CASE REPORT

# Lung Cancer and Immunotherapy: When the Immune System Becomes the New Challenge

## *Cancro do Pulmão e Imunoterapia: Quando o Sistema Imunitário se Torna o Novo Desafio*

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# ABSTRACT

Pembrolizumab is an immune checkpoint inhibitor. With the introduction of this therapeutic class, the adverse-event profile of antineoplastic therapy has changed, creating new challenges in the longitudinal management of patients with cancer.

We report the case of a 75-year-old man with metastatic lung adenocarcinoma (PD-L1 expression 90%, *KRAS G12C* mutation) who started treatment with pembrolizumab 2 mg/kg every three weeks. Nine months later, he presented with acute hyperglycemia (939 mg/dL) without ketoacidosis, interpreted as autoimmune diabetes secondary to immunotherapy, requiring intensive insulin therapy. Subsequently, he developed bilateral immune-mediated keratitis, treated with artificial tears, topical corticosteroids and antibiotics, as well as systemic corticosteroids. After clinical stabilization, Pembrolizumab therapy was reinstated, with adequate glycemic control and controlled ocular symptoms.

This case illustrates multisystem immune-mediated adverse reactions associated with pembrolizumab and the importance of multidisciplinary management for the success of cancer therapy and improvement of patients' quality of life.



# *RESUMO*

*O pembrolizumab é um inibidor de checkpoint imunológico. Com a introdução desta classe terapêutica, o perfil de acontecimentos adversos da terapêutica antineoplásica alterou-se, criando novos desafios na gestão longitudinal dos doentes com cancro.*

*Apresentamos o caso de um homem de 75 anos com adenocarcinoma pulmonar metastático (expressão de PD-L1 de 90%, mutação KRAS G12C) que iniciou tratamento com pembrolizumab na dose de 2 mg/kg de três em três semanas. Nove meses depois, apresentou hiperglicemia aguda (939 mg/dL), sem cetoacidose, interpretada como diabetes autoimune secundária à imunoterapia, tendo sido necessária insulinoterapia intensiva. Posteriormente, desenvolveu queratite bilateral imunomediada, tratada com lágrimas artificiais, corticosteroides tópicos e antibióticos, bem como corticoterapia sistémica. Após estabilização clínica, o tratamento com pembrolizumab foi reiniciado, mantendo-se um adequado controlo glicémico e os sintomas oculares controlados.*

*Este caso ilustra reações adversas imunomediadas multissistémicas associadas ao pembrolizumab e evidencia a importância de uma abordagem multidisciplinar para o sucesso da terapêutica oncológica e para a melhoria da qualidade de vida dos doentes.*



**Keywords:**
Carcinoma, Non-Small-Cell Lung/drug therapy; Drug-Related Side Effects and Adverse Reactions; Immune Checkpoint Inhibitors/adverse effects; Immunotherapy; Lung Neoplasms/drug therapy; Lung Neoplasms/immunology

***Palavras-chave:***
*Carcinoma do Pulmão de não Pequenas Células/tratamento farmacológico; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Imunoterapia; Inibidores de Checkpoint Imunológico/efeitos adversos; Neoplasias do Pulmão/imunologia; Neoplasias do Pulmão/tratamento farmacológico*


# INTRODUCTION

T lymphocytes play a critical role in the immune response against infections and neoplasms. Immune checkpoints are feedback mechanisms that limit expansion of the effector phase of the immune response.[1] Inhibitory receptors expressed on T lymphocytes, such as cytotoxic T-lymphocyte-associated antigen 4 and programmed cell death protein 1 (PD-1), are key components of the immune checkpoint system. When activated by their ligands expressed on tumour cells, these receptors downregulate T-cell function and facilitate immune evasion by the tumour.[2]

Pembrolizumab is a humanised IgG4 kappa anti-PD-1 monoclonal antibody approved by the U.S. Food and Drug Administration in 2015,[3] and by 2023 it had more than 20 approved therapeutic indications.[4] By inhibiting the PD-1 signalling cascade, it enhances T-cell activation.

The most common adverse events associated with pembrolizumab are fatigue, pruritus, and anorexia. Among the most frequent immune-related adverse events, hypothyroidism occurs in 6.9% of patients, pneumonitis in 3.6% (grade >=3 in 1.8%), and infusion-related reactions in 3%.[5] Grade 3 or 4 events, according to the Common Terminology Criteria for Adverse Events (CTCAE)[6] occur in approximately 5% of patients.[3]

The endocrinopathies most commonly associated with pembrolizumab are thyroiditis and hypophysitis.[7] More rarely, pembrolizumab has been associated with primary adrenal insufficiency, diabetes mellitus (DM), hypercalcaemia, and hypoparathyroidism. When diagnosed early, these endocrinopathies tend not to be severe and only rarely require treatment discontinuation. There is no evidence that corticosteroid therapy alters the natural history of pembrolizumab-induced endocrinopathies.[8]

The incidence of DM in clinical trials has been estimated at 0.1%. However, real-world experience since approval of the drug suggests a higher incidence, although it remains below 1%. Pembrolizumab-associated DM is caused by more rapid and aggressive pancreatic beta-cell destruction than that seen in classical type 1 diabetes mellitus. It does not respond to corticosteroid therapy and develops, on average, 7-17 weeks after treatment initiation. Clinically, it is characterised by abrupt-onset hyperglycaemia, ketosis, rapid decline in C-peptide levels, and marked glycaemic variability. Diabetic ketoacidosis is the presenting manifestation in 38%-70% of cases.[4]

Regarding ocular adverse events, these are estimated to occur in up to 10% of patients receiving immune checkpoint inhibitors (ICIs).[9] Dry eye syndrome is the most common ocular adverse event, occurring in approximately 1%-4% of cases, followed by anterior uveitis.[10]

## CASE REPORT

A 75-year-old man, active smoker with an estimated cumulative smoking exposure of 60 pack-years, and a medical history of chronic obstructive pulmonary disease, stable ischaemic heart disease, and atrial fibrillation, presented to his primary care physician with a 2-week history of left-sided sciatica. Initial investigation included computed tomography (CT) of the lumbar spine, which showed an L5-S1 disc herniation without lytic lesions. He subsequently underwent chest radiography and thoracic CT, which revealed a mass in the right upper lobe (RUL), a nodule in the right lower lobe (RLL) with a small ipsilateral pleural effusion, and a well-defined lobulated nodule in the left lower lobe (LLL), which had already been present since 2020 and had shown indolent growth.

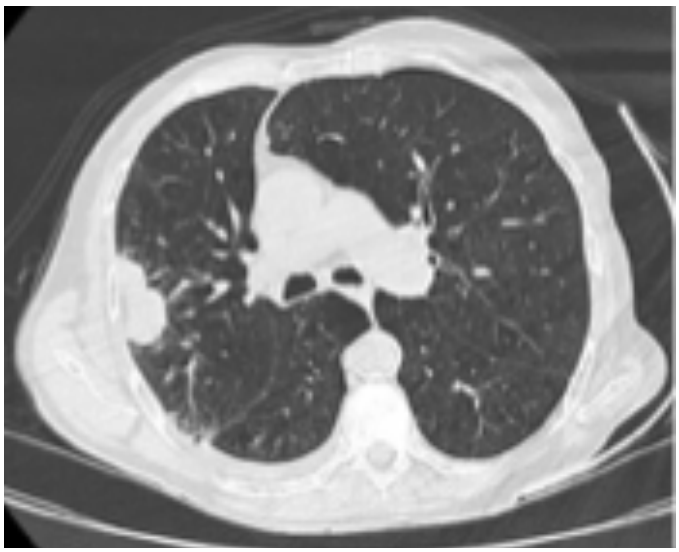

**Figure 1** Thoracic CT at diagnosis, September 2024: right upper lobe mass measuring 43 x 54 mm, in contact with the lateral costal pleura.

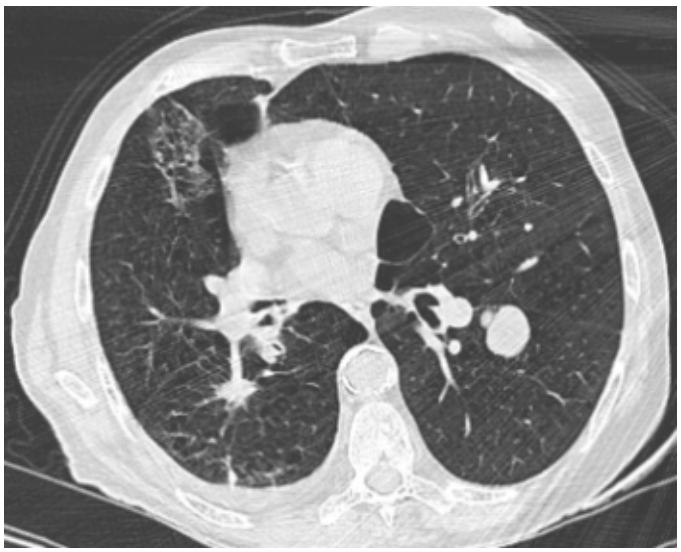

**Figure 2** Thoracic CT at diagnosis, September 2024: well-defined left lower lobe nodule with low suspicion and suspicious spiculated right lower lobe nodule.

For diagnostic assessment of the RUL lesion, transthoracic biopsy was performed in September 2024. Histopathology showed lung adenocarcinoma, with 90% PD-L1 expression and next-generation sequencing (NGS) demonstrating a KRAS exon 2 G12C mutation. Brain CT revealed no metastatic lesions. Positron emission tomography demonstrated increased uptake in the RUL lesion (SUV 18.8), the RLL nodule (SUV 4.2), a 4R lymph node (SUV 4.2), and multiple osseous foci (left second rib, D1 vertebral body, D7 spinous process, left acetabulum, and an extensive lesion involving most of the left sacral ala and left iliac wing).

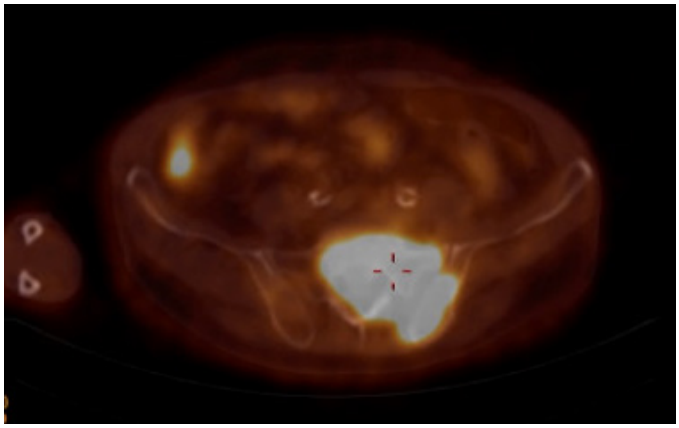

**Figure 3** Baseline 18F-FDG PET-CT: extensive hypermetabolic lesion involving most of the left sacral ala and left iliac wing (SUVmax 14.1).

The patient was therefore diagnosed with lung adenocarcinoma, stage cT4 (nodules in different lobes), N2 (4R nodal involvement), M1c (multiple bone metastases). Functionally, he had an Eastern Cooperative Oncology Group performance status of 1 and reported anorexia and poorly controlled sciatic pain.

He was started on palliative treatment for uncontrolled pain with dexamethasone 2 mg and palliative radiotherapy targeting the sacral lesion and associated soft tissue component, which allowed progressive corticosteroid tapering once pain control was achieved. Pembrolizumab at a dose of 2 mg/kg every 3 weeks was initiated in December 2024.

On response-assessment chest CT in March 2025, partial response according to RECIST criteria was observed, with reduction of the RUL mass to a 20-mm residual scar-like focus and decrease in the size of the RLL nodule, without mediastinal lymphadenopathy.

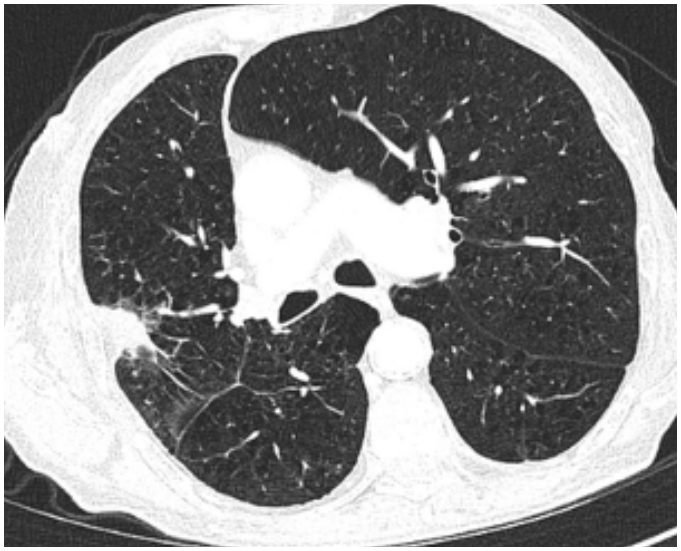

**Figure 4** Thoracic CT 3 months after treatment initiation: favourable response of the right upper lobe lesion.

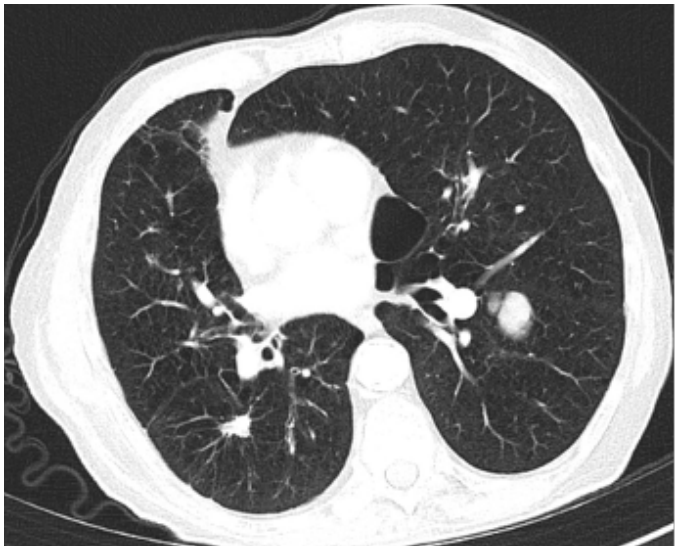

**Figure 5** Thoracic CT 3 months after treatment initiation: favourable response of the right lower lobe lesion; the left lower lobe nodule remains unchanged.

Treatment was continued without further complications until September 2025, when routine pre-treatment laboratory testing revealed a serum glucose level of 939 mg/dL. On clinical assessment, the patient did not report weight loss, polyuria, polyphagia, or polydipsia. Blood ketones were negative, and blood gas analysis showed no evidence of metabolic acidosis.

The case was discussed with the Endocrinology team, given the fulminant presentation and clinical behaviour resembling type 1 diabetes, with the need for high initial insulin doses, including 12 units of long-acting insulin at breakfast and a preprandial rapid-acting insulin correction regimen. New-onset pembrolizumab-associated diabetes, grade 3, was assumed in a patient with no personal or family history of diabetes and who was no longer receiving corticosteroids at that time.

After optimisation of insulin therapy and achievement of adequate glycaemic control, pembrolizumab was resumed at the previous dose and schedule.

Response reassessment CT in September 2025 showed further decrease in the RUL and RLL lesions, without suspicious mediastinal or hilar lymphadenopathy. The LLL lesion remained unchanged, with stability of the remaining findings.

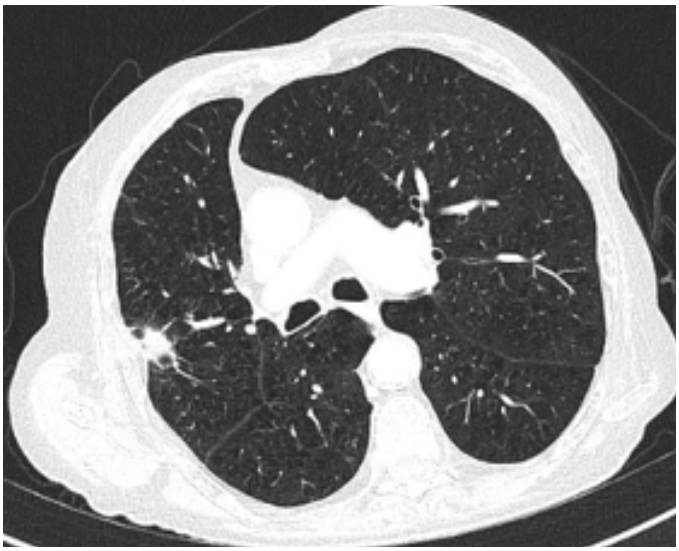

**Figure 6** Thoracic CT 9 months after treatment initiation: reduction in the right upper lobe lesion.

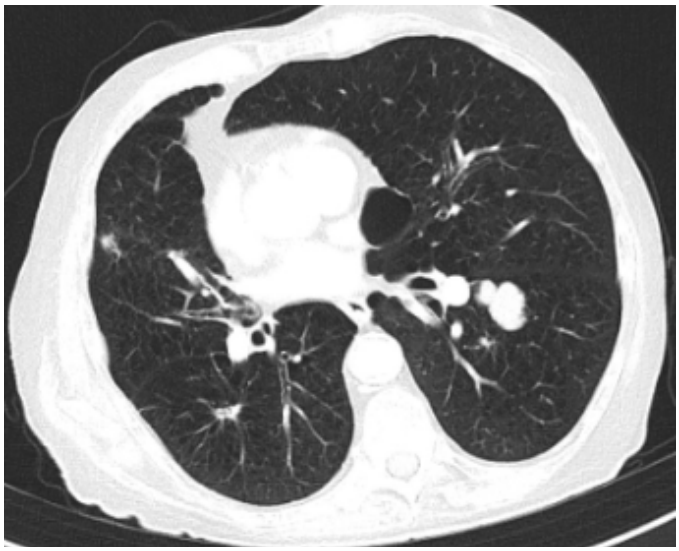

**Figure 7** Thoracic CT 9 months after treatment initiation: reduction in the right lower lobe lesion; the left lower lobe lesion remains unchanged.

In October 2025, the patient was admitted with pneumonia and partial respiratory failure. During hospitalisation, he developed blurred vision and photophobia, with conjunctival hyperaemia on examination. Ophthalmology consultation was obtained, and severe blepharitis with extensive punctate keratitis and bilateral corneal oedema was diagnosed. An immune-mediated ocular adverse event secondary to immunotherapy was presumed, and treatment was initiated with artificial tears, topical corticosteroids and antibiotics, together with systemic corticosteroid therapy (prednisolone 30 mg for 10 days).

At reassessment two weeks after discharge, the patient showed improvement in ocular symptoms while maintained on artificial tears, as well as improvement in anorexia and fatigue. He was undergoing outpatient physiotherapy, with motor recovery, and maintained good glycaemic control on insulin therapy. After discussion with the Ophthalmology team, pembrolizumab 2 mg/kg was restarted, with no further complications.

## DISCUSSION

The present case was intended to illustrate rare immune-related adverse events associated with anti-PD-1 therapy, namely diabetes mellitus and keratitis, and to review the optimal management of these toxicities and the handling of antineoplastic treatment in this setting.

Although rare, with an incidence of <1%, pembrolizumab-associated diabetes follows a more rapid and aggressive clinical course than classical type 1 diabetes because of drug-induced beta-cell destruction[5]. Accordingly, the initial approach to such cases should focus on ruling out diabetic ketoacidosis and promptly initiating appropriate insulin therapy. Temporary interruption of immunotherapy is recommended until the endocrinopathy improves to grade 2 or less.

In the present case, Endocrinology support was essential for insulin management and enabled treatment rechallenge with pembrolizumab, which was considered to have a favourable benefit-risk profile in view of the partial response observed according to RECIST criteria.

With regard to dry eye syndrome, this condition occurs when tear production is reduced or tear quality is impaired. As a result, the corneal surface becomes more vulnerable to irritation and injury, predisposing to keratitis. At the same time, meibomian gland dysfunction may occur, with obstruction of the glandular orifices and gland inflammation, culminating in blepharitis and perpetuating a vicious cycle.[11] Although not life-threatening, this adverse event can significantly impair patient quality of life.

Management of dry eye syndrome includes administration of artificial tears every 2-4 hours, lubricating ointment at night, and environmental measures such as humidification of indoor spaces. From grade 2 onwards, pembrolizumab interruption and topical corticosteroid therapy are recommended, while systemic immunosuppression should be considered on a case-by-case basis.[12] Given the specific nature of ocular manifestations, diagnosis, treatment, and management of ocular immune-related adverse events must be multidisciplinary and include Ophthalmology input. In this case, following joint discussion and considering the extent of ocular and periocular involvement, systemic corticosteroid therapy was deemed warranted.

There is some evidence from retrospective meta-analyses suggesting an association between immune-related adverse events and improved overall survival and progression-free survival. These adverse events appear to be strong predictors of survival, particularly when multiple toxicities occur, and the association seems stronger for thyroiditis or other endocrine toxicities, as well as gastrointestinal and cutaneous adverse events. The authors recommend caution in interpreting these findings because of the risk of immortal time bias, which precludes exclusion of reverse causality. There is also some evidence that grade >=3 toxicity may be associated with poorer long-term outcomes.[13-15]

The authors therefore wish to emphasise the importance of endocrine and ophthalmological toxicities associated with ICIs, particularly pembrolizumab, and to raise awareness of pembrolizumab-induced diabetes as a rare but clinically relevant adverse event. Unlike the more frequent endocrinopathies, such as thyroiditis and hypophysitis, pembrolizumab-induced diabetes is notable for its potential severity, including frequent presentation with diabetic ketoacidosis.

Management of immunotherapy-related toxicities represents a new clinical challenge, particularly given the tendency of these manifestations to become chronic. Multidisciplinary care is therefore more important than ever and should involve physicians from different specialties, as well as nurses, nutritionists, psychologists, and social workers. Patients themselves also assume a more active role in recognising common adverse-event manifestations, for which they should be appropriately informed and educated, and in their monitoring and treatment. A high index of clinical suspicion for immune-related adverse events is imperative, as early diagnosis is critical for timely initiation of appropriate therapy.

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