Uncommon metastases from differentiated thyroid carcinoma

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Abstract

Differentiated thyroid carcinoma (DTC) usually behaves in an indolent manner with low metastatic potential. The major sites of distant metastases are the lung and bone. Metastases to the brain, eye, breast, liver, kidney, muscle and skin are rare or relatively rare. These metastases have almost always appeared in patients with advanced disease and are often associated with poor prognosis but overlooked in clinical practice. Recognizing them has a significant impact on clinical decision-making and prognosis of the patients. Treatment in these patients should be individualized and an alternative therapeutic approach should be considered. Care should be taken to determine whether a ^{131}I uptake focus found at an unexpected site of ^{131}I-whole body scan (WBS) is a DTC metastasis or a false-positive ^{131}I uptake. Imaging with ^{131}I-SPET/CT is of incremental value in the finding of rare metastases from DTC. *In conclusion*, DTC can have unusual metastatic presentations and patterns. Post-therapy ^{131}I-WBS and ^{131}I-SPET/CT play an important role in the management of patients with DTC.

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Introduction

Papillary (PTC) and follicular (FTC) thyroid carcinomas are follicular cell-derived carcinomas. They are differentiated forms of thyroid carcinoma and are characterized by slow growth and an indolent biological behavior. Eighty percent of differentiated thyroid carcinoma (DTC) patients respond to total thyroidectomy, radioiodine-131 (^{131}I) ablation and levothyroxine suppression treatment [1]. These cancers usually remain localized in the thyroid gland. Metastases are mainly to regional lymph nodes, followed by the lung and bone. When combined with distant especially widespread metastases, the quality of life is compromised and the overall survival rate is significantly decreased. Among the factors responsible for distant metastases and increased mortality in DTC patients are age over 45 years and the involvement of multiple organs, both of which are independently associated with cancer mortality [2]. DTC metastases to the brain, eye, breast, liver, kidney, muscle, and skin are rare or relatively rare and often overlooked in clinical setting. Rare metastases have almost always appeared in patients with advanced disease are often associated with a poor prognosis and recognizing them has a significant impact on clinical decision-making and prognosis. In this review, we reviewed the relevant literature of rare metastases developing after DTC with emphasis on ^{131}I whole body scan (^{131}I-WBS) and ^{131}I-single photon emission tomography/computed tomography (^{131}I-SPET/CT) and discussed their clinical features, diagnosis, treatment and prognosis.

Head metastases

Brain metastases

Brain metastases are extremely rare; however, the brain was the most frequent locus of secondary metastases from DTC in a study of a large cohort of patients [3]. Researchers have noted that approximately 18% of patients with distant metastases from PTC developed brain metastases during their disease course. Brain metastases occur more frequently in the cerebral hemispheres, while other sites for intracranial metastases are the cerebella and pituitary. Cerebellar metastases are exceptional, to our knowledge, only six cases were reported in the literature. Two were in the cerebellopontine angle [4, 5] and four in the cerebellar hemisphere [6-9]. There have been 12 well-documented case reports on pituitary metastases so far [10-20]. In most cases, brain metastases are asymptomatic, and only a few have suggestive symptoms, including headache and numbness of feet. Three instances of hypopituitarism have been reported [12-14].

Brain metastases from DTC rarely accumulate radioactive iodine, presumably due to the blood brain barrier or to being less differentiated than the primary tumor [21]. In such cases, the ^{131}I scan may not be reliable. A high serum thyroglobulin (Tg) may be helpful but not specific, as it is usually high in all metastatic DTC. If there is a suspicion of brain metastasis, we strongly argue the need for a head computed tomography (CT) or magnetic resonance imaging (MRI) (Fig. 1), which would provide a more accurate diagnosis.

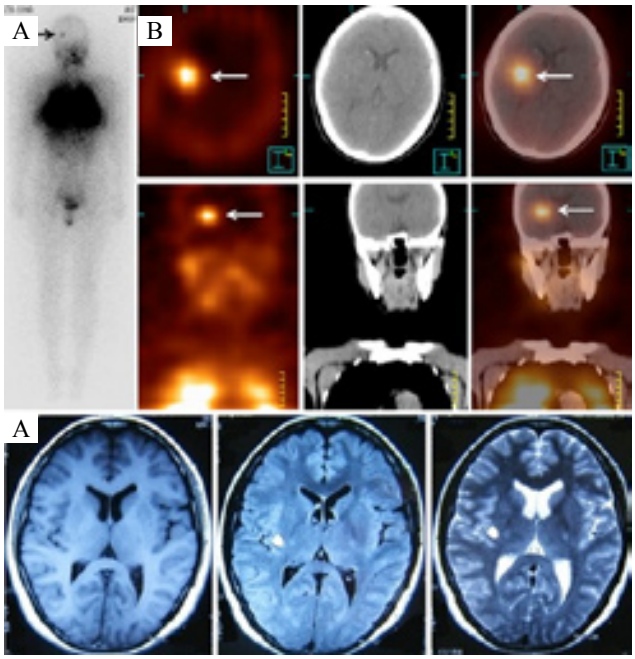

Figure 1. A patient with lung metastases was treated with ^{131}I. Posttherapeutic ^{131}I-WBS showed intense ^{131}I uptake in the lungs. There is a small and faint ^{131}I accumulation lesion in the right brain (A, arrow), which could have been easily overlooked. The subsequent ^{131}I-SPET/CT revealed that was a small ^{131}I-avid mass in the right brain (B, arrows) and MRI further demonstrated that it was a small lesion in the right brain of basal ganglia (C), which corresponded well to the ^{131}I-SPET/CT images and could precisely localize the foci of ^{131}I uptake.

There is no clearly defined protocol concerning the management of intracranial metastases from DTC, which is possibly due to their rarity. Surgery, radiotherapy [22], and ^{131}I treatment have been used with varying results. According to our experiences from a solitary lesion, the best therapeutic option seems to be surgery resection and gamma knife radiotherapy. Patients with DTC who underwent resection of one or more foci of brain lesions had longer survival than those who did not [23]. Treatment with ^{131}I is recommended for ^{131}I-avid brain metastatic lesions. Chemotherapy has only a limited role.

There is a general consensus that brain metastasis is a negative prognostic factor with a tendency for recurrence [9] and thus, a close follow-up is mandatory.

Eye metastases

Ocular spread carcinoma of DTC is unusual, with a predilection for the orbit rather than the globe and uvea [24]. Researchers have reviewed 520 cases with uveal metastases and found only two cases with choroidal metastases originating from the thyroid [25]. Within the uveal structure, the choroid is more commonly involved than iris. In reviewing the literature, we found reports of 13 clinically well-documented cases of choroidal metastases [26-38] and 4 cases of iris metastasis [30, 39-41]. Eye involvement typically presents in the setting of widely disseminated metastatic disease. However, ocular lesions as the initial presentation can occur, and in such instances, a thorough search for additional sites of metastatic disease is recommended. Researchers have described a case with no prior diagnosis of thyroid malignancy presenting with red iris, choroidal and skin metastatic lesions [30]. Others reported another patient of PTC, who initially presented with a choroidal metastasis [32]. Most of these subjects presented with unilateral ocular metastasis. Bilateral synchronous metastases is a rare occurrence and only four such cases have been documented [26, 27, 30, 31].

Related symptoms mainly include pain and impairment of visual ability. According to our clinical observation, reddish or orange color is a commonly observed feature of the uveal metastases from DTC. Eye metastasis may cause blindness with a rapid degradation of the patients' quality of life. Therefore, after abrupt or progressive changes in visual acuity, funduscopy examination and ocular ultrasound are recommended for identification and monitoring of ocular metastases. Fine-needle aspiration biopsy can offer the final diagnosis.

It is a clinical challenge the treatment of ocular metastases from thyroid carcinoma. Treatment with ^{131}I, although unlikely to cure the metastatic deposits, may be followed by improvement of vision and decreased size of the lesions [37]. In the case of ^{131}I-refractory tumors, as demonstrated by negative ^{131}I-WBS, ocular external beam radiation remains a therapeutic option [33]. Brachytherapy is particularly effective in administering a high-dose to a single lesion of small volume. Enucleation should be considered in the presence of a painful eye with secondary neovascular glaucoma [27]. These treatments may improve the patients' quality of life, and their life expectancy.

Due to the low incidence of ocular spread of metastases from DTC, it is important to recognize that DTC can metastasize to the eye, especially in the differential diagnosis of an ocular mass of unknown origin.

Neck metastases

Parapharyngeal metastases

Two relatively large number studies of DTC cases with parapharyngeal metastases have been described, suggesting that the incidence rate of parapharyngeal metastases is extremely low. One study presented parapharyngeal metastases in 3 of 696 DTC cases (0.43%) [42]. The other study was published by our team [43]. In this report, a total of 14 cases were found to have parapharyngeal metastases out of 561 DTC (2.5%) patients. Up to date, 37 cases from papillary [42-45] and 4 cases from follicular thyroid carcinoma [43, 46] have been reported.

The parapharyngeal space has roughly the shape of an inverted pyramid. Due to the expansive nature of the space, the clinical picture of a patient with parapharyngeal tumor is often nonspecific or asymptomatic when the tumor does not exceed 3.0cm in size [45]. Frequently, patients complain of a mass in the neck or the oropharynx that causes dysphagia. Rarely, patients are presented with a cranial nerve paresis, reflex otalgia, or trismus [44].

In our work, physical examination of the oral cavity with neck palpation was an important step to diagnose a parapharyneal tumor. However, as said before, only tumors larger than 2.5 to 3.0cm can be detected [42]. The ^{131}I-WBS has a higher sensitivity for finding DTC metastases than anatomic imaging modalities and ^{131}I-SPET/CT can offer an incremental diagnostic value [43, 47]. Peroral fine needle aspiration cytology is a simple, fast, and cost-effective method for the diagnosis of parapharyngeal metastases [45]. Surgery is an efficient treatment. The surgical approach for a parapharyngeal space neoplasm depends on the site and location of the mass, in relation to the major vessels [48]. For ^{131}I-avid patients, ^{131}I treatment can achieve better treatment outcomes.

Thorax metastases

Breast metastases

Metastases to the breast from extramammary primary cancer comprise only 0.5% to 2% of all breast tumors [49]. Mammary metastases from DTC are rarer. To our knowledge, only 7 cases have been described in the literature [50-56], all female, having papillary [50, 52-54] and 3 follicular types of DTC [51, 54, 56]. Breast metastases usually occur in the setting of disseminating metastases. However, researchers [53] reported a unique case of a follicular variant of papillary thyroid carcinoma (FV-PTC), with three cutaneous and one breast metastasis spread over a time of 11 years, in the absence of a locally invasive tumor or of other sites of dissemination.

It seems that metastatic disease to the breast tends to be superficial and usually located at the upper outer quadrant. Axillary lymph nodes may be involved. A firm breast lump, partially fixed to the chest wall, is the most common clinical manifestation. Differentiating primary mammary disease from metastatic may be difficult on clinical examination alone. In our diagnostic process, after knowing the history of patients, mammography or ultrasound examination may be suggested and is usually helpful. Although it is suggested that the presence of microcalcifications on mammography could potentially rule out metastatic disease to the breast [49], based on our clinical experience, DTC metastases to the breast may be accompanied by calcification, which needs further investigate. Immunohistochemistry plays an important role in the accurate identification of metastatic lesions.

To patients with breast metastases of DTC, we generally recommend surgical resection, which is the most effective treatment. Metastases which concentrate ^{131}I respond well to ^{131}I treatment.

Esophagus metastases

Esophagus metastases from DTC are an extremely rare event and only one case has been reported by Lee et al. [57]. It was one metastatic lesion from FTC that was detected by ^{18}F-fluordeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) scanning. The patient was a 55 years old male presented with persistently raising Tg levels despite negative ^{131}I-WBS. An initial ^{18}F-FDG-PET/CT scan showed moderate focal uptake in the upper esophagus, which was initially thought to be normal. However, a subsequent comparative ^{18}F-FDG-PET/CT scan showed more intense uptake. Finally, a diagnostic endoscopy revealed a 2.0cm pedunculated polyp in the esophagus, which histologically was metastatic FTC. This case highlights that ^{18}F-FDG-PET/CT has a role in ^{131}I-WBS negative patients with elevated Tg.

Abdominal metastases

Liver metastases

Differentiated TC very rarely presents with metastases to the liver and a reported frequency was 0.5% [58]. A review of the literature revealed that only ten cases have been documented. Three were males and seven females with an average age of about 63 years (range from 32 to 85 years). Histologically, the primary tumor was identified as papillary in four patients [59, 60], follicular in five [60-64], and Hűrthle cell TC in one patients [66]. In two cases, the metastatic histological type was inconsistent with the primary tumor. The primary tumors were FTC and PTC, while both their metastatic lesions were a FV-PTC [59, 60]. Transformation of histopathologic types may occur in liver metastases from DTC, therefore, a careful retrospective histological study is recommended.

Metastatic liver involvement from DTC is nearly always multiple or diffuse and is usually found along with other distant metastases. We found that most liver metastases from DTC were asymptomatic and were usually discovered incidentally. The ^{131}I-WBS combined with ^{131}I-SPET/CT scan plays an important role.

Surgical resection has been reported to offer the best chance for prolonged survival [67]. A unique treatment has been reported by other researchers [62]. It was the combination of percutaneous interstitial LASER photocoagulation and ^{131}I treatment, because the metastatic lesion was huge and surgically unresectable. The survival rate after liver metastases is poor; however, it cannot be attributed to liver metastases alone, because it generally appeared after more metastases at other sites.

Pancreas metastases

The pancreas is an organ where malignant tumors are almost always primary, metastases being very rare. To date, only 7 cases of pancreas metastases developing after DTC [50, 68-73] have been reported in the literature. They were all of the papillary type; five were conventional PTC [50, 68-70, 73] and 2 were of tall cell variant PTC [71, 72]. More interesting, among these patients, 6 were male and only 1 female with an average age of 61 years old (range from 34 to 82). In most cases, pancreas metastases developed several years after the primary tumor had been diagnosed. Researchers have described a unique patient whose thyroid gland was intrathoratic and initial clinical symptoms were due to pancreatic metastasis [50].

The common clinical symptoms include abdominal pain, fullness (abdominal distension), and anemia. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is recognized to be one of the most sensitive tests for the detection of both primary and metastatic lesions of the pancreas. It is capable of both detecting and facilitating the biopsy of small (less than 2cm) lesions within the pancreas [71].

In selected patients pancreatectomy for metastatic disease should be considered for alleviation of the symptoms and prolongation of survival.

Intestinal metastases

The intestine is a highly unusual destination for DTC metastases. Indeed, only 2 cases of PTC [70, 73] and 1 case of FTC [74] with metastases to the intestine have been described. Researchers [74] have reported a case of FTC metastasized to the sigmoid colon 17 years after initial treatment. Interestingly, except for increased Tg level, the patient remained asymptomatic; ^{131}I-WBS was negative as well as the CT scan, bone scintigraphy, and ^{18}FDG-PET scan. The location was detected by somatostatin receptor scintigraphy. Another case report described by other researchers [70] presented a patient with symptomatic anemia due to a bleeding duodenal metastasis from PTC. The patient was treated by partial duodenopancreatectomy. More interesting is a case with PTC presented with a hoarse voice and rectal bleeding. A barium enema revealed a lesion within the colon [73].

Our experience suggests that gastrointestinal metastases can be overlooked when using a traditional ^{131}I-WBS, because of the confounding presence of physiologic enteric radioactivity. For suspicious patients, ^{131}I-SPET/CT should be recommended for further examination, especially for patients with a high level of Tg. For DTC metastases invading the intestine, complete surgical resection followed by ^{131}I treatment offers an opportunity for palliation.

Renal metastases

Clinical detection of renal metastases from DTC is infrequent. To the best of our knowledge, only 25 cases have been reported in the literatures. Most of these subjects were female aged more than 45 years. Seven had conventional PTC, 6 had FV-PTC [75, 76], 11 had FTC and 1 had thyroid "adenoma" [77], which could have a highly differentiated FTC. Others [75] have reported the first and only case of metastatic PTC (microcarcinoma) to the kidney in a patient with wide metastatic dissemination (including renal, pulmonary and pelvic bony metastases). Autopsy showed that, in all DTC, the frequencies of bilaterality and multiplicity kidney metastases were as high as 71-81% [78]. Nevertheless, in our department, most of renal metastases from DTC were solitary and unilateral (Fig. 2). These metastases can be developed several years (occasionally decades) after removal of the primary DTC. This finding is consistent with the slow course of DTC. However, renal metastases as an initial presentation can occur and have been reported by others [79].

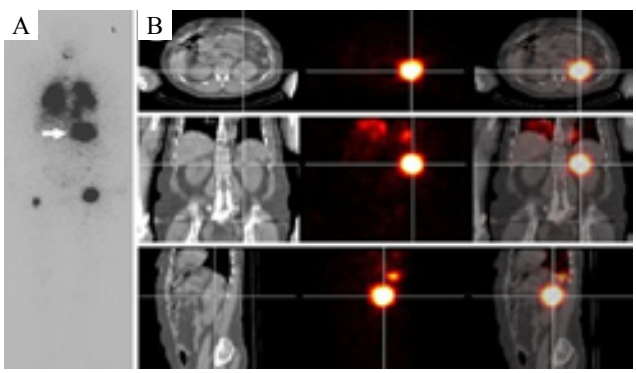

Figure 2. A patient with a history of FTC presented with lungs metastases and received ^{131}I treatment. Posttherapeutic ^{131}I-WBS images demonstrated bilateral lungs ^{131}I uptake. An additional area of high focal tracer uptake was noted in the left upper quadrant (A, arrow), which was initially thought to be related to the bowel. This was further evaluated with ^{131}I-SPET/CT and a lesion localized in the left kidney was revealed (B). The activities projected over the lower limbs were bone metastases.

In the few cases reported, patients have usually presented with hematuria, abdominal discomfort, or a renal mass. However, based on our experience, most patients are asymptomatic and (DTC metastases) are detected incidentally after posttherapeutic ^{131}I-WBS and/or ^{131}I-SPET/CT. Intense ^{131}I uptake by ^{131}I-WBS in the upper abdomen should not be simply assumed to be physiological gastrointestinal uptake or a false-positive finding. The presence of foci of ^{131}I accumulation in the renal bed area, especially a "star" effect due to a renal metastasis should be well investigated [76].

We recommend that a comprehensive treatment regimen, which includes resection of the renal lesion(s) and repeated high-dose ^{131}I treatment, should be instituted in patients harboring such metastases. This combined treatment modality may be useful in delaying disease progression.

Adrenal metastases

Adrenal gland is also an uncommon site for DTC metastases. There are 11 cases [79-84] documented in the literature. Five were of the follicular type, four were papillary and two were Hűrthle cell carcinoma. Others [80] have reported the first case of a patient with an adrenal metastasis secondary to Hűrthle cell carcinoma identified by ^{131}I-WBS. The adrenal metastasis is often associated with lung or bone metastases. Concomitant adrenal and renal metastasis from DTC is exceptional. Only two such cases have been reported [81, 83].

Usually, adrenal metastasis from DTC is asymptomatic. Most of them are detected by post-treatment ^{131}I-WBS. Thus, in the presence of a positive ^{131}I-WBS with foci of ^{131}I accumulation in the upper abdomen, a high index of suspicion of metastases to an intraabdominal organ should be raised and effectively excluded by correlative anatomical imaging or by ^{131}I-SPET/CT.

In general, surgical resection is recommended for solitary, resectable adrenal lesions [84]. Further therapeutic doses of ^{131}I can prolong the survival by delaying the disease progression or by ablating the lesion.

Ovarian metastases

The rarity of ovarian metastases from DTC is supported by review of the literature, where only three cases have been reported [85-87]. The first case was reported by others [85], who described a young woman with ovarian spread of FTC 12 years after the primary tumor had been removed. Because of the long interval since the thyroid cancer was diagnosed, the diagnosis of a malignant struma ovarii was initially considered. Others [86] presented another case of a PTC, which recurred as a cystic metastasis to the ovary 11 years after the original diagnosis. In this case, the initial clue was elevation of serum Tg, while ^{131}I-WBS identified the site of metastasis. Both of these cases were unilateral ovarian metastases from DTC. Bilateral ovarian metastases have been reported by others [87] in a 38 years old woman who underwent thyroidectomy 7 years before.

In the diagnosis of ovarian metastases of DTC, the possibility of false-positive must be ruled out. We have reported two cases with cystadenoma of the ovary [88, 89] occasionally found by ^{131}I-WBS and identified by ^{131}I-SPET/CT. It seems that ovarian metastases from DTC tend to occur many years after the primary tumor is diagnosed. Because of the long intervals, a woman with a cystic ovarian mass may usually suffer from benign cystadenoma of the ovary, struma ovarii and ovarian metastasis from DTC [90]. A history of prior thyroid carcinoma is critical.

Uterus metastases

Differentiate TC metastasizes so rarely to the uterus that only one case has been reported by researchers [91]. The patient was a 77 years old woman, who was performed a near-total thyroidectomy seven years before for an aggressive FTC. Histopathological examination at that time revealed extensive extracapsular and vascular involvement. Seven years later, she underwent a transabdominal hysterectomy and bilateral salpingo-oophorectomy because of an uterine tumor suspected of being endometrial cancer. However, the specimen was consistent with the diagnosis of Hűthle cell cancer metastatic to the uterus. The patient died six months later from widespread metastases and multi organ failure. This case illustrates the possible occurrence of DTC metastases to an unusual site.

Muscle and skin metastases

Muscle metastases

Although more than 40% of the human total weight is comprised of skeletal muscle, hematogenous metastasis to skeletal muscles is extremely rare. One hypothesis is that skeletal muscles are a hostile environment for the retention and proliferation of cancer cells, including muscle motion, unadapted pH and the muscle's ability to remove tumor-produced lactic acid [92]. Skeletal muscle metastasis from DTC is rare and tends to be found in patients with advanced-stage neoplasm (Fig. 3). A retrospective review of the literature revealed only 10 reports [93-95] of muscle metastases arising from DTC, 7 of papillary and 3 of follicular carcinoma. It seems that DTC is prone to metastasize to the erector spinae. Three of the 10 cases were erector spinae metastases and 2 of them were reported by our team [94, 95]. Muscle metastases are generally associated with other distant metastases. One elderly hyperthyroid patient was presented with single metastasis in the right biceps muscle without any other synchronous metastasis [92].

Skeletal muscle metastases usually are neither painful nor palpable; therefore, tend to be an incidental finding by post-therapeutic ^{131}I-WBS. A scan by ^{131}I-SPET/CT has great value in further identifying of the ^{131}I-WBS findings.

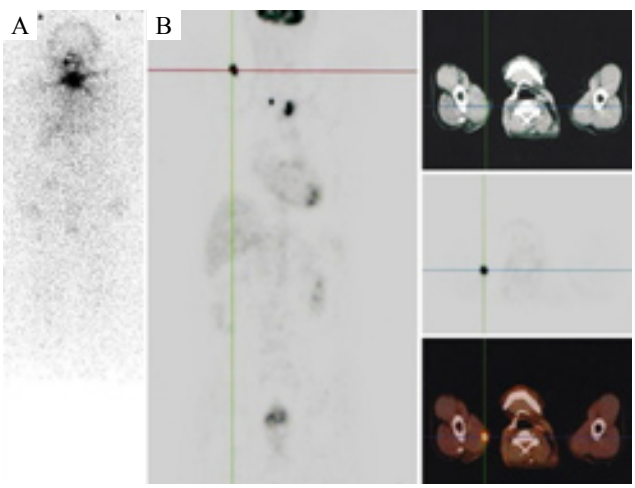

Figure 3. A patient with a history of PTC underwent a ^{18}F-FDG-PET/CT examination, because of a negative posttherapeutic ^{131}I-WBS image (A) but with elevated Tg level. Unsuspected muscle metastases were detected by ^{18}F-FDG-PET/CT (B, cross line). The ^{18}F-FDG-PET/CT was helpful in this case.

Skin metastases

Cutaneous metastasis from DTC is also a rare manifestation of disseminated DTC disease. A review on roughly 60 cases of DTC skin metastases, which have been documented in the literatures, stated that PC has a greater preponderance for skin metastases. These tumors arise with approximately equal frequency in men and women with a mean age of 63 years. They can be the initial manifestation of an occult thyroid cancer [96]. Dermal lesions typically present as slowly growing erythematous or purple plaques or nodules, usually on the scalp, face, or neck. Clinically, scalp is the most common site for cutaneous metastases. This may relate to local vascular factors essential for the highly complex nature of metastases [97]. The lesions may be solitary or multiple and are almost always asymptomatic. Ulceration is not common. However, researchers [98] have reported three clinically interesting cases of PTC presenting with skin ulceration. Cutaneous metastases in the genital area are extremely rare. Others [99] have reported the first case of ulcerated skin nodules in the scrotum from Hűrthle cell carcinoma of the thyroid.

Clinically, we suggest that the investigation of a flash color skin nodule, particularly in the scalp area, should include the possibility of metastatic DTC. This is most important when the patient has a history of DTC. Tests like ^{131}I-WBS and ^{131}I-SPET/CT are usually helpful. Fine needle aspiration biopsy of the suspicious lesions and application of Tg immunostain will readily provide the diagnosis.

The presence of cutaneous metastases in patients with DTC indicates a poor prognosis and most treatments are palliative. Recognizing and understanding the clinical findings may determine the overall management of the patients.

In conclusion, DTC, which ordinarily behaves in an indolent manner, can have unusual metastatic presentations and patterns. Post-therapy ^{131}I-WBS, ^{131}I-SPET/CT and Tg play an important role in the management of patients with DTC. As most of DTC metastases are ^{131}I-avid, ^{18}F-FDG PET/CT is generally not recommended. However, ^{18}F-FDG-PET/CT has a role in ^{131}I-WBS negative patients with elevated Tg. Reports related to DTC rare metastases are limited. Rare metastases from DTC may be not as rare as we once thought. Care should be taken to determine whether a ^{131}I uptake found at an unexpected site is a DTC metastasis or false-positive uptake.

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The authors declare that they have no conflicts of interest.

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