Case Report

Skull metastasis from follicular thyroid carcinoma: report of three cases and review of literature

Jun Shen1, Sufen Wang2, Xintong Zhao1, Xuefei Shao1, Xiaochun Jiang1, Yi Dai1, Shanshui Xu1, Xianwen Pan1

Departments of 1Neurosurgery, 2Pathology, Yi-Ji Shan Hospital of Wannan Medical College, Wuhu, Anhui, China

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Abstract: Three patients’ medical history, clinical manifestation, imaging characteristic, therapy and prognosis of calvaria metastasis from follicular thyroid carcinoma (FTC) in our hospital were retrospectively analyzed by reviewing medical literature. In case one, the tumor in frontal bone and fossa orbital was total resected, no further treatment was performed, the patient gave up on therapy and died of extensive metastasis at 22 months after the initial operation. In case two, the tumor in parietal and occipital bone was total resected, the subtotal resection of bilateral thyroid gland and isthmus was performed and combined with therapy of Levothyroxine and 131I radio-iodine therapy, no evidence of tumor recurrence at 30 months after the primary operation. In case three, the tumor in occipital bone was gross total resected, total resection of bilateral thyroid gland and clearance of lymph node was performed after two months, adjunctive therapy with Levothyroxine, 131I radio-iodine and skull radiotherapy, no evidence of tumor recurrence at 21 months after the primary operation. Correct diagnosis of calvaria metastasis from FTC preoperative is difficult because it’s rarity, patients can survive for years after synthetic therapy including total resection of metastatic tumor, radical operation of thyroid carcinoma, adjunctive therapy of Levothyroxine, 131I radio-iodine and skull radiotherapy.

Keywords: Thyroid carcinoma, papillary thyroid carcinoma, follicular thyroid carcinoma, calvaria, skull base

Introduction

The calvarium is a common site for metastasis, accounting for 15%-25% of all cancer patients [1]. The most common primary malignancy is breast cancer, followed by lung cancer, prostate cancer, and malignant lymphoma, but from thyroid cancers is extremely rare [1, 2], only a small number of reports are found in the literature. The largest series of skull metastasis from thyroid carcinoma described a frequency of only 2.5% among 473 patients. The majority of skull metastasis from thyroid cancers is of the follicular subtype [3]. Both skull base and calvaria can be invaded by thyroid carcinoma, it is hard to be diagnosed correctly preoperative for its atypical clinical manifestation and imaging findings. Primarily because of the rarity of skull metastasis with thyroid carcinoma, the role of standard postoperative therapy for this situation has not been definitively established. In this article, we report on three cases of skull metastatic lesions form follicular thyroid carcinoma (FTC) and reviewed the pertinent literature.

Cases report

Case 1

A 67-year-old man without remarkable medical history was found to have a painless mass in the right frontal region since 3 months and gradual blurred vision in the right eye since 7 months. Physical examination showed a palpable, immobile and hard tumor in right frontal region measured 2 cm in sagital and 2 cm in coronal directions and 0.6 cm in vertical dimension. Visual acuity test showed that the left eye vision was 1.3 and 0.8 vision in his right eye. Orbital computed tomography (CT) revealed an isodense tumor with osteolytic characteristic in the right frontotemporal region (Figure 1A, 1B), the magnetic resonance imaging (MRI) of the brain disclosed a 2.8×3.4×3.5-cm homogeneously enhanced, well-demarcated extradural mass (Figure 1C). A diagnosis of extroverted meningioma or metastatic carcinoma was taken in our consideration preoperative. The patient underwent a right frontotemporal craniotomy, after skin incision, a redness, hyper vascular,
soft mass was exposed, the tumor was invaded the sclerotin of right roof of orbit and frontal sinus and was strongly adherent to the dura mater, both the tumor and invaded bone were total resected and cranioplasty was performed with digital shaping titanium mesh which prepared preoperative (Figure 1D). Histopathological examination showed the diagnosis of metastatic FTC (Figure 2A, 2B). Immunochemical studies demonstrated that immunonegative for glial fibrillary acidic protein (GFAP) but some of the cells were immunopositive for thyroglobulin (TG) (Figure 2C, 2D). Postoperative course was uneventful, the patient manifested normal physical and mental development and no neurological deficits. The patient was discharged for refusing further treatment. The patient was admitted to another hospital again with thoracicodynia 20 months later, CT of the chest in the hospital revealed extensive disease including neck, stethidium and mediastina; she gave up on therapy and died 22 months after the initial surgery.

Case 2
A 61-year-old female presented to our hospital with a complaint of gradual exaggerated mass
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Figure 2. (A, B) Histopathological examination showed the diagnosis of metastatic FTC (HE×100). Immunohistochemical studies demonstrated that immunonegative for glial fibrillary acidic protein (GFAP) (×100) (C), but some of the cells were immunopositive for thyroglobulin (TG) (×100) (D).

Figure 3. A. MRI demonstrated an extradural tumor with bone destruction and enhanced homogeneously by gadolinium. B. Postoperative CT of brain revealed the tumor was total resected and cranioplasty by digital shaping titanium mesh was performed.
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in her right parietooccipital region in the last year. She had a history of thyroid adenoma and total excised at another hospital 3 years ago. Physical examination showed an 8.0 cm×8.0 cm, firm, painless, and immobile mass of the parietal and occipital area. MRI demonstrated an extradural tumor with bone destruction and enhanced homogeneously by gadolinium (Figure 3A). A tumor completely resection and cranioplasty by digital shaping titanium mesh was performed (Figure 3B). Intraoperative observation, a beige, abundant vascular, soft mass was found, the tumor adjacent to the superior sagittal sinus (SSS) and strongly adherent to the dura mater but not invaded it. Histopathological examination showed the diagnosis of metastatic FTC (Figure 4A, 4B). Thyroid ultrasonography was performed and revealed multiple nodules in the right thyroid lobe. The patient underwent a right total thyroidectomy and left near total thyroidectomy two weeks later. The histopathological examination confirmed the diagnosis of FTC and demonstrated that some of the cells were penetrated the thyroid capsule (Figure 5A, 5B). Postoperatively levels of thyroid hormones were normal. The patient received thyroid replacement therapy with 125 μg L-thyroxine daily and underwent adjuvant radioiodine treatment using $^{131}$I. The patient was discharged without discomfort or clinical symptoms. To date, she is alive without evidence of tumor recurrence or metastasis at 30 months after surgery.

Case 3

This healthy 67-year-old male was admitted to our emergency room with ulcerated and dura-tive bleeding in his occipital mass which gradu-
Figure 6. A. Head CT scan exhibited an occipital mass, 6.0 cm×8.0 cm in size, isodense with central necrosis, and with osteolytic destructive features. B. The tumor was gross total resected.

Figure 7. (A, B) Histological examination revealed the diagnosis of FTC and osseous tissue can be found encircled by some of the tumor cells (HE×100). The tumor cells were positive staining for thyroid transcription factor-1 (TTF-1) (×100) (C), and thyroglobulin (TG) (×100) (D).
al exaggerated in the last 4 months. A head CT scan exhibited an occipital mass, 6.0 cm×8.0 cm in size, isodense with central necrosis, and with osteolytic destructive features (Figure 6A). Intraoperative observation found a hypervascular, beige-colored mass, a large amount of blood was gushed out when we resect the tumor, about 2000 ml in a short time, the tumor was gross total resected (Figure 6B). Histological examination revealed the diagnosis of FTC with positive staining for thyroid transcription factor -1 (TTF-1) and thyroglobulin (TG), and osseous tissue can be found encircled by some of the tumor cells (Figure 7A-D). Thyroid ultrasonography revealed thyromegaly accompanied of multiple cystic-parenchyma lesions. Total resected of bilateral thyroid gland and clearance of lymph node was performed after two months, Histopathological examination showed the diagnosis FTC and the tumor cells penetrated the thyroid capsule and vessels (Figure 8A, 8B). The patient received thyroid replacement therapy with 125 μg L-thyroxine daily, underwent adjuvant radioiodine treatment using $^{131}$I, and skull radiotherapy to residual tumor. At present, the patient is alive symptom-free and without evidence of tumor recurrence or metastasis 21 months after the primary operation.

**Discussion**

Thyroid cancer is the most common endocrine malignancy and its incidence has been increasing dramatically throughout the world in the past few decades. Thyroid cancers are divided into four major histological subtypes, papillary, follicular, medullary, and anaplastic. The most common subtype of thyroid cancer is papillary thyroid cancer (PTC). The second most common subtype is follicular thyroid cancer (FTC). Together, papillary and follicular cancers are termed differentiated thyroid cancer (DTC) which accounts for 90% of all thyroid cancers [4, 5]. Despite an overall excellent prognosis and survival in patients of DTC, 5-23% of patients have distant metastasis, which confers on them a relative poor prognosis despite of adequate treatment [4, 6]. Bone was the most common single site for FTC and the second most common single site for PTC [6]. Bone metastases from FTC are more often to the long bones, such as the femur and flat bones, particularly the pelvis and sternum, the bones most often involved in metastasis of PTC are ribs, vertebrae and sternum, while skull metastasis form both FTC and PTC are extremely rare, accounting for 2.5% of all bone metastasis, the majority of skull metastasis from thyroid cancers is of the FTC, followed by PTC [3, 7, 8].

Calvaria metastases from DTC can occur at any age, the youngest patient was just 18 years old [9], but most patients are between 60 and 70 years old [3]. The age of patients with skull base metastasis from FTC ranges from 23 to 74 years (mean, 54.6 years), and that of those from PTC ranges from 35 to 73 years (mean, 53.5 years) [10]. Both calvaria and skull base metastases from DTC revealed a female pre-dominance [3, 10]. Mean period from initial diagnosis of thyroid carcinoma to calvaria...
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metastasis was 23.3 years, ranging from 4 to 52 years [3]. Mean period from initial diagnosis of FTC to skull base metastasis was 3.9 years, ranging from 0 to 18 years, mean period from initial diagnosis of PTC to skull base metastasis was 6.8 years, ranging from 0 to 18 years [10].

Anatomically, calvaria metastatic lesions are most frequently located at the midline of the frontal and parietooccipital region [9, 11-19], skull base metastatic lesions are most frequently located over the clivus [10, 20, 21], petrous ridge, sella turcica, sphenoid sinus, cavernous sinus and infratemporal fossa can also be found in the literature [10, 20-24]. To our best knowledge, metastatic DTC arising from the orbit communicate to frontal sinus (case 1) has not previously been reported, just two cases of DTC metastasis to the orbital have been described [25, 26].

The diagnosis of metastatic DTC of the skull base is a challenge prior to surgical intervention, to date, only 28 cases of skull base metastasis from DTC have been reported. The most common symptom of skull base metastasis from DTC is cranial nerve dysfunction. The metastatic lesion is usually revealed bone destruction and local invasion to the surrounding soft tissues on radiological examination, so that skull base metastasis from DTC is often mistaken as chordoma, chondrosarcoma, melanoma and other metastatic cancers [10, 20-29].

The calvarium is more favorite than skull base by DTC invasion, which usually presents as a soft painless slow growing scalp mass, growth of the disease causes the brain compression can result in increased intracranial pressure and neurological symptoms including headaches, neurological deficits, meningeal irritation, and seizures [3, 9, 11, 16, 30], it occasionally causes scalp ulceration and bleeding (case 3). Combined with our three cases, we reviewed the pertinent literature and summarized the radiological characteristics of calvarium metastasis from DTC. (i) most of the lesions were single, (ii) the tumors were total extradural and not invaded dura mater, but can invade the subcutaneous tissue, (iii) the lesions were oval or round-shaped with clear boundaries and revealed osteolytic feature, (iv) the tumors usually disrupt both the inner and outer tables of calvarium and the length-diameter of the tumor is longer than the bone defect, (v) the lesions mimicked a meningioma in both CT and MRI, and enhanced homogeneously, central necrosis can be found if the tumor growth voluminous [3, 9, 11-19, 31]. However, those features can also be found in other calvarium metastatic carcinoma such as hepatocellular carcinoma [32]. If a gradual exaggerated scalp mass with the radiological characteristics aforementioned, a diagnosis of calvarium metastasis should be taken in our consideration and the SPECT and biopsy should be performed [9, 12, 19].

Total or nearly total thyroidectomy and removal of as much of the metastatic lesions remain the first choice whenever possible, however, total excision in most cases of skull base metastasis is hazardous because of the presence of vital structures and profuse bleeding [3, 10, 16]. Bleeding is often profuse during surgical resection of calvarium metastasis which still interfered the tumor total resection [9, 16], in our case three, the tumor was just gross total resected for about 2000 ml of blood was gushed out in a short time when we resect the tumor. Adjunctive radiation with 131I and replacement therapy with L-thyroxine should be performed postoperative [3, 9, 11]. External radiotherapy should be administered for unresectable or residual tumors [3, 20]. Kotecha et al reported that Gamma Knife surgery (GKS) is an effective treatment modality for patients with metastases to the calvarial bones or skull base [1]. Patients with larger lesions near vital structures or in a previously irradiated field might benefit from the fractionated stereotactic radiation technique [2]. Measurement of circulating TG to predict the recurrence of the DTC during follow up may be useful [20]. Despite a synthetical therapy, the outcomes for patients with skull metastasis form DTC are relatively poor, Nagamine et al reported that the mean survival time was 4.5 years, ranging from 5 months to 17 years in a series of 12 patients [3]. Li X et al reviewed the previous reports and calculated that overall survival among patients undergoing definitive treatment ranged from 14 months to 3.5 years from the discovery of the skull metastasis, the survival of untreated patients was even shorter [12].

In conclusion, we further contribute to the literature on the rare occurrence of skull metastasis from DTC, discussed the clinical manifes-
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tation, imaging characteristics, differential
diagnosis and postoperative management, and
highlight that a systematical and multidisci-
plinary therapy of this rare entity should be
performed.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jun Shen, Depart-
ment of Neurosurgery, Yi-Ji Shan Hospital of Wannan
Medical College, Zheshan West Road on The 2nd,
Wuhu, Anhui, China. Tel: (0086) 553-5739594; Fax:
(0086) 553-5739594; E-mail: shenyuanziyan@163.com

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