Reactivation of Pulmonary Tuberculosis in a patient with Oropharyngeal Cancer Treated with Nivolumab: Case Report

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Reativação de Tuberculose Pulmonar em uma Paciente com Câncer de Orofaringe Tratada com Nivolumabe: Relato de Caso

Reactivación de la Tuberculosis Pulmonar en una Paciente con Cáncer de Orofaringe Tratado con Nivolumab: Informe de Caso

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ABSTRACT

Introduction: Immune checkpoint inhibitors (ICI) are a class of drugs that are increasingly used to treat cancer. However, they have been associated with an increased risk of tuberculosis (TB) reactivation in patients with latent TB infection (LTBI). **Case report:** 61-year-old woman with oropharyngeal cancer who developed TB reactivation while receiving Nivolumab. The reactivation of TB in patients receiving ICI is thought to be due to the inhibition of the PD-1 pathway, which plays a role in the control of LTBI. The incidence of TB reactivation in patients receiving ICI is higher than in the general population. **Conclusion:** The increasing use of ICI is likely to lead to an increase in the number of cases of TB reactivation. It is suggested that routine screening for LTBI should be performed in patients who are being considered for treatment with ICI, especially in countries with a high incidence of TB.

Key words: immune checkpoint inhibitors; tuberculosis, pulmonary; latent tuberculosis.

RESUMO

Introdução: Os inibidores de *checkpoints* imunológicos (ICI) são uma classe de medicamentos cada vez mais utilizados para tratar o câncer. No entanto, eles têm sido associados a um risco aumentado de reativação da tuberculose (TB) em pacientes com infecção tuberculosa latente (ILTB). **Relato do caso:** Mulher, 61 anos, com câncer de orofaringe desenvolveu reativação de TB pulmonar enquanto recebia nivolumabe. Acredita-se que a reativação da TB em pacientes em ICI seja em virtude da inibição da via PD-1 que desempenha um papel no controle da ILTB. A incidência de reativação da TB em pacientes em ICI é maior do que na população geral. **Conclusão:** O uso crescente de ICI provavelmente levará a um aumento no número de casos de reativação da TB. Sugere-se proceder ao rastreamento rotineiro para ILTB nos pacientes que estão sendo considerados para tratamento com ICI, especialmente em países com alta incidência de TB.

Palavras-chave: inibidores de *checkpoint* imunológico; tuberculose pulmonar; tuberculose latente.

RESUMEN

Introducción: Los inhibidores de puntos de control inmunológico (ICI) son una clase de medicamentos que se utilizan cada vez más para tratar el cáncer. Sin embargo, se han asociado con un mayor riesgo de reactivación de la tuberculosis (TBC) en pacientes con infección tuberculosa latente (ILTB). **Informe del caso:** Mujer, 61 años, con cáncer de orofaringe que desarrolló reactivación de tuberculosis pulmonar mientras recibía Nivolumab. Se cree que la reactivación de la tuberculosis en pacientes con ICI se debe a la inhibición de la vía PD-1, que desempeña un papel en el control de la ILTB. La incidencia de reactivación de la tuberculosis en pacientes con ICI es mayor que en la población general. **Conclusión:** El uso cada vez mayor de ICI probablemente conducirá a un aumento en el número de casos de reactivación de la tuberculosis. Se sugiere realizar pruebas de detección sistemática de ILTB en los pacientes que están siendo considerados para recibir tratamiento con ICI, especialmente en países con una alta incidencia de tuberculosis.

Palabras clave: inhibidores de puntos de control inmunológico; tuberculosis pulmonar; tuberculosis latente.

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INTRODUCTION

Immune checkpoint inhibitors (ICI), anti-PD-1 or PD-L1, are currently the main classes of drugs used in the treatment of solid and hematological neoplasms. Nivolumab is a PD-1 inhibitor indicated for the treatment of several solid tumors, such as lung cancer, head and neck cancer, melanoma, kidney, urothelial, and lymphomas. The toxicity profile of ICI is better when compared to conventional cytotoxic chemotherapy, but it is based on immune-mediated effects, the most common being hypothyroidism, and others less common, such as colitis, hepatitis, nephritis, and pneumonitis.

Recently, there has been an increasing number of publications drawing attention to tuberculosis (TB) diagnoses in the form of casereports[1,2], reviews on the topic[3-6], including systematic reviews on TB reactivation in patients treated with ICI[7].

Much has been studied and hypothesized, but reactivation, as well as the severity of TB, is most likely related to the role of PD-1 in the control of latent tuberculous infection (LTBI), as suggested in preclinical trials[8-10].

Concern about TB reactivation and the increasing use of ICI has raised questions about how to conduct LTBI screening in this population, and the publication of regional experiences are examples of this[11,12]. Screening for early treatment of latent *Mycobacterium tuberculosis* (M tuberculosis) infection is routine, for example, prior to initiation of treatment with anti-tumor necrosis factor (TNF)-alpha agents in the management of psoriasis, Crohn's disease, and rheumatoid arthritis[13,14].

According to the World Health Organization (WHO) report on TB in 2022, a quarter of the world's population is infected with the TB bacillus, with the incidence of the disease higher in developing countries. In Brazil, in 2021, the incidence coefficient was 32.0 cases/100,000 inhabitants[15]. Because of this high incidence rate (over ten cases), it is important to identify LTBI in cancer patients who are candidates to start treatment with drugs that can reactivate the disease.

Based on the increased data in the literature on TB reactivation in ICI-treated patients, we report the case of a Brazilian patient with malignant neoplasm of the oropharynx who was diagnosed with TB during treatment with nivolumab. It is understood that case reports in this context will provide a future understanding of the need for LTBI screening before initiating treatment with this class of drugs, especially in countries where TB incidence is high.

This research was approved by the Research Ethics Committee (CEP) of the São José dos Campos Institute of Science and Technology of Universidade Estadual Paulista (Unesp) under opinion number 6506181 (CAAE: 75367923.0.0000.0077) and followed all ethical requirements related to studies involving human beings, necessary for its success and protection related to the confidentiality of information, as evidenced in Resolution nº. 466/12[16] of the National Health Council.

CASE REPORT

Patient, female, 61 years old, diagnosed with malignant neoplasm of the oropharynx confirmed by excisional biopsy of level II cervical lymph node with moderately differentiated squamous cell carcinoma (SCC) – p16 positive. History of more than 40 pack-years of tobacco use and absence of other relevant comorbidities; denied previous treatment or prophylaxis for TB. Initial staging was without distant metastatic disease. The patient underwent curative treatment with radiotherapy and chemo sensitization with cisplatin.

One year after the end of treatment, the patient presented mediastinal lymph node enlargement, evidenced by computed tomography (CT); the largest of the left pulmonary hilum measuring 2.7x2.0 cm, in addition to pulmonary nodules suggestive of secondary involvement, the largest in the right lower lobe of 2.5x1.6 cm (Figure 1A). It was then considered a distant relapsed disease, and treatment with carboplatin, fluorouracil and cetuximab was started, with stable disease for six months of treatment, when it evolved with progression of lung and lymph node disease, and second-line treatment with paclitaxel was started. These lesions showed partial response in the second line, during 15 months of treatment, and grew back (Figure 1B).

Due to the progression of the disease and the patient's excellent *performance status,* nivolumab was proposed as the third line of treatment. The pulmonary and mediastinal lesions went into almost complete and lasting response for about 37 months (Figure 1C), when he presented a new enlargement of the single left perihilar mediastinal lymph node, called oligoprogression. The lesion was submitted to stereotactic body radiotherapy (SBRT) and treatment with nivolumab was maintained, with excellent local control for another four months. As immunotherapy-related toxicity, the patient developed levothyroxine-controlled hypothyroidism about four months after starting treatment.

Two months after the end of radiotherapy, productive cough and episodes of bronchospasm began, and CT showed an image of pulmonary consolidation with air bronchogram in the left lower lobe without cleavage plane and associated lymph node enlargement in the

pulmonary hilum on the same side (Figure 2A). She received sequential treatment with azithromycin and ceftriaxone, however, with the worsening of respiratory symptoms with dyspnea, weight loss and night sweats, there was a need for hospitalization for clinical support (Figure 2B). The hypothesis of active TB was raised, confirmed with the research of the alcohol-resistant acid bacillus (AFB) in sputum. After starting the rifampicin-isoniazid-pyrazinamide-ethambutol (ripe) regimen of treatment for TB, the patient showed significant clinical improvement.

Due to treatment funding issues, until the last contact with the patient – approximately three months after the start of anti-TB treatment – immunotherapy had not been restarted. Imaging control after four months of treatment for TB showed excellent recovery from lung infection, but already with a suggestion of lung metastasis growth (Figure 2C).

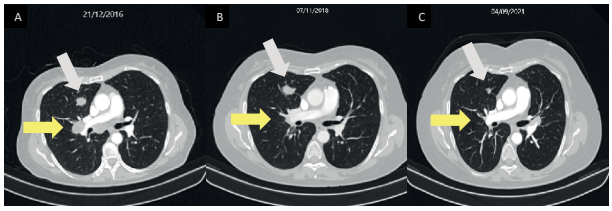

Figure 1. Presence of pulmonary nodule in the right lower lobe (white arrow) and right hilar lymph node enlargement (yellow arrow), considered the beginning of recurrent metastatic neoplastic disease (A). Imaging tests before starting treatment with nivolumab, after having already received two different lines of chemotherapy with partial response (B). Imaging control, after about 37 months of treatment with nivolumab, showing excellent pulmonary response (C)

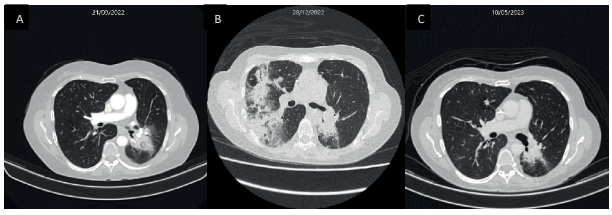

Figure 2. Onset of symptoms with productive cough and bronchospasm, two months after undergoing stereotactic radiotherapy-SBRT in the right hilum (A). Image of hospitalization after clinical worsening with productive cough, dyspnea, weight loss and night sweats (B). Image control after four months of anti-TB treatment (C)

DISCUSSION

The diagnosis of pulmonary TB in this patient during treatment with nivolumab, without other risk factors for the development of the infection, led to a review of the literature on the relationship between ICI use and LTBI reactivation. Several reports were found[7,17,18] raising concern about the consequences, severity and how to prevent similar new cases in the future.

Most TB reactivations in ICI-treated patients appear to be pulmonary, as in the case inquestion[7], but most cases are diagnosed with reactivation within the first three months of treatment[17]. The patient in the present case had already been under treatment for almost 40 months when she started experiencing respiratory symptoms and night sweats. He reacted well and promptly to anti-TB treatment, as in most of the described patients treated, despite reports of rapid and fulminant evolutions.

We reviewed reports of screening experiences for LTBI and a recent published series of 70 patients at a dermatology-oncology service in Germany[19]. A country with a low incidence of TB evaluated adherence to screening for latent TB during the two-year period in patients who would receive treatment with *checkpoint inhibitors* with the following result: 73% of patients were evaluated and 9% tested positive for latent infection.

Liu K et al.[7], in their systematic review of 27 studies, showed 35 cases of TB in patients treated with *checkpoint inhibitors,* and were able to calculate the estimated incidence of TB cases in patients undergoing ICI therapy – the incidence can reach an incredible 2,000 cases/100,000 inhabitants, 35 times higher than in the general population. However, the data collected were predominantly from countries with a low incidence of TB – considered low when it is less than ten cases/100,000 inhabitants.

In Brazil, in 2021, 68,271 new cases of TB were reported in the general population, while in countries such as France and the United States, this number does not reach ten thousand in the same period[18], which leads us to believe in the importance of discussing preventive measures against the reactivation of this infection in patients who will receive ICI.

Immune control of LTBI requires a balance of immune cells to inhibit the growth of the bacillus, but at the same time does not generate an intense inflammatory response to the point of causing tissue damage. Inhibition of the PD-1 pathway can stimulate multiple types of immune cells in the granuloma, resulting in the collapse of this structure with loss of control of latent infection[18,20,21]. Tereza et al.[9], in a three-dimensional cell culture model of human TB, demonstrated that PD-1 regulates the immune response in TB, and PD-1 inhibition accelerates the growth of *M. tuberculosis* through excessive secretion of TNF-α.

Screening for LTBI and, consequently, TB chemoprophylaxis are already well established in patients at high risk for the development of active TB, for example, before treatments with anti-TNF-α[22-24] medications, either in the form of the tuberculin skin test (PPD) and more recently by the interferon-gamma release test (IGRA), due to the potentially fatal consequences of TB reactivation.

Currently, there is no practical recommendation for screening or chemoprophylaxis for patients being considered for ICI treatment suggested by specialized societies. In the current literature, only one published clinical recommendation was found, sponsored by the Chinese health department, which discusses recommendations for the diagnosis and management of infections related to the use of ICI[25]. In fact, in the survey of the case study by Langan et al.[19], the authors detail that the research protocols during the development of some ICIs did not include screening tests for LTBI in patients who developed active TB.

In Brazil, the PPD test has long been used. More recently, the IGRA test has also been made available in the public network for patients at elevated risk of developing TB (children ≥ 2 years <10 years who had contact with cases of active TB, HIV patients with CD4-lymphocyte count >350 cells/mm^3 and candidates for stem cell transplantation)[13].

In addition, it is important to include TB as a differential diagnosis for patients who develop pulmonary disease on PD-1[26-28] inhibitors, in addition to immune-mediated pneumonitis – the latter a rare situation –, with a frequency of less than 1%, whose treatment includes the use of corticosteroids, sometimes in high doses.

The current case was also a challenge to conduct, as there is still no general consensus on whether ICI therapy should be continued, temporarily interrupted, or permanently suspended in the context of acute *M tuberculosis* infection or reactivation[19]. According to a systematic review, the time to restart immunotherapy ranged from one to four months and there was no interference of anti-TB treatment on the effectiveness of antineoplastic treatment[12].

CONCLUSION

The number of reports of association of TB reactivation with treatment with PD-1 inhibitors has been increasing with the globalization of the use of these drugs, so it is suggested, with this typical case, to raise the discussion about the routine indication of screening for latent infection, especially in countries with a high incidence of TB such as Brazil, prior to treatment with ICI medications.

CONTRIBUTIONS

All authors contributed substantially to the design and/or planning of the study; in the collection, analysis and/or interpretation of the data; in the writing and/or critical review; and approved the last version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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