CBD: "Tuberculosis associated with Triplet therapy for lung cancer".

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DC: A 58-year-old UK-born Caucasian male was referred to the chest clinic with a swollen neck, dilated veins and shortness of breath, which had developed slowly over the preceding months. A CT scan of the thorax revealed a necrotic 66mm right upper lobe mass which encased the right middle and upper lobe bronchus, right pulmonary artery and was invading the mediastinum (Figure 1A and B). The mass was extrinsically compressing the Superior Vena Cava (SVC). There were enlarged supraclavicular fossa, mediastinal, hilar and axillary lymph nodes and a necrotic 32mm mesenteric mass with associated abdominal lymph nodes. Endobronchial ultrasound was performed and fine needle aspiration of the station 4R Lymph node diagnosed an adenocarcinoma, which was TTF-1 positive and PD-L1 negative (0%), with no recognised driver mutations identified. MRI of the spine demonstrated C1 and T1 bone metastases. The initial management was high dose dexamethasone, palliative radiotherapy to the spine (C7-T2 8Gy 1F) and anticoagulation with dalteparin. He then commenced Triplet therapy with Carboplatin (AUC 5), Pemetrexed (500mg/m^2) and Pembrolizumab anti-PD-1 immune checkpoint inhibition (200mg).

EK: Immunotherapy has dramatically changed the landscape in treating lung cancer. Checkpoint inhibitors, anti-programmed death (PD-1) and its ligand anti-PD-L1, have shown significant improvements in overall survival of both non-small cell lung cancer (NSCLC) and small cell lung

cancer (SCLC). Depending on PD-L1 expression, checkpoint inhibitors can be used either as monotherapy or in combination with chemotherapy in first line treatment of NSCLC. A recent Phase 3 trial has shown significantly longer overall survival and progression-free survival with addition of immunotherapy to standard chemotherapy from the outset in patients across subgroups of PD-L1 expression levels, including those with scores <1% (1). Therefore, Triplet therapy combining chemotherapy and immunotherapy has become the first line treatment of choice for metastatic NSCLC. Patients on Triplet therapy present with a higher incidence of adverse events, management of which often requires a multidisciplinary approach.

DC: The patient completed the first two cycles of Triplet therapy. However, when he attended for review prior to cycle three, 44 days after commencing treatment, he was unwell complaining of feeling light-headed, shaky and described a new cough producing clear sputum. He denied haemoptysis, chest pain or increased shortness of breath. On physical examination, his Eastern Cooperative oncology group performance status had reduced to 3, from a baseline of 1. He was febrile with a temperature of 38^{o}C, blood pressure was 106/70mmHg, heart rate was 96 bpm and oxygen saturation was 96% on room air. Chest auscultation revealed crackles throughout the right lung. Blood tests showed a new anaemia (Hb 94 g/L), hyponatraemia (Na 128 mmol/L) and raised transaminase (ALT 107 IU/L).

CT Chest performed prior to clinic review showed a partial treatment response of the tumour and a new small pulmonary embolism (PE) in the right lower lobe despite anticoagulation. New areas of consolidation had developed in the right upper zone (Figure 1C and D). At this point, these changes were felt to be possibly in keeping with treatment-induced pneumonitis as the patient also had a raised transaminase. He was admitted directly from clinic and started on intravenous amoxicillin/clavulanic acid and oral prednisolone (40mg). His anticoagulation with dalteparin was increased due to the new PE.

RB: The differential diagnosis at this stage included community acquired pneumonia, immunotherapy-related pneumonitis and atypical infections. Immune checkpoint inhibition has a very different adverse-effect profile compared to standard cancer chemotherapy, including colitis, hepatitis, nephritis, skin inflammation and endocrinopathies (2). The commonest pulmonary side effect is pneumonitis. Although the mechanism is not fully elucidated, this reaction is thought to be mediated by dysregulated effector and regulatory T cells in the pulmonary interstitium, ultimately leading to an inflammatory response (3). In this case his Triplet therapy was held, and he was treated with antibiotics to cover for a community-acquired pneumonia and simultaneously with prednisolone to cover for a possible immunotherapy-related pneumonitis. On review of his clinical history and imaging, pneumonitis was felt less likely than an infective process.

DC: Following admission, his temperature remained intermittently raised despite a week of intravenous antibiotics. Multiple blood, urine and sputum samples showed no bacterial growth. His chest X-ray showed ongoing dense consolidation in the right upper zone and some ill-defined opacities in the right mid-zone**.** Spontaneous sputum was sent for acid fast bacilli (AFB) staining and this was smear positive. Nucleic-acid amplification testing demonstrated a positive PCR for *Mycobacterium tuberculosis*, with no rifampicin-resistance conferring mutations. He commenced treatment with rifampicin, isoniazid, pyrazinamide and ethambutol and improved clinically within 48hrs. His prednisolone was tapered, and he was discharged to continue his anti-TB medications in the community. Further questioning revealed that several years previously a work colleague had been diagnosed with pulmonary TB and he had undergone contact-tracing with a chest X-ray, but was not given chemoprophylaxis. His Triplet therapy was held whilst anti-TB treatment was initiated. He was seen in the chest clinic two weeks post-discharge and was clinically much improved. He had gained 2 kilograms in weight and liver function tests had returned to normal. He has since recommenced his Triplet therapy, whilst continuing his anti-TB antibiotics.

PE: The number of cases of TB associated with immune checkpoint inhibition is rapidly expanding with over a dozen now reported (4, 5). However, these published cases may be a significant under-representation of the true incidence. The interval between admission and requesting appropriate diagnostic tests in our case reflects the novelty and consequent lack of awareness of this complication. Such a delay may lead to suboptimal care, nosocomial transmission of infection, and in some cases death. The patient we describe is the first following Triplet therapy, which is now standard of care for disseminated NSCLC (1). In all anti-PD-1-related TB cases, a potential confounder is the immunosuppression caused by the underlying malignancy and frequent co-administration of corticosteroids. However, corticosteroids only marginally increase the risk of TB, and the rapidity of TB development in these immune checkpoint-associated cases strongly suggests a direct mechanistic link. Furthermore, the hyper-susceptibility of PD-1 deficient mice to Mtb infection, which die even more rapidly than interferon-γ deficient mice, indicates that the PD-L1/PD-1 axis is critical in maintaining immune homeostasis in TB infection.

In this case, if the sputum AFB stain had not been performed, then the diagnosis would simply not have been made and the patient would have been palliated, despite having a treatable condition. We suspect that there may be a large number of undiagnosed cases of TB associated with anti-PD-1 treatment, as cancer progression and pulmonary TB can present very similarly, with new chest X-ray infiltrates, fever, haemoptysis and weight loss. Furthermore, as these immunotherapies are deployed in high TB incidence settings such as India, the frequency is likely to increase exponentially.

Mechanistically, the rapidity of TB progression suggests that immune checkpoint inhibition is generating a highly permissive environment for TB progression. Understanding the underlying process is critical. Immune checkpoint inhibition will increase secretion of diverse cytokines and chemokines, leading to a pro-inflammatory environment. Zebrafish studies using *Mycobacterium*

marinum suggest that the recruitment of permissive monocytes to granulomas may increase Mtb growth (6). In patients, accelerated TB progression is likely to involve multiple factors including excessive inflammatory cell infiltration and extracellular matrix destruction, but this requires further mechanistic dissection. The majority of side effects of cancer immunotherapy are immune related adverse events (IRAEs) (2), which are typically autoimmune in nature. These clinical observations support recent hypotheses that events leading to active TB disease may be fundamentally "loss of tolerance" or "autoimmune" in nature. The insights generated from the biological era are further demonstrating that an excessive immune response in TB is just as harmful, and perhaps even worse, than an insufficient response to the pathogen.

In summary, TB reactivation is increasingly recognised as an adverse effect of immune checkpoint inhibition. However, the reported cases are likely to represent the tip of the iceberg due to under-diagnosis, as TB will often mimic progression of the underlying malignancy. Sending appropriate clinical samples for mycobacterial testing is essential to initiate antibiotics for this treatable complication and prevent nosocomial transmission. Potentially, screening for latent TB and treating those who have positive results with chemoprophylaxis alongside immune checkpoint inhibition may be indicated, as occurs prior to anti-TNF therapy. Estimating the risk-benefits will require better knowledge of the true incidence of this phenomenon, and so the authors are establishing a UK national register to capture all cases and inform guideline development.

Figure 1: Development of pulmonary TB. Chest X-ray at start of Triplet chemotherapy shows right upper lobe apical tumour (A), while 56 days later extensive right upper lobe consolidation has developed (C). Comparison of diagnostic CT scan performed 2 weeks before initial Chest X-ray (B) with the CT scan on readmission shows response of the tumour with immune checkpoint inhibition but new consolidation with cavitation (D).

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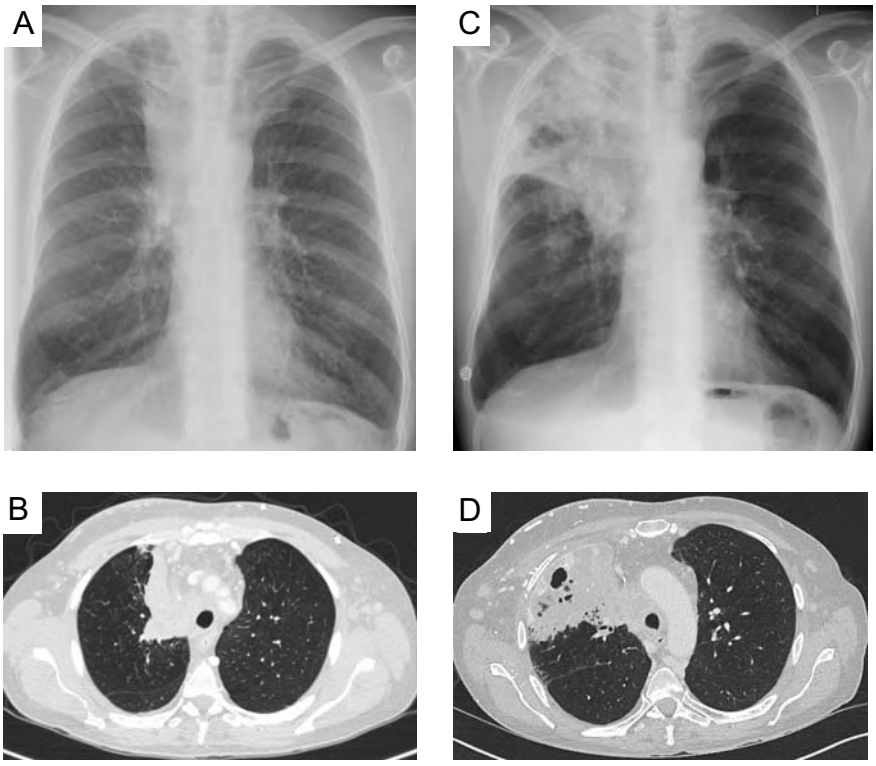
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