# AT LAST! It was not a progression!

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## ABSTRACT

**Introduction:** Nivolumab is approved in Portugal for non-small cell metastatic lung cancer, as one of the indications, after progressing on chemotherapy. As an immune checkpoint inhibitor (ICI) immune-related adverse events (irAE) are possible reactions.
**Case report:** A 64-year-old man with stage III lung adenocarcinoma who progressed after chemoradiotherapy and first line metastatic chemotherapy started nivolumab. Approximately 16 months after starting treatment he is admitted to the hospital with suspected brain metastasis due to vomiting, prostration and altered mental state. Brain-CT showed no abnormalities, but analyses showed decreased levels of ACTH and cortisol, which supported the diagnosis of hypophysitis. Nivolumab was stopped and high-dose hydrocortisone was initiated with good response. After discharge, patient showed disease stability and maintained vigilance.
**Discussion:** Hypophysitis is an uncommon endocrine irAE of nivolumab. It appears on average 6 months after starting treatment and shows nonspecific symptoms often misjudged as disease progression. Only a high degree of suspicion can lead to appropriate investigation and treatment.

**Key-words:** adenocarcinoma, hypophysitis, nivolumab



## BACKGROUND/INTRODUCTION

The use of ICI in lung cancer (LC) is recent.[1] In Portugal the ICI approved for non-small cell lung cancer (NSCLC) are the anti-programmed cell death 1 molecules (anti-PD-1) nivolumab and pembrolizumab, the anti PD-ligand 1 (anti-PD-L1) atezolizumab and durvalumab, anti-cytotoxic T-lymphocyte-associated antigen 4 (anti-CTL-4).

The PD-1 molecule is expressed on the surface of T lymphocytes and its stimulation blocks lymphocyte activation and leads to apoptosis.[2] PD-L1 expression value is variable in NSCLC patients and each patient should be classified

according to their PD-L1 expression status – high PD-L1 levels (PD-L1≥50%), mild levels (1%≤PD-L1<50%) and negative levels (PD-L1<1%). This classification has important therapeutic implications as it might dictate whether an ICI is used or not and if it must be combined with other drugs such as chemotherapy (Ch).

These drugs have demonstrated unequivocal clinical benefit in different disease stages[1]. In the particular case of nivolumab, it has demonstrated an increased overall survival in NSCLC metastatic patients who progressed after chemotherapy (Ch) when compared with docetaxel, and also showed a better tolerability profile.[3,4] Nevertheless, as every drug, its safety is hampered by its adverse events (AE), which in case of immunotherapy are mainly immune related AE (irAE).

The authors present a case of endocrine irAE associated with nivolumab.

## CASE REPORT

A 64-year-old man from Brazil, living in Portugal for several years, with personal history of Hashimoto's thyroiditis since 2011, medicated with levothyroxine 125mcg, was diagnosed with lung cancer by transthoracic biopsy (TTB) in November 2018 with adenocarcinoma, PDL1 <1%, with no known driver mutations on next generation sequencing (NGS), located in the right upper lobe (RUL) cT4 cN3 cM0, stage IIIC according to the 8th edition of the American Joint Committee on Cancer (AJCC) criteria.[5] The patient was submitted to concomitant chemoradiotherapy (ChRT) with cisplatin and vinorelbine plus RT 60Gy/33 fractions until February 2019 with partial response as the best response.

In November 2019, due to persistent pain in the right thigh and hip, he had a bone scintigraphy showing Tc-99m uptake in the upper third of the right femoral diaphysis. Chest CT performed at this time showed no local progression. The multidisciplinary tumor board staged the patient as IVB and Ch with carboplatin + pemetrexed was started with palliative radiotherapy on the bone (8Gy/1f). A total of 4 cycles with stable disease as best response was achieved, without maintenance of pemetrexed due to renal function impairment.

In August 2020 the patient had a pathological fracture of the right femur treated with surgery with intramedullary nailing. The chest CT showed a new solid component near the irradiated region with roughly 20 mm of greater diameter. The multidisciplinary board decided to re-irradiate the bone metastasis and start second line treatment with Nivolumab, which he began in October 2020 with a fixed dose of 480 mg 28/28 days, with complete response in the lung.

At the beginning of January 2022, the patient presented with nausea, vomiting, altered state of consciousness and worsening of his general condition which aggravated within 3 weeks. At that time, the patient was examined in the pulmonology clinic and hospitalized with suspected cerebral metastasis. On admission he was prostrated, with impaired mobilization, drowsy and confused. The hip pain was partially controlled with medication and there were no other findings upon examination. Initial blood tests showed CRP 3.62 mg/dL, T4L 1.44 nd/dL and TSH 0.14 µUI/mL.

During hospitalization, brain CT excluded space-occupying lesions (SOL) or other alterations, CT of the lumbar spine revealed severe lumbar spinal stenosis at L3-L4, moderate stenosis at L4-L5 and left foraminal stenosis at L5-S1, and awake electroencephalogram (EEG) showed normal activity. Thoracoabdominal CT-Scan revealed new left pulmonary hilar lymph node with

10 mm, micronodule 3 mm in the left lower lobe (LLL), moderate right pleural effusion, cardio-phrenic lymph nodes, the largest on the right with 6 mm, circumferential thickening of the cecum, with densification of adjacent fat and locoregional ganglia, the largest with 8 mm, and several hepatic nodules the largest with 8 mm. A lumbar puncture (LP) was also performed with colorless cerebrospinal fluid (CSF) that showed high protein levels, normal glucose, was sterile for microbiological and mycological tests and negative for cancerous cells.

Once he presented fasting glycemia values 68-89 mg/dl, and vomiting the support of endocrinology team was requested and analysis were repeated with the whole endocrine panel. Patient had hypoNa+ 129 mmol/L, hypoK- 3.3mmol/L, hypoCl- 95 mmol/L, hypoMg2+ 1.3 mg/dL, CRP 7.5 mg/dL, glycemia 62 mg/L, insulin 224 µUI/mL, peptide C 0.3 ng/mL, ACTH <5 pg/mL, cortisol <0.8µg/dL, thus validating the diagnosis of hypophysitis secondary to nivolumab. The drug was suspended and hydrocortisone (HC) 50mg 8/8h was started, with improvement of fasting glycemia 85-130 mg/dl and symptoms, keeping that improvement after reducing the dose of HC to 10 + 5 + 5 mg, which he maintains. The patient was discharged from the hospital at the 29th day of hospitalization.

After the acute event he performed (on April 2022) a Brain MRI that showed slight nodular thickening of the pituitary stalk, pituitary gland within normal dimensions, with a small superficial nodular component externalizing from the anterosuperior part of the gland – a small hyperproteic cyst with 2 mm, although it was not possible to exclude cystic metastasis or cystic microadenoma hypothesis, Rathke's pouch cyst, and moderate leukoaraiosis with possible small ancient infarcts. He also underwent colonoscopy that revealed no endoscopic lesions and a chest CT in June 2022, which showed pulmonary stable disease and at liver level only steatosis.

The multidisciplinary board decided to maintain clinical and imaging surveillance of the patient without reintroduction of nivolumab nor other therapy due to pulmonary disease stability, despite not being able to fully exclude brain metastasis and the recent episode of hypophysitis immune-mediated adverse event grade 3.

## DISCUSSION

Endocrinopathies as irAE of nivolumab are present in 3–24% of patients, with different grades of severity.[2,6-8] Thyroid disorders are the most common, rarely exceeding grade 2, followed by hypophysitis, adrenal insufficiency and diabetes.[2]

The inflammation of the pituitary gland is more common with anti-CTLA-4, nevertheless, it occurs in 0.5-1% of anti-PD-1/PD-L1 monotherapy patients.[9] It can result in primary dysfunction of the gland, leading to deficiency in one or more hormones secreted by the anterior pituitary gland.[10] One of the proposed mechanisms of hypophysitis relates to a type II hypersensitivity reaction. Pituitary glands express CTLA-4 in a subset of cells what might explain why anti-CTLA-4 therapy, but only rarely PD-1/PD-L1 blockade, results in hypophysitis.[9] Interestingly, some recent reports showed that the presence of irAE, especially with radiologic manifestations, was associated with a better response to immunotherapy.[11] Also, the development of pituitary-irAE predicted better prognosis for both NSCLC and malignant melanoma (MM) when patients were treated with physiological doses of HC.[12]

Patients are not all at the same risk of developing ICI irAE. History of autoimmune diseases

diagnosed prior to immunotherapy and dual ICI therapy confer higher risk.[2,13] Older age, sex, or metastasis seem not to confer a higher risk, but older patients with melanoma or non-small cell lung cancer, or on dual ICI therapy, may be at higher risk of fatal neurologic irAEs.[13] HLA-DR15, B52 and Cw12 are possible predisposing factors for pituitary irAEs. HLA-DR15 is reportedly associated with autoimmune disease via interleukin-17 regulation, suggesting its involvement in pituitary irAE development. Whether using HLA haplotypes to screen patients who have predisposition to have pituitary irAE could be a good clinical tool is still unknown, but it would give physicians the possibility to identify patients at higher risk and follow them closely.[14] Another interesting finding in a recent case series of renal cell carcinoma patients under nivolumab, was that eosinophil count raised in some patients before the onset of hypopituitarism, regardless of symptoms presentation. Further studies are needed to validate if hyper eosinophilia is an early predictor of hypopituitarism and could be used in clinical practice.[15]

Median time to presentation is 26 weeks (around 6 months) and usually appears 5 to 36 weeks after initiation of ICI therapy, but may arise any time on therapy and has been reported as late as 19 months post treatment start or even several months after therapy discontinuation.[9,16] Symptoms are often unspecific and may be confound with cancer natural history. The primary differential diagnosis is with cerebral metastasis since the majority of symptoms are from neuro-compression (e.g. fatigue, nausea, emesis and headache, or even include diplopia or visual defects). In rare severe cases the presentation could be with hypotension or adrenal crisis precipitated by a concurrent illness. Secondary hypothyroidism and least frequently secondary hypogonadism could also occur.[9]

When the clinical suspicion of hypophysitis is high, a full endocrine workup should be performed, along with a brain MRI with or without contrast with pituitary/sellar cuts.[16-18,20] Pituitary morphology commonly changes during the course of hypophysitis although a normal MRI does not exclude the diagnosis. It starts with mild to moderate enlargement with stalk thickening, followed by atrophy and finally empty sella in the most severe cases.[16] Nevertheless, not all hospitals could readily perform a brain MRI so a brain-CT could be performed instead, although it has lower sensibility either to pituitary gland inflammation as to the presence of metastasis.

Management should be based on clinical presentation and endocrine evaluation.[17] As thyroid disorders are the most frequent, thyroid hormones integrate the analysis panel for NSCLC patients treated with ICI in our hospital, but the other hormones are not routinely assessed. The diagnosis of hypophysitis is therefore frequently delayed since symptoms are unspecific and the appropriate analysis are performed late in the diagnostic investigation. Complete hormone panel analysis is only performed if there is a high suspicion on the diagnosis and sometimes it is obtained after the introduction of corticosteroids interfering with subsequent endocrine testing results.[18]

The first tests to assess the diagnosis of hypophysitis are adrenocorticotropic hormone (ACTH), morning cortisol, and thyroid hormones – triiodothyronine (T3), unbound thyroxine (fT4) and thyroid-stimulating hormone (TSH). ACTH and TSH deficiency are the most common manifestations of hypophysitis, When both adrenal insufficiency and hypothyroidism are present, cortisol screening enables hydrocortisone replacement treatment and it should start several days before administering thyroid hormones to prevent precipitating an adrenal crisis.[17-20] The lest

frequent hormone deficiencies are hypogonadotropic hypogonadism and, more rarely, diabetes insipidus due to deficient vasopressin as a result of pituitary damage and insulin-like Growth Factor 1 (IGF1).[16,17] Sexual hormones deficiency – luteinizing hormone (LH), follicle-stimulating hormone (FSH), total and free testosterone and estradiol, is usually accompanied by low libido, mood changes, or fatigue. If applicable, the hormone deficits should receive replacement therapy.[17]

If untreated, hypophysitis may lead to permanent endocrine organ dysfunction.[17,18] Generally grade 1 hypophysitis does not require withholding of ICIs, but with grade 2 and/or grade 3 it should be withheld with resumption following stabilization on replacement hormones. Permanent discontinuation of nivolumab is recommended for grade 4 events.[17] Corticosteroids are usually used to treat grade 3/4 events, beginning with 1 to 2 mg/kg oral prednisone or equivalent and then gradually tapering over 1 to 6 weeks. (14 e 8) Compressive symptoms (e.g., severe headaches, diplopia, visual field defects) could also be treated with prednisolone 1-2mg/kg or equivalent with rapid taper (over 1-2 weeks).[9,17]

All patients with endocrine irAE, must have an endocrinology appointment. Ideally, all patients undergoing ICI therapy should have endocrinologic follow-up and perform a pretreatment diagnostic panel with ACTH and cortisol, TSH, FT4, electrolytes, glucose and glycated hemoglobin (HbA1c).[17]

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