

Follicular Thyroid Carcinoma Metastasis to the Skull and Brain: Case Series with Literature Review

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ABSTRACT

Distant metastasis is more common in follicular thyroid carcinomas (FTC) than papillary thyroid carcinomas (PTC), as vascular invasion is often characteristic of FTC. Lung, bone, brain, liver, bladder, and skin are potential sites of distant metastases. On the other hand, lymph node involvement is much less common (8–10%) in cases of FTC compared to PTC. The therapy of patients may be significantly impacted by learning more about the epidemiological features of thyroid metastases at uncommon sites.

In our experience, metastases in uncommon sites do not always indicate a poor prognosis for differentiated thyroid carcinoma (DTC), which might be due to the disease patterns. Every year, around 5% new FTC patients are registered, treated with radioiodine, and followed up in the thyroid division of National Institute of Nuclear Medicine and Allied Sciences (NINMAS). Four FTC patients (F=3, M=1) with skull bone and brain metastases are discussed in this case series. All of them were post thyroidectomized and were referred to NINMAS for radioiodine ablation therapy (RAIT). Two of them had skull and brain metastases, third patient had extensive skull, facial bone and pubic bone invasion, whereas, fourth patient had multiple skull metastases.

Keywords: Follicular thyroid carcinoma, Skull metastasis, Brain metastases, Radioiodine ablation therapy.

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INTRODUCTION

Follicular thyroid carcinoma (FTC) is the second most common thyroid cancer after papillary carcinoma (PTC), making up 10–15 percent of all thyroid carcinomas (TC). FTCs are malignant epithelial tumors that show evidence of follicular cell differentiation but lack the diagnostic nuclear features of PTCs (1, 2). Both are well-differentiated thyroid carcinomas (WDTC), FTC

typically being more aggressive with a female-to-male incidence ratio of 4:1 and more likely to show distant metastasis compared to PTC (3). The incidence of distant metastasis in FTC has been reported to be 6-20%, with the bones and lungs being the most common locations (4).

Long bones, such as the femur and flat bones, particularly the pelvis and sternum, are more frequently involved in bone metastases from FTC, whereas the ribs, vertebrae and sternum are the bones most frequently involved in PTC (3, 4). Skull metastases from both FTC and PTC are extremely rare, accounting for only 2.5% of all bone metastases, the majority of skull metastases are from FTC, followed by PTC (5, 6).

In this article, we report on four unusual cases of skull metastatic lesions from aggressive FTC with poor outcomes and reviewed the pertinent literature.

CASE SERIES

This study is a retrospective review of four cases with unusually aggressive thyroid cancer variants. They all arrived at our institute for the first time between 2021 and 2022. During the analysis of each patient's chart, particular attention was paid to the following factors: 1) clinical presenting symptoms, 2) physical examination findings, 3) thyroid ultrasound, CT, and MRI scan findings, 4) preliminary cytopathology results obtained via FNAC or excisional biopsy, 5) thyroid specimen pathology post-operatively, 6) all treatments provided, and 7) final results in terms of local control and

disease-free survival. The nuclear medicine department received referrals for all 4 patients from other medical professionals in related fields. Two patients had an abnormal mass over the skull that later turned out to be an unusually aggressive form of FTC. Other two patients had no visible skull lesions.

CASE 1

A 45-year-old woman with no notable medical history presented with a longstanding swelling in the front of the neck and recent complaints of a severe headache. In April 2021, a non-enhanced CT scan of the brain suspected an atypical malignant meningioma with a large soft tissue component and a small intra-diploe component involving the left parietal bone with infiltration of the underlying leptomeninges (Figure 1). The differential diagnosis for this brain mass was osteosarcoma with soft tissue extension and histopathological correlation was recommended. The patient then underwent an MRI of the brain and the report revealed a strongly enhancing extra-axial mass along the left parietal bone with surrounding soft tissue (suspected intraosseous meningioma). The differential diagnosis was hemangiopericytoma (Figure 2). Upon resection of the skull tumour in June 2021, post-operative histopathology reported metastatic follicular carcinoma of thyroid origin. High resolution

ultrasound (HRUS) of the neck revealed a fairly big heterogeneous mass in the left lobe measuring about 65 X 36 mm and a tiny solitary nodule in the right lobe measuring about 3.0 X 2.2 mm (Figure 3). Total thyroidectomy was done in January 2022 and minimally invasive FTC was reported in histopathology. Upon registration at NINMAS, the patient underwent the pre-therapeutic investigations according to the Society of Nuclear Medicine, Bangladesh (SNMB) guideline (ref) including HRUS of the neck, 99m Technetium thyroid scan, radioactive iodine (¹³¹I) uptake and blood profile. Ultrasound showed few prominent lymph nodes on both sides of the neck. The largest node in level III of right neck measured about 29 X 11 mm. Faint radiotracer uptake in the left thyroid bed was present in ^{99m}Tc thyroid scan and ¹³¹I uptake was 3.6% (Figure 4). Laboratory tests revealed serum TSH=119 mIU/L, serum thyroglobulin (Tg)=14.2 ng/ml, anti Tg-antibody = 1.30 IU/ml. Serum Calcium and Parathormone (PTH) levels were normal. Even though the patient achieved the target serum TSH level for the administration of RAIT, a repeat non-contrast CT scan of the brain was recommended beforehand to check the status of the brain and skull lesion. As there was no evidence of residual brain lesion she received 150 mCi of RAIT safely with an uneventful stay in isolation.

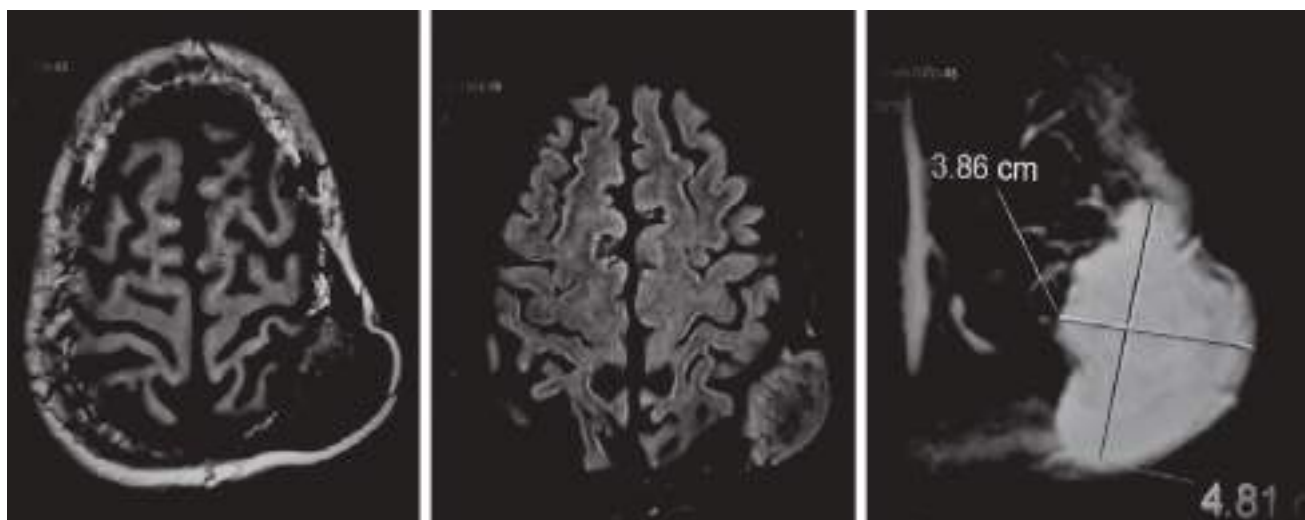


Figure 1: Pre and post contrast CT of brain showing large soft tissue lesion (48 X 39 cm) involving the left parietal bone with infiltration of the underlying leptomeninges

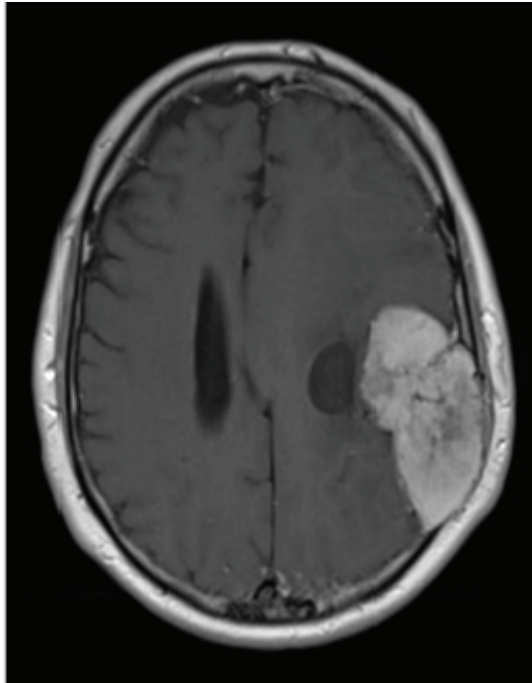


Figure 2: Collected contrast CT image of a hemangiopericytoma shared by Di Muzio B et al. to compare the similarity with the brain lesion of case 1 (see Figure 1)

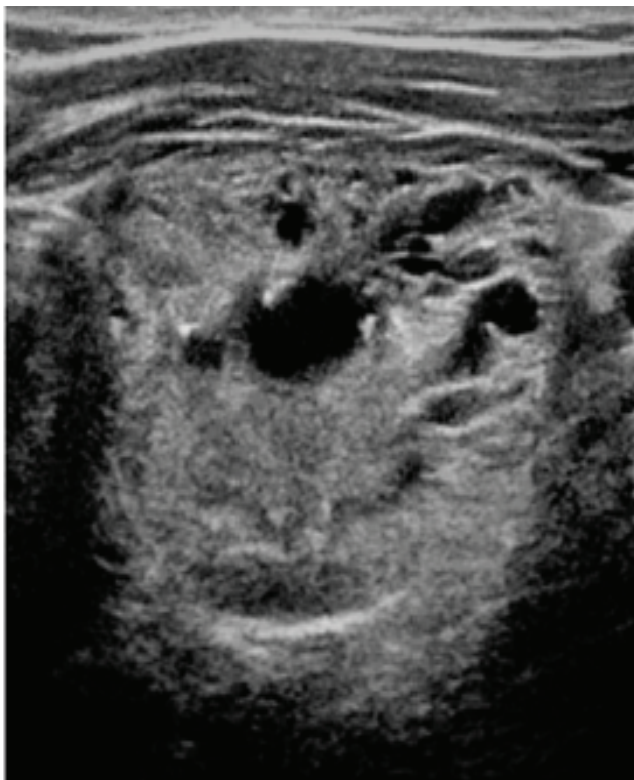


Figure 3: High resolution ultrasound image showing big heterogenous nodule (65 X 36 cm) occupying almost whole of left lobe of thyroid gland

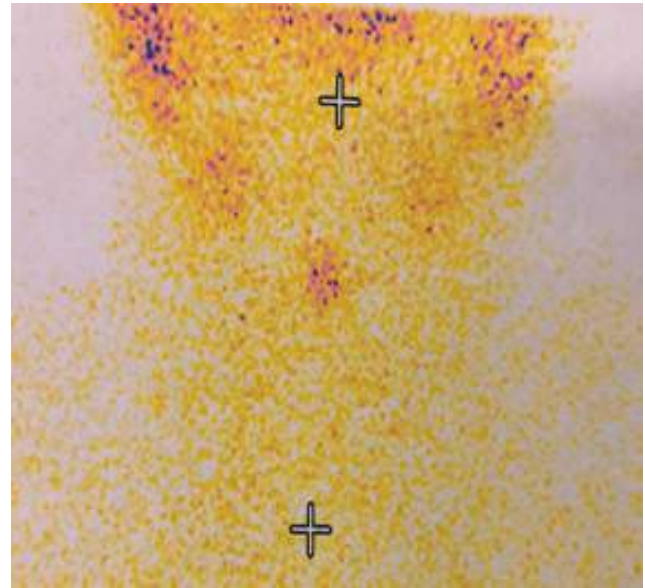


Figure 4: Post-thyroidectomy ^{99m}Tc scan showing faint tracer concentration at thyroid bed

CASE 2

A 32-year-old woman initially had a mass removed from her gum in October 2021. Histopathology reported a giant cell tumor of the buccal mucosa. The assigned clinician wanted to explore more. Abdominal ultrasound revealed mild splenomegaly (bipolar length 11.9 cm) and bilateral multiple renal calculi with bilateral nephrocalcinosis. HRUS of the thyroid gland showed mild thyromegaly with a mixed echogenic, predominantly solid, soft tissue mass posterior to the left lobe of the gland, measuring about 48 X 27 mm, which was suspected to be a parathyroid adenoma (Figure 5). Mild cardiomegaly in echocardiography and a few pus cells in a routine urine test were detected. Total thyroidectomy followed by histopathology in two different laboratories were done due to differences with diagnosis and ultimately convinced the diagnosis to be medullary thyroid carcinoma. So, the patient started thyroxine and steroids under the supervision of an otolaryngologist. Oncologist recommended a ^{99m}Tc-MDP whole-body bone scan which revealed increased tracer uptake in right and left mandible, left parietal, occipital, right occipito-temporal regions of the skull (Figure 6). Lesions were also found in the right pubic bone, that looked like infiltrative bony lesions. HRUS of neck revealed bilateral cervical and submandibular lymphadenopathy, whereas,

abdominal ultrasound was normal. Tumor marker for medullary carcinoma of the thyroid, serum calcitonin was <1 pg/ml (normal value 1-11.8 pg/ml) which was surprisingly low and made the clinician request for a re-check of the histopathology slides. Re-evaluation of the slides in a third lab of a different institute confirmed follicular carcinoma of the thyroid and repeated in a fourth lab for reconfirmation. Finally, the patient was diagnosed as a case of follicular carcinoma of the thyroid with multifocal capsular invasion and extensive bone metastasis. After being referred back to NINMAS her

pre-therapy investigations were partially done except radioiodine uptake and ^{99m}Tc thyroid scan as she was a nursing mother but unfortunately RAIT decision was postponed as brain metastasis was suspected. But later on CT scan of brain confirmed no brain involvement. (Figure 7) Also pre-therapy ^{99m}Tc thyroid scan revealed faint radiotracer uptake in the thyroid bed and ^{131}I uptake was 4.0%. The patient got 150mCi RAIT without any further complications. Her post therapy scan (RxWBS) showed single focal radiotracer concentration in thyroid bed. (Figure 8)

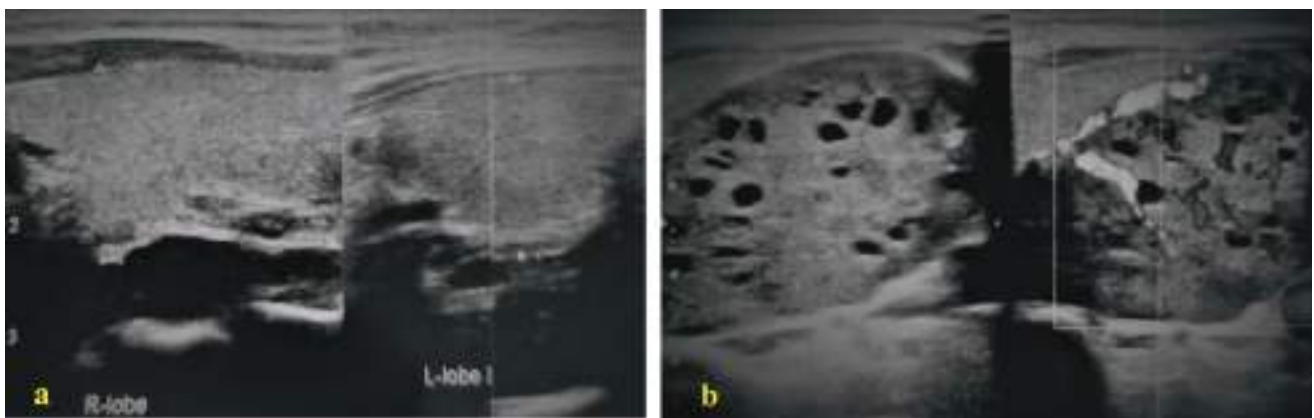


Figure 5: a) High resolution ultrasound image of intact lobes of thyroid gland & b) suspected parathyroid adenoma

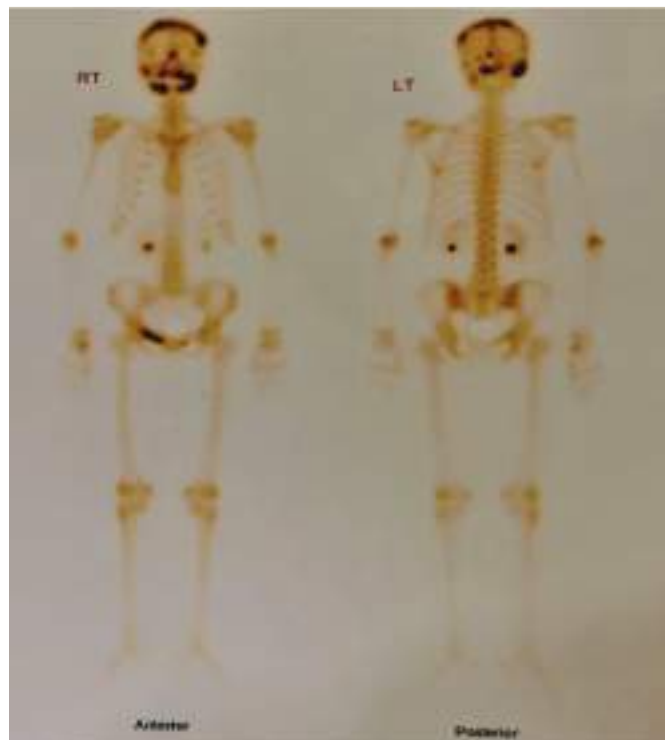


Figure 6: ^{99m}Tc Technetium-MDP whole body bone scan images showing increased tracer uptake in right and left mandible, left parietal, occipital, right occipito-temporal regions of the skull

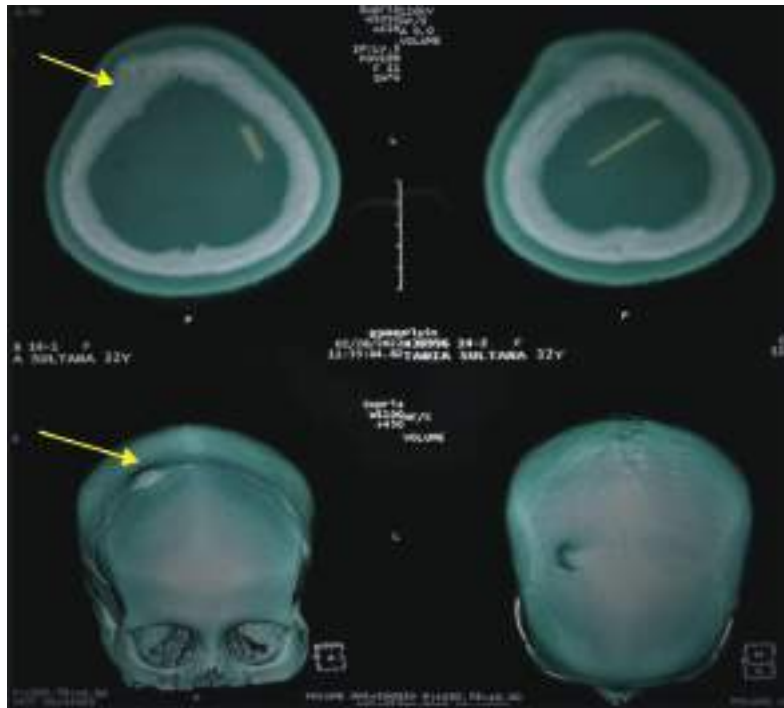


Figure 7: CT scan image of skull mass (yellow arrow) showing no involvement of brain

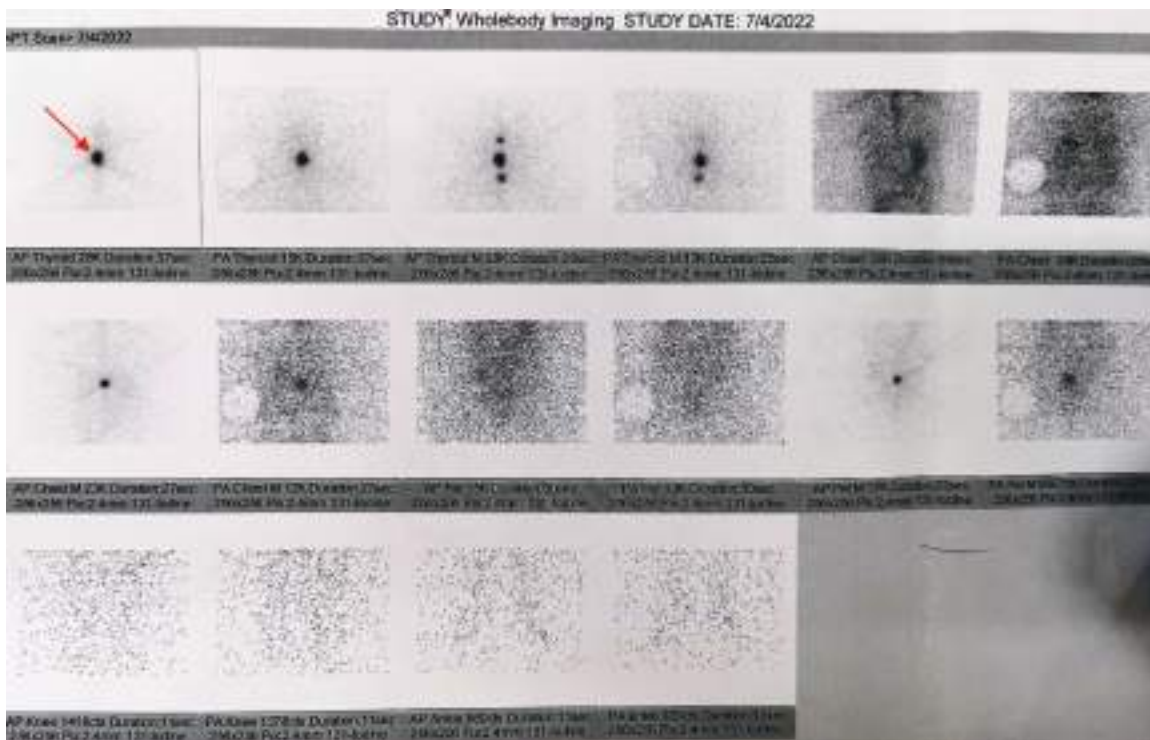


Figure 8: Post therapy whole body scan showing single focal radiotracer concentration in thyroid bed

CASE 3

A 55-year-old woman presented with a long-standing, untreated thyroid nodule that had been present for 10–12 years. Simultaneously, she had a gradually

growing swelling in the parietal bones over a period of 1–1.5 years, which she tried to treat with homoeopathic medications.

A team of head and neck surgeons performed a left hemi-thyroidectomy only, as the skull mass was un-resectable. Postoperative and pre-therapeutic investigations were started at NINMAS. A ^{99m}Tc thyroid scan and HRUS of the neck showed intact right thyroid lobe (Figure 9). Duplex ultrasound of the skull swelling revealed a large, irregularly outlined soft tissue mass with increased vascularity, measuring approximately 55 X 32 mm. Extensive skull erosion was reported in a

contrast-enhanced CT scan, where the large skull metastasis involved both parietal regions and invaded the adjacent parietal lobes of the brain (Figure 10). FNAC from the skull mass confirmed metastatic FTC. A significantly high level of circulating Tg (26678.0 ng/mL) was also discovered. RAI ablation could not be performed due to brain involvement. The patient was finally referred to an oncologist and treated with the oral Tyrosine Kinase Inhibitor (TKI), Lenvatinib.

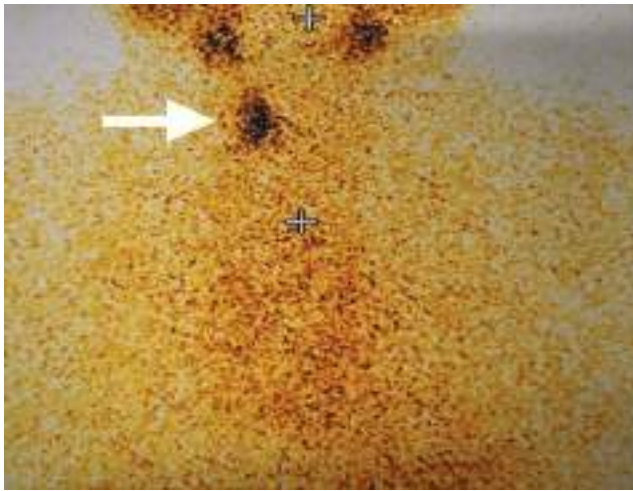


Figure 9: Postoperative ^{99m}Tc - thyroid scan image of a 55 year-old woman with an intact right lobe of thyroid gland.

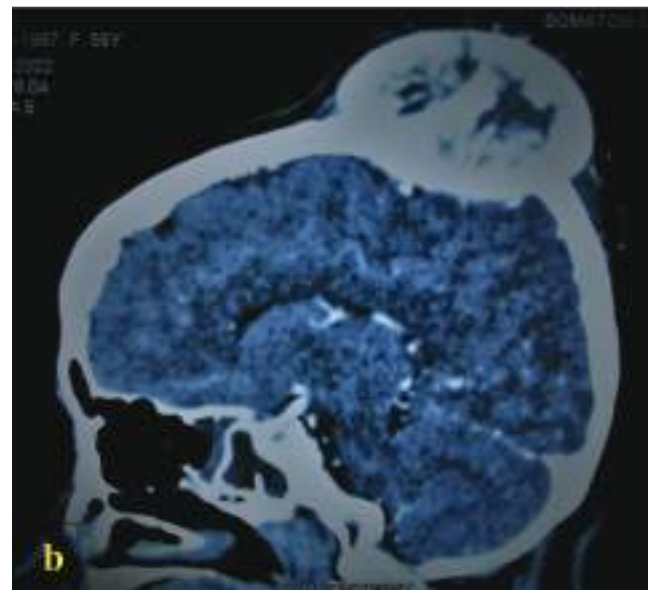


Figure 10: b) CT image of the lesion showing the heterogenous mass indenting deep to the skull bone and partially invaded brain



Figure 10: a) Fairly big, visible and palpable mass lesion on the parietal bone of skull.

CASE 4

A 46-year-old hypertensive man underwent hemi-thyroidectomy in 2015, which was reported as multinodular goiter. In 2019, he developed a scalp swelling in the occipital region. A CT scan of the brain showed a large expansile mass lesion, approximately 3.1 X 4.7 X 4.6 cm in size, in the right side of the occipital bone (Figure 11) which was more in favor of an intra-osseous meningioma. Excision of the mass revealed metastatic follicular carcinoma in histopathology. Completion thyroidectomy with central compartment clearance was done in 2019 followed by RAIT with 50 mCi of ^{131}I outside Bangladesh 1.5 months after the second surgery. Post-therapy scan (RxWBS) showed abnormal tracer uptake in the left thyroid bed with no distant metastasis. In 2020, a large-dose scan

(DxWBS) revealed functioning remnant tissue in the thyroid bed with skeletal metastases involving the skull and left clavicle. During follow-up in 2021, his TSH level was 0.9 mIU/Lon-levothyroxine), serum Tg was less than 0.2 ng/mL and anti-TgAb level was less than 1.30 IU/mL. Both the serum calcium and the serum parathormone were unremarkable. Neck ultrasound reported empty right thyroid bed but a 1.7X 1.1 cm sized hypoechoic area in the left thyroid bed. Follow-up CT scan of the brain showed no abnormality at the same time. Between 2020 and 2022, the patient received four additional RAIT doses (200, 150, 200, and 150 mCi, respectively) with a total of 750 mCi of ¹³¹I till now. However, the latest RxWBS in 2022 showed multiple small foci of tracer concentration in the skull, more in the occipital, parietal, and temporal bones, and also a single focal area at the sternal end of the left clavicle, while the thyroid bed being empty (Figure 12) and serum Tg level being normal (1.97 ng/ml).



Figure 11: Brain CT image of a 46 year old man showing a large expansile mass lesion in the right side of the occipital bone

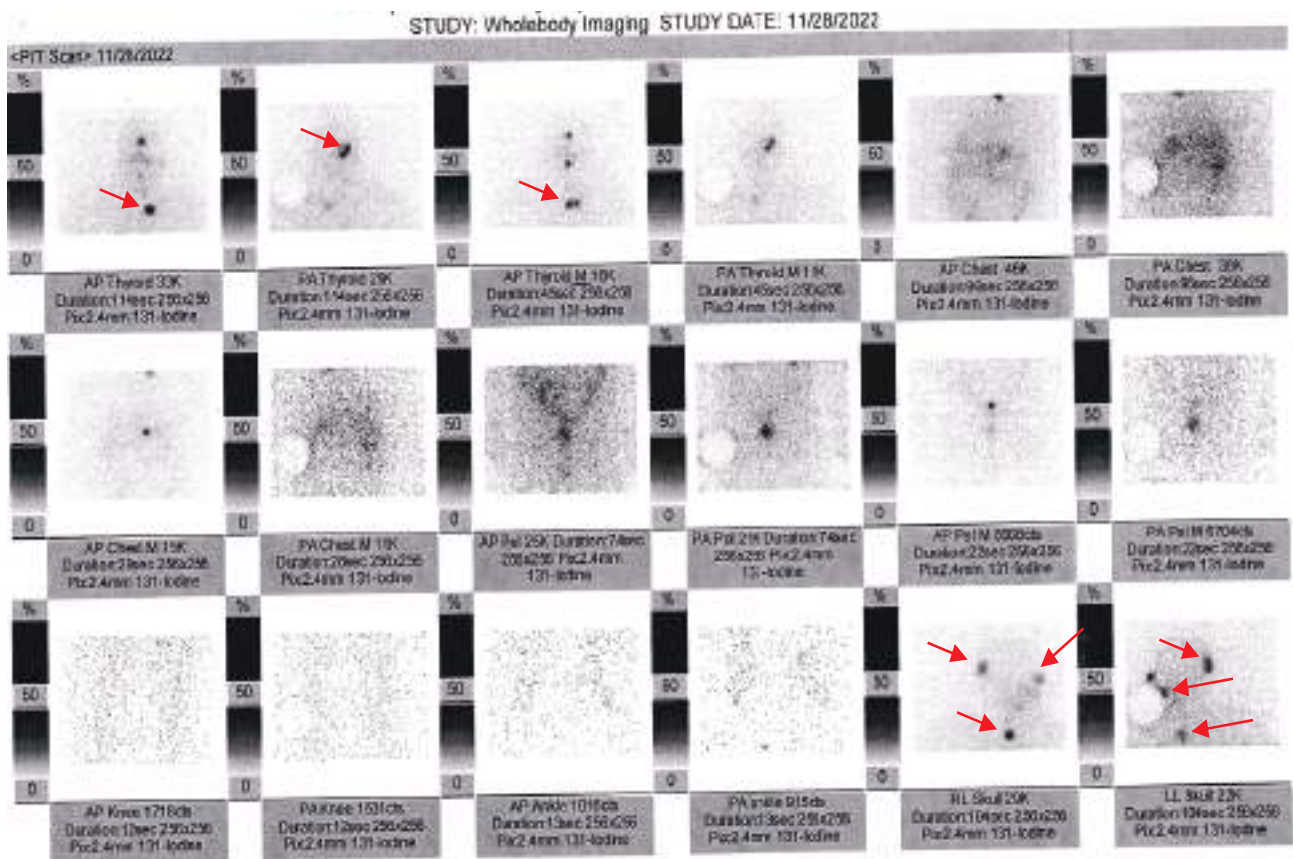


Figure 12: Post therapy ¹³¹I whole body scan (latest) showing empty thyroid bed with multiple small foci of radioiodine concentrations in the skull (more in the occipital, parietal, and temporal bones) and also a single focal area at the sternal end of the left clavicle.

DISCUSSION and LITERATURE REVIEW

Distant metastasis in DTC has been reported at 10–20% in various studies (4, 7, 8). FTC is the second most common subtype of DTC after PTC and accounts for around 10%–15% of all thyroid cancers. This subtype disseminates hematogenously via angioinvasion and metastasizes in advanced cases. The preferred metastatic targets include bone (25%) and lungs (49%), and the less common sites are brain, liver, bladder, and skin (2, 9). Flat bones such as the scapula, sternum and irregular bones like the ilium, vertebrae, and long bones are mostly affected (2, 10). By contrast, skull metastasis in FTC is extremely rare and has been reported in only a few case reports (7, 11, 12). Most authors found a single, quite large and protruding metastatic lesion in the skull, but there is only one report of multiple skull metastases (13). In this study, three cases had lesions only in the skull, with the largest lesion being 5.5 cm, whereas one patient showed multiple bony involvement. Three out of four cases received RAIT, while one patient with a huge unresectable skull and brain lesion did not. Patients reported no pain in their skull lesions, but one reported hip pain with long walks or prolonged standing. FTC typically shows a higher occurrence in women aged 40–60 years (1, 5), but this study demonstrated an age range of 32–55 (mean 44.5) years and a female preponderance (M = 1, F = 3).

Skull metastasis in FTC can be difficult to diagnose before operation, especially in single lesion, because of slightly high-density masses on CT. There are many overlaps between epidural metastasis and meningiomas (5,8,13). Clinical and imaging characteristics are somewhat similar in both epidural skull metastases of FTC and meningiomas, but the main difference is osteolytic destruction of the skull and subcutaneous tissue in the metastasis of FTC. Liu Y et. al found out that, in cases with osteolytic bone destruction and subcutaneous invasion occurring in the shape of a sandwich, cookie, or hamburger, first consideration should be the possibility of metastasis (13).

A contrast enhanced CT scan of the brain in Case 1 was suggestive of an atypical malignant meningioma with a

large soft tissue component and a small intra-diploe component involving the left parietal bone infiltrating the underlying leptomeninges. The differential diagnosis was osteosarcoma with soft tissue extension. MRI of the brain revealed a strongly enhancing extra-axial mass along the left parietal bone with surrounding soft tissue suggesting intraosseous meningioma or hemangiopericytoma. The second patient did not have a CT scan. Case 3 showed a large skull metastasis involving both parietal regions, invading the adjacent parietal lobes of the brain with extensive skull erosion. In the fourth patient, a large expansile mass lesion in the right side of the occipital bone was noted, which was more in favour of an intra-osseous meningioma. Whole-body bone scan with ^{99m}Tc MDP revealed increased tracer uptake in the right and left mandibles, left parietal, occipital, and right occipito-temporal regions of the skull, along with the right pubis, suggestive of infiltrative bony lesions in Case 2.

Two of the four cases underwent skull and brain mass excision, and histopathology confirmed metastatic FTC. The other two cases were diagnosed by FNAC at suspected metastatic sites. One of them had the skull defect reconstructed with a bone-impacted flap (Case 1). These metastatic lesions in the skull (Cases 1 and 2) and other bones (Case 3) correspond with the RxWBS findings too. Surgical-based treatment offers the best survival outcomes for isolated facial skeleton metastasis and a combination of metastatectomy, RAIT, EBRT and total thyroidectomy are regarded as most effective (10, 14, 15). However, total excision is impossible and hazardous in most cases. TSH suppression therapy is recommended for DTC, and central and lateral node resection is recommended for patients with palpable lymphadenopathy. Three of the patients presented here were treated with neck dissection followed by RAIT in high doses. NINMAS follows the SNMB protocol as the recommended guideline and usually 200 mCi ^{131}I is administered in cases of bone metastases from DTC (16)

Three patients in this series received RAIT; two of them were initially diagnosed with bone metastasis and received a single dose (150 mCi and 200 mCi,

respectively). One was diagnosed with bone metastasis later in therapy and had five doses of RAIT (a total of 750 mCi). One patient was unfit for RAIT, so she got none. Instead, this patient was referred to an oncologist and was treated with a Tyrosine Kinase Inhibitor. None of the patients has undergone EBRT for palliative purposes till date.

When the disease is limited to the thyroid gland, the overall 10-year survival rate is 90%; however, when cervical lymph nodes and/or distant sites are involved, this percentage is reduced to 70% and 20%, respectively (17, 18). Silaghi H et. al. reported that, DTC patients presenting with initial distant metastasis had relatively favorable outcomes compared with those, who developed after initial treatment. Two patients of this study also presented with initial metastasis and had better prognosis than the other patients who developed metastasis after initial treatment. RAIT, EBRT, chemotherapy, or palliative therapy can be considered in these patients (19, 20). Survival analysis suggests that surgical resection of involved craniofacial structures with or without adjuvant treatment is the optimal treatment for FTC metastases with convincing significance (21, 22). Treatment plans should be formulated with a multidisciplinary team involving surgical oncology, radiology, pathology, endocrinology, medical oncology, radiation oncology, and possibly palliative care.

Two-thirds of DTC patients with distant metastases would be classified as radioactive iodine-refractory (RAIR-DTC), evolving into a poor outcome (21, 22). Advanced or progressive RAIR-DTC is usually treated with multi-targeted tyrosine kinase inhibitors (TKIs). Lenvatinib and Sorafenib are FDA-approved first-line TKIs used worldwide, including Bangladesh (23). Case 3 was getting TKI as a last resort. Anti-angiogenic drugs, including single-targeted TKIs, are currently being evaluated as alternative therapy in the case of first-line TKI failure. (13, 22, 23)

CONCLUSION

The treatment of bone metastasis associated with FTC represents a tough challenge. Severe bone pain, areas of bony involvement, iodine non-avidity, late diagnosis, negligence and non-treatable cases are particularly

associated with poor prognosis. RAIT combined with total thyroidectomy and possible metastatectomy appears to be the most effective treatment protocol. However, total excision in most cases are not possible. EBRT in inoperable residual tumours and TKI in radioiodine refractory cases are helpful options. A multidisciplinary approach with early detection, appropriate doses of RAIT seems to improve the survival rate and quality of life of patients with bone metastases from DTC.

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