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## CASE REPORT

# Nivolumab Induced Acute Severe Toxicity in Lung Adenocarcinoma

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### Abstract:

#### Background:

Immunotherapy has recently revolutionized the world of oncology. Nivolumab an IgG4 targeting PD-1 receptor has been approved in metastatic melanoma, renal cell carcinoma, Hodgkin lymphoma and non-small cell lung cancer. It works as a checkpoint inhibitor, allowing the immune system to clear cancer, and it is this mechanism of action which explains its toxicity also named as immune-related adverse events.

#### Case Presentation:

This report describes the case of a 65-year-old female with metastatic lung adenocarcinoma treated with nivolumab. After 19<sup>o</sup> cycle she presented acute severe toxicity with pneumonitis, hypophysitis and thrombocytopenia. She was successfully treated with high dose steroids and immunoglobulins.

#### Conclusion:

Immune-related adverse events associated with nivolumab are usually nonspecific, with lots of differential diagnosis. They often resolve with prompt management, however, they may get severe if treatment is not retired and systemic immunosuppression with corticosteroids is initiated. As shown in this case, we must be attentive throughout the treatment and even after the end of the treatment, since not all cases occur according to what is described in the literature.

**Keywords:** Nivolumab, Immune-related adverse events, Pneumonitis, Hypophysitis, Thrombocytopenia, Lung Adenocarcinoma.

## 1. BACKGROUND

Lung cancer causes the greatest number of cancer deaths, globally (1.59 million deaths/year) [1]. Non-Small Cell Lung Cancer (NSCLC) accounts for 85-90% of lung cancers [2]. In advanced disease, conventional treatments such as surgery, chemotherapy or radiotherapy, are rarely curative. Nevertheless, they provide symptom relief and benefit in survival. Immunotherapy has revolutionized the landscape of cancer therapy, showing durable remissions and prolonged survival. Based on the CHECKMATE 063 [3] and CHECKMATE 017 [4] studies in squamous histology and a phase III trial in non-squamous [5], nivolumab was approved by the FDA and EMA for second-line treatment of NSCLC. Nivolumab is an Ig G4 monoclonal human antibody targeting Programmed Cell Death -1 (PD-1) receptor and blocking its interaction with its ligands PD-L1 and PD-L2. Receptor PD-1 is a negative regulator of T-lymphocytes controlling the immune response and immunity homeostasis in physiological conditions. This mechanism of action explains its toxicity, commonly known as immune-related Adverse Events (irAEs). In general, as with pembrolizumab (another anti-PD1, which has also demonstrated activity in melanoma, NSCLC and bladder cancer), the severity of irAEs is mild to moderate with a frequency of grade 3-4 adverse drug reactions of  $\leq 2\%$  for any event term. This case describes some of these irAEs in a woman who had been treated with nivolumab for 19 cycles.

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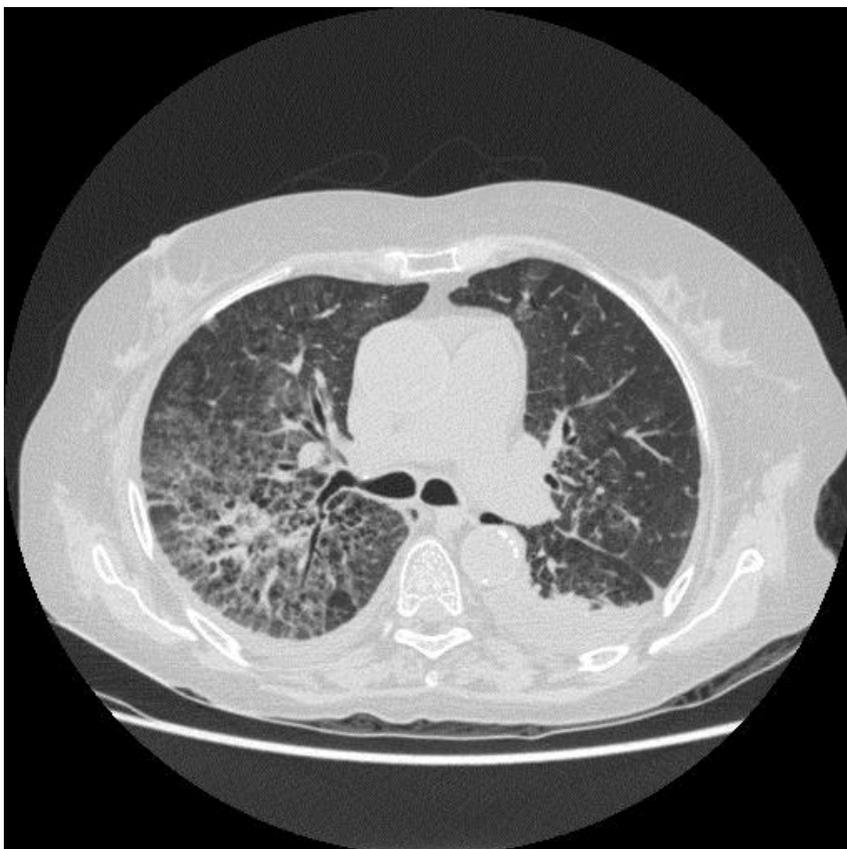
## 2. CASE REPORT

In August 2015 a 65-year-old woman with hypertension and asymptomatic severe aortic stenosis, was diagnosed with metastatic lung adenocarcinoma (cT4 N3 M1b; infradiaphragmatic lymph node metastasis) without EGFR mutation or ALK translocation susceptible of target treatment. She received first-line treatment with cisplatin-pemetrexed and bevacizumab [6, 7] presenting progressive disease with the appearance of new pulmonary nodules after the third cycle.

Within a widespread use, on January 2015, she started Nivolumab (3mg/kg every two weeks) achieving radiological partial response according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.

On September 2016, after 18 cycles, she was admitted to hospital due to a severe headache. She was diagnosed with 2 brain metastasis while she maintained partial response outside the Central Nervous System (CNS). On October 2016, she received radiosurgery (20Gys) to both lesions. During this period of time, the treatment with Nivolumab was withheld and she received high doses of corticosteroids.

In November 2016, a new CT scan evaluation was performed where she maintained stable disease. The treatment with Nivolumab was reassumed (19<sup>o</sup> cycle) and soon after, she was admitted to hospital with a 5-day history of progressive dyspnea without cough, expectoration or fever. On admission, she was afebrile, with normal blood pressure (125/63 mmHg) and cardiac rhythm (79 beats/min). Her respiratory rate was 24 breaths/min, with an oxygen saturation of 88% by pulse oximetry while breathing room air and 93% while receiving supplementary oxygen at a flow of 4 liter per minute. Cardiac auscultation revealed a regular rate and rhythm. Lung auscultation revealed general hypoventilation with dry bilateral crackles. On examination of extremities, no cyanosis or peripheral edema was noted. Arterial blood gas revealed a normal pH and PaCO<sub>2</sub> but significant hypoxemia with a PaO<sub>2</sub> of 40 mm Hg while breathing room air. The rest of laboratory testing was normal except for anemia grade 2. The chest radiograph revealed diffuse bilateral interstitial infiltrates on both sides, and a CT scan of the chest Fig. (1) showed patchy opacification, predominantly involving perihilar segments, and bilateral pleural effusion.



**Fig. (1).** CT scan of Chest showing patchy opacification and bilateral pleural effusion.

The differential diagnosis was consistent with hydropic decompensation, diffuse infectious disease, respiratory distress or nivolumab-induced pneumonitis.

Due to the suspicion of nivolumab induced pneumonitis treatment with prednisone, 1mg/kg/day was initiated with antibiotherapy with ceftriaxone and trimethoprim-sulfamethoxazole to cover a possible opportunistic infection. However, there was no improvement after 72 hours, so the dose of prednisone was elevated to 3 mg/kg/day. Also, a bronchoscopy with a Bronchoalveolar Lavage (BAL) was performed which revealed the presence of *P. jiroveci* without finding its antigen. Cytology of BAL, as well as other microbiological studies (including serologies) was negative. With these results and due to their uncertain significance, the patient was evaluated by infectious disease department who indicated continuing treatment with trimethoprim-sulfamethoxazole. After 10 days she improved and was able to walk long distances without supplementary oxygen.

Nevertheless, she started with neurological alterations such as disorientation and oscillating confused state. She denied having visual alterations or headache. Laboratory testing revealed hyponatremia grade 3 (sodium (Na) 126mEq [ 135 - 145 mEq]), thrombocytopenia grade 4 (21000 platelets/ $\mu$ L [135000 - 450000 ]) and panhypopituitarism that was not present on admission with T4 0.3 ng/dL [0.8 - 1.8 ], T3 0.5 pg/mL [1.4 - 4.4 ], TSH (Thyrotropin) 0.40  $\mu$ U/mL [0.5 - 6.3 ], Thyroperoxidase (TPO) Ac. 3. A cranial CT and a magnetic resonance Fig. (2) were performed with the presence of the 2 previously treated metastases without change but with no radiologic evidence of hypophysitis.



**Fig. (2).** Cranial CT and a magnetic resonance showing a normal pituitary gland.

Because of the hyponatremia, autoimmune adrenalitis was one of the first differential diagnoses, which was rapidly dismissed when normal aldosterone levels were found. Thus other differential diagnoses were considered such as syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) or cerebral salt wasting. Hyponatremia was resolved with hydroelectrolyte reposition, which reinforces the later hypothesis.

Trombocytopenia was suspected to be iatrogenic, therefore trimethoprim-sufametoxazole was discontinued after completing 15 days of treatment.

In order to dismiss other causes, a bone marrow biopsy was performed. It showed a medullar hypoplasia. Also, PF4hepAc were negative, so low molecular weight heparin as a cause was rejected.

Corticosteroid treatment was not enough as there was no improvement, so immunoglobulins were administered. After a week the patient started improving gradually but with a severe steroid myopathy. She started rehabilitation at hospital and continued in a rehabilitation hospital center where she died several weeks later with a liver failure due to new multiple hepatic metastases.

### 3. DISCUSSION AND CONCLUSION

Immunotherapy is usually better tolerated than chemotherapy. Its toxicity (also known as immune-related adverse events) is rarely severe in intensity and it is believed to arise from general immunologic enhancement. If grade 2 toxicity is presented, treatment should be withheld; On the other hand, if patients experience grade 3 or 4 toxicity, like

in our case, treatment cessation and immunosuppression with systemic corticosteroids is required.

Several IrAEs have been associated with nivolumab including, fatigue, hypersensitivity, infusion reactions and other organ-specific toxicity such as skin, gastrointestinal, pulmonary, endocrine, renal, liver or hematologic [8]. The median time of onset of these IrAEs varies depending on the affected organ: pneumonitis has been related on 9 weeks, endocrine from 4 to 18 weeks. In the reported case all of them started after the 19<sup>o</sup> cycle of nivolumab (+/-40 week after the beginning of this treatment) and were grade 3.

In what concerns our case, the initial suspicion was a nivolumab-induced pneumonitis, which is described in up to 10% of patients treated with nivolumab, but only 2% were grade 3 or more. As commented before this diagnosis is a diagnosis of exclusion, thus either pulmonary infection or progressive disease needed to be excluded first [9]. The clinical presentation of pneumonitis, is often unspecific, as patients usually complaint of unproductive cough and dyspnea, with or without hypoxemia. CT scan of the chest may show multiple radiologic images. Bronchoscope with BLA may help rule out pulmonary infection.

In order to exclude pulmonary infection (including opportunistic infections) empiric antibiotic therapy was started from the beginning with ceftriaxone and trimethoprim-sulfamethoxazole.

Although *Pneumocystis jiroveci* DNA was present in BAL, no antigen was found by immunofluorescence, and quantitative DNA copies did not rule out an infection, because colonization is also possible. In fact, *Pneumocystis* organisms are commonly found in healthy individuals' lungs, but it is only when both cellular and humoral immunity are defective, that disease occurs. In this sense, it is important to note that National Comprehensive Cancer Network guidelines for the prevention and treatment of cancer-related infections recommend considering *Pneumocystis* prophylaxis with trimethoprim-sulfamethoxazole, atovaquone, or pentamidine for patients treated with 20 mg of prednisone equivalent daily for at least four weeks [10].

After respiratory symptoms improved, she referred fatigue and started with neurologic alterations. Once CNS progression was excluded, other differential diagnoses had to be ruled out. These neurological events could be due to nivolumab since a range of neurological events have been described, including polyneuropathy, facial and abducens nerve paresis and demyelination [9]. However in our case symptomatology was unspecific and the possibility of hypophysitis had to be evaluated, as early diagnosis help avoid serious consequences.

In the case of hypophysitis, symptomatology may range from mild fatigue, arthralgias, loss of libido to more serious symptomatology like headache, visual changes, profound dizziness and nausea [11].

If suspected, MRI is recommended: The main finding is usually pituitary enlargement and nodularity, however normal pituitary gland (like in our case) or atrophy does not rule out hypophysitis. Laboratory testing usually shows low levels of the hormones produced by the pituitary: Adrenocorticotropic Hormone (ACTH), TSH, FSH, LH, Growth Hormone (GH), prolactin.

It is possible to have one or more axes affected. These findings also help differentiating hypophysitis from primary adrenal insufficiency and primary hypothyroidism. Taking into account all the results, we were facing a hypophysitis. Nevertheless, we cannot forget that the patient had received cerebral radiosurgery. In fact, radiotherapy may also cause hypophysitis, although in our case the dose and localisation were different. Also of note is that endocrinopathies are usually not reversible and patients often require long-term supplementation of the affected hormones, as our patient.

With the appearance of hyponatremia, adrenal insufficiency was suspected. This is the most critical endocrinopathy which can cause dehydration, hypotension, and electrolyte imbalances.

However, in our case, as we were using high doses of corticosteroid ACTH was presumably low, so aldosterone was measured. Aldosterone levels were normal so primary adrenalitis was ruled out. One of the differential diagnoses for the hyponatremia was cerebral salt-wasting syndrome. Differentiation of this disorder from SIADH, can be difficult because both can present with hyponatremia and concentrated urine with natriuresis. However, distinguishing between the 2 disorders is important because treatment options differ [12]. In our case hyponatremia was solved with suerotherapy.

Hematologic toxicity when nivolumab is used is more commonly seen in lymphoma studies. There are two main causes of thrombocytopenia: insufficient production in bone marrow (due to folic or vitamin b12 deficit, infections, myelodysplastic disease and drug-induced bone marrow toxicity) or excessive destruction (hiperesplenism, drugs, CID). In our case a bone marrow biopsy was performed which showed medullar hypoplasia and PF4hepAc were negative, so

the low molecular weight heparin as a cause was rejected. The possibility of drug induced thrombocytopenia should be considered as trimethoprim sulfamethoxazole has been related as its cause [13]. In our case, the drug cessation was not enough and immunoglobulins were needed.

In conclusion, IrAes, are a unique spectrum of toxicity to which we are not yet used to, but we will have to face them more and more often. Most of the symptomatology is mild and nonspecific, with lots of differential diagnosis, however, they may get severe unless prompt treatment. It is essential for both patients and physicians to prevent this toxicity (knowing the toxicity spectrum, identifying dysimmunity risk factors), to anticipate their development, to detect them, and when this toxicity is present it is essential to treat it together with organs' specialists. As shown in this case, we must be attentive throughout the treatment and even after the end of the treatment, since not all cases occur according to what is described in the literature.

## LIST OF ABBREVIATIONS

NSCLC	=	Non-Small Cell Lung Cancer
irAes	=	immune-related Adverse Events
RECIST	=	Response Evaluation Criteria in Solid Tumors
CNS	=	Central Nervous System
BAL	=	Bronchoalveolar Lavage
TSH	=	Thyrotropin
TPO	=	Thyropoxidase
LH	=	Lutropin
FSH	=	Folitropi
ACTH	=	Adrenocorticotropic Hormone
GH	=	Growth Hormone
SIADH	=	Inappropriate Antidiuretic Hormone Secretion

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## HUMAN/ANIMAL RIGHTS

No Animal/Humans were used for studies that are basis of this research.

## CONSENT FOR PUBLICATION

Informed written consent was obtained from the patient for publication of this case. Consent is available on request.

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## AUTHORS' CONTRIBUTIONS

JA and EA wrote the manuscript. IR, SC and GL proofread the manuscript. AM, JA and EA primarily took care of patient. All authors read and approved the final manuscript.

## COMPETING INTERESTS

The authors declare that they have no competing interests.

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None declared.

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