NEUROLOGICAL SIDE EFFECTS OF CHECKPOINT INHIBITOR TREATMENTS: A CASE OF IPILIMUMAB-RELATED POLYRADICULONEUROPATHY

A PICCA[1], L DIAMANTI[1], G BERZERO[1], P BINI[1], A PICHIECCHIO[2], E ALFONSI[3], C PORTA[4], A FERRARI[4], E MARCHIONI[1]

[1]Department of Neuroncology, C. Mondino National Neurological Institute, Pavia, Italy
[2]Department of Neuroradiology, C. Mondino National Neurological Institute, Pavia, Italy
[3]Department of Neurophysiopathology, C. Mondino National Neurological Institute, Pavia, Italy
[4]Department of Medical Oncology, I.R.C.C.S. San Matteo University Hospital Foundation, Pavia, Italy

Introduction

Immune checkpoints are molecules involved in preventing autoimmunity and maintaining self-tolerance by inhibiting T-cell activation. Tumor cells are capable to escape from immune system via the activation of immune checkpoints. Inhibition of immune checkpoints may increase T-cell immune response against tumor by blocking this aberrant downregulation. Ipilimumab is a monoclonal antibody that blocks CTLA-4 (cytotoxic T-lymphocyte antigen-4); it is approved for patients with stage III or metastatic melanoma.

Use of checkpoint inhibitors, however, can disrupt patient immune system balance leading to **immune-related adverse events** (irAEs). Most common Ipilimumab adverse events are immune-related and involve skin, gastro enteric tract, liver and to a lesser extent pituitary gland (autoimmune hypophysitis). As the use of these agents increases, atypical immune-related side-events are seen, also involving central and peripheral nervous system.

Here, we describe the case of neurological adverse event in a patient treated with Ipilimumab for metastatic melanoma.

Case report

D.R., a 69-years-old woman, started immunotherapy with Ipilimumab according to standard schedule (3 mg/kg e.v. every 3 weeks for a total of 4 doses) for a metastatic melanoma.

After third cycle she experienced mild paresthesia in lower limbs, not reported to the physicians. The day after fourth cycle she developed paresthesia in lower limbs, and to a lesser extent the hands (fig.1). She then suffered gait impairment and distal weakness. Symptoms were progressive over two weeks, then stabilized. Pregabalin did not improve symptoms. He has been addressed to our service and subsequently hospitalized. Clinical and instrumental findings are reported in Table 1, column A.

For suspected immune-mediated etiology related to Ipilimumab, she has been treated with high dose intravenous methylprednisolone (1 g i.v. /die for 6 days) followed by oral tapering. The patient improved quickly, with disappearing of lower limbs symptoms and recovery of a normal gait. She returned home, with only mild hands paresthesias remaining.

A second hospitalization one month later confirmed the ongoing improvement (Table 1, column B).

Patient is in follow up at the moment, free from neurological relapses.

Conclusions

This case confirm that **neurological immune-related adverse events** are uncommon but possible **during checkpoint inhibitors treatment**. They can **range widely**, including Guillain-Barré-like syndromes, chronic immune demyelinating polineuropathy, polyradiculitis, meningitis, encephalitis, enteric neuropathy, myastenia gravis-like syndromes and transverse myelitis. Immune-related adverse event should always be suspected in patients treated with checkpoint inhibitors who develop new neurological symptoms.

CSF analysis (showing increased proteins and white blood cells count, mostly lymphocytes) and **MRI scans** (ruling out metastases and showing inflammatory findings like contrast enhancement and swelling) can be helpful.

Temporal onset of neurological adverse events is still to define, but commonly they arise after third or fourth cycle. Given the long-term action of Ipilimumab, irAEs can occur even after treatment termination.

If an immune-related adverse event is suspected, rapid start of high-dose of **steroids** may lead to recovery. **Intravenous immunoglobulins or plasmapheresis** has also been reported effective. If no relevant benefits are seen, a second-line treatment with different immunosuppressors should be explored.

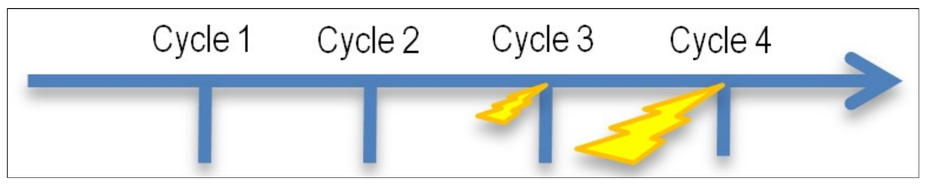

Fig.1: symptoms timeline related to Ipilimumab cycles

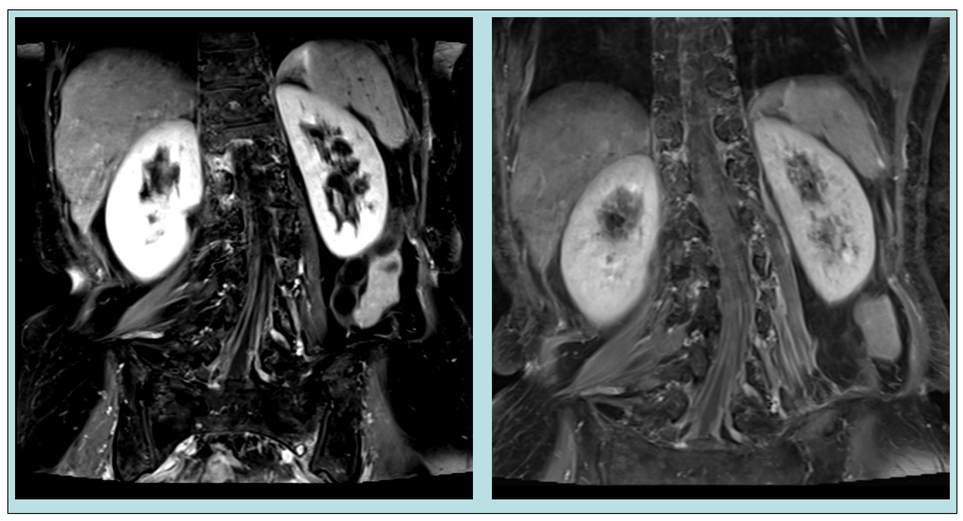

Fig.2: T1 cor post Gd at baseline shows cauda equina enhancement and thickening

Fig.3: T1 cor post Gd 1 month after treatment shows reduction of cauda equina enhancement

Clinical and instrumental findings	A. At baseline	B. 1 month after treatment
Neurological examination	Diffuse deep tendon areflexia Distal weakness in upper and lower limbs Errors in heel-to-shin and finger-to-nose testing Loss of proprioception Romberg sign Marked gait ataxia	Hypo-areflexia in upper and lower limbs Mild distal hyposthenia in upper limbs Negative Romberg test Normal gait
CSF analysis	CSF albumin: 141 mg/dl CSF to serum albumin ratio: 3.8% CSF cell count: 9 cells/mm^3	CSF albumin: 64 mg/dl CSF to serum albumin ratio: 1.7% CSF cell count: 5 cells/mm^3
MRI scan	Cauda equina contrast enhancement (Fig. 2)	Decrease in cauda equina enhancement (Fig. 3)
EMG/ENG	Predominantly-motor polyneuropathy	Mostly motor, mixed axonal-demyelinating polyradiculoneuropathy

Table 1.

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