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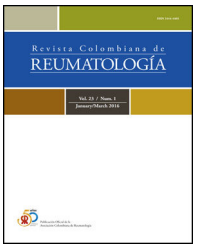

Editorial

Autoantibodies: A manifestation of immune related adverse events of cancer immunotherapy☆

Autoanticuerpos: una manifestación de los eventos adversos inmunológicos de la inmunoterapia en cáncer

Immunotherapies against cancer have changed the landscape of treatment of this disease during the last decades. Among them, the immune checkpoint inhibitors (ICIs) that target PD-1, PD-L1 and CTLA-4, which have been remarkable successful in the treatment of different types of cancer.[1]

ICIs inhibit negative costimulatory signals from T cells and activate the antitumor response to attack cancer cells in a non-antigen-specific manner. However, they can also (re)activate autoreactive T cells, which in turn could lead to a breakdown of T cell tolerance, not only towards tumor antigens but also towards autoantigens, which could result in the activation of autoreactive B cells and, ultimately, in the formation of autoantibodies that could be associated with immune-related adverse events (irAEs). The autoantibodies can bind directly to normal tissues and mediate cell destruction by antibody-mediated cytotoxicity or they can bind to complement and trigger a biochemical cascade of cell lysis and destruction.[2]

The detection of autoantibodies before treatment is associated with the successive development of ICI-related irAEs, supporting a B-cell-mediated etiology for some irAEs. Several irAEs clearly mimic pathological conditions in which the development of antibodies has been implicated, such as bullous pemphigoid, thyroiditis, Raynaud's phenomenon, and dermatomyositis, among others. However, for the majority of irAEs the relationship of initial or increased levels of autoantibodies is still unknown, and the cases have been mainly anecdotal, suggesting that so far undefined autoantibodies may be associated with the development of ICI-related irAEs.[2]

It has been established that the autoantibodies directed against the tumor and the autoantigens could serve as biomarkers of antitumor response and autoimmunity, to the extent that they can be routinely measured in the serum of the patients. Thus, some patients with irAE may have preexisting subclinical autoimmune conditions that manifest clinically as a full-blown autoimmune disease after the therapy with ICI. For example, analyses of pre-treatment and post-treatment sera have put into evidence that, regardless of the status of the antibodies before ipilimumab, the patients with positive autoantibodies after treatment experienced more irAEs than patients who did not developed them. However, no significant association was observed between autoantibody positivity and the development of irAEs, except in patients who developed antithyroid antibodies after ipilimumab, and who subsequently received anti-PD-1 therapy, and presented thyroid dysfunction.[3] Similarly, no correlation was found between pre-existing ANAs and the development of cutaneous alterations, thyroid dysfunction, interstitial pneumonitis, hypophysitis and diabetes, except for a close relationship between pre-existing ANAs and the development of colitis.[4] Similarly, it has been reported that pre-existing antithyroid antibodies are highly correlated with thyroid dysfunction,[5,6] while pre-existing antibodies against the acetylcholine receptor are closely related to the development of myasthenia *gravis*.[7] In another study, the pre-existence of antibodies was independently associated with the development of irAEs in patients with non-small squamous cell lung cancer (NSCLC)

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treated with nivolumab or pembrolizumab, but, interestingly, they had a better clinical benefit.[8] Likewise, in other studies with NSCLC patients it was observed that the early detection of anti-ANA, ENA or ASMA autoantibodies associated with ICI therapy can be a surrogate marker of autoimmunity, in addition, it can be strongly predictive of the response to treatment with nivolumab in terms of progression-free survival and overall survival.[9]

Currently, with the development of new technologies, using a human protein array (HuProt), the baseline levels of antibodies of patients with melanoma treated with ICI were analyzed to identify antibody signatures previous to treatment which could predict the development of irAE, finding antibody signatures associated with apoptosis, immunity/autoimmunity, including TNFα signaling, Toll-like receptor signaling and microRNA biogenesis with the appearance of irAE associated with PD1 blockade, with a precision, sensitivity and specificity >90.[10] In another study, using a Luminex® matrix, which evaluates the presence of antibodies against 832 antigens, 333 patients treated with ICI were analyzed for the detection of serum antibodies, and it was found that the antibodies against the fibroblast growth factor receptor 1 (FGFR1) were associated with a lower rate of irAEs and a shorter survival, while the antibodies against the melanoma-associated antigen B4 (MAGEB4) were associated with a higher rate of irAEs and a longer survival.[11]

In conclusion, despite the large number of studies, there is still no strong evidence to argue for recommending universal screening for autoantibodies before starting ICI, since even if an individual has a positive screening test, it would not be a contraindication for treat him with ICI for cancer therapy. However, in patients with a personal or family history of autoimmune disease, or in those who had signs or symptoms suggestive of an underlying autoimmune disease, screening for autoantibodies may be considered before starting treatment with ICI, since these patients have an increased risk of developing a full-blown autoimmune disease after treatment and, therefore, they should be followed-up more closely.

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