Title

Testing for latent tuberculosis before starting patients on immune checkpoint inhibitors

Author

Dhar, Chirag

Publication Date

2020-06-09

Peer reviewed

Testing for latent tuberculosis before starting patients on immune checkpoint inhibitors

Chirag Dhar✉, Departments of Medicine and Cellular and Molecular Medicine, University of California, San Diego, USA

Dear Editor, *Indian Journal of Cancer*

Multiple case reports have been published on the risk of tuberculosis activation in patients on immune checkpoint inhibitors (ICPIs) and have come to my attention. To this matter, I caution clinicians to test for latent tuberculosis (LTB) before starting their patients on ICPIs.

The 2018 Nobel Prize in Medicine and Physiology was awarded to Tasuku Honjo and James Allison for their discovery of ICPIs, a revolutionary new cancer therapy.[1] An important yet often overlooked phenomena when using ICPIs though is the risk of infection reactivation due to immunosuppression. Activation of asymptomatic and undiagnosed LTB is a significant concern as demonstrated by multiple case studies.[2-8] One possible mechanism for reactivation of tuberculosis (TB) in patients on anti-PD-1 therapy[9] is pictorially depicted in Figure 1. Briefly, PD-1 expressing T-cells bind to PD-L1 on cells infected with *Mycobacterium tuberculosis*. These cells remain quiescent until anti-PD-1 therapy for an unrelated malignancy is started. This blocking of the immune handshake may reactivate LTB leading to pulmonary/disseminated TB.

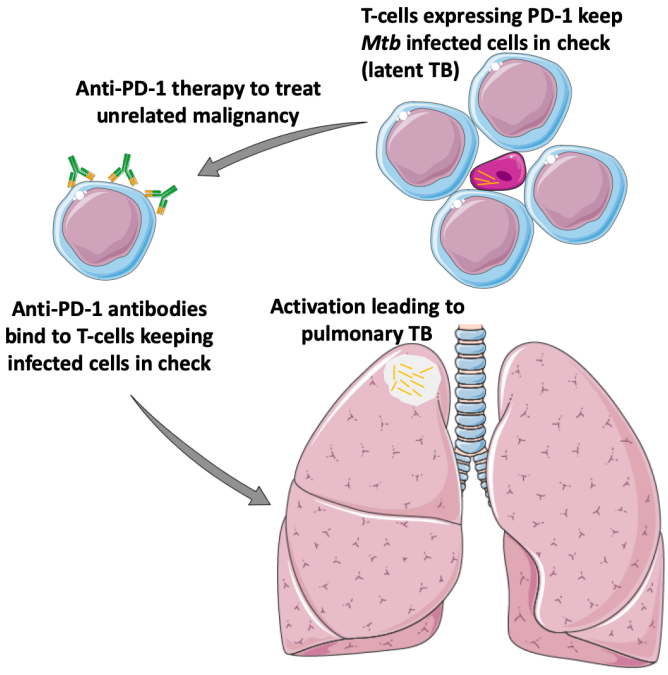

Figure 1: Pictorial depiction of one possible mechanism for TB activation by anti-PD-1 immunotherapy. Yellow rods indicate Mycobacterium tuberculosis (Mtb) Image created with objects sourced from Servier Medical Art (http://smart.servier.com/), licensed under a Creative Common Attribution 3.0 Generic License.

In light of all these studies, it is imperative that physicians test for LTB before starting patients on ICPIs. This caution is especially targeted to physicians practicing in countries where TB is endemic. The established way to test for asymptomatic LTB is by Interferon-γ release assays such as the QuantiFERON-TB Gold test (high specificity of >99%)[10] as was used in a recent study.[11] Newer methods such as host gene expression profiles[12] and differences in cellular phenotypes[13] are also being studied as possible ways to diagnose LTB.

If a diagnosis of LTB is established, further therapeutic decisions should be taken in consultation with a pulmonologist/TB specialist. A 4-week isoniazid chemoprophylaxis is one possible method to treat LTB and has been successful in preventing TB reactivation in patients on anti-TNF therapy.[14] Finally, the potential risk to benefit ratio of ICPIs should also be taken into consideration on a case-by-case basis in patients with untreated LTB. Longer follow ups of patients on ICPIs and pre-clinical model studies are likely to throw further light on these matters.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Chirag Dhar

Departments of Medicine and Cellular and Molecular Medicine, University of California, San Diego, U.S.A.

Correspondence to: Dr. Chirag Dhar, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA-92093, U.S.A. ✉E-mail: cdhar@ucsd.edu or chirag@worldviewofmedicine.org

How to cite this article: Dhar C. Testing for latent tuberculosis before starting patients on immune checkpoint inhibitors. Indian J Cancer (in press)

References

1. Huang PW, Chang JW. Immune checkpoint inhibitors win the 2018 Nobel Prize. Biomed J 2019;42:299-306.

2. Takata S, Koh G, Han Y, Yoshida H, Shiroyama T, Takada H, *et al*. Paradoxical response in a patient with non-small cell lung cancer who received nivolumab followed by anti-Mycobacterium tuberculosis agents. J Infect Chemother 2019;25:54-8.

3. Picchi H, Mateus C, Chouaid C, Besse B, Marabelle A, Michot JM, *et al*. Infectious complications associated with the use of immune checkpoint inhibitors in oncology: Reactivation of tuberculosis after anti PD-1 treatment. Clin Microbiol Infect 2018;24:216-8.

4. Lee JJ, Chan A, Tang T. Tuberculosis reactivation in a patient receiving anti-programmed death-1 (PD-1) inhibitor for relapsed Hodgkin's lymphoma. Acta Oncol 2016;55:519-20.

5. Fujita K, Terashima T, Mio T. Anti-PD1 Antibody treatment and the development of acute pulmonary tuberculosis. J Thorac Oncol 2016;11:2238-40.

6. Chu YC, Fang KC, Chen HC, Yeh YC, Tseng CE, Chou TY, *et al*. Pericardial tamponade caused by a hypersensitivity response to tuberculosis reactivation after Anti-PD-1 treatment in a patient with advanced pulmonary adenocarcinoma. J Thorac Oncol 2017;12:e111-4.

7. van Eeden R, Rapoport BL, Smit T, Anderson R. Tuberculosis infection in a patient treated with nivolumab for non-small cell lung cancer: Case report and literature review. Front Oncol 2019;9:659.

8. Barber DL, Sakai S, Kudchadkar RR, Fling SP, Day TA, Vergara JA, *et al*. Tuberculosis following PD-1 blockade for cancer immunotherapy. Sci Transl Med 2019;11:eaat2702.

9. Ahmed A, Adiga V, Nayak S, Kumar JAJU, Dhar C, Sahoo PN, *et al*. Circulating HLA-DR+CD4+ effector memory T cells resistant to CCR5 and PD-L1 mediated suppression compromise regulatory T cell function in tuberculosis. PLoS Pathog 2018;14:e1007289.

10. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Kenneth C, *et al*. Updated guidelines for using interferon gamma release assays to detect mycobacterium tuberculosis infection - United States, 2010. MMWR Recomm Rep 2010;59:1-25.

11. Langan EA, Graetz V, Allerheiligen J, Zillikens D, Rupp J, Terheyden P. Immune checkpoint inhibitors and tuberculosis: An old disease in a new context. Lancet Oncol 2020;21:e55-65.

12. Sambarey A, Devaprasad A, Mohan A, Ahmed A, Nayak S, Swaminathan S, *et al*. Unbiased identification of blood-based biomarkers for pulmonary tuberculosis by modeling and mining molecular interaction networks. EBioMedicine 2017;15:112-26.

13. Rakshit S, Adiga V, Nayak S, Sahoo PN, Sharma PK, van Meijgaarden KE, *et al*. Circulating mycobacterium tuberculosis DosR latency antigen-specific, polyfunctional, regulatory IL10+ Th17 CD4 T-cells differentiate latent from active tuberculosis. Sci Rep 2017;7:11948.

14. Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, Montero D, Pascual-Gómez E, Mola EM, *et al*. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. Arthritis Rheum 2005;52:1766-72.

