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Endocrinology Quiz – Case 10

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A 54-year-old lady presented to the endocrine clinic with tiredness, dyspnea and weight gain. She had a history of lung adenocarcinoma with bone metastases for which she underwent lobectomy and of a right hemithyroidectomy 25 years ago for unclear reasons. She was receiving chemotherapy with carboplatin and pembrolizumab, alongside zolendronic acid therapy, whereas she was previously treated with carboplatin, premetrexed and pembrolizumab. Other medical history included hypertension, diabetes and recently diagnosed "hyperthyroidism". Medications included metformin, insulin glargine, insulin glulisine, losartan and amlodipine. General examination revealed some generalized swelling with a heart rate at 60 bpm and regular, but no other signs.

Further investigations showed prominent hypothyroidism with TSH >100 mIU/L, free T4 (fT4) 1.54 pmoL/L and free T3 (fT3) <0.3 pg/mL. Her thyroid function tests (TFTs) two weeks prior to her presentation showed ft4 21.51 pmoL/L and TSH 0.03 mIU/L which led her family doctor to diagnose "hyperthyroidism", whereas they were normal when she was first initiated on chemotherapy. Her thyroid peroxidase antibodies (TPO) were high at 65.3 IU/mL. Accordingly, the carbimazole was stopped and she was commenced on levothyroxine 50 μg which was gradually up-titrated to 100/125 μg on alternate days. Her TFTs normalized within five months. A thyroid ultrasound scan (USS) revealed heterogeneity and multiple small hypoechoic areas (likely pseudonodules) up to 7.2 mm, with no overtly concerning features. Pituitary function tests were also performed and showed a normal post-menopausal pattern.

Comment

The above case is typical of pembrolizumab-induced thyroiditis. Pembrolizumab is a humanized monoclonal immunoglobulin (Ig) G4 antibody directed against human cell surface receptor programmed cell death 1 (PD-1).

Programmed cell death-1 (PD-1) ligand (PD-1-L) and PD-2-L which are found on antigen presenting cells can interact with PD-1 receptors on white blood cells, a process that causes an inhibition of the immune system. PD-1-L is also expressed by neoplastic cells and can interact with PD-1 antigens on white blood cells and this also causes inhibition of the immune system (reduced apoptosis threshold, anergy and T cell depletion). The use of PD-1 or PD-L1 inhibitors in oncology causes disinhibition of the immune system and hence an anti-neoplastic effect. However, note that these same receptors are also important for self-tolerance. Consequently, immune system activation increases the risk of various immune-related adverse events (irAEs), e.g. thyroid dysfunction, hypophysitis, colitis, hepatitis and dermatological complications. Pembrolizumab is an IgG4 monoclonal antibody, an Ig subclass not associated with antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. Hence, it has been proposed that it is unlikely that pembrolizumab triggers an immune response via its interaction with the PD-1 receptor expressed by the thyroid gland. Overall, the exact mechanisms involved in pembrolizumab-induced thyroiditis need to be elucidated.

The currently available PD-1 inhibitors include nivolumab and pembrolizumab; for PD-L1 inhibitors atezolizumab, avelumab and durvalumab are available. Given their favorable efficacy comparative to traditional chemotherapy, their utilization is increasing with time.

Hypothyroidism is most common endocrine irAE with PD-1 inhibitors, occurring in 6–15% of patients treated with such medications. It is always prudent to differentiate from secondary hypothyroidism, which can also occur, albeit less commonly, with these medications. It is therefore important to ensure no cortisol deficiency before giving levothyroxine and, if in doubt, treatment with glucocorticoid medications should commence first.

Thyrotoxicosis is also common, occurring in 1–12% of patients treated with PD-1 inhibitors. Thyrotoxicosis is most commonly due to thyroiditis and it therefore often follows the pattern of initial thyrotoxicosis (often 3–8 weeks post-PD-1 inhibitors) with spontaneous reversion to hypothyroidism after many weeks (usually about two months and up to three years). Graves' disease is uncommon; notwithstanding, it is recommended that a thorough examination and workout is followed to exclude such an important differential diagnosis, e.g. by checking for Graves' ophthalmopathy and emphasis on checking TSH-receptor antibodies (TRAb). Radioiodine scan and thyroid USS may be used, but beware their caveats. In particular, although RAI may be used, given that these patients are often loaded with iodinated contrast media for computed tomography (CT) scans then the test becomes inaccurate. USS may show increased vascularity in Graves' disease and reduced vascularity in thyroiditis but there is a lot of overlap between the

two. 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) shows diffusely increased uptake consistent with thyroiditis, but sometimes the same pattern may be seen with Graves' disease and chronic lymphocytic thyroiditis.

As mentioned thyrotoxicosis develops earlier and hypothyroidism later and this probably reflects the nature of this condition which is invariably a (silent) thyroiditis. Thyroid peroxidase (TPO) and anti-thyroglobulin (Tg) antibodies are often present. It is hypothesized that a destructive thyroiditis is at play, mediated by autoreactive T cells against the thyroid gland. Polymorphic variants in the PD-1 gene in some individuals may predispose to thyroid irAEs. Combination therapies with PD-1 inhibitors and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) antagonists (e.g. ipilimumab) have additive effect on irAEs, including thyroid irAEs, e.g. with hypothyroidism occurring in 14% of patients treated with combination immunotherapy. It has reported an even higher rate of complications with up to 50% of patients with PD-1/CTLA4 inhibitor combination therapy having any type of thyroid dysfunction and including milder thyroid dysfunction. Similarly, Barroso-Sousa et al showed that combination therapy significantly increases the different endocrine side-effects, but grade 3 hypo- and hyperthyroidism were rare at 0.2%. The hypothyroidism occurrence in order of increasing incidence followed the following order: CTLA4 antagonists < PD-1 inhibitors < combination of CTLA4 antagonists and PD-1 inhibitors; the same trend was observed for hyperthyroidism but the difference between PD-1 inhibitors and CTLA4 antagonists failed to reach statistical significance.

Nevertheless, given the apparent higher rate of objective tumoral response with combination treatments it is likely that such therapies will be increasingly utilized in the future. On the other hand, irAEs including endocrine irAEs have been linked to improved survival, but this may relate to selection bias as those who survive longer have longer follow-up and hence more likely to develop irAEs during that time. Nevertheless, this observation ought to be clarified in the near future.

Hypothyroidism is usually permanent and requires levothyroxine therapy. If subclinical hypothyroidism with TSH <10 mIU/L, then the patients may be managed conservatively with no levothyroxine. Beta-blockers can be utilized for symptomatic relief during the thyrotoxic phase of thyroiditis. As with other thyroiditis, the use of anti-thyroid drugs is discouraged as they are ineffective. If severe symptoms develop, immunotherapy can be withheld. Moreover, for severe symptomatology and or pre-existing cardiac disease in thyrotoxicosis, glucocorticoids may be given together with the discontinuation of the immune-complex inhibitor.

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