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Immune Checkpoint Inhibitors-induced Thyroid Dysfunction in Patients with Advanced Malignancies

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Abstract

Background: Immune checkpoint inhibitors (ICIs), including antiprogrammed cell death receptor-1, antiprogrammed cell death ligand-1, and anticytotoxic T-lymphocyte-antigen 4, have improved patients' outcome in advanced malignancies. These agents are associated with immune-related adverse events, including skin toxicity, gastrointestinal toxicity, hepatotoxicity, renal toxicities, and endocrinopathies.

Method: We retrospectively reviewed the electronic medical records of patients treated with ICIs for advanced malignancies from two tertiary cancer care centers in the Emirate of Dubai, United Arab Emirates (UAE), including Dubai Hospital and American Hospital from November 2015 to January 2019. The patients were identified through the hospital cancer registry. We retrospectively collected data regarding the subjects' demographics, cancer type, type of ICIs, thyroid-related adverse events, and duration of treatment.

Results: In the present paper, 43 patients received ICI and 19 (44%) developed thyroid dysfunctions. The median age of ICI-receiving subjects was 60 (27-80) years; 26 of them were male and 17 were female. Pembrolizumab was the most used agent (42%). Pretreatment thyroid functions were normal for all the patients. Following treatment initiation, 19 (44%) patients developed thyroid abnormalities, including overt hypothyroidism (n = 11, 57%), overt hyperthyroidism (n = 2, 11%), subclinical hypothyroidism (n = 4, 21%), and subclinical hyperthyroidism (n = 2, 11%). Thyroid abnormalities developed in 56% of them treated with Pembrolizumab and 37% treated with Nivolumab.

Conclusion: Hypothyroidism was the most prevalent thyroid adverse event in the patients treated with ICIs in our study and the majority of thyroid dysfunction encounters took place in the first 6 weeks after ICI initiation. The treatment was well tolerated and there were no treatment-related discontinuations or deaths.

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Introduction

The immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment with significantly improved outcomes in patients with advanced malignancies. The ICIs are classified into anti-programmed cell death receptor-1 (PD-1), antiprogrammed cell death ligand receptor-1 (PDL-1), and anticytotoxic T-lymphocyte antigen 4 (CTLA-4). The immune checkpoints are a group of proteins binding to T-cells surface receptors and inhibiting their function (mostly the CTLA-4) or proliferation (mostly PD-1) within the tumor microenvironment. The inhibition of T-cell operation can cause tumor growth. Therefore, the inhibition of CTLA-4, PD-1, and PDL-1 would in turn dampen the tumor growth upregulation due to T-cells activation; it will maintain the endogenous tumor cells destruction ability of T-cells.[1,2,3] Immune checkpoint inhibition may unavoidably lead to a broad spectrum of side-effects termed as immune-related adverse events (irAEs), including skin toxicity, gastrointestinal toxicities, hepatotoxicity, renal toxicities, and endocrinopathies.[4,5] Immune checkpoint inhibitors-induced thyroid dysfunction is usually a primary autoimmune disorder caused by anti-PD-1 and less commonly by anti-CTLA-4 antibodies. However, autoimmune hypophysitis has been reported to mainly occur as a consequence of the anti-CTLA-4 administration.[6] It is hypothesized that the T-cells unleashed due to inhibition of immune checkpoints may attack the normal endogenous self-antigens, including healthy cells leading to autoimmune destruction of the targets. Numerous studies reporting ICIs adverse events were retrospective, while few of them were observational or randomized trials.[7] Due to the increased use of immunotherapy in cancer patients, it is expected that further patients attend the emergency department with irAEs. Hence, it is of paramount importance for the general and emergency physicians to be aware of adequate management of these toxicities. To the best of our knowledge, there is no research publication on this subject in the Middle East; thus, the findings of this study would add further knowledge to the already-existing literature. Herein, we aimed to evaluate the incidence of thyroid dysfunction after ICIs administration in our population. This study was conducted in two tertiary oncology units in the Emirate of Dubai, UAE. The oncology departments in Dubai Hospital and American Hospital are the main tertiary cancer referral centers in Dubai, where the bulk of the complicated oncology cases are often seen; and therefore, prescription of the ICIs is more frequently used. This study mainly focused on thyroid disorders induced by administration of anti-PD-1 (Nivolumab, Pembrolizumab) and anti-PD-L1 (Atezolizumab, Durvalumab).

Materials and Methods

This is a retrospective cohort observational study, where we reviewed the electronic medical records of the patients treated with ICIs for advanced malignancies from two tertiary cancer treatment centers in the Emirate of Dubai, UAE, including Dubai Hospital and American Hospital, from November 2015 to January 2019. The study was approved by Dubai Scientific research ethics committee (ethics code: DRSEC-05/2018_12). Eligible cases were identified through the hospital cancer registry. Data regarding the participants' demographics, cancer type, type of ICIs, details of the thyroid-related adverse events, time of occurrence, and the type of dysfunctions were identified. The data were analyzed utilizing the SPSS program in order to report the thyroid dysfunction based on different parameters, such as time of thyroid dysfunction occurrence and involvement of the pituitary gland in the thyroid dysfunction. All the patients who had received at least one cycle of ICIs and had one thyroid function test (TFT) performed within six weeks of initiating the therapy were included in this study. The ICIs used included Nivolumab, Atezolizumab, Pembrolizumab, and Durvalumab. The subjects with pre-existing thyroid disease and unavailable baseline TFT results were excluded. Those who did not undergo TFTs within six weeks of the treatment initiation were not included in the data analysis. The biochemical diagnosis of hypothyroidism and subclinical hypothyroidism were based on TSH and FT4

Table 1. Timing of thyroid dysfunction occurrence after immunotherapy use

	Subclinical Hyperthyroidism	Subclinical Hypothyroidism	Overt Hyperthyroidism	Overt Hypothyroidism
Within 6 weeks	0	3	0	7
Within 12 weeks	2	1	1	2
Within 18 weeks	0	0	1	2

levels. Hypothyroidism was defined as a TSH level of over 10 uIU/ml and the patients with TSH levels of between 4.2 to 9.9 uIU/ml were categorized as subclinical hypothyroid. Hyperthyroidism and subclinical hyperthyroidism were likewise defined as the presence of suppressed TSH and high free T4 or only suppressed TSH with normal free T4, respectively. The reference ranges for TSH (0.27-4.2 uIU/ml), FT3 (3.1-6.8 pmol/l), and FT4 (12-22 pmol/l) were used in this study. Secondary hypothyroidism was defined as a low TSH and low free T4 after initiation of ICI.

Results

A total of 43 patients received ICI, 19 (44%) of whom developed thyroid dysfunctions; their median age was 60 years. There were 26 (60%) male and 17 (40%) female subjects. Metastatic lung cancer was the most common prevalent (n = 24, 56%), followed by renal cell cancer (n = 6.14%), malignant melanoma (n = 5, 12%), bladder cancer (n = 3, 7%), Hodgkin's lymphoma (n = 3.7%), and other malignancies (n = 2, 4%) (Figure 1). Nivolumab was employed for treatment in 19 (44%) patients, Pembrolizumab in 18 (42%), Atezolizumab in four (9%), and Durvalumab in two (5%) patients.

All the cases had TFTs checked prior to starting ICI, and then with each cycle of ICI. Pretreatment TFTs were normal for all the patients. After treatment initiation, 19 (44%) subjects developed thyroid abnormalities, including overt hypothyroidism in 11 (57%) patients, overt hyperthyroidism in two (11%), subclinical hypothyroidism in four (21%), and subclinical hyperthyroidism in two (11%) of them. The majority of the thyroid dysfunctions (n = 10, 52%) were noted in the first six weeks of ICI initiation, including seven patients with overt hypothyroidism and three with subclinical hypothyroidism. Six patients developed thyroid abnormalities between weeks 7 to 12 of ICI initiation. This included overt hypothyroidism (n = 2), subclinical hypothyroidism (n = 1), overt hyperthyroidism (n = 1), and subclinical hyperthyroidism (n = 2). Two patients developed overt hypothyroidism and one overt hyperthyroidism in weeks 13 to 18 of ICI initiation (Table 1).

Pembrolizumab was the most common thyroid dysfunction-causing ICI in 56% of the patients and Nivolumab in 37% of them. All of the patients developing hyperthyroidism and subclinical hyperthyroidism received Pembrolizumab and similarly, all of those developing secondary hypothyroidism were treated with Nivolumab. Hypothyroidism was noted in five subjects treated with Pembrolizumab and six treated with Nivolumab (Figures 2 and 3). Immune-mediated thyroid toxicities in both hospitals were managed according to the guidelines of NCCN (National Comprehensive Cancer Network). No ICI-associated treatment discontinuations, severe morbidity, or mortality was noted.

Discussion

In the current study, we found that the ICIs augment the risk of thyroid dysfunction to a large extent. Hypothyroidism was the most common thyroid adverse event in the patients treated with ICIs. Half of the hypothyroidism cases were induced by Nivolumab.

ICI-related endocrine glands autoimmunity causes dysfunction of the thyroid, pituitary, adrenal glands, and the pancreas. Manifestations of immune-mediated endocrine gland dysfunction include hypothyroidism, hyperthyroidism, hypophysitis, type I diabetes mellitus, and primary adrenal insufficiency.[8,9] ICIs have been reported to cause both primary and secondary thyroid

dysfunctions. Distinguishing primary thyroid disorders from secondary hypothyroidism (secondary to hypophysitis) is critical before initiating the treatment.[10] The underlying pathogenic mechanism of ICI-induced thyroid dysfunction has not been clearly established to date. It is postulated that it could be due to either an autoimmune or a non-autoimmune pathological process or a combination of both. The majority of cases of primary thyroid dysfunction are related to thyroiditis, which can be seen as diffuse uptake on a positron emission tomography scan.[11] Thyroiditis can present initially as thyrotoxicosis due to the release of thyroid hormone from inflamed thyroid tissue. This can subsequently result in hypothyroidism from inflammatory damage following cytotoxicity induced by these agents against the thyroid gland. There is no previous data available on the prevalence of the endocrinopathies associated with different ICIs in the UAE. Our study covered only the dysfunction of the thyroid gland among the other endocrinopathies with ICIs, but it is value-adding scientific information for our region in view of paucity of research in this specific subject of emerging importance in the Middle East. In the pretreatment, thyroid function tests were normal for all the patients. Following the treatment initiation, 44% (n = 19) of them developed thyroid abnormalities significantly higher as compared with the published data.[12] Recent studies looking specifically for primary thyroid dysfunction after PD1 inhibition have noted that the rate of thyroid abnormalities could be as high as 14%-20%, especially following combination ICIs therapy.[13] A meta-analysis examined the incidence of endocrine dysfunction across 38 randomized trials enrolling 7551 patients treated with immunotherapy. It reported that the incidence rates for hypothyroidism were 3.8%, 7.0%, 3.9%, and 13.2% with Ipilimumab, Nivolumab or Pembrolizumab, Atezolizumab, and the combination of Ipilimumab plus Nivolumab, respectively. Regarding the subtypes of thyroid dysfunction, this systematic review showed that among the recipients of ICI monotherapy, anti-PD1 and anti-PD-L1 caused further thyroid-related adverse events than anti-CTLA-4.[14] There was no statistically significant difference concerning the risk of hypothyroidism between PD-L1 and PD-1 inhibitors. Our study revealed a higher incidence of hypothyroidism, including overt hypothyroidism and subclinical hypothyroidism.

Interestingly, all cases of secondary

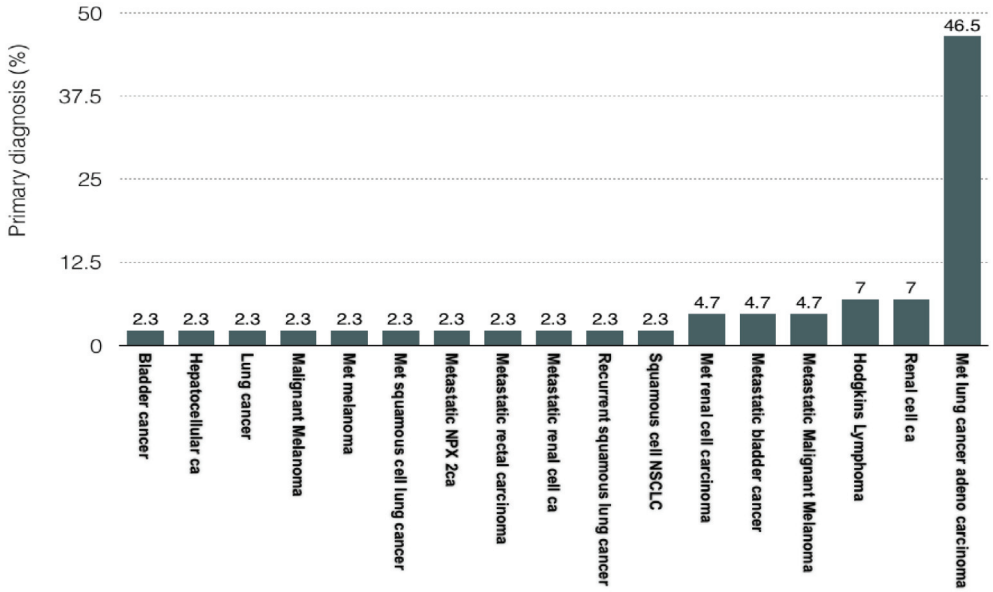

Figure 1. This figure shows the primary cancer diagnosis in the patients treated with immunotherapy.

hypothyroidism (which points towards ICI-induced hypophysitis) are from the Nivolumab group. In their meta-analysis, Barroso et al. reported that the overall incidences of hypophysitis were 6.4% for combination therapy, 3.2% for CTLA-4 inhibitors, 0.4% for PD-1 inhibitors, and below 0.1% for PD-L1 inhibitors. This may necessitate more diligent surveillance of pituitary function in the first few months after the treatment initiation, especially with Nivolumab. In our study, PD-1 inhibitors (Nivolumab, Pembrolizumab) indicated a higher rate of various thyroid abnormalities. Another interesting finding in this systematic review was the higher incidence of hyperthyroidism in the patients on PD-1 inhibitors (OR, 5.36; 95% CI, 2.04-14.08; adjusted P = 0.002). Herein, overt hyperthyroidism was seen in 4.5% of the patients and subclinical hyperthyroidism in 4.5% of them. All of these cases were linked with the use of Pembrolizumab (PD-1 inhibitors).

A retrospective study from the University of Texas by Priyanka et al., in 2018, looked into the prevalence of immune-related thyroiditis (irT). The patients received a combination of Ipilimumab + Nivolumab (40%), Nivolumab (33%), Pembrolizumab (21%), and other ICIs (7%). They showed that thyrotoxicosis phase is mostly asymptomatic and usually followed by the development of hypothyroidism in 84% of cases after ICI therapy. The patients in this study had a period of thyrotoxicosis lasting from 2.6 to 39.7 weeks.[15] A French registry looked for the development of thyroiditis in the recipients of Nivolumab, Pembrolizumab, and Ipilimumab before April 2017.[16] Their database showed 110 cases of thyroid dysfunction, 42.7% of whom were asymptomatic, and unlike our study, where there was a high incidence of hypothyroidism compared to hyperthyroidism, they reported an equal proportion of hyperthyroidism and hypothyroidism. Only 16% of the patients had positive antithyroid antibodies. A higher prevalence of hyperthyroidism was also documented by a Japanese study in 2017, where they observed the change in thyroid function test after the use of Nivolumab in 72 cases with previous normal biochemistry. They found 15.3% cases of hyperthyroidism and subclinical hyperthyroidism and only 4.2% of subjects developed hypothyroidism and subclinical hypothyroidism.[17] While we did not observe any single case of

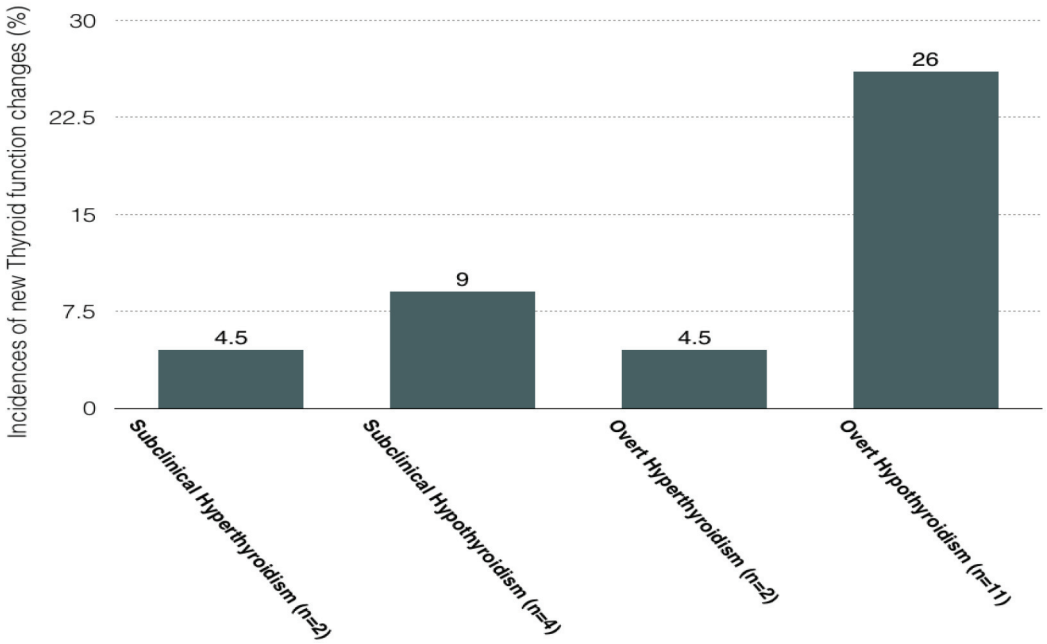

Figure 2. This figure shows thyroid dysfunction with immunotherapy use.

hyperthyroidism in our population after Nivolumab administration, 37% of our patients had Nivolumab-associated primary or secondary hypothyroidism.

In our study, Pembrolizumab showed a higher rate of thyroid dysfunction (56%) relative to other agents. A recent study involving a large cohort of 10,280 cases, by Johnson et al. also reported a slightly higher incidence of thyroid dysfunction with Pembrolizumab (20.8%) than Nivolumab (18%) despite a significantly higher prescription of Nivolumab (54.3%) compared with that of Pembrolizumab (35.8%).[18] On the contrary to this distinct finding in our study, several previously published data showed no significant differences in terms of the incidence of thyroid dysfunction with Nivolumab and Pembrolizumab (6.5% and 7.9%, respectively).[19]

We observed a relatively lower T3 level than T4 in our research and out of all the patients, three had an isolated low T3 level, which improved with time. This feature could be part of a spectrum of the endocrine disruption by these agents or due to sick euthyroid syndrome linked with any underlying cancer or critical illness. A recent study reported better disease progression-free interval and median survival in patients who develop irAEs and have low FT4. The authors linked this association with PD-L1 single nucleotide polymorphism.[20] Confirmation of this finding needs further prospective investigation in different subpopulations to validate the results. Our study revealed that the majority of thyroid abnormalities occur in the first six weeks after ICI initiation. These findings are consistent with the published data showing the median time to onset of endocrinopathy with PD-1 inhibitor monotherapy to range from 1.4 to 4.9 months.[21]

In spite of the interesting findings concerning thyroid dysfunctions after ICI treatment, our study has the limitations of a retrospective research; the data were collected from only two cancer treatment centers in Dubai and the sample size was small. The results may not reflect ICI treatment effects in other patient populations. However, the findings shed light on relatively high rates of ICI-induced adverse effects on thyroid in our population. To the best of our knowledge, this is the first study to assess the rate of ICI-induced thyroid toxicities in the Middle East.

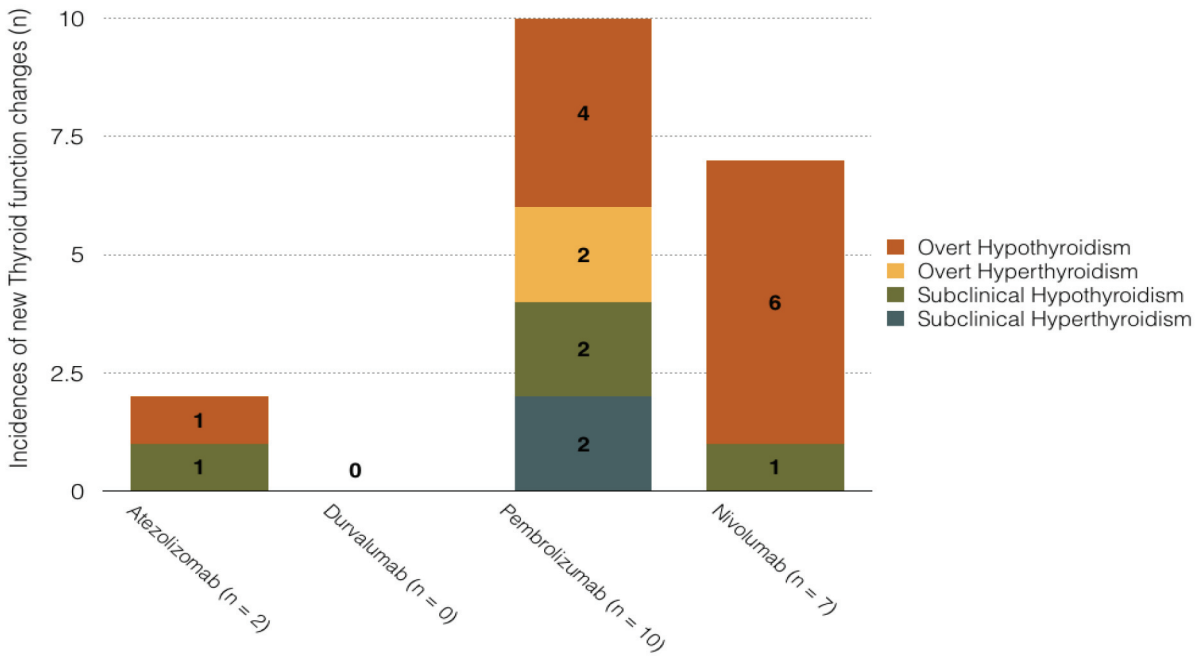

Figure 3. This figure shows thyroid dysfunction with immune checkpoint inhibitors' use based on the immunotherapy type.

Conclusion

ICIs augment the risk of inducing thyroid dysfunction to a large extent. Hypothyroidism was the most prevalent thyroid adverse event in patients treated with ICIs. Half of the hypothyroidism cases were induced by Nivolumab. All the cases of hyperthyroidism or subclinical hyperthyroidism were induced by Pembrolizumab. The majority of the ICI-induced thyroid abnormalities were observed in the first 6 weeks after the treatment initiation. The treatment was well tolerated, and there were no thyroid immune-related adverse events leading to immunotherapy discontinuation or mortality. ICIs-induced thyroid dysfunction is believed to be underestimated, which needs diligent surveillance after initiation of treatment.

Conflict of Interest

None declared.

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