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► To cite this version:

Morgane Lacour, Lou Grangeon, Jasmine Flament, Anne-Bénédicte Duval-Modeste, Aline Zaréa, et al.. Ipilimumab-induced severe meningoradiculitis. *Journal of Clinical Neuroscience*, 2019, 62, pp.246 - 247. 10.1016/j.jocn.2018.12.009 . hal-03486181

HAL Id: hal-03486181

<https://hal.science/hal-03486181>

Submitted on 20 Dec 2021

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Case report

Ipilimumab-induced severe meningoradiculitis

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Words count excluding figure legends: 1060

Character count for the title: 42

Number of references: 7

Number of figures: 0

Keywords: Ipilimumab, immune checkpoint inhibitors, adverse effect, meningoradiculitis

Morgane Lacour reports no financial disclosures

Lou Grangeon reports no financial disclosures

Jasmine Flament reports no financial disclosures

Anne-Bénédicte Duval-Modeste reports no financial disclosures

Aline Zaréa reports no financial disclosures

Maxime Guillaume reports no financial disclosures

Romain Lefaucheur reports no financial disclosures

Authors contributions:

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Introduction:

Immune checkpoint inhibitors (ICIs) have greatly improved the survival of patients with several types of cancer by enhancing the anti-tumor immune responses by blocking signals from receptors exerting negative regulatory effects on T-cell activation. Serious neurological immune-related adverse events (irAEs) with these treatments are rare (<1%) but may be severe and require rapid recognition and treatment. Ipilimumab is a cytotoxic T-lymphocyte antigen-4 monoclonal antibody (anti CTLA4) approved for the treatment of metastatic and stage III melanoma [1]. We here report two rare cases of patients presenting ipilimumab-induced meningoradiculitis.

Case 1

A 51-year-old male, underwent surgical removal of a dorsal melanoma (Breslow 1,2, Clark IV, BRAF negative) with no evidence of metastases. Subcutaneous metastases and right inguinal lymphatic nodes appeared 20 months later. Nivolumab was initially introduced but was poorly tolerated and switched after two courses to Ipilimumab. Five weeks later, he presented with a painful distal sensory and motor weakness of both lower limbs, spreading to the upper limbs. Deep tendon reflexes were absent. Proprioception and cranial nerves were normal.

Routine blood tests were normal. Further investigations revealed positive antiganglioside anti-Gm1 IgG antibodies and positive antinuclear antibodies (80 CU). CSF was remarkable for a lymphocytic meningitis (73 leukocytes/mm³, with 96% of lymphocytic cells), elevated protein level at 2.87 g/L (N<0.5 g/L) and normal glucose CSF level (= 0.6 g/L; 0.5< N< 0.8 g/L). PCR screening tests performed on CSF for HSV, VZV, CMV, EBV, HHV-6, enterovirus, adenovirus and Lyme disease were all negative. CSF cytologic tests were negative for malignancy. CT scan revealed then right inguinal adenopathy with progression of the

subcutaneous metastatic lesions. Lumbar magnetic resonance imaging (MRI) showed enhanced gadolinium contrast of the equine cauda roots. No evidence of brain metastases was found on brain imaging. Electrophysiological nerves conduction study (NCS) and electromyography (EMG) of all 4 limbs showed acute sensorimotor demyelinating neuropathy compatible with the diagnosis of polyradiculoneuropathy.

Ipilimumab was stopped and intravenous (IV) immunoglobulins (0.4 g/kg per day during five days) were introduced. Pain and motor weakness mildly improved and the patient was sent to a rehabilitation center one month after symptoms' beginning. Two months later, repeated NCS and EMG showed a worsening of sensory and motor nerve conduction velocities, as well as a decrease of sensory and motor nerves amplitudes, with persistent fibrillation potentials. The patient still experienced distal hypoesthesia and distal motor weakness of all 4 limbs. Repeated CSF analysis disclosed 10 leukocytes/mm³ and proteins level at 1.32 g/L. CSF cytologic tests for malignancy remained negative.

Four months later, neurological examination showed persistent absent reflexes with hypoesthesia of both lower limbs. Repeated NCS and EMG showed an improvement of sensory and motor nerves conduction velocities and amplitudes but persistent fibrillation potentials. Third-line chemotherapy with dacarbazine was started and the patient continued to improve. Six months after initial neurological symptoms, he could walk with a stick. In contrast, PET/CT showed increased FDG uptake in several muscles, liver, lungs, kidney, and bones. The patient finally died 27 months after the melanoma diagnosis.

Case 2

A 65-year-old man was followed for a metastatic melanoma (Breslow 7.5, Clark IV) of the left arm evolving for 2 years with an initial left axillar lymphatic node, multiple para-aortic nodes and left suprarenal metastasis. A PET/CT had recently showed disease progression with

peritoneal carcinomatosis. Nivolumab immunotherapy was then stopped after the 26th regime and replaced by Ipilimumab. After the second infusion of Ipilimumab, the patient presented with a progressive and symmetrical painful weakness of lower limbs. Neurological examination revealed painful tactile hypoesthesia of the two legs, severe motor proximal and distal weakness predominantly involving the left lower limb, and areflexia. There was no autonomic dysfunction or cranial nerve impairment. CSF analysis revealed 47 leukocytes/mm³ with numerous lymphocytic cell, proteins level at 3.78 g/L, glucose CSF level at 0.8 g/L; (0.5 < N < 0.8 g/L). NCS and EMG showed acute sensorimotor demyelinating neuropathy at 4 limbs compatible with the diagnosis of polyradiculoneuropathy without fibrillation potential. IV immunoglobulins (0.4 g/kg per day for five days) were introduced. Neurological examination worsened 3 days after with the appearance of a left facial nerve palsy associated with a swallowing disorder. IV methylprednisolone (1 g daily for 3 days) was given followed by tapering oral prednisone (1 mg/kg daily), which led to an overall improvement. He could walk with assistance two weeks post admission. Corticosteroids were gradually decreased. Dacarbazine was introduced after a PET-scanner showing a disease progression with new FDG uptake sites. Repeated NCS 5 months later was similar to the first one and EMG was mildly improved. Six months after the neurological symptoms onset, the patient was able to walk alone with no residual disability.

Discussion

Here we report two cases of ipilimumab-induced meningoradiculitis. Neurological irAEs with anti CTLA4 are uncommon. A systematic review of 59 trials reported an incidence of 3.8% of neurological irAES following anti-CTLA-4 therapy [2]. The majority of these neurological side effects was low-grade and consisted of non-specific symptoms such as headaches and/or

dizziness. High-grade (\geq grade 3) neurological irAEs occurred in $< 1\%$ of patients and included autoimmune encephalitis, aseptic meningitis, myasthenia gravis, Guillain- Barre syndrome (GBS), peripheral sensorimotor neuropathies, myositis, and posterior reversible encephalopathy syndrome [3]. Our observation highlights the wide clinical range of these neurological irAES with the report of these two cases of meningoradiculitis. To our knowledge, only three similar cases of meningoradiculitis have been reported [4] [5] [6].

A prompt diagnosis of neurological irAES is necessary in order to start a suitable treatment as soon as possible. These adverse events usually occur within 6–12 weeks after initiation of CTLA4 therapy. After exclusion of differential diagnosis (infection, tumor invasion and/or paraneoplastic syndromes), ipilimumab therapy should be interrupted. Corticosteroids should be considered as the first-line treatment of choice for all neurological irAEs, even for conditions in which steroids are not usually indicated (e.g. Guillain–Barre syndrome) [7]. Our observations reinforce these guidelines. Indeed, we can note that our second patient who has been treated with corticosteroids recovered much faster than the first one. Patients who are unresponsive or only partially responsive to corticosteroids can be additionally treated with IVIg, plasmapheresis, anti-TNF-alpha antibodies, mycophenolate, and rituximab [3]. Finally, patients who experience severe neurological irAEs with ipilimumab treatment appear to have higher tumor response rates and increased survival compared to those without irAEs. Recent reports show that ICIs treatments are not formally prohibited in these patients with severe neurological irAES and that a different ICI may be proposed [6].

In conclusion, ICIs are new and highly effective treatment used in several malignancies. Physicians must be aware of the associated neurological irAES that can occur in order to start a suitable treatment as quickly as possible.

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