Seronegative chorea as a rare Immune-Related Neurological Adverse Event induced by Nivolumab: *a case of multisystemic irAE with divergent therapeutic response*

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Introduction

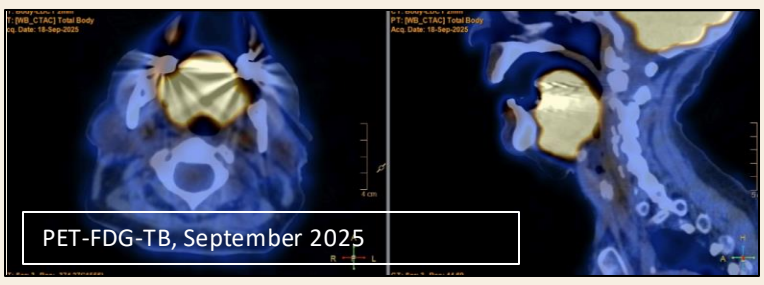
Movement disorders (MDs) represent rare neurological manifestations among immune-related adverse events (irAEs) associated with immune checkpoint inhibitors (ICIs). In the literature, ICI-related MDs constitute approximately **3-5%** of neurological complications, with choreo-athetosis movements described only **anecdotally**.

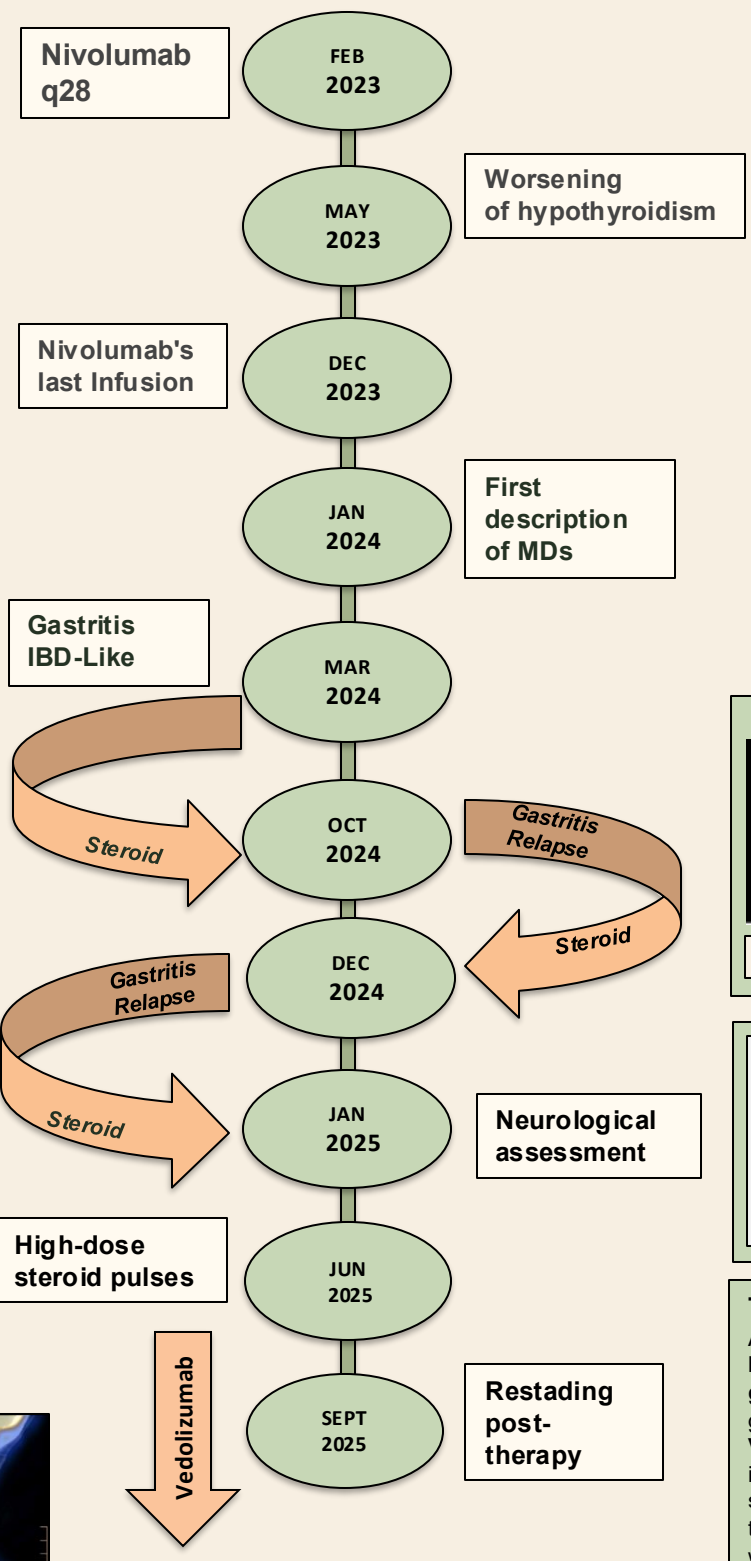
Case Report

This paper presents a case study of a 77-year-old female patient diagnosed with **BRAF-mutated metastatic melanoma**. The patient was treated with **nivolumab** at 28-day intervals, and was subsequently referred to gastroenterology colleagues due to **recurrent IBD-like** nivolumab-related **gastritis**. The patient then developed a hyperkinetic movement disorder of the **choreo-athetosis** type, mainly involving the pelvis, which began **one month after** the last drug administration. The gastroenterological condition demonstrated clinical and endoscopic improvement following corticosteroid therapy, with no neurological benefit observed. The patient subsequently underwent a course of high-dose steroid pulses, followed by restaging with whole-body PET/CT, neurophysiological testing, neuraxis MRI, and lumbar puncture. This sequence of procedures was conducted two months after the high dose steroid trial.

Diagnostic Approach:

A polygraph test was conducted, which revealed **dyskinetic activity** with bursts at 1-2 Hz of the mm gluteus maximus, biceps femoris. A whole-brain and spine MRI with contrast was also performed, which yielded a negative result. Furthermore, an autoimmune panel was conducted, which included ANA, ENA, ANCA, anti-CCP, and LAC. In addition, infectious, neoplastic, and deficiency (B12, B9, E vitamins) as well as onconeural and neuronal-surface antibodies (all wnl) were investigated. A diagnostic spinal tap showed only the presence of **OCBs** pattern **2+** on CSF. In consideration of the data pertaining to cerebrospinal fluid,a therapeutic intervention involving the administration of **high-dose steroid boluses** was undertaken, though this did not result in any clinical improvement.





Clinical Classification of hyperkinetic movement disorder

Historical Features

- 77 aa
- Medical, family and physiological history was unremarkable until December 2022, when lymphadenopathy was detected and found to be compatible with metastatic melanoma
- Sudden onset with a static progression observed one month after the final dose of Nivolumab q28.
- The movement disorder did not respond to the following pharmaceutical interventions Benzodiazepines (e.g. alprazolam, Rivotril), Steroids, Antipsychotics, Alcohol

Chorea Characteristics

- The disorder involves Gluteus maximus, Biceps Femoris, Lower Face, left arm
- Involuntary movements occurring at rest and disappearing during sleep and voluntary motor activity
- Frequency 1-2 Hz, pseudo-rhytmic, high amplitude

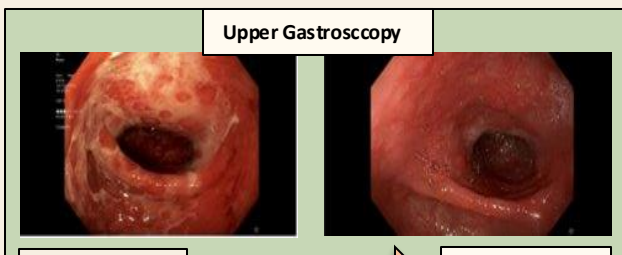
Associated Signs

- Hypothiroidsm
- IBD-Like Gastritis
- Mild ataxia, Left-sided bradykinesia
- Left-sided pyramidal sign (Hoffmann, Achilles Clonus, Hyperreflexia)

Additional Findings

- Brain and Spine MRI with Contrast agent (neg)
- Blood Exams (LAC, aCL,β2GPI, ANA, ENA, ANCA, anti-CCP3, Vit B12, B9, Vit E, Calcium, Celiac disease panel)
- LCS (Glu 2,3 mmol/L, Oligoclonal band positive pattern 2+)

Upper Gastrosccopy



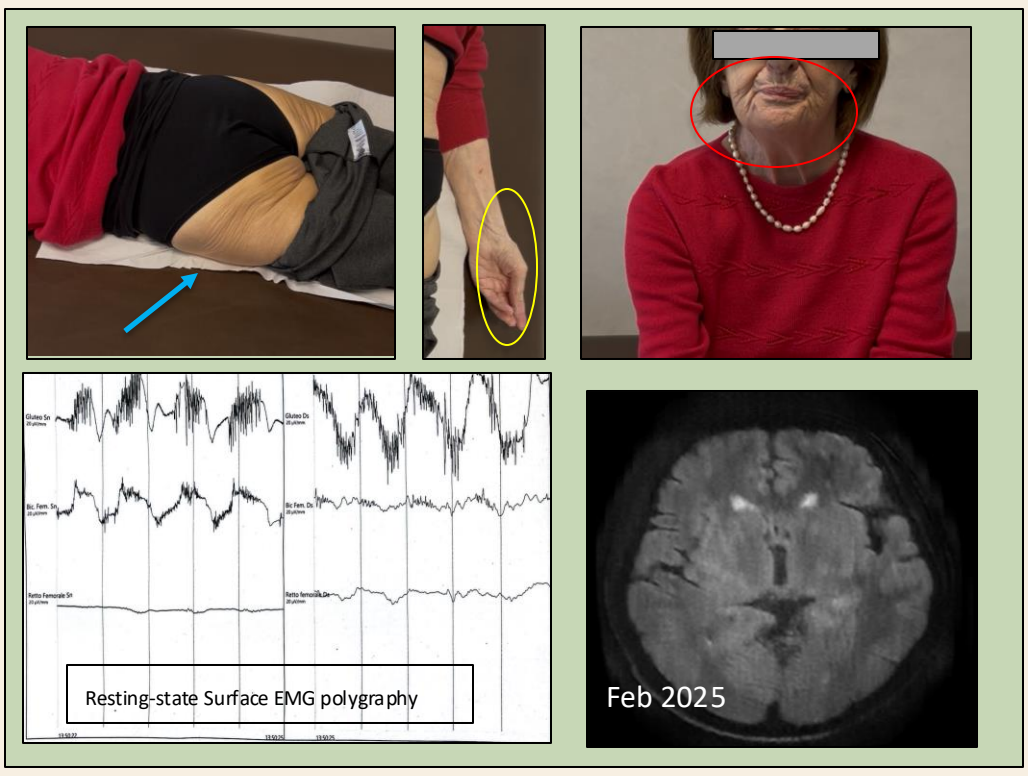
December 2023 → *Steroid* → July 2025

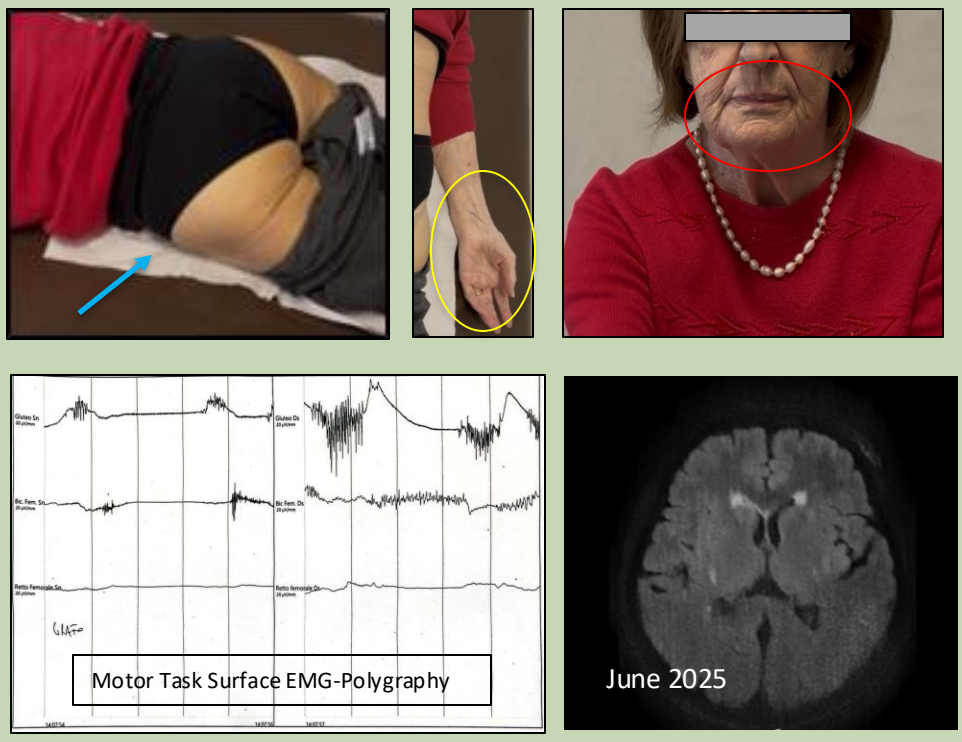
Anticorpo	Siero	Liquor
HuD (ANNA 1)	Negativo	Negativo
Ri p54 (ANNA 2)	Negativo	Negativo
Yo	Negativo	Negativo
Amfifisina	Negativo	Negativo
PNMA2 (Ma2/Ta)	Negativo	Negativo
CV2	Negativo	Negativo
Recoverina	Negativo	Negativo
SOX1	Negativo	Negativo
Titina	Negativo	Negativo
Zic4	Negativo	Negativo
GAD65	Negativo	Negativo
Tr (DNER)	Negativo	Negativo

Anticorpi	Siero	Liquor
Anti-NMDAR	Negativo	Negativo
Anti-AMPA1/2	Negativo	Negativo
Anti-DPPX	Negativo	Negativo
Anti-CASPR2	Negativo	Negativo
Anti-LGI1	Negativo	Negativo
Anti-GABARB1/B2	Negativo	Negativo

Therapy and Outcomes

A trial was conducted in which patient was administered high-dose intravenous steroids (**methylprednisolone 1 g/day** for 3 days) withouta clear clinical response. From a gastroenterological perspective, the initiation of **Vedolizumab** resulted in favourable outcomes for the gastric involvement. Since May, following the commencement of steroid therapy, we have conducted repeated MRI scans of the neuraxis, in addition to a rheumatologic panel and a whole-body PET/CT scan which revealed **FDG-avid lesion** at the tonguel, which is currently under further investigation. It was planned that a follow-up would take place in September 2025. This would consist of a repeat lumbar puncture, blood tests and a neurophysiological assessment.





Discussion

Chorea is an uncommon manifestation among the IRAEs associated with ICIs, and its recognition is important for the management of patients. Despite the existence of isolated case reports, the underlying pathophysiology remains largely hypothetical. According to the extant literature, irAEs affecting the CNS induced by anti-PD-1 antibody treatment are rare, and the vast majority of observed irAEs affecting the CNS have been related to **anti-CTLA-4**. In the present case, the absence of paraneoplastic or autoimmune encephalitis-specific autoantibodies renders direct attribution to an immune-mediated mechanism more complex. However, the finding of OCBs in CSF supports the hypothesis of **intrathecal immune activation**, consistent with the evidence that only a proportion of irAEs are caused predominantly by T-cells. The ineffectiveness of high-dose intravenous corticosteroid therapy has also been reported in other cases of post-ICI MD, including chorea. In such cases, the response appears to be **slower** and **less pronounced** than that observed in other irAEs. In some cases, the administration of additional immunosuppressive drugs, such as infliximab, is required. In contrast to the management algorithms outlined in Schneider et al. for encephalitic presentations, there is currently a paucity of specific guidance for ICI-related movement disorders. This underscores the necessity for both shared clinical experience and individualised multidisciplinary management.

Conclusion

The paucity of clinical experience with ICIs continues to present a significant challenge in the recognition and management of rare neurological iRAEs. Movement disorders, including chorea, are uncommon and require meticulous diagnostic procedures to rule out alternative etiologies. This case report describes a rare, serum-negative, nivolumab-associated chorea, which was instrumentally documented and characterised by the presence of BOC in the CSF, in the absence of known autoantibodies or structural brain changes. This finding serves to expand the existing body of knowledge pertaining to the spectrum of neurological irAEs associated with ICIs. The concomitant IBD-like gastritis, which demonstrated a positive response to corticosteroids, emphasises a multiorgan IRAe with divergent therapeutic behaviour, suggesting the presence of distinct immunopathogenic pathways. This case underscores the significance of early recognition, multidisciplinary discussion, and customised diagnostic and therapeutic approaches in the management of multisystem immune-related adverse events.

Latest Updates:

- **CSF:** 13 cells/ perMicroL (62% MNCs, 38% PMNs); glucose 2.5 mmol/L;
- **Under Evaluation:** MEPs, SSEPs, surface EMG polygraphy, flow cytometry (FC), OCBs, ONAs, NSAbs, ENT evaluation.
- **Clinical status:** neurological manifestations stable; improved systemic response.
- **Oncology:** no evidence of melanoma relapse; follow-up ongoing. Worsening of hypothyroidism
- **Gastroenterology:**Vedolizumab induction dose stopped; maintenance therapy initiated.

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