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Editorial

Pathophysiology of Sjögren's-like syndrome induced by cancer immunotherapies: similarities and differences with classical Sjögren's syndrome

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Cancer immunotherapy based on checkpoint inhibition has offered a new therapeutic avenue, although it is associated with a broad spectrum of adverse events as a result of immune system activation (1). Immune checkpoint inhibitor (ICI) therapy for the treatment of cancer refers to the modulation of the regulatory component of acquired immunity, involving mainly the CD80/CTLA-4 pathway and the PD1/PD-L1 axis. This is most easily achieved by administration of blocking monoclonal antibodies such as anti-CTLA-4, anti-PD1 and anti-PD-L1 respectively (1, 2). Naïve anti-tumour CD8+ and CD4+ cells, after tumour antigen recognition in an MHC restricted manner through their TCR receptor (signal 1), must be activated by co-stimulatory signals (signal 2) before reaching their mature effector phenotype. This second critical signal is ensured by binding of CD80/86 on antigen presenting cells (APC) to CD28 on naïve T cells which are then differentiated into the various CD4+ subtypes and the CD8+ cytotoxic cells (2). To limit immune activation, effector CD4+ and CD8+ T cells may express co-inhibitory molecules, such as CTLA-4 and PD1. The CTLA-4 inhibitory 'immune checkpoint' binds CD80/86 on APCs more efficiently than CD28, delivering a suppressive signal to T cells and preventing excessive activation. Similarly, PD1 receptor expressed by activated T cells may engage its PD-L1 ligand on APCs, mediating an inhibitory signal on T cells to control immune activation.

In order to evade immune surveillance, tumour cells manipulate the surrounding microenvironment by promoting an inhibitory background against the orchestrated anti-tumour immune response. Indeed, cancer enables the same mechanisms the immune systems employ to control excessive activation of both cellular and humoral immunity (2, 3). Tumour cells may express PD-L1 themselves, or induce PD-L1 expression by APCs, resulting in dampening of the anti-tumoral T cell responses. Anti-PD1 or PD-L1 monoclonal antibodies employed in immune checkpoint inhibitor therapy block these PD1/PD-L1 interactions, reversing the inactivation of anti-tumour T cells induced by cancer. Tumour cells can also recruit Tregs within the tumour lesion, which may suppress CD4+ and CD8+ T cell activation by regulating APC maturation through CTLA-4 mediated trogocytosis (4), via secretion of inhibitory cytokines stimuli such as IL-10, TGF-beta and IL-35 (5) or by IL-2 deprivation (6).

Anti-CTLA-4 antibodies employed in immune checkpoint inhibitor therapy act in different ways against cancer, by blocking CTLA-4 on activated anti-tumour T cells, by binding to CTLA-4 on Tregs preventing their regulatory effects upon activated anti-tumour T cells and by mediating antibody dependent cellular cytotoxicity (ADCC) of Tregs after binding to the Fc receptor on APCs (7).

The net effect of ICI therapy, either by CTLA-4 or PD-1/PD-L1 blockade, is to unleash the suppressed anti-tumoral T cell response and promote efficient tumour elimination. To a lesser extent, humoral immunity may be also affected by ICI therapy. B cell maturation during the germinal centre (GC) reaction is mainly based on an interplay among follicular dendritic (fDCs), T follicular helper (Tfh) and B cells though the CD80/86–CD28, CD40L–CD40, and PD-L1/PD-1 pathways (8, 9). Excessive recruitment by cancer of

Tfh regulatory cells expressing CTLA-4 molecules on their surface, may suppress Tfh and B cell interaction, leading to impaired humoral immunity and antibody production against tumours (10). Thus, ICI may ameliorate B cell responses against cancer by attenuating the inhibitory effects of Tfh regulatory cells.

Since ICI therapy at least in part, inhibits the mechanisms of peripheral tolerance, autoreactive T and B cell clones may be activated and mediate autoimmune phenomena with subsequent tissue injury (1). Thus, immune related adverse events are expected to emerge and cancer patients receiving ICI may experience autoimmune manifestations including post-ICI sicca symptoms/ Sjögren's syndrome (11, 12). In clinical terms, ICI treated patients may present mainly with isolated sicca symptoms, Sjögren's-like syndrome and less commonly frank idiopathic primary SS (3, 13-15). Recent studies have been focused on the pathophysiology and differences between post-ICI Sjögren's like syndrome and pSS (13-16). It has been clearly shown that these 2 entities share common features but seem to be distinct clinical syndromes. Post ICI-SS patients are usually males of the sixth decade of life as opposed to the female predominance of pSS patients whose symptoms first appear at their 40s or 50s (13). However, the differences in age and sex may reflect the relevant distribution of the underlying malignancy in the post-ICI-SS group and not a true feature of this particular entity. Another important clinical aspect is the acute onset of sicca symptoms among post ICI-SS patients, since approximately 50% of them develop dryness within the first 3 months of ICI treatment (3). On the contrary, in pSS patients, the disease course follows a slowly progressive pattern most likely associated with the limiting effect of the regulatory component which is significantly and acutely abrupted after ICI therapy. It is also noteworthy that extra-glandular manifestations are less prevalent and limited mainly to the cutaneous and musculoskeletal domains compared to typical pSS patients (3, 13, 17). Interestingly, B cell mediated manifestations are rare as supported by the fact that cryoglobulins have not been detected among post-ICI patients and the prevalence of the classical autoantibodies such as anti-Ro/SSA and anti-La/SSB is much lower, suggesting less systemic and B cell activation in this group of patients (13, 15).

The histologic landscape of minor salivary labial gland biopsy (MSGB) of post-ICI SS is quite heterogenous, encompassing nonspecific lesions of chronic sialadenitis, dispersed lymphocytic infiltration and less commonly the typical focal sialadenitis of pSS (14). It is also noteworthy that different histologic patterns may be observed even in the same specimen while in some cases, it seems that the acinar cells are involved rather than the typical ductal cells of pSS (16). Regarding the composition of lymphocytes, post-ICI SS biopsies disclose T cell rich infiltrate with CD4+ and CD8+ cells and paucity of B cells (14, 15) which are present at different degrees in pSS patients depending on the severity of the inflammatory lesions within the MSGs (18). In accordance, no GC are formed within the MSGB of post ICI SS patients, a finding consistent with the low production of autoantibodies and the lack of B cell manifestations in this group (15). Recently, it has been proposed that the post-ICI IFN-γ increase due to enhanced T cell responses, may induce the expression of PD-L1 on epithelial cells capable of mediating a protective "reverse signalling" after anti-PD-L1 engagement. These actions may interfere with the intrinsic turnover of the salivary epithelium leading to the premature exhaustion of the progenitors of acinar cells, with subsequent dysfunction of the epithelium (15). However, this hypothesis must be further investigated in post-ICI SS cases.

Taken together, it seems that management of post ICI SS, is an important clinical unmet need. The acute onset of symptoms, the predilection for skin and joint manifestations, the limited prevalence of B cell manifestations and the underlying neoplasia, impose a different therapeutic strategy compared to idiopathic pSS. In such cases, history, physical examination and laboratory evaluation including immunologic, viral, oral and ocular functional tests should be performed before any intervention. In general, management depends on severity of clinical manifestations, disease extent, co-morbidities, immunologic profile, performance status as well as the underlying malignancy (19). In case of mild sicca symptoms, local treatments may be useful and ICI therapy can be continued. In more severe symptoms ICI therapy can be withheld while corticosteroids may be considered in low or moderate doses to control arthritis or relevant skin rashes. Persistent and severe sicca symptoms or severe involvement of internal organs may require permanent ICI therapy discontinuation. On the contrary, the improvement of sicca symptoms may allow to resume ICI therapy. The lack of data on this issue, limits the development of strict recommendations, and management should be tailored according to patient's profile, physician's experience and the general principles mentioned previously.

So far, cumulative data point out that the post-ICI SS and pSS are pathogenetically distinct but some patients from both groups may share common features. In this context, specific scientific questions are risen: a) Do seropositive post-ICI patients and typical pSS share common autoantigens and genetic background? Future studies on this direction are expected to map the involved autoantigens and genetic elements implicated in immune mediated responses against the salivary epithelium leading to organ specific limited disease with sicca symptoms, b) Since post-ICI SS patients produce autoantibodies to some extent but lack GC within MSGB, where these autoantibodies are produced? It is obvious that regional lymph nodes are involved in this process and patients with head and neck cancer who relapse are perfect candidates to study such phenomena in their lymph nodes which can be surgically excised as standard of care, c) Why post-ICI SS patients develop a disease confined to the salivary glands with limited B cell manifestations, given that both T and B cell autoimmune responses are augmented after

ICI therapy? Since autoreactive B and T cell clones are activated, a broad autoimmune response involving both cellular and humoral immunity is anticipated and post-ICI SS patients should present with several autoantibodies; limited autoantibody production implies still active regulatory mechanisms in post-ICI patients which may control efficiently the excessive B cell hyperactivity, providing a model to study potential therapeutic interventions in pSS patients and d) What is the long term outcome and prognosis of post-ICI SS patients? If this particular syndrome is well controlled and remitted after ICI therapy, it is possible that the autoreactive clones are efficiently suppressed as before the ICI administration; therefore, studying the regulatory component of the immune system by multi-omics approaches at the time point of cancer diagnosis and after ICI therapy, may reveal the effector elements to control pSS disease and potentially identify predictors for developing post-ICI SS. In conclusion, the immune related adverse events of ICI therapy may provide insights into the regulatory mechanisms of systemic autoimmunity and reveal hidden pathogenetic associations with strong therapeutic potential.

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