Letter to the Editor

Open questions between immune checkpoint inhibitors and tuberculosis incidence

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We read with great interest the recent publication "A narrative review of the controversy on the risk of mycobacterial infections with immune checkpoint inhibitor use: does Goldilocks have the answer?" (1). We agree with Vaddi *et al.* for their vital insight on the controversial association between mycobacterial infections and the use of immune checkpoint inhibitors (ICIs). We also have some concerns about the following issues.

Firstly, only dozens of tuberculosis (TB) cases have been reported during ICI usage until now, although ICIs are widely used for malignant tumor therapy and accidentally used for chronic infection therapy. In a recent publication, an increased TB incidence of 1.58% in the ICIs group was reported, which was higher than 0.68% in the tyrosine kinase inhibitors (TKIs) group (2). Importantly, as one of the high-risk populations for TB incidence, various cancer patients had increased TB occurrence, especially in cancer of the respiratory tract followed by hematology. There was a 1.86% pulmonary TB incidence among patients with lung cancer (3), and the incidence of TB among cancer patients receiving chemotherapy was 3.9% (4). Moreover, in TB endemic areas such as China, the TB incidence was significantly higher in hospitalized patients with latent tuberculosis infection (LTBI) than in the general population. Therefore, from the incidence perspective, the linkage between ICI usage and TB reactivation was still inconclusive, even with increasing case reports and retrospective case series.

Secondly, most ICI-treated patients had previous immunosuppressive therapy experience, which also might result in TB reactivation. Thus, it is important to differentiate immunosuppression-induced TB reactivation from unmasking TB due to dysregulated immunity (5). PD-1 expressions on conventional T cells and regulatory T cells may play opposite immunoregulatory functions in the course of TB development. Besides different levels of PD-1 expression on T cell subsets, other immunological markers should be further investigated to differentiate immune exhaustion (effector function loss) from immune activation-induced immune tolerance (a protective immunity). Patients in an immune exhaustion state may benefit from ICI application due to improved T-cell function (6), while patients in the immune activation-induced immune tolerance state might increase autoimmune risk and unmasking infectious diseases due to hyperinflammation after ICI usage (7). In the lesson from human immunodeficiency virus (HIV) infection, controlling opportunistic infections before antiretroviral therapy (ART) could reduce the occurrence of immune reconstitution inflammatory syndrome (IRIS) among patients with advanced immunodeficiency. Similarly and notably, treatment for reducing antigenic burden is recommended

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before ICI application.

Thirdly, changing morphological patterns of TB pathology were observed in different immune conditions, but the pathological manifestations of ICI-related TB have scarcely been described. Among previous case reports, both classical caseous necrosis and atypical granulomatous inflammation were observed, which were accompanied by high PD-L1 expression on macrophages (8). Surprisingly, the lung pathology of PD-1$^{-/-}$ mice was characterized by obvious bacterial proliferation and focal necrotic areas, infiltrated by apparent neutrophils and a smattering of T and B cells. The typical histological lesion of TB among immunocompetent individuals is the coexisting caseous necrotizing-granulomatous inflammation, multinuclear giant cell reaction, positive acid-fast staining, and high PD-1 expression on CD8^{+} T cells (8). Among cases with advanced HIV infection, the main presentation of TB is atypical granulomatous inflammation with less lymphocyte infiltration. However, large numbers of neutrophils, plasma cells, and lymphocytes are demonstrated in the pathology of TB-IRIS, partly with concurrent suppurative inflammation (9). Furthermore, organizing pneumonia filling with intraalveolar fibrous granulation tissue is also reported as a special manifestation of TB-IRIS (10).

In conclusion, the incidence of TB among patients using ICIs was still low. The pathogen's load, immune status, and pathological manifestation should also be evaluated to differentiate TB reactivation from unmasking TB-IRIS. In the future, prospective case-control studies are urgently needed to identify the precise incidence data, real immune status, and characteristic biomarkers. Although a discrepant proof between infectious diseases guidelines and oncology guidelines, intensive TB screening and initiating TB preventive therapy should be recommended among severely immunocompromised individuals in high TB burden countries.

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Footnote

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