REVIEW

Thyrotoxicosis with concomitant thyroid cancer

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Abstract

Thyrotoxicosis with concomitant thyroid cancer is rare and poorly recognized, which may result in delayed diagnosis, inappropriate treatment and even poor prognosis. To provide a comprehensive guidance for clinicians, the etiology, pathogenesis, diagnosis and treatment of this challenging setting were systematically reviewed. According to literatures available, the etiologies of thyrotoxicosis with concomitant thyroid cancer were categorized into Graves' disease with concurrent differentiated thyroid cancer (DTC) or medullary thyroid cancer, Marine–Lenhart Syndrome with coexisting DTC, Plummer's disease with concomitant DTC, amiodarone-induced thyrotoxicosis with concomitant DTC, central hyperthyroidism with coexisting DTC, hyperfunctioning metastases of DTC and others. The underlying causal mechanisms linking thyrotoxicosis and thyroid cancer were elucidated. Medical history, biochemical assessments, radioiodine uptake, anatomic and metabolic imaging and ultrasonography-guided fine-needle aspiration combined with pathological examinations were found to be critical for precise diagnosis. Surgery remains a mainstay in both tumor elimination and control of thyrotoxicosis, while anti-thyroid drugs, beta-blockers, ^{131}I , glucocorticoids, plasmapheresis, somatostatin analogs, dopamine agonists, radiation therapy, chemotherapy and tyrosine kinase inhibitors should also be appropriately utilized as needed.

Key Words

- thyroid cancer
- thyrotoxicosis
- hyperthyroidism

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Introduction

Thyrotoxicosis, mainly caused by Graves' disease, is a condition that results from inappropriately high thyroid hormone actions in tissues. Although it commonly manifests palpitations, shortness of breath, increased appetite, sweating, heat intolerance, etc. (Gilbert 2017), multiple etiologies and potential therapeutic options may be involved. Besides specific clinical symptoms and signs, elevated triiodothyronine (T_3) and/or thyroxine (T_4) as well as suppressed thyroid-stimulating hormone (TSH) facilitate the diagnosis of thyrotoxicosis except central hyperthyroidism, in which TSH is nonsuppressed (Vinagre *et al.* 2014, Perticone *et al.* 2015). Although the ratio of total T_3 to total T_4 can be useful in differential diagnosis (Shigemasa *et al.* 1987, Carle *et al.* 2013), in patients with mild or subclinical hyperthyroidism, T_4 and/or T_3 can be normal, and therefore, measurement of serum TSH with

highest sensitivity and specificity, is the most preferred (de Los Santos *et al.* 1989).

Thyroid carcinoma, however, is usually identified by ultrasonography and then confirmed by ultrasonography-guided fine-needle aspiration (FNA) followed by pathological examinations, which categorize thyroid carcinoma into three groups, DTC, anaplastic thyroid carcinoma (ATC) and medullary thyroid carcinoma (MTC). DTC can be further classified as papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), Hürthle cell carcinoma (HCC) and poorly differentiated thyroid carcinoma. With globally rising incidence, thyroid carcinoma has attracted much more concern than before.

In theory, thyrotoxicosis with suppressed TSH should lead to a lower incidence of thyroid cancer than that observed in euthyroid patients

(Fiore & Vitti 2012). In practice, thyroid cancer is typically less efficient in iodine uptake and thyroxine synthesis than normal parenchymal, and most patients with thyroid cancer present with euthyroid or clinical/subclinical hypothyroidism (Kunawudhi *et al.* 2016). However, an increasing number of studies have demonstrated that more attention should be paid to the management of thyrotoxicosis with concurrent thyroid cancer since the first case of hyperfunctioning thyroid cancer metastases was successfully treated with radioactive iodine (^{131}I) (Seidlin *et al.* 1946). A comprehensive guidance for the clinical management of thyrotoxicosis combined with the neoplastic disease is greatly needed, owing to that misdiagnosis or inappropriate treatment may worsen the prognosis if the etiology and pathogenesis of synchronous thyrotoxicosis in patients with thyroid cancer are not sufficiently recognized (Cerletty & Listwan 1979).

However, there is no extant systematic review or consensus dedicated to thyrotoxicosis with concurrent thyroid cancer, possibly due to its low morbidity and management difficulties. We, therefore, performed a comprehensive PubMed search using the combined terms of 'thyroid cancer' and 'thyrotoxicosis' or 'hyperthyroidism', yielding 762 and 4255 articles prior to December 31, 2018, respectively. The mechanism, diagnosis and treatment according to the etiologies of thyrotoxicosis, including Graves' disease, Marine–Lenhart Syndrome (MLS), Plummer's disease, amiodarone-induced thyrotoxicosis (AIT), central hyperthyroidism, hyperfunctioning metastases of DTC and others, were discussed in detail. Moreover, refined diagnostic schemes and practical treatment options for each condition were recommended as well.

Graves' disease with concomitant thyroid cancer

Graves' disease is an autoimmune disease that results from stimulation of the TSH receptor (TSHR) by thyrotropin receptor antibodies (TRAb). The prevalence of concomitant thyroid cancer occurring in patients with Graves' disease reach up to 17% (Weber *et al.* 2006). Although PTC is the most frequently reported histologic type happened in Graves' disease, MTC with concomitant Graves' disease has also been reported (Habra *et al.* 2004), and other clinicopathological characteristics and survival features of thyroid cancer associated with Graves' disease or euthyroidism remain controversial among studies (Pellegriti *et al.* 1998, Yano *et al.* 2007,

Pazaitou-Panayiotou *et al.* 2012). MLS, defined as concomitant occurrence of autonomously functioning thyroid nodule (AFTN) and Graves' disease (Marine & Lenhart 1911), has the possibility of coexisting DTC as well (Scherer *et al.* 2013). PTC and FTC occurred in MLS only reported by several cases by far (Scherer *et al.* 2013, Sharma 2017).

Mechanism

TRAb, similar to TSH, exhibits agonistic activity to TSHR, leading to the secretion of thyroid hormones and thyrotoxicosis, which is independent of the hypothalamic–pituitary–thyroid axis. In addition, TRAb might play a role in stimulating DTC growth because DTC cells express TSHR like normal thyroid cells do (Preece *et al.* 2014). Furthermore, TRAb stimulates invasiveness and angiogenesis of DTC by upregulating vascular endothelial growth factor, placenta growth factor, and their receptors via the same signaling pathways as TSH-induced cell activation and growth (Filetti *et al.* 1988, Mazzaferri 1990). In addition, TSH plays an important role in regulating DTC cell growth, which is incorporated by the insulin-like growth factor (IGF) system (Malaguarnera *et al.* 2012). Considering the important functional similarities between TSH and TRAb, IGF-1 could also affect the growth of DTC in patients with Graves' disease.

MTC sometimes associates with multiple endocrine neoplasia (MEN) syndromes, however, none of the reported cases of Graves' disease associated with MTC was finally diagnosed as MEN (Habra *et al.* 2004), and the mechanism of Graves' disease associated with MTC is still unclear.

DTCs found in or out of AFTN in MLS are really rare events (Valenti *et al.* 1999, Scherer *et al.* 2013, Sharma 2017, Lombardi *et al.* 2018). The DTC happened in MLS may be related to the stimulation of TRAb or gene mutation such as *BRAF*^{V600E} (Scherer *et al.* 2013).

Diagnosis

Increased TRAb is helpful in distinguishing Graves' disease from other etiologies of thyrotoxicosis, except mild Graves' disease, in which TRAb can be still negative (Carle *et al.* 2013). Radioactive iodine uptake (RAIU) is an alternative testing, which is usually elevated, unless there has been a recent exposure to iodine such as radiocontrast or amiodarone. Thyroid scan displays with diffuse radioisotope uptake, whereas the tumor is generally low uptake as a 'cold' nodule (Basharat *et al.* 2011,

Elnaggar *et al.* 2018). In addition, ultrasonography may be particularly useful through providing representative information of Graves' disease with diffuse, bilateral or isthmus goiter, heterogeneous and hypoechogenicity parenchyma and hypervascularization with the classical aspect so called 'thyroid inferno', and describing the characteristics of malignant thyroid nodule, including taller than wide shape, hypoechogenicity, irregular margins, calcifications, vascularity and extrathyroidal extension (Alzahrani *et al.* 2012, Bogazzi *et al.* 2012, Goichot *et al.* 2018). In such situations, ultrasonography is also the primary diagnostic modality available for a guided FNA cytology/biopsy (FNAC/B) of nodules (Haugen *et al.* 2016).

For MTC with concurrent Graves' disease, beyond the above indicators of Graves' disease and malignant nodule (Kim *et al.* 2017), the diagnosis can be facilitated by testing serum calcitonin and carcinoembryonic antigen with superior efficacy to ultrasonography FNAB (Hahm *et al.* 2001). In addition, computed tomography (CT) of the chest and abdomen can provide evidences of cervical lymphadenopathy, pulmonary or hepatic metastases.

MLS with coexisting DTC is characterized by increased TRAb and RAIU, differentiating from Plummer's disease (Sharma 2017). Tumor manifests hypoecho in ultrasonography with or without microcalcification and presents 'hot' nodule in thyroid scan with comparatively lower but not suppressed uptake of the rest parenchymal tissue. If ultrasonography indicates malignant tendency of the nodule, FNAC is essential to confirm the diagnosis (Scherer *et al.* 2013, Sharma 2017).

Treatment

Surgery is the most appropriate treatment for Graves' disease with concomitant DTC. However, surgery for Graves' disease is recognized to be more challenging due to the increased vascularity of the thyroid gland and has been reported to be associated with higher rates of complications compared with surgery for other benign thyroid conditions (Karamanakos *et al.* 2010). Since thyroid storm may be precipitated by the stress of surgery, anesthesia or thyroid manipulation, pretreatment with anti-thyroid drugs (ATDs) with or without beta-adrenergic blockade is recommended (Ross *et al.* 2016).

Propylthiouracil (PTU) is preferred during the first trimester of pregnancy, for treatment of thyroid storm, and in patients with minor reactions to methimazole (MMI). Apart from that, MMI should be used in virtually every patient who chooses ATDs therapy for Graves' disease.

Compared with MMI, PTU can control thyrotoxicosis faster because it not only suppresses thyroid hormone synthesis by inhibiting thyroperoxidase, but also restrains the conversion of T_4 to T_3 .

Initial daily doses of 10–30 mg are used to restore euthyroidism at the start of MMI therapy, and the dose can then be titrated down to a maintenance level; while PTU is usually administered 50–150 mg 2 or 3 times daily due to its shorter duration of action. During treatment with ATDs tailored to the individual patient, clinicians should monitor blood and hepatic function closely due to the possible side effects of ATDs.

Potassium iodine has been used as a beneficial adjunct to ATDs therapy for Graves' disease, because it attenuates organification and release of thyroid hormones as well as thyroid vascularity and intraoperative blood loss during thyroidectomy (Calissendorff & Falhammar 2017). Compared with MMI alone, potassium iodine together with MMI results in better control of thyrotoxicosis and fewer adverse reactions. In addition, corticosteroids, and potentially cholestyramine can be used to rapidly prepare for emergent surgery (Panzer *et al.* 2004).

Although surgical procedures for DTC vary depending upon the clinical pathological characteristics of the tumor, near-total or total thyroidectomy is now well established as the choice in patients undergoing surgery for Graves' disease to prevent the recurrence (Barakate *et al.* 2002, Sundaresh *et al.* 2017). In addition, cervical lymph nodes are dissected when macroscopically involved or in the presence of extensive invasion of central nodes (Pellegriti *et al.* 2013). For patients with unresectable distant metastases from DTC, ^{131}I therapy is executed subsequently.

For Graves' disease with concomitant MTC, total thyroidectomy under biochemical euthyroidism achieved by administration of ATDs and beta-blockers is appropriate (Habra *et al.* 2004). If the evidence of extrathyroidal tumor extension and metastases existed, adjuvant therapy such as radiation therapy or molecular targeted therapy would be needed (Brierley *et al.* 1996, Solomon & Rischin 2012). The treatment strategies for MLS with concomitant DTC is similar to Graves' disease with coexisting MTC, and subsequent ^{131}I administration is recommended if necessary (Scherer *et al.* 2013, Uludag *et al.* 2016).

Plummer's disease with concomitant DTC

Plummer's disease, which is also known as toxic nodular or toxic multinodular goiter (TMNG) commonly happened in iodine deficient regions, is an active multinodular goiter

associated with thyrotoxicosis (Kang *et al.* 2002, Porterfield *et al.* 2008). The incidence of DTC is higher than expected in Plummer's disease (18.3 vs 3.0%) (Smith *et al.* 2013). The predominant pathological pattern is PTC, follicular variant of papillary thyroid cancer (FVPTC) and FTC are also involved (Ngalob & Isip-Tan 2013, Smith *et al.* 2013).

Mechanism

A long period of iodine deficiency leads to T_4 decreasing, which in turn increases TSH and induces thyroid follicular cell hyperplasia. Besides, thiocyanate from smoking exerts inhibitory effect on iodine uptake and organification (Hegedüs *et al.* 2016). All the above mechanisms account for the appearance of multinodular goiter (MNG). The conversion of MNG to TMNG is attributed to constitutive activation of the cyclic adenosine monophosphate (cAMP) signaling pathway by mutation of TSHR and $G_s\alpha$ protein (Krohn *et al.* 2005). In addition, the extracellular growth factors, such as transforming growth factor β and IGF-1, stimulate growth and dedifferentiation of thyroid epithelial cells, leading to tumorigenesis (Krohn *et al.* 2005, Hegedüs *et al.* 2016).

Diagnosis

Unlike Graves' disease, TRAb in Plummer's disease is negative. Ultrasonography detects solid thyroid nodule with intranodular hypervascularization (Kurita *et al.* 2008). CT provides not only the information of nodule size, calcifications and compression of the adjacent tissue, but also the metastases of lymph nodes, lungs and bones. Magnetic resonance imaging (MRI) is thought to be more precise than CT in the anatomic-topographic evaluation of the substernal goiter (Porterfield *et al.* 2008). Thyroid scan with ^{99m}Tc -pertechnetate presents functioning thyroid nodule with minimal uptake of the rest gland (Ngalob & Isip-Tan 2013). Although 'hot' nodule is generally considered as benign, a higher incidental cancer rate than expected can be found in patients with Plummer's disease compared to historical reports (Smith *et al.* 2013). Hence, if ultrasonography suggests malignant signs such as calcifications and vascularity or metastases, FNAB of primary nodule or metastases should be recommended (Ngalob & Isip-Tan 2013).

Treatment

If patient has a perspicuous diagnosis of Plummer's disease associated with DTC, surgery is the first choice because it

can not only resect the primary tumor and metastases, but resolve compression and thyrotoxicosis symptoms rapidly as well. Biochemical euthyroidism achievement with ATDs before surgery and subsequent ^{131}I therapy for the unresectable metastases are also necessary (Ngalob & Isip-Tan 2013).

AIT with concurrent DTC

Amiodarone is an antiarrhythmic medication used to treat ventricular tachycardia and fibrillation or severe congestive heart failure. AIT occurs in up to 18% patients under amiodarone therapy due to high iodine content deriving from amiodarone in patients with underlying thyroid autonomy in a nodular goiter or Graves' disease (AIT1) and destructive thyroiditis raising from direct toxicity of amiodarone to follicular cells (AIT2) (Bogazzi *et al.* 2001). The pathological patterns of DTC in AIT include PTC and FVPTC, which usually occurred in elderly men (Cattaneo 2000, Saad *et al.* 2004, Mackie & Shulkin 2005, Inaba *et al.* 2012).

Mechanism

Thyrotoxicosis, including AIT, is positively related to the tumorigenesis of thyroid cancer (Stocker & Burch 2003, Preece *et al.* 2014). Thyroid cancer has been observed to occur more frequently in rats administered amiodarone, owing to amplified radiation toxicity (Inaba *et al.* 2012). In addition, investigators have demonstrated that amiodarone is directly carcinogenic to human (Su *et al.* 2013).

Diagnosis

If thyroid nodules are found in patients with a long history of amiodarone administration, clinicians should be highly vigilant for the malignant possibility of the nodules. The absolute levels of free T_4 (FT_4) and free T_3 (FT_3) at presentation have no discriminatory value between AIT1 and AIT2, although they tend to be higher in AIT2. Thyroperoxidase antibody (TPOAb), thyroglobulin antibody and TRAb are often positive in AIT1 but negative in AIT2, although their presence does not necessarily allow a diagnosis of AIT1 (Cattaneo 2000, Saad *et al.* 2004, Franklyn & Gammage 2007, Inaba *et al.* 2012). Interleukin-6 (IL-6) appears to be a better marker for thyroid gland destruction and is markedly elevated in AIT2 (Bartalena *et al.* 1994). However, falsely low IL-6 levels

are often encountered in AIT2, limiting its usefulness. In addition, several preexisting disorders of the thyroid such as Graves' disease can give rise to high IL-6 levels. Therefore, at present, the role of IL-6 in differentiating type 1 and type 2 AIT remains unclear (Sudheer Ahamed & Mathew 2009).

RAIU is usually reduced or nil in patients with AIT2 and ranges from low-normal to an increased uptake in those with AIT1 (Bartalena *et al.* 2018). Before performing RAIU, patients are needed to exclude the influence of iodine, which could induce false-negative or -positive results. In addition, ^{99m}Tc sestamibi (^{99m}Tc-MIBI) scans have been reported to be helpful in differentiating between the two principal types of AIT, with normal or increased uptake in AIT1 and decreased uptake in AIT2 due to the destruction of thyroid follicular cells by amiodarone (Piga *et al.* 2008, Elnaggar *et al.* 2018).

In thyroid ultrasonography, goiter or nodules are generally found in AIT1 but not in AIT2; and AIT1 usually presents as hyperechoic parenchyma, while AIT2 displays hypoechogenic. Doppler sonography also provides a noninvasive, real-time assessment of thyroid vascularity as well as nodules, and is helpful in demonstrating the destructive nature of AIT2 without parenchymal hypervascularity (Alzahrani *et al.* 2012).

Treatment

AIT is frequently resistant to ATDs, increasing morbidity and mortality (Yiu *et al.* 2009). It is suggested to halt amiodarone during the management of AIT to improve the efficacy of anti-thyroid treatment (Bogazzi *et al.* 2010). However, arrhythmias in cardiac patients increase the risk of surgery and anesthesia, and amiodarone remains the only option and needs to be continued or re-introduced in resistant tachyarrhythmia, especially in patients with heart failure. In addition, amiodarone with a half-life of up to 100 days, is accumulated within the adipose tissue and should be interrupted for at least 6 months to be eliminated (Bogazzi *et al.* 2010). Moreover, despite interruption of amiodarone administration, spontaneous remission of thyrotoxicosis is rare (Elnaggar *et al.* 2018). Thus, one can suggest that its interruption or continuation might not influence AIT management. Presently, amiodarone interruption in AIT1 is recommended to improve the response to ATDs, but in patients with AIT2, this is not compulsory (Maqdasy *et al.* 2018).

It is important to distinguish between both types of AIT as the therapy differs for each. AIT1 is primarily treated using ATDs such as thionamides

(carbimazole, methimazole or propylthiouracil) to suppress excess hormone synthesis. Long durations and large doses of thionamide treatment (40–60 mg/day of methimazole or equivalent doses of propylthiouracil) may be necessary to establish euthyroidism even if amiodarone is halted (Bogazzi *et al.* 2010). Patients on thionamides should be cautious about the serious side effect, including bone marrow suppression and the possible symptoms of sore throat, mouth ulcers and febrile illness. To increase the sensitivity and response of the thyroid gland to thionamides, a 4- to 6-week course of potassium perchlorate at doses not exceeding 1 g/day, which could decrease the entry of iodine into the thyroid and competitively inhibits thyroid iodine uptake, has been used (Wiersinga 2010, Ahmed *et al.* 2011, Bartalena *et al.* 2018).

AIT2 is usually treated with glucocorticoids for their anti-inflammatory and membrane-stabilizing effect. The proposed initial dose is 40–60 mg/day of prednisone (or equivalent doses of other glucocorticoids), which is then tapered based on clinical and/or biochemical euthyroidism (Narayana *et al.* 2011). Another agent that has been tried in the treatment of AIT2 is lithium carbonate, which inhibits thyroid hormone secretion, but this is not backed by adequate scientific evidence.

In fact, some patients manifest a 'mixed type' AIT in which single treatment is insufficient, and a combination of thioamides, perchlorate and glucocorticoids is necessary to control thyrotoxicosis (Maqdasy *et al.* 2018). In patients with life-threatening thyrotoxicosis or in individuals refractory to medical treatment, plasmapheresis may be used to decrease the perioperative risks associated with thyroidectomy by rapidly restoring a clinical and biochemical euthyroid state (Tonnelier *et al.* 2017).

Surgery is a valid therapy for patients with AIT accompanied by DTC and for patients with severe symptoms that are resistant to combined therapeutic strategies or in cases of drug contraindications (Zhu *et al.* 2016, Tonnelier *et al.* 2017). In fact, thyroidectomy feasibly yields in an immediate reversal of AIT with rapid resolution of symptoms (Houghton *et al.* 2004, Saad *et al.* 2004). As remnant tissue poses a risk for recurrent or persistent thyrotoxicosis, total thyroidectomy is recommended (Williams & Lo Gerfo 2002, Kaderli *et al.* 2016). Some authors performed thyroidectomy using local or general anesthesia in critically ill patients with AIT (Williams & Lo Gerfo 2002, Kaderli *et al.* 2016), which showed no increased risk for morbidity or mortality. In contrast, a series of 34 patients from Mayo Clinic demonstrated elevated morbidity and mortality (Houghton *et al.* 2004).

Therefore, if at all possible, thyroid hormones should be normalized before surgery to minimize the peri-operative complications.

Central hyperthyroidism with coexisting DTC

Central hyperthyroidism, which has been defined as secondary hyperthyroidism, is possibly associated with DTC. Central hyperthyroidism with coexisting DTC can be divided into two categories: TSH-secreting pituitary adenoma (TSHoma) with concomitant DTC and pituitary resistance to thyroid hormone (PRTH) with coexisting DTC. Both of them present symptoms and signs of hyperthyroidism with nonsuppressed TSH. TSHoma is a very rare disorder, which accounts for about 0.5–3% of all pituitary adenomas (Perticone *et al.* 2015). PRTH induced thyrotoxicosis mainly involves the heart and brain. In the last years, several cases of central hyperthyroidism associated with DTC have been reported. The pathological patterns of DTC occurring in central hyperthyroidism include PTC and FTC (Vinagre *et al.* 2014, Perticone *et al.* 2015).

Mechanism

So far, the pathogenesis of TSHoma is unclear. Possible mechanisms involve over-expression of Pit-1 gene and the basic fibroblast growth factor as well as posttranscriptional defects and function alterations in thyroid hormone receptor (TR) of tumoral thyrotropes (Beck-Peccoz *et al.* 2009).

The revealed pathogenesis of PRTH includes mutations in the thyroid hormone transporters (organic anion transporting polypeptide 14 and monocarboxylate transporter 8), the restricted expression of the deiodinase type 2, and the disruption of specific TRb2 contact mechanisms (Suzuki *et al.* 2011).

As described earlier, a prolonged period of unregulated and inappropriately high levels of TSH induced by TSHoma or PRTH may have a stimulatory effect on thyroid neoplasia (Vinagre *et al.* 2014, Perticone *et al.* 2015).

Diagnosis

The confounding factors, such as antibodies against TSH or thyroid hormones as well as abnormal forms of albumin or transthyretin, should be excluded before confirming the diagnosis of central hyperthyroidism (Beck-Peccoz *et al.* 2009, Amlashi & Tritos 2016). To exclude

thyroid diseases, TRAb and TPOAb are of value, and they are generally negative in central hyperthyroidism (Vinagre *et al.* 2014, Perticone *et al.* 2015).

There are no significant differences in TSH and free thyroid hormone levels between patients with TSHoma and those with PRTH, making differential diagnosis difficult. Moreover, although pituitary hypersecretion of α -glycoprotein (α -GSU) and elevated α -GSU/TSH ratio are detected in most TSHoma patients, it is more frequently normal in microadenomas than in macroadenomas (Ness-Abramof *et al.* 2007, Yamada *et al.* 2014). Sometimes, the diagnosis of TSHoma can be facilitated by the presence of neurological symptoms such as visual defects and headache or clinical characteristics of concomitant hypersecretion of other pituitary hormones such as acromegaly and amenorrhoea/galactorrhoea (Kiatpanabhikul *et al.* 2017). In addition, carboxyterminal crosslinked telopeptide of type I collagen and sex-hormone-binding globulin are increased in patients with TSHoma but normal in patients with PRTH (Beck-Peccoz *et al.* 2009). Furthermore, the findings of similar biochemical data in relatives definitely indicate the diagnosis of PRTH, since familial cases of TSHoma have not been documented (Beck-Peccoz *et al.* 2009).

It is proposed that dynamic tests are of value to make a distinction between TSHoma and PRTH. T_3 suppression test is most sensitive and specific to assess the presence of TSHoma with no inhibition of TSH secretion compared with PRTH. Of note, this test is contraindicated in elderly patients or patients with coronary heart disease. In addition, a blunted TSH response to the thyrotropin-releasing hormone (TRH) stimulation test has also been seen in most patients with TSHoma, in contrast to PRTH patients who generally show a rise in TSH levels after TRH administration. On the contrary, increased α -GSU after TRH test is positive in TSHoma but negative in PRTH (Tjornstrand & Nystrom 2017). Besides, long-acting somatostatin analogs (SSAs) has been proposed as a distinguishing mean between TSHoma and PRTH, owing to that FT_4 and FT_3 significantly reduce in patients with TSHoma but not in those with PRTH after SSAs administration (Mannavola *et al.* 2005).

Hypophyseal mass with suprasellar extension at MRI or CT scan strongly supports the diagnosis of TSHoma. However, it may be difficult to distinguish TSHoma from PRTH if the tumor was very small or empty sella. Pituitary scintigraphy with radiolabelled octreotide has also been shown to successfully localize TSHoma expressing somatostatin receptors. Unfortunately, the specificity of octreotide scan is low in both secreting and

non-secreting pituitary mass (Losa *et al.* 1997, Amlashi & Tritos 2016). Positron emission tomography/computed tomography (PET/CT) of gallium-labeled SSAs has been increasingly used in the evaluation of neuroendocrine tumors with successful results in diagnosing ectopic pituitary adenoma (Naswa *et al.* 2012, Yang *et al.* 2017). The primary thyroid cancer associated with central hyperthyroidism presents as intranodular hypoecho and vascularization in ultrasonography and 'cold' nodule in thyroid scan. The nodule FNAB will be of value for diagnosing thyroid cancer (Paragliola *et al.* 2011, Perticone *et al.* 2015).

Treatment

Administering SSAs, ATDs and beta-blockers before surgery can control thyrotoxicosis, which reduces the risk during surgery (Beck-Peccoz *et al.* 2009). The optimal surgery strategy in patients of TSHoma with coexistent DTC has not been established (Calle-Pascual *et al.* 1991, Kishida *et al.* 2000, Perticone *et al.* 2015). Thyroid surgery is performed before pituitary adenomectomy in some cases, even if it could lead to a progression of TSHoma (Calle-Pascual *et al.* 1991, Perticone *et al.* 2015). On the contrary, performing pituitary adenomectomy before thyroidectomy may avoid a theoretically possible growth of the TSHoma and remove a stimulus for DTC progression (Kishida *et al.* 2000). Another reason for this strategy is that performing pituitary surgery first could be helpful to control thyrotoxicosis as well as neurological symptoms induced by a large and/or invasive TSHoma quickly and effectively. Nevertheless, the therapeutic strategy should be individualized for every single patient, taking into account all the relevant associated comorbidities.

For PRTH patients with concomitant DTC, thyroidectomy is performed to remove the primary neoplasm. If patients have thyrotoxicosis, PTU is preferred because it inhibits deiodinase activity, which is expected to reduce the intracellular content of T_3 in peripheral tissues. The levothyroxine therapy should be conducted considering the clinical condition of these patients and imitating as much as possible the preoperative hormonal pattern for serum T_4 and T_3 even if optimal TSH suppression cannot be achieved (Paragliola *et al.* 2011). Other drugs of interest which can suppress TSH secretion include triiodothyroacetic acid and dopamine agonists (Aguilar Diosdado *et al.* 1991, Dulgeroff *et al.* 1992).

Hyperfunctioning metastases of DTC

Patients with thyroid cancer are generally clinically euthyroid, and the cancer itself is relatively hypofunctional compared to normal thyroid tissue. Hyperfunctioning metastases of DTC, however, occurs more frequently than previously thought. Although most hyperfunctioning metastases are FTC-derived, metastases from PTC can also induce thyrotoxicosis (Danilovic *et al.* 2015, Biyi *et al.* 2016). The major sites of hyperfunctioning metastases are pulmonary and bone (Haq *et al.* 2007, Nishihara *et al.* 2010, Biyi *et al.* 2016), and the rare metastases site of the liver was also reported (Takano *et al.* 2006, Kunawudhi *et al.* 2016). According to the study of Qiu, 0.71% DTC patients present with hyperfunctioning metastases, and the 10-year survival rate of patients with hyperfunctioning metastases was 65.79%, patients younger than 45 years at occurrence of distant metastases, those with only lung metastases, and patients with PTC had better prognoses (Qiu *et al.* 2015).

Mechanism

Iodine-induced thyrotoxicosis due to an underlying defect in intrathyroidal iodine regulation, which is referred to as Jöð-Basedow phenomenon, may also exist in DTC metastases (Lorberboym & Mechanick 1996, van Der Molen *et al.* 2004, Mackie & Shulkin 2005).

As described earlier, DTC cells are derived from thyroid follicular cell, and express TSHR as normal thyroid cells do. The TSHR in metastatic DTC, then, acts as an antigen of TRAb, and the TRAb, in turn, stimulates the metastases to produce thyroid hormones (Yoshimura Noh *et al.* 1997). In addition, the presence of a base substitution at codon 633 in exon 10 of the TSHR gene in thyroid cancer cells can constitutively activate the cAMP cascade and thereby play a role in cancer hyperfunction (Russo *et al.* 1997). Another possibility is that cancerous thyroid tissue itself is capable of causing overproduction of thyroid hormones. In cases of metastases that induce thyrotoxicosis, metastatic tumors are usually bulky, suggesting that a large mass of cancerous thyroid tissue is necessary to overproduce thyroid hormone (Sundaraiya *et al.* 2009, Tan *et al.* 2009).

Generally, iodothyronine deiodinases are expressed in various normal organs or benign thyroid nodules, but low expression in PTC (Bianco *et al.* 2002, de Souza Meyer *et al.* 2005). Whereas some cases of FTC with multiple large metastases demonstrated a decrease in FT_4 accompanied

by an increase in FT₃, resulting in T₃ thyrotoxicosis, which may be due to high activities of deiodinases in massive metastatic follicular cancers (Takano *et al.* 2006, Miyauchi *et al.* 2008). Recently, this mechanism has been further confirmed by molecular targeted therapy of radioiodine refractory metastases from FTC, which demonstrated that lenvatinib and sorafenib could rapidly control thyrotoxicosis by inhibiting D1 and/or D2 activity (Danilovic *et al.* 2015).

Diagnosis

Measurement of serum thyroglobulin levels is important to monitor DTC metastases, which are commonly located in lung, bone and liver (Miyauchi *et al.* 2008, Tan *et al.* 2009). Although chest and abdominal CT, MRI or ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET/CT have been used to rule out the possibility of metastases from other organs, metastases biopsy accompanied by pathological examination is most reliable to verify the origin from thyroid.

In patients with hyperfunctioning DTC metastases, elevated serum thyroid hormones and suppressed TSH are usually found. Interestingly, metastatic FTC commonly presents T₃ predominant (Rosario *et al.* 2005, Takano *et al.* 2006). Certain criteria should be met to reach a diagnosis of thyrotoxicosis due to the overproduction of hormones by metastatic tissue: (a) the exclusion of hyperfunctioning thyroid goiter; (b) the demonstration of uptake function of metastatic lesion; (c) failure of thyrotoxicosis to resolve after adequate thyroidectomy and (d) thyroid hormones levels still higher than normal without excessive exogenous levothyroxine intake after thyroidectomy.

According to the above mechanisms of hyperfunctioning DTC metastases, several etiologic diagnoses of thyrotoxicosis may be involved including iodine-containing compounds, DTC metastases *per se* and/or via TRAb and deiodinases. If thyrotoxicosis happened in patients with DTC metastases who received an imageologic examination or amiodarone due to cardiac disorder recently, the diagnosis of iodine-containing compound induced thyrotoxicosis in DTC metastases should be firstly considered. Otherwise, an elevated TRAb level supports the diagnosis of TRAb-induced thyrotoxicosis in patients with DTC metastases. To date, thyrotoxicosis in DTC metastases caused by deiodinases is difficult, since the measurement of deiodinases activity is not readily available.

The hyperfunctioning metastases of DTC generally are well differentiated, displaying excellent

^{99m}Tc-pertechnetate and ¹³¹I uptake (Chantadisai & Kingpetch 2014). As we have demonstrated previously, ^{99m}Tc-pertechnetate whole-body scan should be recommended for diagnoses as well as predicting the efficacy of ¹³¹I therapy (Liu *et al.* 2017). Figure 1 shows practical management procedures of a representative case with hyperfunctioning DTC metastases.

Treatment

The therapy for DTC with hyperfunctioning metastases is aimed at treating both the thyrotoxicosis and the neoplastic disease itself, as both are major causes of morbidity and mortality. Treatment of thyrotoxicosis with ATDs is often temporarily effective, whereas normalization of hormonal values and prompt clinical recovery can usually be achieved by ¹³¹I therapy after total thyroidectomy (Salvatori *et al.* 1998) (Fig. 1).

Before ¹³¹I treatment of metastases, patients are advised to undergo total or completion thyroidectomy to remove possible lesion(s) and eliminate the interference of thyroid gland when undergoing ¹³¹I treatment as well as avoid complications caused by destruction of excessive gland (Tan *et al.* 2009, Nishihara *et al.* 2010, Biyi *et al.* 2016). In addition, surgical debulking can be performed on any large and accessible metastatic lesions, which alleviates thyrotoxicosis to a certain extent (Geliebter *et al.* 2017). For the hyperfunctioning metastases, thyrotoxicosis can be alleviated with ¹³¹I therapy despite a persistently low TSH level (Biyi *et al.* 2016). In the study by Kunawudhi and colleagues (Kunawudhi *et al.* 2016), the patient was injected with recombination human TSH (rhTSH) before ¹³¹I therapy. According to the American Thyroid Association guidelines for the treatment of hyperthyroidism, however, rhTSH should be avoided in these patients (Ross *et al.* 2016).

Based on previous studies, the prescribed activity of ¹³¹I to treat hyperfunctioning metastases of DTC varies from 13 mCi to 200 mCi (Tan *et al.* 2009, Nishihara *et al.* 2010, Kunawudhi *et al.* 2016). Although there is no clear criterion for the dose of ¹³¹I in treatment of functional metastases, it should be noted that high doses of ¹³¹I could cause a large amount of tumor cell destruction, releasing a burst of thyroid hormones and causing thyrotoxic storm if the patients were not prepared adequately before and after ¹³¹I treatment.

To avoid the occurrence of thyrotoxic storm that could become more frequent in seriously ill patients, glucocorticoids and ATDs (prefer PTU) should be used prior to surgery and ¹³¹I treatment, as well as during ¹³¹I

Figure 1

Representative diagnosis and treatment procedures of a case with hyperfunctioning metastases of differentiated thyroid cancer. A 67-year-old female, who had received 'thyroid adenoma' resection due to compression symptoms and a 'hot' mass in thyroid radioiodine scan (A) with normal thyroid hormones and radioactive iodine uptake (RAIU) 24 years before, was referred to our hospital for further management of severe weight loss and heart failure. Since robustly enhanced thyroid hormones (T₃-predominant) and undetectable TSH but normal RAIU were identified, ^{99m}Tc-pertechnetate whole-body scan (WBS) was performed, which displayed abnormal uptake in chest with thyroid remnant accumulation (B). ^{99m}Tc-pertechnetate SPECT/CT was then immediately added, which revealed multiple ^{99m}Tc-avid pulmonary nodules suggesting metastases from DTC (C). Six weeks after the beginning of the medications of propylthiouracil (PTU, 100 mg, tid, p.o.) and propranolol (10 mg, tid, p.o.) when symptoms and signs relieved, complete thyroidectomy was performed with the above medications sustained for another 2 weeks. After 2 weeks of withdrawal of PTU only, the levels of thyroid hormones increased significantly, demonstrating the diagnosis of hyperfunctioning DTC metastases, a 3.7 GBq (100 mCi) of ¹³¹I was administered accompanied by prednisone (40 mg, tid, p.o.) for 3 days and then switched to PTU (200 mg, tid, p.o.) and propranolol (20 mg, qid, p.o.). Post therapeutic WBS combined with ¹³¹I SPECT/CT exhibited robust ¹³¹I accumulation in the pulmonary lesions (D, ¹³¹I WBS; E, ¹³¹I SPECT/CT fusion imaging). Definitive therapeutic effects were verified by shrinkage of metastases, relief of heart failure (F, computed tomography before initial ¹³¹I therapy; G, computed tomography six month post initial ¹³¹I therapy), decreasing levels of thyroid hormones and subsequent levothyroxine replacement (H), warranting more courses of ¹³¹I therapy. A full colour version of this figure is available at <https://doi.org/10.1530/ERC-19-0129>.

treatment via inhibiting thyroid hormone synthesis and peripheral conversion of T₄ to T₃ (Cerletty & Listwan 1979). The recommended doses of glucocorticoids are 300mg/day hydrocortisone or 8mg/day dexamethasone (or equivalent doses of other glucocorticoids) (Bacuzzi *et al.* 2017). If the patient exhibits tachycardia and increased blood pressure, propranolol can then be used to control these comorbidities.

Hyperfunctioning lung metastases are found to be more sensitive to ¹³¹I therapy than those of bone, in which radiation therapy is an excellent alternative used to relieve symptoms (Qiu *et al.* 2015). In addition, since a small number of patients are accompanied by liver metastasis, which is less ¹³¹I-avid, preliminary debulking of a large liver metastasis by percutaneous interstitial

laser photocoagulation treatment followed by ¹³¹I therapy could achieve effective management (Guglielmi *et al.* 1999).

Others

Except for etiologies mentioned above, thyrotoxicosis induced by ATC, HCC and FVPTC have also been described (Kumar *et al.* 2005, Bommireddipalli *et al.* 2010, Ruggeri *et al.* 2013, Rees *et al.* 2015, Daroszewski *et al.* 2018). Additionally, painless thyroiditis-induced thyrotoxicosis has been reported to be associated with PTC (Valentini *et al.* 2016). Moreover, subacute thyroiditis associated with PTC has been found to mainly happened

Figure 2

Algorithm for differential diagnoses of thyrotoxicosis with concomitant thyroid cancer in patients with specific medical history. AIT, amiodarone-induced thyrotoxicosis; ATC, anaplastic thyroid cancer; CRP, C-reactive protein; DTC, differentiated thyroid cancer; ESR, erythrocyte sedimentation rate; FNAB, fine-needle aspiration biopsy; fT₄, free tetraiodothyronine; IHC, immunohistochemistry; n*, normal; PAX8, paired box gene 8; PTC, papillary thyroid cancer; RAIU, radioiodine uptake; T₃, triiodomethylamine; ^{99m}Tc, ^{99m}Tc-pertechnetate; ^{99m}Tc-MIBI, ^{99m}Tc-sestamibi; Tg, thyroglobulin; TgAb, thyroglobulin antibody; TPOAb, thyroperoxidase antibody; TRAb, thyrotrophin receptor antibody; TS, thyroid scan; TSH, thyrotrophin; TTF1, thyroid transcription factor 1; URI, upper respiratory infection; USG, ultrasonography; WBS, whole-body scan.

in older female and the tumors' size occurred in subacute thyroiditis varies from 0.05 cm to 1.2 cm (Gul *et al.* 2018). The prevalence of PTC occurring in subacute thyroiditis is 4.4% regarding a study with 137 patients, which may be much higher than previous finding of 0.43% (5/1152) (Nishihara *et al.* 2008, Gul *et al.* 2018).

Mechanism

The rapid growth of the primary tumor may cause non-specific thyroiditis, which has been deemed as the current mechanism of ATC induced thyrotoxicosis. However, reported cases of thyrotoxicosis associated with ATC show that the etiologies are non-specific, such as ATC associated with Graves' disease, autonomous thyroid nodules, and silent thyroiditis (Papapetrou & Jackson 1975, Mazzaferri *et al.* 1977, Mazzaferri 2000, Phillips *et al.* 2007), and the underlying mechanism for thyrotoxicosis with concomitant ATC remains unclear.

HCC of the thyroid is an infrequent neoplasm, and rarely trap iodine. HCC induces thyrotoxicosis primarily

because of a base substitution at codon 677. This *TSHR* mutant shows constitutive activity of cAMP, which may then be responsible for thyrotoxicosis (Russo *et al.* 1999). Thyroid cancer associated with scintigraphic 'hot' lesion may be explained by the presence of an incidental focus of nonfunctioning cancer cells coexisting within or close to the hyperfunctioning benign nodule or rarely, due to hyperfunctioning cancer cells *per se*.

For the mechanism of thyrotoxicosis with concurrent FVPTC, activation of the cAMP signal transduction system followed by the mutation of the TR gene, which is now thought to cause thyrotoxicosis, has been demonstrated in a great number of autonomously hyperfunctioning thyroid nodules (Bommireddipalli *et al.* 2010).

The mechanism of painless thyroiditis may be due to high dietary iodine intake (Caturegli *et al.* 2014). Cellular damage because of reactive alterations in stromal cells secondary to chronic inflammation has been recognized as the underlying mechanism of DTC development in patients with Hashimoto's thyroiditis (Farrell *et al.* 2017).

Although viral infections and genetic factors are assumed to be related to the etiologies of subacute thyroiditis (Luotola *et al.* 1998), the pathogenesis of subacute thyroiditis with concomitant DTC has not been illuminated.

Diagnosis

Patients with thyrotoxicosis accompanied by ATC usually present symptoms of thyrotoxicosis with neck swelling due to a rapidly enlarging thyroid mass. Elevated free thyroid hormones and suppressed TSH can also be found (Daroszewski *et al.* 2018). Thyroid ultrasonography provides rapid evaluation of the primary thyroid tumor, allows assessment of the involvement of central and lateral lymph node basins, and assists in evaluating airway patency. Neck and chest CT should also be performed to assess the extent of disease. If accessible, ^{18}F -FDG PET/CT is particularly valuable in evaluating metastases.

Only approximately 5% of HCC show 'hot' nodular lesions on the $^{99\text{m}}\text{Tc}$ -pertechnetate thyroid scan, and less

than 10% of HCC take up radioiodine. Furthermore, a discordance uptake in HCC exists between $^{99\text{m}}\text{Tc}$ -pertechnetate and radioiodine (Wong *et al.* 2003). In some cases of HCC, elevated thyroglobulin levels have been found, which could reflect recurrence of the malignancy. $^{99\text{m}}\text{Tc}$ -MIBI has been shown to be taken up by HCC, and the $^{99\text{m}}\text{Tc}$ -MIBI whole-body scan has been reported to be a sensitive marker for detecting metastases in those patients with elevated thyroglobulin (Yen *et al.* 1994). In addition, ^{111}In labeled octreotide scan has been utilized to investigate HCC since 1998 (Gulec *et al.* 1998).

The final diagnosis of FVPTC reported are based on postoperative pathological examination, since the features of thyrotoxicosis induced by FVPTC are similar to those in benign AFTNs (Wong *et al.* 2003, Smallridge *et al.* 2012, Rees *et al.* 2015).

Elevated levels of TPOAb and decreased RAIU can generally be found in painless thyroiditis with concurrent DTC. Ultrasonography demonstrates diffuse hypoechoic pattern in the thyroid gland, which made it impossible to differentiate nodular with irregular

Figure 3

Algorithm for differential diagnoses of thyrotoxicosis with concomitant thyroid cancer in patients without specific medical history. α-GSU, α-glycoprotein; CNB, core needle biopsy; CT, computed tomography; DTC, differentiated thyroid cancer; FNAB, fine-needle aspiration biopsy; FNAC, fine-needle aspiration cytology; FVPTC, follicular variant of papillary thyroid carcinoma; GD, Graves' disease; HCC, Hürthle cell carcinoma; ICTP, telopeptide of type I collagen; MLS, Marine–Lenhart Syndrome; MTC, medullary thyroid cancer; PRTH, pituitary resistance to thyroid hormone; RAIU, radioiodine uptake; SHBG, sex-hormone-binding globulin; SSAs, somatostatin receptor analogs; T₃, triiodomethylamine; $^{99\text{m}}\text{Tc}$, $^{99\text{m}}\text{Tc}$ -pertechnetate; Tg, thyroglobulin; TPOAb, thyroperoxidase antibody; TRAb, thyrotrophin receptor antibody; TRH, thyrotrophic hormone-releasing hormone; TS, thyroid scan; TSH, thyrotrophin; USG, ultrasonography; WBS, whole-body scan.

Table 1 Recommendations on the strategies for the management of thyrotoxicosis with concomitant thyroid cancer regarding each etiology.

Etiology	Diagnosis	Therapy
GD with concomitant DTC	TSH↓, TRAb↑; RAIU↑; TS: 'cold' nodule; US: GD signs (diffuse, bilateral and isthmus goiter, heterogeneous and hypoechogenicity parenchyma with hypervascularization in CDF) and malignant nodule signs (irregular margins of hypoechoic nodule with calcifications, taller than wide shape, evidence of ETE); nodule FNAB (+)	Surgery assisted by ATDs, beta-blockers, potassium iodine, corticosteroids, and cholestyramine ¹³¹ I administration for unresectable metastases
GD with concomitant MTC	TSH↓, TRAb↑, calcitonin↑, CEA↑; RAIU↑; TS: 'cold' nodule; US: GD and malignant nodule signs	Surgery assisted by ATDs and beta-blockers Adjuvant therapy (radiation therapy and molecular targeted therapy)
MLS with concomitant DTC	TSH↓, TRAb↑, RAIU↑; TS: 'hot' nodule; US: GD and malignant nodule signs; nodule FNAC (+)	Surgery with euthyroidism by ATDs and beta-blockers Subsequent ¹³¹ I administration if necessary
Plummer's disease with concomitant DTC	Long period of iodine deficiency, TSH↓, TRAb (n*); TS: 'hot' nodule(s); US: normal echogenicity with increased intranodular vascularization; CT/MRI: metastases/substernal goiter; nodule FNAB (+)	Surgery with euthyroidism by ATDs ¹³¹ I administration for unresectable metastases
AIT1 with concurrent DTC	Long history of arrhythmia and amiodarone administration; TSH↓, TRAb↑, TPOAb↑, TgAb↑; US: malignant nodule signs and parenchymal goiter, nodules and hyperecho with increased vascularity; ^{99m} Tc-MIBI: normal/increased parenchymal uptake	Discontinue amiodarone if possible Surgery assisted by ATDs, beta-blockers, potassium perchlorate, corticosteroids, and lithium carbonate alone or combination
AIT2 with concurrent DTC	Long history of arrhythmia and amiodarone administration; TSH↓, TRAb (n*), TPOAb (n*), TgAb (n*); RAIU↓; US: parenchymal hypoecho with reduced vascularity and malignant nodule; ^{99m} Tc-MIBI: decreased parenchymal uptake	Plasmapheresis for emergency
TSHoma with coexisting DTC	TSH (n*/↑), TRAb (n*), TPOAb (n*), α-GSU↑, ICTP↑, SHBG↑; T ₃ suppression test (–), TRH stimulation test (–); pituitary CT/MRI (+); ¹¹¹ In-DTPA-Octreotide: uptake in hypophyseal mass; SSAs test (+); TS: 'cold' nodule; nodule FNAB (+)	SSAs, ATDs and beta-blockers before surgery Pituitary adenomectomy and thyroidectomy
PRTH with coexisting DTC	TSH (n*/↑), TRAb (n*), TPOAb (n*), T ₃ suppression test (+), TRH stimulation test (+); pituitary CT/MRI (–); SSAs test (–); TS: 'cold' nodule; similar biochemical results in relatives; nodule FNAB (+)	Thyroidectomy assisted by PTU The levothyroxine therapy mimicking preoperative hormonal pattern TRIAC and dopamine agonists alone or in combination
Iodine-containing compound induced thyrotoxicosis by DTC metastases	Recent iodine-containing compound administration, thyroid surgery history (+/–); TSH↓, TRAb (n*), Tg↑; CT/MRI: metastases; ^{99m} Tc-pertechnetate/ ¹³¹ I WBS (+); metastases biopsy (+)	Stop intaking exogenous iodine-containing compound if possible Thyroidectomy with possible metastasectomy
Thyrotoxicosis induced by DTC metastases <i>per se</i> and/or via TRAb	Thyroid surgery history (+/–); TSH↓, TRAb (n*/↑), Tg↑; CT/MRI: metastases; ^{99m} Tc-pertechnetate/ ¹³¹ I WBS (+); metastases biopsy (+)	¹³¹ I therapy assisted by ATDs, corticosteroids and beta-blockers for unresectable metastases Debulking less ¹³¹ I-avid metastases
Deiodinases-induced thyrotoxicosis by DTC metastases	History of DTC, levothyroxine administration; TSH↓, T ₃ ↑, TRAb (n*), Tg↑; ¹⁸ F-FDG PET/CT (+), ¹³¹ I WBS (–)	TKIs (Lenvatinib and Sorafenib)
Thyrotoxicosis with concomitant ATC	Rapid growth of neck mass; TSH↓, TRAb (n*); ¹⁸ F-FDG PET/CT (+); nodule FNAB + IHC: Keratin (–/+), PAX8 (+/–), Tg (–), TTF1 (–/+), Calcitonin (–)	Surgery assisted by ATDs and beta-blockers if necessary Radiation therapy, chemotherapy, chemoradiation, TKIs (Sorafenib, Lenvatinib) and Fostretabulin for unresectable ATC
Thyrotoxicosis with concurrent HCC	TSH↓, TRAb (n*); TS: 'hot' nodule; ^{99m} Tc-MIBI: nodule uptake; ¹¹¹ In-DTPA-Octreotide: nodule uptake	
Hyperfunctioning FVPTC	TSH↓, TRAb (n*); TS: 'hot' nodule; nodule FNAC (+)	

(Continued)

Table 1 Continued.

Etiology	Diagnosis	Therapy
Painless thyroiditis associated with DTC	TSH↓, TRAb (n*), TPOAb↑; RAIU↓; US: parenchymal hypoecho with decreased vascularity and malignant nodule; nodule FNAB (+)	Surgery after controlling thyrotoxicosis with beta-blockers
Subacute thyroiditis with concomitant PTC	TSH↓; CRP↑, ESR↑; TS: not or poorly visualization, RAIU↓; US: parenchymal hypoecho and malignant nodule; FNAB (+)	Surgery after anti-inflammatory medications

α-GSU, α-glycoprotein; AIT, amiodarone-induced thyrotoxicosis; ATC, anaplastic thyroid cancer; ATDs, anti-thyroid drugs; CDF, color Doppler flow; CEA, carcinoembryonic antigen; CRP, C-reactive protein; CT, computed tomography; DTC, differentiated thyroid cancer; ESR, erythrocyte sedimentation rate; ETE, extrathyroidal extension; ¹⁸F-FDG PET/CT, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography; FNAB, fine-needle aspiration biopsy; FNAC, fine-needle aspiration cytology; FVPTC, follicular variant of papillary thyroid carcinoma; GD, Graves' disease; HCC, Hürthle cell carcinoma; ICTP, telopeptide of type I collagen; IHC, immunohistochemistry; MLS, Marine–Lenhart Syndrome; MRI, magnetic resonance imaging; MTC, medullary thyroid cancer; n*, normal; PAX8, paired box gene 8; PRTH, pituitary resistance to thyroid hormone; PTU, propylthiouracil; RAIU, radioiodine uptake; RRDTC, radioiodine refractory differentiated thyroid cancer; SHBG, sex-hormone-binding globulin; SSAs, somatostatin receptor analogs; T₃, triiodomethylamine; ^{99m}Tc-MIBI, ^{99m}Tc-sestamibi; Tg, thyroglobulin; TgAb, thyroglobulin antibody; TKIs, tyrosine kinase inhibitors; TPOAb, thyroperoxidase antibody; TRAb, thyrotrophin receptor antibody; TRH, thyrotrophic hormone releasing hormone; TRIAC, triiodothyroacetic acid; TS, thyroid scan; TSH, thyrotrophin; TSHoma, TSH-secreting pituitary adenoma; TTF1, thyroid transcription factor 1; US, ultrasonography; WBS, whole-body scan.

borders and microcalcification from inflammatory lesion. It is recommended to get another ultrasonography examination when the symptoms have resolved and laboratory values have recovered in order to rule out an underlying nodular disease (Nishihara *et al.* 2008). In cases with indeterminate thyroid nodule, FNAB is recommended (Valentini *et al.* 2016).

Swelling with pain in the thyroid gland are the clinical finding in patients of subacute thyroiditis associated with DTC. Elevated C-reactive protein, erythrocyte sedimentation rate, FT₄, and decreased TSH are commonly found (Nishihara *et al.* 2008, Gul *et al.* 2018). Not or poorly visualization thyroid in thyroid scan, as well as low RAIU are helpful to confirm the diagnosis of subacute thyroiditis (Fatourehchi *et al.* 2003). It is difficult to point out the coexistence of DTC with subacute thyroiditis, because unspecific focal with indefinite borders or diffuse hypoechoic parenchyma at initial ultrasonography could obscure the coexistence of tumor, however, microcalcifications in parenchyma and unnormal cervical lymph nodes are clues of suspicious malignancy in the presence of adjacent hypoechoic areas. Color Doppler flow is not particularly helpful for differential diagnosis between subacute thyroiditis and tumor, because approximately 30% of PTC are hypovascular and subacute thyroiditis only in the recovery phase presents slightly increased vascularization (Hiromatsu *et al.* 1999, Chan *et al.* 2003). Bekir Ucan *et al.* considered that elastography may assist in the diagnosis and monitoring of subacute thyroiditis as well as deciding biopsy requirement in subacute thyroiditis coexistent with suspicious nodules (Ucan *et al.* 2014). Owing to the characteristics of subacute thyroiditis with concurrent DTC, postponing assessment of the nodule until a complete recovery from subacute thyroiditis is

sensible. In addition, FNAB is indispensable in cases of lesions which are seen as a focal mass mimicking thyroid cancer.

Treatment

The treatment criteria for thyrotoxicosis associated with ATC has not yet been established due to its rare incidence, rapid progression, poor response to therapies and dismal prognosis. Even with intervention, survival benefits are limited (Kumar *et al.* 2005, Phillips *et al.* 2007, Daroszewski *et al.* 2018). ATDs and beta-blockers are generally administered to control thyrotoxicosis (Daroszewski *et al.* 2018). Management, however, remains most challenging for the primary tumor. Although in appropriate cases complete resection of tumor is the single intervention that improves survival, rather than debulking (Akaishi *et al.* 2011), the clinical presentation of ATC limits surgical treatment in the majority of patients (Heymann *et al.* 2005, Phillips *et al.* 2007, Daroszewski *et al.* 2018). Owing to improvement of central compartment palliation, surgery should be considered even in the presence of distant disease (Smallridge *et al.* 2012).

Reduced mortality and improved survival have been shown in postoperative radiation therapy with a radiation dose of >45 Gy (Pierie *et al.* 2002). For patients who are not suitable for surgery, the primary tumor, as well as metastases, can be treated palliatively with external beam irradiation (Heymann *et al.* 2005, Kumar *et al.* 2005).

Chemoradiation has been shown to be superior to radiation alone (Sugitani *et al.* 2012), and doxorubicin is the most commonly used drug. To improve the outcome, clinical trials have been conducted with several combinations. The commonly used combinations are

taxanes (paclitaxel or docetaxel) and/or anthracycline (doxorubicin) and/or platins (cisplatin or carboplatin), in combination with radiotherapy. Although the prognosis for most patients with ATC continues to be poor, multimodality therapy can significantly improve the survival (Akaishi *et al.* 2011).

With the best knowledge of ATC tumor biology, there are a few new drugs tested for ATC treatment, which may also be used in ATC patients associated with thyrotoxicosis. Sorafenib and fosbretabulin have been used in the treatment of ATC but show limited efficacy (Sosa *et al.* 2014, Thomas *et al.* 2014). Lenvatinib, another multikinase inhibitor, has demonstrated clinical activity and manageable toxicities in patients with ATC (Tahara *et al.* 2017).

Total thyroidectomy should be offered in patients with HCC. The efficacy of ^{131}I treatment is unclear because most HCC do not trap iodine. Patients with thyrotoxicosis induced by FVPTC can be treated with ATDs to attenuate symptoms and signs of thyrotoxicosis. In general, patients with FVPTC-induced thyrotoxicosis undergo near/total thyroidectomy; and ^{131}I is subsequently administered not only for postsurgical thyroid remnant ablation and/or metastases therapy but for convenient periodical surveillance as well (Bommireddipalli *et al.* 2010, Rees *et al.* 2015).

Thyrotoxicosis induced by painless thyroiditis is deemed to be caused by the preformed thyroid hormones released from the destructed follicular. Therefore, treatment with beta-blockers, rather than ATDs, is recommended. After clinical recovery, thyroidectomy can be performed to remove the primary tumor (Farrell *et al.* 2017).

Subacute thyroiditis is self-limited disease and often resolves spontaneously or may improve with anti-inflammatory medications (Jhaveri *et al.* 2003). Subsequent thyroidectomy with neck dissection if needed is the choice for thyroid cancer (Nishihara *et al.* 2008, Ucan *et al.* 2014).

Conclusion

The understanding of the causal relationship between thyrotoxicosis and thyroid cancer is critical for accurate diagnosis and appropriate treatment. After discussion of underlying mechanisms in terms of each etiology, efficient management means are recommended, yielding diagnostic mind mapping flowcharts with regard to the presence (Fig. 2) or absence (Fig. 3) of specific medical history and refined therapeutic strategies (Table 1).

For Graves' disease, MLS, AIT, Plummer's disease, central hyperthyroidism, painless thyroiditis or subacute thyroiditis associated with DTC, Graves' disease with concurrent MTC and primary hyperfunctioning thyroid cancer (HCC or FVPTC), surgery after controlling thyrotoxicosis with medications remains the first choice. If unresectable DTC metastases exist, adjuvant modalities major in ^{131}I therapy are needed. For hyperfunctioning DTC metastases, medications-aided ^{131}I therapy after thyroidectomy with possible metastasectomy remains a mainstay. In radioiodine refractory thyroid cancer patients who manifest thyrotoxicosis simultaneously, debulking approaches and molecular targeted therapy are promising to control thyrotoxicosis and prolong survival. For ATC accompanied by thyrotoxicosis, since ATDs and surgery merely relieve symptoms, radiotherapy, chemotherapy as well as neoadjuvant therapy are necessary.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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