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Clinical features and treatment strategies of immune checkpoint inhibitor-related thyroid dysfunction in patients with biliary and ampullary malignancies

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Abstract

Objective: To analyze the clinical characteristics of immune checkpoint inhibitor-related thyroid dysfunction (irTD) in patients with biliary and ampullary malignancies, explore its pathogenesis, diagnostic difficulties and treatment strategies, and thereby provide references for the early recognition, accurate diagnosis and standardized management of this disease.

Subjects and Methods: This is a retrospective study that collected clinical data of patients with biliary and ampullary tumors who received immune checkpoint inhibitor therapy at Xuhui District Central Hospital in Shanghai from January 2024 to December 2025, aiming to identify potential influencing factors of irTD. In addition, by integrating the clinical data of two typical cases of irTD, the clinical characteristics, diagnosis, treatment process, and prognosis of this disease were elaborated in detail.

Results: A total of 15 patients with abnormal thyroid function were included in the study, and a case-control cohort was established at a 1:2 ratio. It was found that there were no significant differences in age, gender, tumor type, tumor surgical condition, tumor stage, drug type, diabetes, baseline free triiodothyronine, and baseline free thyroxine ($P > 0.05$).

In contrast, statistically significant differences were observed in thyroid stimulating hormone (TSH, $P = 0.009$), anti-thyroid

peroxidase antibody (TPOAb, $P < 0.001$), and anti-thyroglobulin antibody (TgAb, $P = 0.001$). Univariate and multivariate logistic regression analyses indicated that TPOAb was the most important independent risk factor affecting irTD. ($P < 0.05$). Abnormalities could significantly increase the risk of thyroid function abnormalities in patients receiving ICIs treatment. Analysis of two typical cases—one with drug-induced hypothyroidism complicated with pericardial effusion and the other with drug-induced hyperthyroidism complicated with hyperthyroid heart disease—demonstrated that the dynamic change trend of TPOAb could reflect the degree of thyroid damage and prognosis. It could also serve as an early warning indicator for irTD and a reference indicator for adjusting treatment regimens, which further optimizes the monitoring and treatment strategies for irTD.

Conclusion: The results of this study provide significant clinical implications for the management of irTD. In clinical practice, it is crucial to pay attention to TPOAb. For high-risk individuals, the frequency of monitoring thyroid function should be increased simultaneously, and early intervention should be carried out to avoid serious complications. During treatment, close monitoring of TPOAb changes provides a reliable reference for timely adjustment of treatment regimens, thereby improving the standardized management level of irTD in clinical practice.

Keywords: Immune checkpoint inhibitors; Immune-related adverse events; Biliary Tract Neoplasms

Introduction

Biliary tract neoplasms (BTC) and ampullary carcinoma (AC) are both highly malignant tumors of the digestive system. Due to the insidious early symptoms and strong invasiveness, most diagnoses are made at the middle or advanced stage, missing the opportunity for radical surgery. In recent years, immunotherapy, represented by immune checkpoint inhibitors (ICIs), has emerged as a core treatment option for patients with advanced BTC and AC, leveraging its unique immune regulatory mechanism. It holds an irreplaceable and crucial position in the comprehensive treatment of this highly malignant disease.

However, while ICIs activate the body's anti-tumor immune response, they also disrupt the body's own immune tolerance, triggering a series of immune-related adverse events (irAEs). Among these, immune checkpoint inhibitor-related thyroid dysfunction (irTD) is the most common endocrine system adverse reaction [1-2]. It is mostly caused by destructive thyroiditis, resulting in hypothyroidism, or it can be hyperthyroidism and thyroiditis, and in some cases, it can manifest as Graves' ophthalmopathy, thyrotoxic crisis, and severe myxedema [3].

The specific mechanism of irTD remains unclear. Currently, there is no unified conclusion. Some studies have found that factors such as individual genetic susceptibility, thyroid stimulating hormone (TSH), thyroid autoantibodies such as anti-thyroid globulin antibody (TgAb) or anti-thyroid peroxidase antibody (TPOAb), and the state of the tumor immune microenvironment (such as circulating immune cell phenotypes like T cells, NK cells, CD56, CD16) are related[4-5]; In addition, for BTC and AC patients, tumor consumption and biliary obstruction may lead to metabolic disorders and nutritional deficiencies, which already confer a potential risk of endocrine system dysfunction. The application of ICIs may further exacerbate this abnormality and even affect the treatment process and patient prognosis.

Currently, most research on irTD focuses on high-incidence tumors such as lung cancer and melanoma. There

are relatively few data available for the specific and rare group of patients with BTC and AC. This contrasts sharply with the indispensable and irreplaceable role of ICIs in the treatment of such diseases, resulting in a lack of sufficient theoretical support for clinical diagnosis and treatment. This article explores the pathogenesis and treatment strategies of the disease, providing references for early identification, precise diagnosis, and standardized management. It is of great significance for ultimately improving patients' survival prognosis and quality of life.

Subjects and Methods

1.1 Study population:

The clinical, laboratory and imaging data of patients with BTC and AC who received ICIs at Shanghai Xuhui District Central Hospital between January 2024 and December 2025 were retrospectively collected. Patients with irTD were enrolled into the case group, while patients with normal thyroid function receiving ICIs during the same period were recruited as the control group. A 1:2 matched case-control cohort was established to explore potential influencing factors for irTD. This study was conducted in accordance with the Declaration of Helsinki and the ethical standards of the Medical Ethics Committee of Shanghai Xuhui District Central Hospital. The study protocol was approved by the Medical Ethics Committee of Shanghai Xuhui District Central Hospital. Written informed consent was obtained from all participants.

Inclusion criteria: (1) With clear histological or cytological diagnostic basis; (2) No restrictions on whether traditional chemotherapy drugs are combined or not; (3) Complete clinical data.

Exclusion criteria: (1) Incomplete medical records; (2) Patients with pre-treatment thyroid dysfunction (excluding thyroid nodules, TPOAb+ or TGAb+); (3) Positive for thyroid-stimulating hormone receptor antibody (TRAb)

1.2 Data Collection:

The system collected the clinical data of BTC and AC patients who received ICIs, specifically including: (1) Basic clinical characteristics: gender, age, surgical history (tumor-related surgery); (2) Tumor and treatment-related information: pathological type and whether there is distant metastasis, drug type; (3) Baseline thyroid data and post-treatment data: TSH, free triiodothyronine (FT3), free thyroxine (FT4), TPOAb, TgAb, and TRAb; (4) Previous diseases: diabetes or not; The study aims to identify potential influencing factors for irTD in BTC and AC patients, and to screen out independent risk factors. Additionally, for the clinical data of 2 patients with severe thyroid dysfunction-related complications, the clinical characteristics, diagnosis, treatment process, and prognosis results were analyzed. This was done with the aim of providing practical and feasible clinical reference data for optimizing the early identification and treatment of severe thyroid adverse reactions associated with immune checkpoint inhibitors in clinical practice.

1.3 Statistical Analysis:

All data were processed by SPSS 27.0 statistical software. Continuous variables with normal distribution were expressed as mean $\pm$ standard deviation (SD), while those not meeting the normality criterion were represented by

median (Median, M) and interquartile range M (P25, 75). Independent sample T-tests were used to compare normal measurement data, and otherwise, Wilcoxon Mann-Whitney and Kruskal-Wallis rank sum tests were employed. Univariate and multivariate logistic regression analyses were conducted to calculate OR values and correlation coefficients to identify factors influencing TPOAb. $P < 0.05$ indicated statistical significance. Receiver operating characteristic (ROC) curves were drawn to predict the indicators of TPOAb changes.

Results

Factors influencing thyroid function:

A total of 15 patients with drug-induced thyroid dysfunction and 30 patients with normal thyroid function were included in the study. Table 1 compared the changes in thyroid function after drug treatment and screened the influencing factors of irTD: age ($P=0.881$), gender ($P=0.832$), disease type ($P=0.435$), tumor surgery status ($P=0.314$), drug type ($P=0.994$), diabetes ($P=0.737$), presence or absence of distant metastasis ($P=0.95$), FT3 ($P=0.435$), FT4 ($P=0.84$) showed no significant differences, while TSH ($P=0.009$), TPOAb ($P<0.001$) and TgAb ($P=0.001$) showed statistically significant differences between the two groups ($P<0.05$);

Further single-factor and multi-factor Logistic regression analysis (Table 2) was conducted to show that TPOAb ($P=0.03$) was the most significant independent risk factor for irTD ($P<0.05$), and abnormal levels of TPOAb could significantly increase the risk of irTD.

To clarify the predictive efficacy of TPOAb for irTD, ROC curve analysis was used to determine the optimal cut-off value. As shown in Figure 1, the area under the ROC curve (AUC) of the baseline level of TPOAb was 0.861, and the critical value was determined to be 2.67 IU/l. At this time, the diagnostic sensitivity of this indicator was 78.6% and the specificity was 89.7%, suggesting that the baseline level of TPOAb has a good predictive value for the occurrence of irTD.

Introduction of case analysis:

Two representative cases were analyzed as follows (Table 3).

Case 1: A 69-year-old male, after surgery for ampoidal malignant tumor (adenocarcinoma), staged pT2N0M0 (IB stage), with a history of cholecystitis and gallbladder stones, received PD-1+ teggio treatment after surgery; Before medication administration, his thyroid function was normal, with positive TPOAb, negative TGAb, and negative TRAb. Color Doppler ultrasound indicated bilateral thyroid nodules (TI-RADS 3 category). After 16 weeks (4 cycles) of medication, the patient felt significantly weak, accompanied by a significant increase in creatine kinase, hypothyroidism, a significant increase in TPOAb, and a small amount of pericardial effusion. The use of PD-1 was suspended, and levothyroxine tablets were used for replacement therapy. Subsequently, the dosage of levothyroxine was adjusted, and the administration of ICI was reinitiated. A maximum dose of 250 μg levothyroxine per day was required to maintain normal thyroid function. In addition, after treatment, the thyroid color Doppler ultrasound of the patient showed diffuse reduction of the thyroid gland (left lobe $11\times 7\text{mm}$, right lobe $13\times 7\text{mm}$, isthmus 2mm).

Case 2: A 73-year-old male with malignant tumor of the hilar bile duct (T4N1M0 stage IIIC, adenocarcinoma), with a history of hypertension. His thyroid function was normal before treatment. TPOAb and TGAb were positive, while TRAb was negative. The thyroid ultrasound is normal. He was treated with cadonilimab + gemcitabine + cisplatin. Two weeks after the treatment, he experienced palpitations and chest tightness. The examination indicated atrial fibrillation, heart dysfunction, and hyperthyroidism. TPOAb and TGAb significantly increased. It was considered as hyperthyroid-induced heart disease. He was treated with control of ventricular rate, improvement of heart function, and glucocorticoid therapy. The symptoms have significantly improved and the electrocardiogram has returned to normal. One week later, the condition turned into hypothyroidism. Substituted treatment with levothyroxine was given, and the immune checkpoint inhibitors were re-administered.

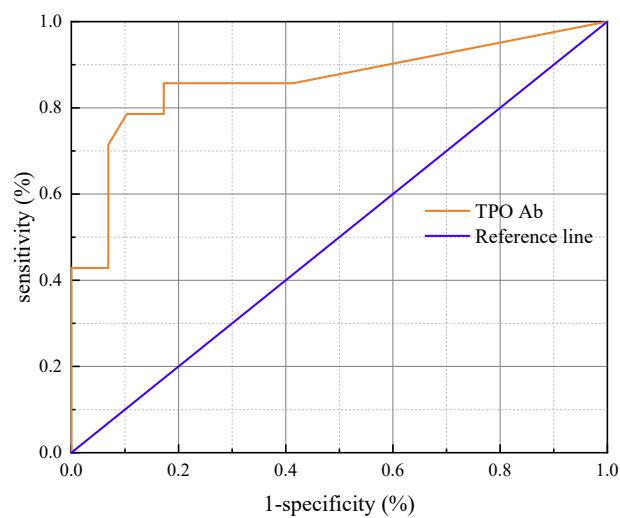
Table 1 Comparison of baseline data between patients with normal and abnormal thyroid function after ICIs treatment

	Normal thyroid function (n=30)	Abnormal thyroid function (n=15)	P
Gender (Male)	17	8	0.832
Age (years)	60.73±9.4	61.2±10.5	0.881
Oncologic surgery (Present, %)	8 (26.7%)	7 (46.7%)	0.314
Type of disease (n/%)			0.435
Cholangiocarcinoma	19 (63.3%)	8 (53.3%)	
Gallbladder cancer	10 (33.3%)	5 (33.3%)	
ampullary carcinoma	1 (3.3%)	2 (13.3%)	
Drug type (n/%)			0.994
Tislelizumab	14 (46.7%)	7 (46.7%)	
Cadonilimab	4 (13.3%)	2 (13.3%)	
Durvalumab	6 (20%)	3 (20%)	
Toripalimab	3 (10%)	2 (13.3%)	
Camrelizumab	3 (10%)	1 (6.7%)	
Diabetes mellitus (None, %)	27 (90%)	13 (86.7%)	0.737
Distant metastasis (None, %)	19 (63.3%)	11 (73.3%)	0.95
Baseline indicators			
TSH (uIU/ml)	1.385(0.96,2.03)	2.65(1.72,3.7)	0.009
TPOAb (IU/ml)	0.25(0.25,0.39)	45.06(12.74,375.54)	< 0.001
TGAb (IU/ml)	0.9(0.9,0.9)	1.05(0.9,22.7)	0.001
FT3 (pmol/L)	3.83(3.49, 4.04)	3.92(3.65,4.34)	0.435
FT4 (pmol/L)	15.73(13.83,16.68)	15.73(13.83,17.83)	0.84

Table 2: Univariate and multivariate Logistic regression analysis of the influencing factors of irTD

Reference value	Univariate analysis			Multivariate analysis		
	B	OR (95% CI)	P	B	OR (95% CI)	P
Gender	-0.135	0.874(0.252,3.04)	0.832			
Age	0.005	1.005(0.942,1.073)	0.878			
Oncologic surgery	0.878	0.21(0.66,8.81)	0.185			
Distant metastasis	0.465	1.59(0.41,6.23)	0.504			
Diabetes mellitus	0.325	1.39(0.26,9.32)	0.74			
Drug type	-0.18	0.982(0.62,1.55)	0.94			
TSH	0.72	2.05(1.12,3.78)	0.021	0.419	1.52(0.68,3.403)	0.308
TPOAb	0.035	1.036(1.005,1.07)	0.024	0.036	1.036(1.003,1.07)	0.03
TGAb	0.27	1.31(0.99,1.74)	0.059			
FT3	-0.083	0.92(0.582,1.46)	0.72			
FT4	-0.025	0.98(0.733,1.29)	0.867			

Figure 1: ROC curve of TPOAb for predicting irTD



(Note: AUC = 0.861, 95% CI: 0.722 - 0.999, $P < 0.001$; The optimal cut-off value is 2.67 IU/l, with a sensitivity of 78.6% and a specificity of 89.7%)

Table 3: Analysis of Clinical Characteristics of Two Patients with Severe irTD

	Case 1	Case 2
Gender / Age	Male / 61	Male / 73
Tumor type / Pathology	Ampullary carcinoma (adenocarcinoma)	Hepatopancreatic ductal carcinoma (adenocarcinoma)
ECOG	1	1
Tumor staging	pT2N0M0IB	T4N1M0 IIIC
Previous illness	Gallbladder stones, cholecystitis	Hypertension
Drug type	Tislelizumab	Cadonilimab
Chemotherapy drugs	Tegison	Gemcitabine + Cisplatin
Baseline indicators		
TSH (uIU/ml)	0.545	3.431
TPOAb (IU/ml)	21.65	564.5
TGAb (IU/ml)	<0.90	41.4
TG(ng/ml)	3.95	0.4
FT3 (pmol/L)	4.29	3.65
FT4 (pmol/L)	14.32	14.33
TRAb (IU/L)	Negative	Negative
Thyroid ultrasound	Bilateral thyroid nodules (TI-RADS category 3)	Normal thyroid ultrasound
Changes in thyroid function	Hypothyroidism	Hyperthyroidism - Hypothyroidism
Duration of medication	16 weeks	2 weeks
Changed indicators		
TSH (uIU/ml)	49.57	0.011
TPOAb (IU/ml)	655.78	> 1000
TGAb (IU/ml)	<0.90	> 2500
TG (ng/ml)	0.33	3.61
FT3(pmol/L)	1.35	25.35
FT4(pmol/L)	3.86	> 77.22
Immune thyroid function grading	Level 3	Level 4
Adrenal cortex function	Normal	Normal
Symptoms and Complications	Fatigue, significantly elevated creatine kinase levels, and pericardial effusion;	Chest tightness, atrial fibrillation, heart failure;
Intervention measures	Suspend ICIs and use hormone replacement therapy (maximum dose 250 µg/d);	Control the ventricular rate, correct heart failure, and use glucocorticoids;
Prognostic outcome	Persistent hypothyroidism, restarting ICIs, thyroid ultrasound indicates diffuse thyroid shrinkage	Converted to hypothyroidism (one week later), continue the original treatment plan

Figure 2: Changes in thyroid function and TPOAb antibody levels

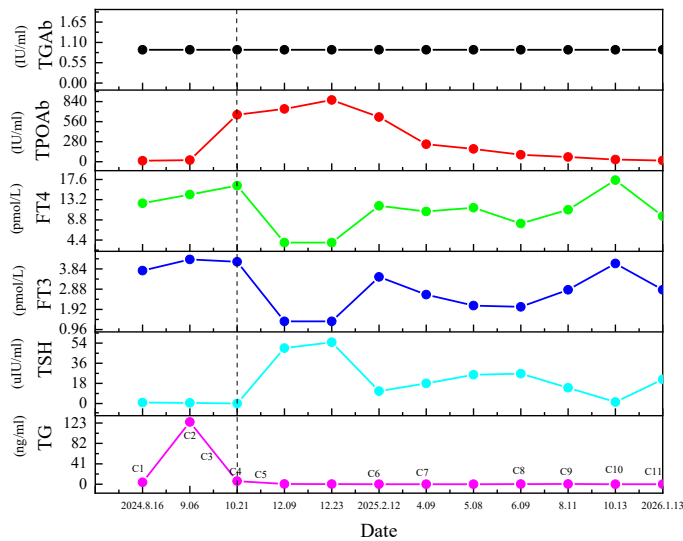


Figure 2a: Presents as a progressive increase in TPOAb, a progressive decline in thyroid function, and a persistently extremely low level of TG; After drug treatment, the antibodies gradually decrease, and thyroid function gradually returns to normal.

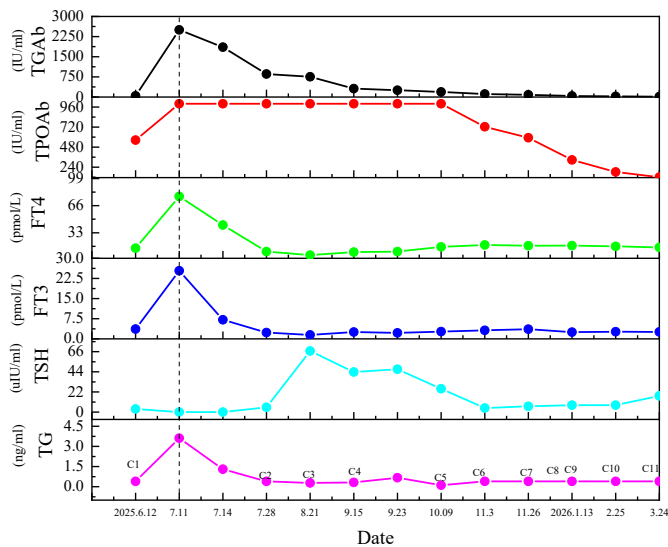


Figure 2b: After the treatment, TPOAb levels rose sharply. The patient experienced a process of hyperthyroidism and hypothyroidism. The antibody levels gradually decreased, and the thyroid function underwent a rapid transition from "hyperthyroidism" to "hypothyroidism".

Discussion

Ampullary carcinoma accounts for 0.2%–2% of all digestive tract tumors, with a 5-year survival rate of approximately 20%–40%. Biliary tract malignancies constitute about 3% of digestive system cancers, and their overall 5-year survival rate is less than 5% [6-7]. In recent years, immune checkpoint inhibitors have evolved into a novel therapeutic strategy for these aggressive malignancies. International multicenter phase III trials, including TOPAZ-1 and KEYNOTE-966, have demonstrated prominent breakthroughs in first-line chemoimmunotherapy for advanced BTC [8-9]. Nevertheless, the widespread use of ICIs is accompanied by a variety of immune-related adverse events. Relevant clinical data concerning such adverse reactions in patients with these rare tumors remain limited. This study systematically investigates the clinical features and adverse impacts of irTD in BTC and AC. The findings validate the critical value of routine TPOAb monitoring during immunotherapy, providing high-level evidence for optimizing immunotherapy management and establishing individualized safety intervention strategies for patients with BTC and AC.

This study demonstrated that positive TPOAb serves as a valuable indicator for irTD. As humanized monoclonal antibodies, ICIs eliminate inhibitory signals of T-cell activation, allowing tumor-reactive T cells to exert potent anti-tumor effects [10]. While fighting tumors, it may involve normal tissues or organs of the body, causing immune-related adverse reactions, among which thyroid damage and hypophysitis are more common [11-12]. Immune-related thyroiditis is pathologically characterized by lymphocyte infiltration, follicular cell loss and focal necrosis, indicative of destructive thyroiditis [13-15]. Prior studies have confirmed that TPOAb-positive individuals have inherent susceptibility to autoimmune thyroid diseases. By restoring anti-tumor immunity, ICIs may trigger cross-reactive immune responses against thyroid antigens, impairing follicular cells and driving the progression from autoimmune thyroiditis to overt thyroid dysfunction [16]. The disrupted balance between thyroid injury and repair further accelerates disease progression. Accordingly, adequate pretreatment counseling on potential endocrine toxicities is essential for patients with abnormal thyroid autoantibodies. Close longitudinal monitoring of thyroid function during ICI treatment is also recommended to prevent severe complications [17].

Baseline TPOAb positivity has the utility of predicting irTD, and its dynamic changes can reflect the severity of thyroid damage and long-term prognosis. Studies have shown that TPOAb can serve as an early warning biomarker for abnormal thyroid function [18]; the level of TPOAb reflects the activity of thyroid autoimmunity, and higher titers are associated with more severe thyroid tissue damage and endocrine dysfunction [19], while continuous elevation indicates persistent autoimmune activation, and active intervention measures are required [20]. A decrease in TPOAb level usually indicates the alleviation of thyroid inflammation and can be used as a reference indicator for adjusting treatment plans [21]. In summary, dynamic monitoring of TPOAb helps to optimize the monitoring strategies and treatment plans for ICI-related thyroid dysfunction [22]. In case 1, TPOAb acts as a "marker" of autoimmune damage. Its level gradually increases as the degree of damage worsens, and at the same time, the secretory function of follicular cells also declines, manifesting as the gradual aggravation of hypothyroidism. In Case 2, the sharp elevation of TPOAb triggered rapid infiltration of abundant autoreactive T cells into the thyroid, leading to acute follicular injury and massive thyroid hormone release, which ultimately resulted in destructive hyperthyroidism. Subsequent extensive follicular cell necrosis and impaired secretory

function further progressed to hypothyroidism. Persistently high TPO titers indicated ongoing autoimmune attack on the thyroid, hindering follicular repair and eventually causing permanent hypothyroidism. Moreover, exhaustive thyroid follicular reserve suppressed new thyroglobulin secretion, accompanied by irreversible structural damage to the thyroid gland.

Most patients with irTD will experience a brief period of hyperthyroidism, during which the symptoms are usually mild or absent. The median duration from hyperthyroidism onset to disease resolution or progression to hypothyroidism is approximately 4 to 7 weeks [23]. Accordingly, thyroid function monitoring every two weeks is generally recommended throughout this course [24-15]. In Case 2, the patient progressed from hyperthyroidism to hypothyroidism within just one week. This indicates that a thyroid function monitoring plan should be tailored according to individual circumstances. For high-risk individuals, monitoring should be intensified and the follow-up interval shortened when necessary. In Case 1, the patient's thyroid gland was significantly atrophied. 250 micrograms of levothyroxine were administered daily to maintain normal thyroid function and a stable clinical condition. This suggests that a higher replacement treatment dose may be required for patients with irTD.

It should be noted that studies have shown that patients who experienced irAEs after ICIs treatment generally exhibited better tumor treatment responses, with significant improvements in overall survival, overall response rate, and progression-free survival, suggesting a close relationship between autoimmunity and the anti-tumor effects of ICIs [26]; For such diseases with a high degree of malignancy, the application value of immune checkpoint inhibitors is relatively high. Regarding adverse drug reactions, this study suggests that objective evaluations should be conducted, and attention should be paid to the long-term prognosis assessment of the disease. Individualized anti-tumor plans and thyroid injury treatment plans should be formulated as much as possible to maximize the benefits for patients.

Conclusions

The results of this study provide significant clinical implications for the management of irTD. In clinical practice, it is crucial to pay attention to TPOAb. Pre-treatment TPOAb screening and evaluation are strongly recommended, particularly for high-risk patients, with intensified thyroid function monitoring to enable early intervention and prevent severe complications. Serial TPOAb monitoring during treatment is critical for whole-course surveillance and comprehensive assessment of immune-related thyroid dysfunction.

Research limitations

This study was a single-center retrospective study. Due to the low incidence rate of the disease, the sample size was relatively small, which may have led to selection bias. The influence of differences in ICI drugs and chemotherapy regimens on thyroid dysfunction were not clearly defined. The relationship between thyroid dysfunction and the therapeutic efficacy and long-term survival of patients' tumors was not explored. At the same time, there was a lack of pathological data from thyroid tissue examination to support the pathological types of thyroid damage. In the future, multi-center, large-sample prospective studies should be conducted to further verify the predictive value of TPOAb and provide higher-level evidence for the safety management of ICIs treatment in patients with BTC and AC.

Conflicts of interest

There are no conflicts of interest.

Author contributions:

Qi Song is responsible for data collection, processing and summary; Qi Song and Taomin Su are responsible for writing and revising the article; Zhuojun Liao, Jinyan Zhao and Shulong Zhang are responsible for providing and summarizing the cases; Yan Wang, Houbao Liu are responsible for reviewing and revising the article.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions

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