Infectious Diseases Associated with the Use of IMT

Subjects: Oncology

Contributor: Ranferi Ocaña-Guzmán , Diego Osorio-Pérez , Leslie Chavez-Galan

In the last decades, immunotherapy (IMT) added Immune Checkpoint Inhibitors (ICI) as one of the most potent tools developed recently to improve traditional oncology treatment. ICI consists of using monoclonal antibodies to inhibit the immune checkpoints (IC)-ligand binding, and, consequently, the activation of the immune cells is conserved.

immune checkpoint immunotherapy cancer IRAE ICI

1. Tuberculosis (TB)

TB is an infectious disease caused by the bacilli *Mycobacterium tuberculosis* (M.tb). The immune response develops a cellular structure called granuloma to contain the M.tb infection. TNF (Tumour Necrosis Factor) is an inflammatory cytokine necessary to maintain and form granuloma [1][2]. TNF was one of the first molecules selected as a target in the treatment of rheumatoid arthritis (RA) to limit chronic inflammation; infliximab is an anti-human monoclonal antibody (chimeric mouse–human) that inhibits soluble TNF in both the monomeric and trimeric form, and etanercept is a fully human recombinant molecule consisting of two subunits of the TNF receptor 2 to block the trimeric form of TNF [3]. From 1998 to 2001, 70 TB cases were associated with using infliximab; from these, 12 patients died [4].

Now in the era of ICIs, reports indicate a substantial risk of latent TB reactivation associated with using blockers of the PD-1 pathway. Using a mouse model knockout for PD-1, E. Lázár-Molnár et al. reported that the loss of the PD-1 pathway favours an excessive inflammatory state, increasing the necrotic damage and reducing the infiltration of T and B cells, which affects the capacity to control M. tb proliferation [5].

A growing number of reports show a reactivation of pulmonary TB in humans using IMT, for instance, after using PD-1 inhibitors such as Pembrolizumab and Nivolumab [6][7][8]. The frequency of TB reactivation is higher in patients with haematological malignancies compared to solid tumours [9][10]. A meta-analysis by K. Liu et al. indicates that patients treated with PD-1/PD-L1 blockers had a 35 times higher probability of reactivating TB than the general population, and the mortality was extremely high because 30% of these patients that experienced reactivated TB died [10].

Even patients with uncommon cancer, such as nasopharyngeal carcinoma and Merkel cell carcinoma, developed TB following PD-1 blockade therapy; authors described that pembrolizumab disturbs the T cell response because,

although they observed specific Th1 lymphocytes CD4+, others such as Th17, CD8+, and FoxP3+ T-cells did not show an increase over time [6].

The limited evaluations of specific T cells to cancer cells and M.tb suggest an imperative need for animal models at a basic level and the clinical caution to test cancer patients for latent TB before starting ICI treatment, especially in countries with a high incidence of TB.

2. Aspergillus fumigatus Infection

Aspergillus fumigatius is a fungus, causative of several diseases, mainly in the respiratory airways due to the high presence of spores in the airborne particulate matter [11]. As a result of the immune status of the host, *Aspergillus fumigatius* spores can lead to a broad spectrum of diseases, including invasive aspergillosis, frequently affecting patients with chronic obstructive pulmonary disease. Other forms are chronic pulmonary aspergillosis and allergic bronchopulmonary aspergillosis, which show a high incidence among asthma and cystic fibrosis patients [12]. Diverse reports have demonstrated isolated cases of patients with *Aspergillus fumigatus* infection after IMT use.

A 62-year-old man with diabetes mellitus and metastatic renal cell carcinoma was initially treated with monoclonal Nivolumab and Ipilimumab to block PD-1 and CTLA-4, respectively [13]. Posterior to the finish of the scheme, this patient continued using rituximab for the carcinoma treatment [13]. In a separate case from the Brooklyn Hospital Center (New York), a 63-year-old man completed chemotherapy with paclitaxel and carboplatin to treat non-small-cell lung cancer (NSCLC). After three months, four cycles of Durvalumab began to block PD-L1; however, the patient showed difficulty of breath, and *Aspergillus fumigatus* was identified in the pleural fluid culture [14].

Another reported case is a 68-year-old man treated for NSCLC with chemoradiotherapy and subsequently with durvalumab [15]. After the second dose, bacterial pneumonia with fever and IRAE were considered, and *Aspergillus fumigatus* was isolated from bronchoscopy-obtained samples [15]. This patient did not report comorbidities associated with infection susceptibility such as diabetes mellitus; it is important to note this because data suggest that opportunistic infections in patients with IM could be related to metabolic disorders [14].

The exact mechanism by which opportunistic infections occur in patients with IMT is poorly understood. Still, it is possible that the co-infections could result from many immune alterations during ICI administration, such as a hyper-inflammatory state. Usually, to control this paradoxical response, corticosteroids are used to reduce hyper-inflammation. However, this induced immunosuppression also induces another undesirable effect.

3. Pneumocystis jirovecii

Pneumonia caused by the fungus *Pneumocystis jirovecii* is a common opportunistic infection affecting immunosuppressed patients [16]. Currently, there are reports about this infection in patients treated with IMT.

M. Schwarz et al. reported two lethal cases of infection by *Pneumocystis jirovecii* in patients treated with PD-L1 blockers [17]. The first was a man, 79 years old, diagnosed with bilateral NSCLC, posterior to an unsuccessful scheme of six cycles of chemotherapy with carboplatin and gemcitabine, followed by radiotherapy; nivolumab was initiated, but it was stopped twice because of recurrent respiratory infections. A thoracic computerized tomographic (CT) scan showed that the patient had reticular and nodular thickening at the four nivolumab cycles. Nivolumab was retired, and immunosuppressive treatment with corticosteroids was initiated. However, the patient presented severe dyspnoea, dry cough, hypotension, tachycardia, and fever after four weeks, and, using quantitative PCR, the presence of *Pneumocystis jirovecii* was confirmed. The patient was deceased 2 weeks later due to respiratory failure [17].

In the second case, a man of 53 years old was diagnosed with stage IIIA NSCLC. The patient was treated with cisplatin and vinorelbine, followed by a right upper lobe resection [17]. Nivolumab and radiotherapy were used to treat residual mediastinal tumour persistence. By the third cycle of nivolumab, the patient developed dyspnoea and fever, and the CT scan showed evidence of pneumonitis. Nivolumab was suspended from initiating corticosteroid administration, despite an initial improvement; after a month, the patient deteriorated dramatically, and his bronchial alveolar lavage was positive for *Pneumocystis jirovecii* infection and cytomegalovirus positivity [17].

There are reports of complications in younger people than in the previous study. A report of 2020 at the Children's Hospital of Philadelphia describes the case of an 18-year-old woman diagnosed with primary mediastinal B-cell lymphoma (PMBCL) and a previous history of pulmonary embolism. Initially, she was treated with six cycles of rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and hydroxydaunorubicin with a refractory result. Then, the patient began treatment for 8 months with pembrolizumab, and at 11 doses, she started to have respiratory symptoms of exertional shortness of breath, chest tightness, and pleuritic chest pain. *Pneumocystis jirovecii* was detected in the bronchoalveolar lavage fluid, and she was treated with 21 days of high-dose trimethoprim/sulfamethoxazole and steroids. After 7 days, she left the hospital, and two weeks later, she improved [18].

Thus, *Pneumocystis jirovecii* infection is a severe condition that occurs in immunocompromised patients from IMT use, and it often leads to fulminant respiratory failure. At present, it is not clear which immune mechanism is affected to induce IRAEs using IC blockers. researchers suggest that the evaluation of the frequency of T cell subpopulations should be included during the follow-up of patients under IMT schemes. This information could provide relevant knowledge to identify the main cell subpopulation affected when a specific IC is blocked, even though it is not clear whether the cell subpopulations are involved in a specific way with the blocked molecule or if the IRAEs are a consequence of a general immune alteration.

References

1. Beham, A.W.; Puellmann, K.; Laird, R.; Fuchs, T.; Streich, R.; Breysach, C.; Raddatz, D.; Oniga, S.; Peccerella, T.; Findeisen, P.; et al. A TNF-Regulated Recombinatorial Macrophage Immune

Receptor Implicated in Granuloma Formation in Tuberculosis. PLOS Pathog. 2011, 7, e1002375.

2. Robert, M.; Miossec, P. Reactivation of latent tuberculosis with TNF inhibitors: Critical role of the beta 2 chain of the IL-12 receptor. Cell. Mol. Immunol. 2021, 18, 1644–1651.
3. Palacios, Y.; Chavez-Galan, L. Immunosuppressant Therapies in COVID-19: Is the TNF Axis an Alternative? Pharmaceuticals 2022, 15, 616.
4. Keane, J.; Gershon, S.; Wise, R.P.; Mirabile-Levens, E.; Kasznica, J.; Schwieterman, W.D.; Siegel, J.N.; Braun, M.M. Tuberculosis Associated with Infliximab, a Tumor Necrosis Factor Alpha-Neutralizing Agent. Infect. Dis. Clin. Pract. 2001, 10, 498.
5. Lázár-Molnár, E.; Chen, B.; Sweeney, K.A.; Wang, E.J.; Liu, W.; Lin, J.; Porcelli, S.A.; Almo, S.C.; Nathenson, S.G.; Jacobs, W.R. Programmed death-1 (PD-1)–deficient mice are extraordinarily sensitive to tuberculosis. Proc. Natl. Acad. Sci. USA 2010, 107, 13402–13407.
6. Barber, D.L.; Sakai, S.; Kudchadkar, R.R.; Fling, S.P.; Day, T.A.; Vergara, J.A.; Ashkin, D.; Cheng, J.H.; Lundgren, L.M.; Raabe, V.N.; et al. Tuberculosis following PD-1 blockade for cancer immunotherapy. Sci. Transl. Med. 2019, 11, eaat2702.
7. Barber, D.L.; Mayer-Barber, K.D.; Feng, C.G.; Sharpe, A.H.; Sher, A. CD4 T Cells Promote Rather than Control Tuberculosis in the Absence of PD-1–Mediated Inhibition. J. Immunol. 2011, 186, 1598–1607.
8. Suliman, A.M.; Bek, S.A.; Elkhatim, M.S.; Husain, A.A.; Mismar, A.Y.; Eldean, M.Z.S.; Lengyel, Z.; Elazzazy, S.; Rasul, K.I.; Omar, N.E. Tuberculosis following programmed cell death receptor-1 (PD-1) inhibitor in a patient with non-small cell lung cancer. Case report and literature review. Cancer Immunol. Immunother. 2020, 70, 935–944.
9. Bae, S.; Kim, Y.-J.; Kim, M.-J.; Kim, J.H.; Yun, S.-C.; Jung, J.; Chong, Y.P.; Kim, S.-H.; Choi, S.-H.; Kim, Y.S.; et al. Risk of tuberculosis in patients with cancer treated with immune checkpoint inhibitors: A nationwide observational study. J. Immunother. Cancer 2021, 9, e002960.
10. Liu, K.; Wang, D.; Yao, C.; Qiao, M.; Li, Q.; Ren, W.; Li, S.; Gao, M.; Pang, Y. Increased Tuberculosis Incidence Due to Immunotherapy Based on PD-1 and PD-L1 Blockade: A Systematic Review and Meta-Analysis. Front. Immunol. 2022, 13, 727220.
11. O'gorman, C.M. Airborne Aspergillus fumigatus conidia: A risk factor for aspergillosis. Fungal Biol. Rev. 2011, 25, 151–157.
12. Knutsen, A.P.; Slavin, R.G. Allergic Bronchopulmonary Aspergillosis in Asthma and Cystic Fibrosis. J. Immunol. Res. 2011, 2011, 843763.
13. Malek, A.E.; Taremi, M.; Spallone, A.; Alvarez-Cardona, J.J.; Kontoyiannis, D.P. Necrotizing soft tissue invasive aspergillosis in a cancer patient treated with immunosupressants due to checkpoint inhibitor-induced hepatitis. J. Infect. 2020, 80, 232–254.

14. Gupta, A.; Tun, A.; Ticona, K.; Baqui, A.; Guevara, E. Invasive Aspergillosis in a Patient with Stage III (or 3a or 3b) Non-Small-Cell Lung Cancer Treated with Durvalumab. Case Rep. Oncol. Med. 2019, 2019, 2178925-4.
15. Taima, K.; Tanaka, H.; Itoga, M.; Ishioka, Y.; Kurose, A.; Tasaka, S. Destroyed lung due to sustained inflammation after chemoradiotherapy followed by durvalumab. Respirol. Case Rep. 2020, 8, e00580.
16. Apostolopoulou, A.; Fishman, J.A. The Pathogenesis and Diagnosis of Pneumocystis jiroveci Pneumonia. J. Fungi 2022, 8, 1167.
17. Schwarz, M.; Kocher, F.; Niedersuess-Beke, D.; Rudzki, J.; Hochmair, M.; Widmann, G.; Hilbe, W.; Pircher, A. Immunosuppression for Immune Checkpoint-related Toxicity Can Cause Pneumocystis Jirovecii Pneumonia (PJP) in Non–small-cell Lung Cancer (NSCLC): A Report of 2 Cases. Clin. Lung Cancer 2018, 20, e247–e250.
18. Si, S.; Erickson, K.; Evageliou, N.; Silverman, M.; Kersun, L. An Usual Presentation of Pneumocystis jirovecii Pneumonia in a Woman Treated With Immune Checkpoint Inhibitor. J. Pediatr. Hematol. 2020, 43, e163–e164.