

Analysis of Thyroid Function Abnormalities Induced by Pembrolizumab in Patients with Advanced Malignancies

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ABSTRACT:

BACKGROUND:

Pembrolizumab is an effective anticancer immunotherapy. It is generally well tolerated although immune-related adverse events can occur. Autoimmune thyroid dysfunction is the most common one among these events. Several evidences suggested that pembrolizumab can induce thyroid dysfunction after several treatment cycles.

THE AIM OF THE STUDY:

Is to evaluate the incidence and risk factors of thyroid function abnormalities related to pembrolizumab therapy.

PATIENTS AND METHODS:

This is a multicenter prospective study including 100 patients with different cancers who initiated pembrolizumab treatment. Demographic data was collected in addition to the number of treatment cycles, history of thyroid surgery, thyroid disease, chemotherapy and steroid treatment. Baseline T3, T4 and TSH were measured and assessed periodically. Patients were distributed into 2 groups, those who maintained euthyroid state and the others who developed thyroid dysfunction. Assessment was analyzed looking for any relationship of this dysfunction with age, gender, dose, underlying diagnosis or previous disease or treatment lines.

RESULTS:

Thyroid dysfunction was reported in 31 patients (31%). Female patients were the predominant affected group, ($P < 0.001$). Intriguingly, 38.75% of patients with euthyroidism were ex/current smokers compared with 19.35% of patients with thyroid dysfunction ($P < 0.028$). The median number of pembrolizumab cycles in patients with euthyroidism and with thyroid dysfunction was 5.0 and 6.5, respectively ($P < 0.028$). Finally, the presence of thyroid disease was more frequent among patients with thyroid dysfunction than those with euthyroidism ($P < 0.005$).

CONCLUSION:

A considerable proportion of patients receiving pembrolizumab can develop thyroid dysfunction. Female gender, number of treatment cycles and history of thyroid disease may be risk factors for thyroid dysfunction in those patients.

KEYWORDS: Pembrolizumab, Thyroid dysfunction, Immunotherapy, malignancies

1.1 INTRODUCTION:

Pembrolizumab, an anti-programmed cell death 1 (PD-1) receptor monoclonal antibody is an effective anticancer therapy. Pembrolizumab is a new evolving drug that has been approved in the treatment of different types of cancer with high

value of response. It was approved for medical use by FDA in 2014. It is IgG4 subclasses. The binding of pembrolizumab to PD-1 reduces the inhibitory pathway causing a physiological shift to immune reactivity and enhancing tumor immune surveillance and anti-tumor immune response⁽¹⁾.

FDA approved immune checkpoint inhibitors include anti-CTLA-4 monoclonal antibody (ipilimumab), anti-PD-1 monoclonal antibody (nivolumab, pembrolizumab), and anti-PD-L1 monoclonal antibody (atezolizumab, avelumab, and durvalumab). While these agents were initially

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approved for the treatment of metastatic melanoma, they have been found to be effective in a wide range of tumors, such as small and non-small cell lung cancer, Hodgkin's lymphoma, renal cell cancer, cervical cancer, bladder cancer, oesophageal cancer and breast cancer⁽²⁾.

These agents' increased immune activation can result in a variety of immune-related side effects. These can affect a number of organ systems, including the skin (rash, itching), GI tract and liver (colitis, autoimmune hepatitis), and endocrine system (hypophysitis and thyroid dysfunction). In terms of endocrine dysfunction, CTLA-4 inhibitors are more likely to cause hypophysitis, while both CTLA-4 and PD-1/PD-L1 inhibitors can cause thyroid dysfunction.⁽³⁾

Thyroid dysfunction under ICPI can present as thyrotoxicosis or hypothyroidism⁽⁴⁾. The incidence of thyroid dysfunction differs between different ICPI classes. In a meta-analysis of 37 studies, the predicted incidence of hyperthyroidism was estimated to be 3.2% with PD1-inhibitors and 8.0% with combined ICPI therapy⁽⁵⁾. The median time to onset of hyperthyroidism is reported to be around 21 days in combination therapy and 47 days in monotherapy with PD1-inhibitors⁽⁴⁾. In another study including 168 patients with non-small-cell lung cancer, renal-cell cancer and melanoma treated with ICPI, the average time to develop thyroid dysfunction was 2.8 months⁽⁶⁾.

The incidence of hypothyroidism was higher with combination therapy (13.2%), and 7% with PDL-1 inhibitors alone, according to the same meta-analysis. The median time to onset in the two regimens is comparable, with 63 days in combination therapy and 70 days in PD-1 inhibitor

monotherapy⁽⁷⁾.

The pathogenesis of thyroid disorders caused by ICPI is not fully understood. Data from observational studies suggest that ICPI-induced thyroid dysfunction is caused by a silent destructive thyroiditis that can progress to hypothyroidism or euthyroidism⁽⁸⁾. However, only a few cases of thyrotoxicosis caused by Graves' disease have been reported in the literature⁽⁹⁾.

The treatment of hypothyroidism is determined by the degree of TSH elevation and the severity of symptoms. Adrenal insufficiency must be ruled out prior to beginning hormone replacement in order to prevent potentially fatal adrenal crises⁽¹⁰⁾. The mainstay of treatment is hormone replacement with levothyroxine at a dose of 1-1.6 mcg/kg/day (depending on age and comorbidities)⁽¹¹⁾. When the TSH is less than 10 mU/L, the decision to use hormone replacement therapy should be made on an individual basis (depending on the presence of symptoms or antibodies)⁽¹⁰⁾. In the case of a high TSH between 5 and 10 mU/L, some clinicians advise checking anti-TPO levels before making a treatment decision.⁽¹²⁾ However, a TSH level greater than 10 mU/L or any TSH rise in the presence of symptoms are indications to initiate treatment.

1.2 AIMS OF THE STUDY

To evaluate the incidence and risk factors of thyroid function abnormalities related to pembrolizumab immunotherapy, and assessment of the clinical characteristics and impact of thyroid dysfunction induced by this immunotherapy among a group of cancer patients.

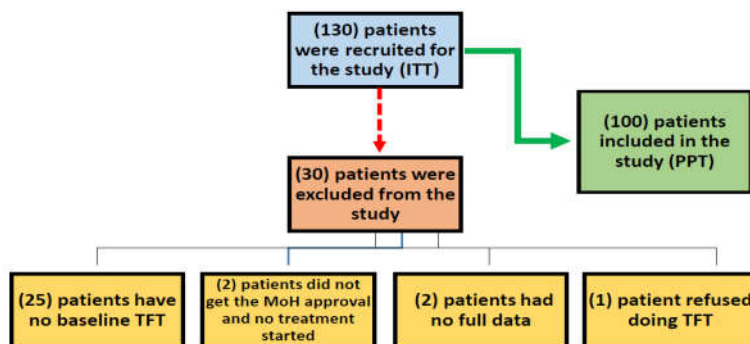


Figure 1: Flow chart of patients recruited for the study.

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PATIENTS AND METHODS:

2.1 Study design and Setting

This is a multicenter cross sectional prospective study including a total of 130 patients, diagnosed with different types of cancers who were prescribed pembrolizumab (in a fixed dose of 200 mg / cycle) according to guidelines throughout the period from the 1st October 2020 till the 31st October 2021.

2.2 Study Population

2.2.1 Inclusion criteria

- Patients with confirmed malignancy (recurrent, Metastatic or Refractory disease).
- On pembrolizumab treatment.
- Different age groups of patients and both gender were included.
- Patient with pre-existing thyroid disease or thyroid surgery having euthyroid function were included.

2.2.2 Exclusion criteria:

- Patients who lacked baseline Thyroid function test (TFT) or could not perform it before starting treatment.
- Patients with no full data.
- Patients with Active autoimmune disease, like (SLE, R.A).

2.3 Ethical consideration

After explaining the purpose of the study, each participant signed a written consent form prior to data collection. Each patient was given the unconstrained right to withdraw at any time. The confidentiality of data was ensured throughout the study, and patients were assured that their data would only be used for research purposes.

2.4 Clinical Examination and Data Collection

For each patient, the following data were collected: age, gender, smoking status, alcohol drinking, comorbidities, type of cancer and date of diagnosis, number of treatment cycles, history of thyroid surgery, thyroid disease, previous chemotherapy and immunotherapy, history of steroid, history of radioactive iodine and history of radiotherapy.

The baseline T3, T4 and TSH were measured prior to initiation of pembrolizumab and the same

measurements were taken every 2-3 cycles. The cumulative dose of pembrolizumab and the time for thyroid dysfunction were calculated from the first dose until the appearance of thyroid dysfunction. The appearance of symptoms and the fate of thyroid abnormalities were registered.

2.5 Follow up and Patients Categorization

Patients were followed-up for 1 year. Thyroid function test was performed regularly. Accordingly, patients were categorized into two groups: those with thyroid dysfunction (clinical and subclinical) and those who maintained euthyroid status.

RESULTS:

3.1 General Characteristics of the Patients

The mean age of the patients was 56.26±15.31 years (range 14-85 years). The male female ratio was 1.38:1. About one-third (35%) of the patients were ex/current smokers, while only 5% of them were alcohol drinkers. Hypertension was the most common comorbidity accounting for 39% of the patients, followed by DM (25%). The mean number of pembrolizumab treatment cycles was 6.37±4.64 with more than one-third of the patients (38%) having 4-6 cycles. Accordingly, the mean cumulative dose was 1090±714.85 mg. A history of radiotherapy, thyroid disease, thyroid surgery, chemotherapy and steroid therapy was reported in 25%, 10%, 2%, 52% and 31%, respectively.

3.2 Evaluation of Thyroid Disorders

The mean baseline concentration of T3, T4 and TSH was 1.69±0.45 ng/ml, 8.95±1.87 µg/dl and 2.42±1.23 mIU/ml, respectively. After the treatment cycles, the mean T3 and T4 did not change significantly (1.41±1.22 ng/ml and 9.54±3.68 µg/dl). However, 14% and 16% of patients had low and high T3, respectively, while 5% and 28% of them had low and high T4, respectively. In contrast, the mean TSH increased sharply (9.72±23.18 mIU/ml) with 13% and 18% of the patients developed low and high TSH, respectively. The mean time to thyroid dysfunction was 130.58±236.84 days with a range of 3.0-1080. Accordingly, thyroid dysfunction (clinical and subclinical) was reported in 31 patients (31%) as shown in (Figure-2).

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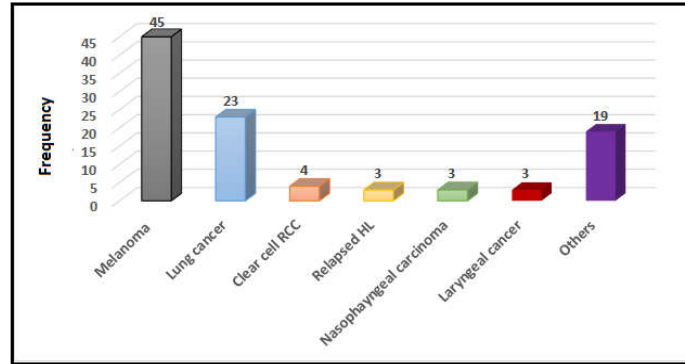


Figure 2: Proportion of the thyroid dysfunction.

3.3 Types of Malignancies

Melanoma was the most common type of malignancy affecting 45 patients (45%) followed by lung cancer (23%). Less common type of malignancies were clear cell RCC, relapsed HL, and Nasopharyngeal carcinoma, laryngeal cancer accounting for 4%, 3%, 3% and 3%, respectively. Sporadic cases of miscellaneous cancers were collectively reported in 19% of the patients (Figure-3). Other cancer including one case of each of

squamous cell carcinoma of the neck, sarcoma/ UPS, malignant thymoma, metastatic parotid adenoid cystic tumor, bladder cancer, sarcomatoid RCC, soft tissue sarcoma, gastric cancer, adrenal cortex cancer, ovarian adenocarcinoma, endometrial cancer, thymic cancer, rectal cancer, uretic urothelial cancer, squamous cell carcinoma of buccal mucosa, colon cancer and cervical cancer.

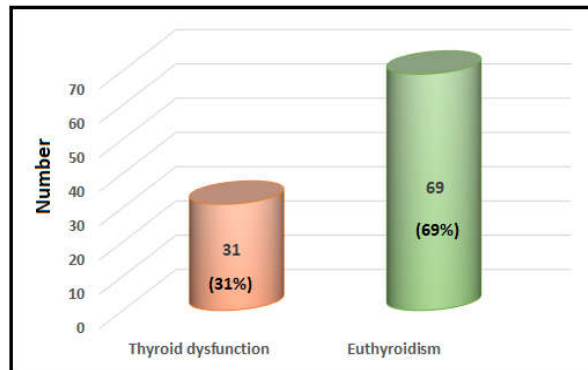


Figure 3: Indication for pembrolizumab use.

3.4 Association demographic and clinical factors with thyroid function

Out of 12 included factors, 4 factors were significantly associated with thyroid dysfunction. Females were more frequent associated with thyroid dysfunction than those with euthyroidism (67.74% vs. 30.43%) with a highly significant difference $p < 0.001$. Intriguingly, 38.75% of patients with euthyroidism were ex/current smokers compared with 19.35% of patients with thyroid dysfunction with a significant difference $p = 0.028$. The median

number of pembrolizumab cycle in patients with euthyroidism and with thyroid dysfunction was 5.0 and 6.5, respectively with a significant difference $p = 0.028$. Finally, the presence of pre-existing thyroid disease was more frequent among patients with thyroid dysfunction than those with no thyroid disease (22.58% vs. 4.35%) with a highly significant difference $p = 0.005$. (Table-1). While none of other parameters like: age, type of malignancy, steroid, etc. showed a significant association.

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Table 1: Association demographic and clinical factors with thyroid function.

Characteristics	Euthyroidism (n=69)	Thyroid dysfunction (n=31)	p-value
Age, years			
Mean±SD	55.32±14.5	56.13±17.22	0.955
Range	14-85	21-83	
Gender			
Male	48(57.97%)	10(32.26%)	<0.001
Female	21(30.43%)	21(67.74%)	
Smoking			
Never	40(%)	25(80.65%)	0.028
Ex/Current	29(38.75%)	6(19.35%)	
Alcohol			
No	40(57.97%)	30(96.77%)	1.585
Yes	29(42.03%)	1(3.23%)	
Comorbidities			
Hypertension	31(44.93%)	8(25.81%)	0.07
Diabetes	21(30.43%)	4(12.9%)	0.061
Heart disease	3(4.35%)	1(3.23%)	0.791
Others (Psoriasis, Asthma)	2(2.9%)	0(0%)	0.487
History of steroid treatment			
No	47(68.12%)	22(71%)	0.741
Yes	22(31.88%)	9(29%)	
Number of treatment cycles			
Mean±SD	5.96±3.76	7.29±6.14	0.028
Median	5.0	6.5	
Range	1.0-20	1.0-33	
Type of malignancy			
Malignant melanoma	31(44.93%)	14(45.16%)	0.532
Lung cancer	15(21.74%)	8(25.81%)	
Clear cell RCC	4(5.8%)	0(0%)	
Relapsed HL	2(2.9%)	1(3.23%)	
Nasopharyngeal carcinoma	1(1.45%)	2(6.45%)	
Ca larynx	3(4.35%)	0(0%)	
Others	13(18.84%)	6(19.35%)	
History of chemotherapy			
No	34(55.74%)	14(45.16%)	0.703
Yes	35(50.72%)	17(54.84%)	
History of radiotherapy			
No	53(76.81%)	22(65%)	0.533
Yes	16(23.19%)	9(35%)	
History of Immunotherapy			
No	52(75.36%)	28(90.32%)	0.084
Yes	17(24.64%)	3(9.68%)	
History of thyroid disease			
No	66(95.65%)	24(77.42%)	0.005
Yes	3(4.35%)	7(22.58%)	

3.5 Multivariate Analysis

In order to find if the number of pembrolizumab cycles is independent risk factor for the development of thyroid dysfunction, multivariate analysis was performed. For this analysis, all factors

demonstrating a significant association with thyroid dysfunction in univariate analysis were entered the multivariate analysis. Furthermore, continuous variable (number of cycles) were categorized into two categories using a proper cut off value.

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The results are shown in table-2. Only history of thyroid disease was independent risk factor for the development of thyroid dysfunction (OR= 6.78, 95%CI=1.53-30.03, p= 0.012).

Table 2: Multivariate analysis.

Characteristics	Euthyroidism (n=80)	Thyroid dysfunction (n=20)	p-value	OR(95%CI)
Gender				
Male	51(63.75%)	3(15%)	0.153	1.0
Female	29(36.25%)	17(85%)		
Smoking				
Never	49(61.25%)	16(80%)	0.414	1.0
Ex/Current	31(38.75%)	4(20%)		
Number of cycles				
≤6	53(66.25%)	10(50%)	0.151	1.0
>6	27(33.75%)	10(50%)		
History of thyroid disease				
No	76(95%)	14(70%)	0.012	1.0
Yes	4(5%)	6(30%)		

3.6 Correlation between Thyroid Function Tests and Number of Cycles

Spearman's correlation test was used to explore the possible correlation between thyroid function test and number of pembrolizumab cycle. None of thyroid hormones had a significant correlation with pembrolizumab cycles.

3.7 Outcome of the Patients

Out of 100 patients treated with pembrolizumab, 31 patients had thyroid dysfunctions which were managed separately (Table-3). All cases of clinical thyroid dysfunctions were reversible after treatment.

Table 3: Outcome of patients who developed thyroid dysfunction when treated with pembrolizumab.

Number of patients	Disorder/ Thyroid dysfunction	Management/outcome
11	clinical hypothyroidism	Given thyroxine therapy
8	subclinical thyroid dysfunction	Did not need treatment
5	preexisting Hypothyroidism	increased prior dose of thyroxine therapy
3	preexisting Hypothyroidism with no prior treatment	started a dose of thyroxine therapy
2	clinical hyperthyroidism	Given carbimazole therapy
2	asymptomatic hyperthyroidism	Did not need treatment
2	withhold pembrolizumab due to renal impairment	Resumed therapy

DISCUSSION:

In the present study, the mean age of the patients was 56.26±15.31 years (range: 14-85 years), 58 of whom were males and 42 were females. This in accordance with a British study including 190 patients with melanoma treated with pembrolizumab. The mean age in those with normal thyroid function was 56.7±15.2 years and

59.0± 13.5 years in those with abnormal thyroid function, but this was not significant (p=0.45). Furthermore, there was a significant gender difference, with 23% of male patients developing thyroid abnormalities compared to 38.3% of female patients (p=0.022)⁽¹³⁾. However, a slightly higher age range was reported among Japanese

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patients receiving pembrolizumab for treatment of different cancers, in which the median age was 71 years (range: 38-83 years). Interestingly, as in our study, there was no significant association of age with the incidence of thyroid dysfunction⁽¹⁴⁾.

In the present study, 31 patients (31%) were recognized to have thyroid dysfunction, (21%) of which were clinically symptomatic and started treatment. However, no treatment was required in (11%). A subset of patients (2%) who developed hypothyroidism have a transient initial hyperthyroid phase (often subclinical). This rate is much higher than that recorded in many studies worldwide.

In an American study, Delivanis et al.⁽¹⁵⁾ 93 patients with advanced cancer (aged 24–82 years; 60% males) who received at least one infusion of pembrolizumab had been analyzed for thyroid disorders using hormonal assay and thyroid imaging modalities. Thirteen patients (14%) developed thyroid immune-related adverse events. In another study including 99 patients with advanced melanoma (aged 26.3–93.6 years; 63.6% females) who received at least (1) administration of pembrolizumab,

de Filette et al.⁽⁸⁾ had reported adverse events of thyroid dysfunction in 17 patients (17.17%).

In a Japanese study, Sakakidaa et al.⁽¹⁴⁾ enrolled 150 patients with metastatic or unresectable advanced cancers who received nivolumab or pembrolizumab in a retrospective study. This study showed that 16.7% of the patients developed immune-related thyroid dysfunction.

In another American study, Osorio et al.⁽¹⁶⁾ found that 10 out of 48 patients (21%) have developed thyroid dysfunction requiring thyroid replacement.

In the KEYNOTE-002 trial, in which melanoma patients received a similar pembrolizumab regime (2 mg/kg every 3 weeks), hypothyroidism was only observed in 5% of patients. Thyroid dysfunction has also been reported at a lower rate in NSCLC patients. In a phase I pembrolizumab trial, 6.9% of NSCLC patients developed hypothyroidism (2 or 10 mg/kg, every 2 or 3 weeks)⁽¹⁷⁾. In a subsequent phase II/III study, 8% of patients (2 or 10 mg/kg) had hypothyroidism, while 4%-6% (2 or 10 mg/kg) had hyperthyroidism⁽¹⁸⁾.

Table 4: Summary of different studies performed to assess frequency of thyroid dysfunction in patients using pembrolizumab.

Number of patients	Disorder/ Thyroid dysfunction	Management/outcome
11	clinical hypothyroidism	Given thyroxine therapy
8	subclinical thyroid dysfunction	Did not need treatment
5	preexisting Hypothyroidism	increased prior dose of thyroxine therapy
3	preexisting Hypothyroidism with no prior treatment	started a dose of thyroxine therapy
2	clinical hyperthyroidism	Given carbimazole therapy
2	asymptomatic hyperthyroidism	Did not need treatment
2	withhold pembrolizumab due to renal impairment	Resumed therapy

Summary of different studies performed to assess frequency of thyroid dysfunction that demonstrate higher proportion in this study compared with other previous studies as shown below (Table-4).

These variations in the incidence of thyroid dysfunction among patients receiving pembrolizumab can be attributed to several factors, the most important of which are the variation in demographic characteristics (age, gender, smoking, BMI), cancer type, treatment regimen and follow up duration.

Of note, there was no significant association between thyroid dysfunction and the type of malignancy in the present study. Although the number of patients in some included malignancies was very small, which could reduce the statistical power, the result reflects the fact that thyroid dysfunction due to pembrolizumab is not affected by the type of malignancy. Unfortunately, most previous studies in this regard used one type of malignancy. Therefore, this result cannot be compared with the other studies.

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In the present study, female gender was significantly associated with the development of thyroid dysfunction in univariate but not multivariate analysis. In accordance with this result is a Swiss study including 380 consecutive patients with melanoma treated either with Ipilimumab, Nivolumab, Pembrolizumab or the combination of Ipilimumab and Nivolumab. There was a significant gender difference, with 23% of male patients developing thyroid abnormalities compared to 38.3% of female patients ($p=0.022$)⁽¹⁹⁾.

There are several feminine factors which predispose women for thyroid dysfunction whether taking Pembrolizumab or not. First of all, the estrogen environment and the peculiar cyclical pattern of hormonal variations are strong promoters for thyroid dysfunctions among females. Second, there is a greater prevalence of autoimmune diseases in females than males⁽²⁰⁾. These factors and may be others make women more prone for adverse thyroid events. Statistically, Smoking had associated with lower incidence of thyroid dysfunction in the studied group where no such remarks had been reported in reviewed literatures yet. However, other disease models were found to get less incidence in correlation to smoking like ulcerative colitis⁽²¹⁾. This effect was attributed to lowering plasma estrogen levels by smoking possibly by induction of estrogen metabolizing cytochrome P450 isoenzymes CYP1A1 and A2 which potentially negating the beneficial effects of estrogen on thrombosis formation and macrophage function⁽²²⁾.

Contradictly, many studies argued this issue in the other way denoting that smoking may increase risk of thyroid disorder development and lower treatment efficacy⁽²³⁾. Thus, the most reasonable explanation for the present result is that most affected patients with thyroid dysfunction were women who are known to have no history of smoking.

The most important finding in the present study was the significant association between number of treatment cycle with pembrolizumab and the development of thyroid dysfunction.

Similar results were frequently reported by many previous studies^(13,14,19, 23). All these studies emphasize the role of pembrolizumab in the development of thyroid dysfunction although with different rate of incidence.

In the present study, the history of thyroid dysfunction was significantly associated with the persistent dysfunction after pembrolizumab treatment. Several studies have shown similar association. De Filette et al⁽⁸⁾ demonstrated that the TPOAb in their patients who developed thyroid dysfunction were already present at baseline in some patients. In another study, Osorio et al⁽¹⁶⁾ showed that the incidence of thyroid dysfunction was not related to the type of tumor nor the type of PD-1 blockade, but was strongly correlated with the presence of anti-thyroid antibodies.

Therefore, patients with thyroid dysfunction who are candidate for pembrolizumab treatment should receive more attention for the possible exacerbated thyroid disease.

5.1 CONCLUSION:

1. A considerable proportion of patients receiving pembrolizumab can develop thyroid dysfunction whether clinical or subclinical.
2. Female gender, number of treatment cycles of pembrolizumab and history of thyroid disease may be risk factors for thyroid dysfunction in those patients.
3. Smoking may have a protective effect against the development of thyroid dysfunction.
4. Thyroid dysfunction induced by pembrolizumab immunotherapy is tolerable and manageable.

5.2 Recommendations

1. Patients treated with pembrolizumab should have a regular checkup of their thyroid function in order to detect and treat the disorder as early as possible as symptoms of thyroid dysfunction are often absent or vague. This will help in prevention of life-threatening consequences.
2. Female patients and those with a history of thyroid dysfunction should have more attention for the possible exacerbation of thyroid disease.
3. Further studies with larger sample size (preferably for each cancer type) are required for more reliable conclusions.
4. Adrenal insufficiency should be ruled out prior to initiating hormonal replacement in pembrolizumab induced hypothyroidism in order to avoid thyroid crises.

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