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Editorial

Immune checkpoint inhibitors in cancer therapy: The leading role of the endocrinologist

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The endocrine, immune, and nervous systems have a close functional relation from the embryonic development until the end of life, nevertheless this important homeostasis can be altered by any stressors such as infections, autoimmune diseases, neoplasms or medications (1).

Immune checkpoint inhibitors (ICPi) have relatively recently emerged as a promising treatment option for several cancers, including advanced melanoma, non–small cell lung cancer, renal cell carcinoma, and colorectal cancer (2). ICPi target immune checkpoints, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death 1 (PD-1) or its ligand (PD-L1). ICPi modulates the immune system with the aim of eradicating cancer cells, but despite their acknowledged anti-cancer efficacy, they can increase the risk of developing autoimmune disorders. In this fashion, the same mechanisms that support tumor regression may favor autoantigen-mediated cytotoxicity and the production of T-cell-dependent autoantibodies (3, 4). Importantly, patients on ICPi may develop endocrine adverse events, even after months or years from the final dose of ICPi, affecting a wide variety of glands. These endocrine adverse events include hypophysitis, diabetes mellitus, hypo and hyperthyroidism, and, adrenal insufficiency. Such toxicities may complicate the clinical course and prognosis of patients, increasing morbidity and mortality if not promptly identified and treated, as they can be life threatening and irreversible (2-4).

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In the current issue, García Ramos et al. report a case that emphasizes how the close interaction between endocrine, immune and nervous systems, may be altered by ICPi therapy with anti CTLA-4 and anti PD-1 in a patient treated for renal cell carcinoma developing hypophysitis and adrenalitis. The susceptibility of endocrine glands, over other organs that are affected with less frequency and intensity, can be explained by the high vascularity of the hypophysis, adrenal gland and thyroid. Furthermore, the pituitary gland expresses CTLA-4, and the generation of CTLA-4 antigens (4).

The authors show the sequence of autoimmune adverse events due to two ICPi, initially expressed with pneumonitis, and later with the involvement of the adrenal and pituitary axis. Interestingly, in the presented case they show the combined use of ICPi as anti-CTL4 and antiPD-1 (ipilimumab + nivolumab) which requires further caution. The incidence of hypophysitis patients treated with the combination of anti-CTLA-4 and anti-PD1 therapy, is higher (6.4 %) than those treated with monotherapy (2). The time of onset and clinical relevance of glandular involvement is variable, from acute to subacute. Hypophysitis usually occurs within 2-3 months after ICPi initiation and symptoms may be not specific with headache and fatigue. The withdrawal of ICPi treatment until hormone replacement is reached, especially in the case of adrenal insufficiency, is often necessary and it may negatively impact on outcomes (2, 4).

Therefore, hormonal monitoring should be accurate, complete, and timely, starting before treatment with ICPi and periodically during treatment, and not exclusively according to clinical manifestations (2, 3). The basal hormonal assessment at the beginning of ICPi therapy should be routinely evaluated, carefully searching for suspicious symptoms for hypophysitis, since hypopituitarism and cancer may show common symptoms and laboratory findings (2).

Unequivocally, endocrinologists play a leading role in the comprehensive management of cancer patients on ICPi, even considering the increasing use of these therapies for different cancers, including rare neoplasms as pheochromocytoma and paraganglioma (5). An effort to identify potential risk factors is required since early diagnosis and management, as in the case reported, are essential to avoid anti-cancer therapy reduction or withdrawal and ultimately to improve patients' outcomes, including progression-free survival.

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