Case report

Isolated adrenocorticotropic hormone (ACTH) deficiency and Guillain-Barré syndrome occurring in a patient treated with nivolumab

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SUMMARY

The increased use of immune checkpoint inhibitors (ICIs) has led to the observation of a variety of immune-related adverse events (irAEs). These irAEs occur usually within the first months after ICIs onset and can involve theorically all organs. We describe two rare irAEs occurring in a 70-year-old caucasian man who was treated with nivolumab for an advanced urothelial cancer of the left kidney. He developed an isolated adrenocorticotropic hormone deficiency that was diagnosed at week 19 and a neurological complication that appeared at week 79 and initially confounded with a lumbar spinal stenosis. Diagnosis of Guillain-Barré syndrome was finally confirmed with the complete resolution of symptoms after 5 days of intravenous immunoglobulin and corticosteroids. We highlight the importance of quickly recognising these potential life-threatening irAEs such as cortisol insufficiency and neurologic adverse events whose initially presentation could be non-specific.

BACKGROUND

Immune checkpoint inhibitors (ICIs) are active against a broad range of malignancies and have significantly changed the treatment landscape for cancer, improving outcome and quality of life of patients. The binding of the checkpoint protein Programmed Death 1 receptor (PD-1), expressed on T-cell, to its ligand PDL-1, expressed on tumour cells, allows cancer cells to escape to immune response, resulting in cancer proliferation. The ICI nivolumab targets PD-1 and prevents its binding to PDL-1, leading to recognition and destruction of cancer cells. Nivolumab has been approved for treating various malignant diseases, including urothelial carcinoma. The increased use of ICIs is currently revealing a large panel of immune-related adverse events (irAEs). All organ can theoretically be affected. In general, irAEs occur quite early, mostly within the first 3 months, but in some cases, the onset of irAEs may be delayed up to 1 year after treatment initiation. The toxicities are usually mild and easily manageable but some, if not rapidly diagnosed and treated, can be life-threatening.[1–3] In this report, we describe the case of a patient who developed, as first toxicity, an isolated adrenocorticotropic hormone (ACTH) synthesis deficiency, followed by cutaneous toxicity and Guillain-Barré syndrome (GBS).

CASE PRESENTATION

A 70-year-old caucasian man with a history of hypertension, nephroangiosclerosis and lumbar discopathy underwent left nephrectomy for a 5-cm renal mass. The histological findings showed locally advanced urothelial carcinoma with positive para-aortic nodes, classified as pT4N1 following tumour, node, metastases (TNM) stage (version 7th). Three cycles of carboplatin–gemcitabine were administered with correct tolerance. Carboplatin was preferred over cisplatin due to decreased glomerular filtration (50 mL/min/1.73 m^2). Nine months after the end of chemotherapy, thoraco-abdominal CT showed metastatic progression with multiple lumbo-aortic lymph nodes and adrenal glands infiltration; cortisol at this time was in normal range, excluding a primary cortisol deficiency. Nivolumab was started at 3 mg/kg intravenously every 2 weeks following standard protocol. The first cycles were well tolerated and our patient did not show any side effect.

The ninth nivolumab administration was followed by rapidly progressing anorexia, nausea and general weakness. Blood test showed hyponatremia (120 mmol/L for a normal range between 130 and 140 mmol/L); haemogram, liver function and glycemia were within a normal range and renal function was stable compared with previous values. Thyroid stimulating hormon (TSH) value was at the upper limit of normal values (3.71 mU/L) and T4, T3, luteinising hormone and follicle stimulating hormone were normal. Morning cortisolemia was very low (40 nmol/L, normal range 126.8–656.5 nmol/L) and ACTH value was inappropriately low (10 pg/mL, normal range 5–49 pg/mL). Thoraco-abdominal CT showed stable disease following response evaluation criteria in solid tumours (RECIST) (version 1.1), with no new lesion and stability of lymph nodes diameter and of adrenal glands infiltration. Cerebral MRI did not show any hypophysis enlargement or inflammation. Low value of cortisol associated with low value of ACTH suggested an ACTH deficiency. The cortisol response to ACTH stimulation supported functioning adrenal glands suggesting that ACTH deficiency was the cause of adrenal insufficiency. As other hormonal tests were within normal range, it was concluded that this is an isolated ACTH deficiency. Hydrocortisone was therefore started at 20 mg in the morning and 10 mg in the evening.

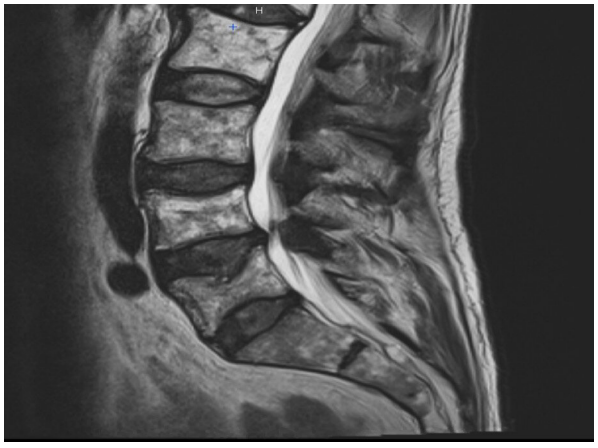
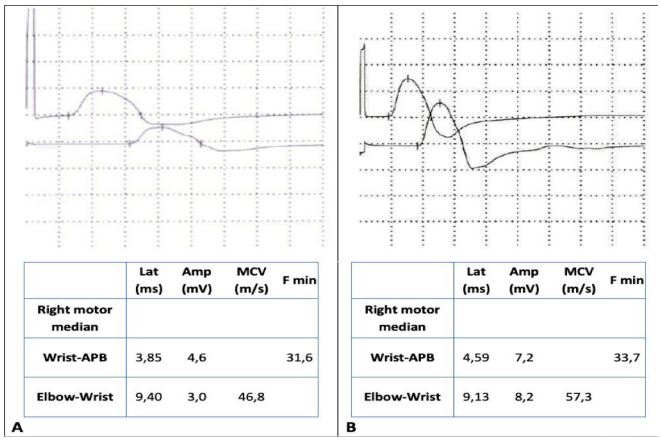


Figure 1 Spinal MRI shows severe L3–L4 and L4–L5 spinal stenosis and foraminal stenosis.



A

	Lat (ms)	Amp (mV)	MCV (m/s)	F min
Right motor median				
Wrist-APB	3,85	4,6		31,6
Elbow-Wrist	9,40	3,0	46,8	

B

	Lat (ms)	Amp (mV)	MCV (m/s)	F min
Right motor median				
Wrist-APB	4,59	7,2		33,7
Elbow-Wrist	9,13	8,2	57,3	

Figure 2 (A) Electromyography at day 0 of intravenous immunoglobulin (IVIG) treatment highlights abnormal velocity of conduction with reduced waves amplitude which was compatible with acute demyelinating polyneuropathy (Guillain-Barré syndrome). (B) At day 5 of IVIG, there was an improvement of initially impaired electromyographic parameters according to clinical status.

Our patient felt rapidly better and clinical symptoms disappeared within the 72 hours. Nivolumab was interrupted for 4 weeks and then restarted. After the 14th administration, our patient developed a grade 2 pruritus, that resolved completely on cetirizine. One week after the 29th administration of nivolumab, grade 2 pruritus reappeared and was associated with rapidly progressing weakness of his lower limbs (Medical Research Council Scale: 3/5) resulting in walking difficulties. Lower limb reflex testing was normal, as well as sensitivity examination. Cranial nerves, cerebellar and upper limb neurological testing was normal. The cognition was preserved. As our patient had a history of chronic low back pain with known lumbar spinal stenosis confirmed by MRI performed 2 years ago, the first hypothesis was a severe stenosis of lumbar spinal canal, as confirmed by a new spinal cord MRI (figure 1). However, this weakness increased over 2 weeks and was associated with rapidly progressing upper limb weakness. Cerebrospinal fluid (CSF) analysis showed an elevated protein concentration (1.05 g/L) and mild leucocytosis (8/mm^3), without any malignant cell. Blood test showed negative testing for Lyme disease, cytomegalovirus (CMV) or HIV; anti-acetylcholine receptor and anti-muscle specific kinase (anti-MuSK) antibodies were negative. Electroencephalogram did not show any sign of encephalopathy or epilepsy. Electromyography (EMG) of upper limbs showed a reduced motor conduction velocity, an increased distal motor latency and a wrong persistence of F-waves without pathologic increment or decrement (figure 2A). These results led us to consider an acute demyelinating polyneuropathy such as GBS. We started intravenous immunoglobulin (IVIG) 0.4 mg/kg once a day for 5 days and methylprednisolone 1 mg/kg during 7 days with degressive schedule and physiotherapy. A rapid clinical improvement was observed within the first 3 days. EMG performed 5 days after IVIG and corticosteroids initiation showed a reduction of abnormalities, confirming the diagnosis of demyelinating polyneuropathy (figure 2B). The patient completely recovered and nivolumab was definitively stopped. Methylprednisone was tapered progressively over 10 weeks. Several attempts to decrease hydrocortisone were associated with fatigue resurgence, reason why our patient remained on initial dose of hydrocortisone.

OUTCOME AND FOLLOW-UP

Six months later, our patient is asymptomatic, still on hydrocortisone and cancer remains stable on CT scan, following RECIST criteria.

DISCUSSION

A large panel of irAEs is currently described with the routine use of ICIs. Skin, gastro-intestinal, hepatic and endocrine events are the most frequent reported irAEs with a median time to onset of 5, 7, 8 and 10 weeks, respectively. However, these irAEs can involve theorically all organs.[1–4] In our patient, interestingly, nivolumab toxicity developed first with endocrine irAE, after 4.5 months of treatment. Skin toxicity developed relatively late, after 14 injections, as well as the neurological toxicity that appeared after the 29 administrations of nivolumab. This sequence of irAEs is rarely reported.

If hypophysitis is a well-known irAE and involves multiple gland axes, isolated ACTH deficiency is rarely reported, particularly as initial event.[5 6] The low level of cortisol associated with an inappropriately low level of ACTH suggested a secondary cortisol insufficiency, which was confirmed by the ACTH stimulation test. As there was no other hormonal axis anomaly, we concluded in an isolated ACTH deficiency. Treatment consists in hydrocortisone supplementation with degressive schedule to reach the lowest effective dose.[7] As our patient did not present adrenal crisis and completely recovered with hydrocortisone substitution, nivolumab was continued. The low level of ACTH and the absence of cancer progression on nivolumab excluded a cancer-related adrenal insufficiency due to metastatic adrenal infiltration.

The second serious irAE was at neurological level. Our patient developed a progressive weakness involving lower and upper limbs. The previous low back pain history of our patient and the MRI showing a lumbar severe stenosis delayed our diagnosis of acute demyelinating polyneuropathy that was suggested by the EMG and the abnormal CSF analysis and that was confirmed by the complete resolution on IVIG. The relationship with nivolumab was based on the fact that our patient was on treatment, by the absence of other demonstrated cause (infection or toxic) and by the synchronous cutaneous rash. Our patient did not undergo recent viral or bacterial infection or vaccination. There was neither metabolic nor electrolyte disorders. Serologic analysis excluded Lyme disease, HIV or CMV infection. No other medication or toxic was added recently.[8–10] Myasthenia gravis was also excluded by the clinical pattern, the EMG and the negative serologic acetylcholine receptors antibodies. The

incidence of serious neurologic irAEs is very low with anti-PDL-1/PD-1 (<1%), particularly for acute demyelinating polyneuropathy with an estimated frequency of 0.1%–0.2%.[11–13] Although neurologic irAEs appear usually rapidly after treatment onset, our patient developed a polyradiculopathy very late in the treatment course, up to 1 year after nivolumab onset. Puwanant *et al* reported a total of 29 ICIs-related peripheral neuropathies and radiculopathies, including 13 diagnosed as GBS. Most of these cases were associated with a high CSF protein concentration but not with high leucocyte value.[13 14] If not rapidly diagnosed, GBS may be life-threatening as it can involve respiratory muscles or induce heart arrythmia.[10] Treatment includes usually IVIG and high dose corticosteroids, following American Society of Clinical Oncology (ASCO) guidelines.[15] In our patient, these treatments completely reversed the symptoms.

Patient's perspective

Treatment could sometimes induce more problems than cancer, reason why I am agree to have a close follow-up. I completely understand the rational to stop definitively nivolumab and I hope that cancer will remain stable.

Learning points

- Isolated adrenocorticotropic hormone secretion deficiency is rarely described but should be considered in any symptom of fatigue during immune checkpoint inhibitor (ICI) treatment.
- Weakness of lower or upper limb should highlight the possibility of neurological complication of ICI.
- Every new symptom must be viewed in connection with the treatment and regarded as an irAE until proven otherwise.
- A close follow-up of patient treated with ICI is mandatory, all along the treatment course.

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