Pulmonary toxicity

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Lung involvement owing to immunotherapy is not a common complication, with an incidence of between 2% and 4%. However, because of the increase in the number of indications of these treatments, an upsurge in the number of cases is anticipated, which is why it is important to recognise this condition.

Pneumonitis is the focal or diffuse inflammation of the lung parenchyma. For its diagnosis, there must be a temporal correlation between the start of treatment, the onset of symptoms and radiological changes. To this end, it is important to ascertain when a patient may begin to manifest symptoms and signs associated with pneumonitis. Immune-mediated pulmonary toxicity is considered a late complication and can occur between three and 19 months after the start of treatment. However, a number of authors have reported immunotherapy-induced pneumonitis two years after the end of this therapy. A further aspect to take into account is the incidence with which the drugs prescribed to the patient may or may not be related to the development of pneumonitis. Pulmonary toxicity by anti-PD-1/PD-L1 is 1.5 to 2 times more common than by anti-CTLA4 in monotherapy; however, when used in combination, the risk of pneumonitis increases threefold. The clinical symptoms that accompany a case of immunotherapy-induced pneumonitis are non-specific (cough, expectoration, dyspnoea, low-grade fever, fever and/or asthenia). Nor is there any pathognomonic radiological pattern. The most common presentation is ground glass opacity (a pattern it shares with other conditions) but it can also occur as organising pneumonia, interstitial pneumonitis, hypersensitivity pneumonitis and even in the form of pulmonary nodules. Due to the non-specific nature of the symptoms, and to the fact that it can be confused with other conditions, it is important to emphasise that pneumonitis secondary to treatment is always a diagnosis of exclusion. To this end, the patient's clinical situation permitting, it is recommended to perform a fibrobronchoscopy with bronchoalveolar lavage (BAL). The sample obtained is sent to microbiology to rule out infection, to pathology to rule out disease progression and to cytohaematology to perform a total and differential cell count. A predominance of lymphocytes or eosinophils in the cell count probably indicates the onset of pneumonitis, but a normal cell count does not rule out this diagnosis.

The following case study illustrates how complex the management of immunotherapy-induced pneumonitis can be. It concerns a patient with a diagnosis of stage IIIA squamous cell carcinoma of the lungs requiring concomitant chemotherapy (CT)-radiotherapy (RT) + nivolumab within a clinical trial. RT was completed in June 2017 and the fifth cycle of nivolumab was administered on 13/12/2017. He was admitted to oncology for the first time in January 2018 with the diagnostic impression of immunotherapy-induced pneumonitis. However, the fact that the patient had received RT probably played a role in the patient's symptoms, and this is due to two reasons: 1) RT leads to the immunogenic death of cancer cells, which, in turn, can lead to pro-immunogenic effects, increasing the

risk of the "autoimmune-like" side effect; and 2) the phenomenon of hypersensitivity owing to RT or "radiation recall", defined as the damage caused to the alveolar endothelium by the RT, which is latent and subsequently manifests through the use of a systemic treatment. It is also important to ascertain whether the cause of pulmonary toxicity is immune-mediated or is due to other treatments, since the guidelines that classify the severity of immunotherapy-induced pneumonitis are different from those employed for CT or RT, in addition to the fact that they provide recommendations as to how the patient should be managed in the event of hospitalisation or home care. The patient in question was classified as grade 3 pneumonitis and the recommendations indicated by the European and American guidelines were followed during his admission, as well as at home, until all symptoms abated and radiological improvement was seen. This enabled corticosteroid treatment to be reduced for six months until onset of an intercurrent non-respiratory event (presence of optic neuritis). It should be noted that treatment with nivolumab was not restarted. In June 2018 when, owing to optic neuritis, treatment with prednisone was reduced from 5 mg/day to 5 mg/48 hours, dyspnoea with respiratory failure occurred. The X-ray was suggestive of pneumonitis with bilateral involvement and he was admitted for the second time with a diagnosis of immunotherapy-induced pulmonary toxicity. As in the first admission, the recommendations indicated by the guidelines were followed but respiratory deterioration was observed, owing to which the dose of methylprednisolone was increased (from 1 mg/kg/day to 2 mg/kg/day) and voriconazole was combined with the antibiotic therapy owing to the presence of a weak positive galactomannan in the BAL, with no improvement 48 hours after the treatment adjustment. For this reason, a second immunosuppressant was started without suspending the corticosteroids, in line with the guideline recommendations, with infliximab being the first choice. A significant improvement was seen two days post-infliximab, with resolution of the respiratory symptoms and a progressive radiological improvement until the disappearance of the pulmonary infiltrates.

Cases like this highlight the importance of a multidisciplinary approach to the management of immune-mediated toxicity, added to the fact that, nowadays, the guidelines advise us on what to do. Despite this, there are still many unknowns, such as: is infliximab the immunosuppressant of choice? And if so, in the event of there being no response, what is the recommended 2nd option? Or how should corticosteroid treatment be tapered after a recurrence of pneumonitis in a patient who was already undergoing corticosteroid therapy?