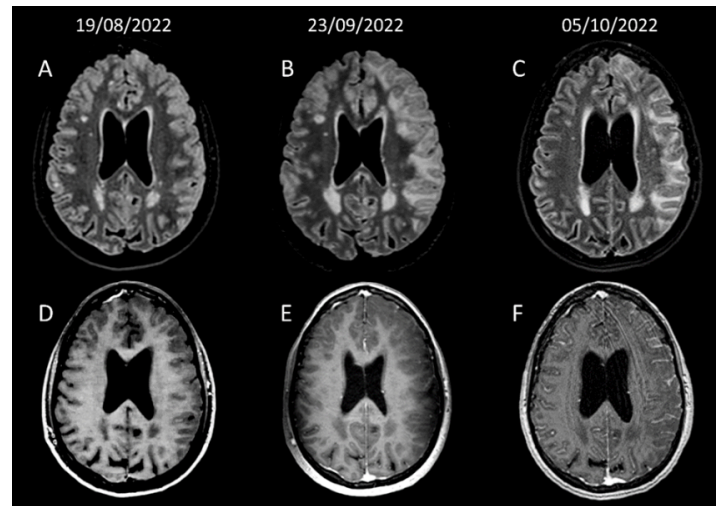


Figure 1: Axial T2 FLAIR (A-C) and axial T1-weighted gadolinium-enhanced (D-F) MRI. August MRI (A, D) show T2 hyper intensity in the cortical region of left frontal lobe with juxtacortical and periventricular white matter hyper intensities without enhancement. September MRI after corticotherapy (B, E) show extension of T2 lesions with edema. October MRI (C, F) show partial reduction of edema but new leptomeningeal enhancement.

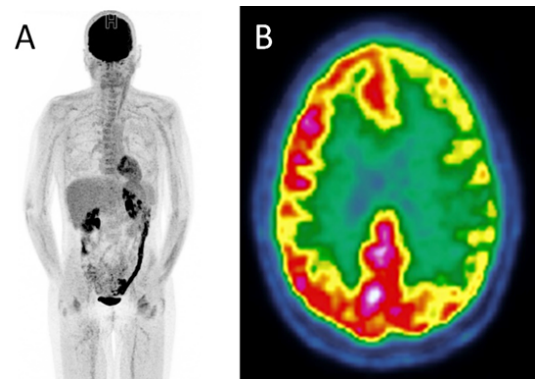


Figure 2: (A) FDG-TEP with extra cerebral complete response and (B) left front-parietal hypo metabolism.

Discussion

We report a rare acute late-onset diffuse encephalopathy secondary to TT. Improvement of cerebral RMI after 5 half-life's of TT suspension, and the absence of differential diagnosis is in favour of an adverse event due to TT. Targeted therapy are prone to give neurological adverse events as IT, but few cases are reported. Severe late grade III-IV irAEs [2] are reported, and neurological irAEs are observed more than 3 years after immunotherapy initiation. Systemic nervous irAEs [5] are described with an incidence rate of 0,1 to 12%, with 80% of them in the first four months of treatment. However, literature reports no encephalopathy incidence in patients treated by TT in second line after immunotherapy. Randhawa and al [6] reported an acute encephalopathy two weeks after TT initiation in a patient who received ICI in first metastatic line combined to chemotherapy, secondarily switched to TT. It was reversible after drug discontinuation. Sabile and al [3] reported a patient initially treated with ICI during four courses, switched to TT, which presented 3 weeks later a drug reaction with eosinophilia and systemic symptoms (DRESS) associated to (PRES). This adverse event was attributed to either delayed immune reaction from immunotherapy, or exacerbated by TT, but not due to TT alone. All cancer therapies were stopped, with PRES and DRESS resolution. Some resolute PRES are described after TT discontinuation, in second line after ICI, [4], but with fatal MM progression [7]. Immunoglobulin are used to treat acute encephalitis. Regarding kinetics of disease progression, Ig should probably have not be fast and efficient enough. Mitoxantrone inhibits T and B cells proliferation and macrophage impairing antigen presentation, and myelin degradation [8]. MTX is used to treat with success multiple sclerosis [9] or acute disseminated encephalomyelitis [10]. Making a pathophysiological parallel that our irAEs were lymphocyte-mediated, we proposed MTX without brain biopsy.

Conclusion

We report a rare case of acute encephalopathy, which occurred under targeted therapy in metastatic melanoma, in second line after immunotherapy; not reversible despite corticosteroid high dose and mitoxantrone. Rare and poorly documented cases of encephalopathy have been reported with TT. We hypothesize that this adverse event could be a delayed immune reaction from

immunotherapy, triggered by TT. Onco-dermatologists should be aware of this adverse effect and mitoxantrone, to manage and monitor these clinical elements with neurologists. Enhanced and prospective pharmacological monitoring would allow to distinguish a delayed side effect of immunotherapy after its discontinuation or a hitherto undescribed side effect under targeted therapy.

Conflict of interest: All authors declare no conflict of interest.

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