# Tuberculous Lymphadenitis in a Patient Receiving Anti-PD-1 Inhibitor For Melanoma

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## Background

Melanoma is a malignancy that primarily derives from melanocytic cells. Tuberculosis (TB) is a worldwide public health problem with being a significant cause of morbidity and mortality. Nivolumab is a well-defined immune checkpoint inhibitor (ICI), which is a fully-humanized IgG4 monoclonal antibody that blocks PD-1 and mainly increases reactivation of anti-tumor immunity. Although opportunistic infections are not expected side effects of ICI, the diagnosis of ICI-related TB has been recently increasing. A recent study with 297 cancer patients reported that the incidence rate of TB during ICI therapy is only 1.7% (5/297). The current report represents the second tuberculous lymphadenitis case in the literature related to anti-PD-1 based monoclonal antibody therapy.

## Case Description

The patient is a 38-year-old Caucasian female who was diagnosed with Stage IIIb malignant melanoma. The excision of the left scapular lesion and axillary dissection was performed. Baseline PET/CT showed no evidence of metastatic disease. After the 5th cycle of Nivolumab treatment, the patient developed 38 ºC fever and grade 2 fatigue. Physical exams, including skin and the respiratory system, were unremarkable. Thyroid function tests, liver function tests, complete blood count, and basic metabolic panel were within normal limits. Respiratory virus panel, EBV, HIV, and Brucella test results were negative. Sarcoidosis is ruled out clinically and radiologically. The patient didn't get any cytotoxic chemotherapy or steroids. Upon completing the 6th cycle, control PET/CT detected a significant metabolic progression in the left cervical region level 2 lymph nodes (Figure.1). The patient didn't have any clinically palpable lymphadenopathy. Left cervical modified radical type 3 dissection was performed. Meanwhile, the patient's fever was continued.

✓ **TB reactivation can occur in various organs as a complication of PD-1 targeted immunotherapy.**

✓ **We recommend TB screening in all patients before starting PD-1 inhibitor therapy.**

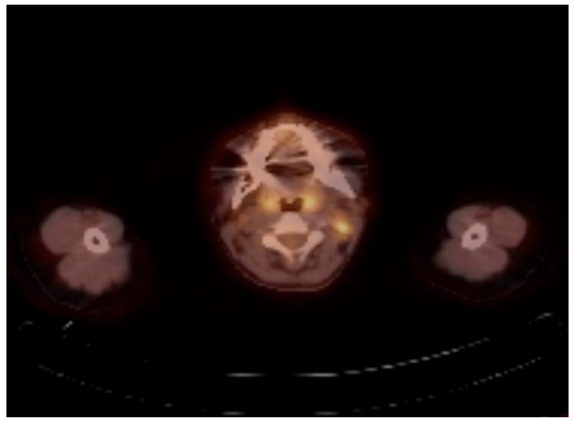

**Figure 1.** F-18FDG PET/CT imaging shows increased metabolic activity and FDG uptake in left level 2 cervical lymph nodes.

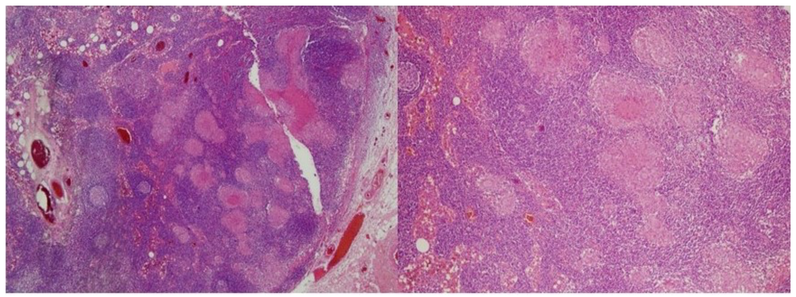

**Figure 2.** The histopathologic evaluation of the left cervical modified radical type 3 dissection material showing caseous granulomatous lymphadenitis.

## Case Description cont'd

The histopathological evaluation of the eight lymph nodes revealed caseous granulomatous lymphadenitis (Figure.2). High resolution computed tomography (HRCT) of the lungs didn't show pulmonary tuberculosis or opportunistic infections. A purified protein derivative (PPD) skin test and Interferon Gamma Release Assay (IGRA) was not performed due to recent immunotherapy. Given persistent fever and caseous granulomatous lymphadenitis, anti-TB treatment was initiated, and subsequently, fever was controlled, and fatigue improved. Concurrently, we continued Nivolumab treatment along with the anti-TB regimen. After six months of anti-TB therapy, the control PET/CT didn't show any recurrence. Anti-TB therapy was discontinued after 12 months. The patient is currently under medical surveillance every three months.

## Discussion

Increasing evidence from current and previous reports suggests that TB reactivation can occur as a complication of ICI therapy. The underlying mechanism has not been elucidated yet. Triggering of excessive inflammatory responses with ICI therapy is a potential cause. This phenomenon is similar to the immune reconstitution inflammatory syndrome (IRIS) associated with antiretroviral treatment. To date, screening for latent tuberculosis before ICIs therapy is not routine yet. Considering increased utilization of ICI based immunotherapies, this issue can cause significant mortality and morbidity, especially in the population with high TB prevalence. TB screening should be carefully considered in all cancer patients before starting PD-1 inhibitor therapy.