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Case Presentation
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Metastasizing Noninvasive Follicular Variant of Papillary Thyroid Cancer: Case Report and Review of the Literature

*Jing Zeng[1], Jinjing Wang[1], Yanwei Hou[1], Juan Zhou[2], Fangni Chen[3], Yun Shao[4] and Yi Fang[1]**

[1]Department of Endocrinology, Fifth Medical Center of Chinese PLA General Hospital, China

[2]Department of Radiology, Fifth Medical Center of Chinese PLA General Hospital, China

[3]Department of Nuclear Medicine, Fifth Medical Center of Chinese PLA General Hospital, China

[4]Department of Pathology, Fifth Medical Center of Chinese PLA General Hospital, China

Abstract

Follicular Variant of Papillary Thyroid Carcinoma (FVPTC) is a hybrid between classic papillary and follicular thyroid carcinoma, with unique tumor features and clinical behaviors. We report a 52-year-old woman who presented with persistent shoulder and back pain accompanied by muscular atrophy of the left upper limb, intermittent headache, and with gradual aggravation for one year. The preoperative diagnosis was difficult and the final postoperative pathological diagnosis was FVPTC. After locoregional and systemic treatments, brain metastasis initially gradually shrank and disappeared, but lung, bone, and brain metastases finally enlarged. Eventually, she died of malnutrition and cachexia. FVPTC always shows benign sonographic features and atypical histological and cytologic characteristics. It is easy to misdiagnose. I-131 ablation may be insufficient in patients with FVPTC at high risk, but can alleviate clinical symptoms, reduce metastasis, improve quality of life, and prolong survival.

Keywords: Follicular variant of papillary thyroid carcinoma; FVPTC; Multiple metastases; I-131 treatment; survival; Papillary thyroid carcinoma

Introduction

Follicular Variant of Papillary Thyroid Carcinoma (FVPTC) accounts for 23% to 41% of PTC [1-3]. FVPTC was first described by Dailey et al. [4-6] in 1950, who characterized FVPTC as having the nuclear features of conventional PTC but with a follicular growth pattern. A definitive preoperative diagnosis of FVPTC based on fine-needle aspiration cytology is not possible, because signs of malignancy depend on the typical nuclear features of conventional PTC [7-9]. In addition, the features of benign and other neoplastic follicular lesions overlap, which can be affected by inter observer variability [10-12].

Patients with FVPTC or conventional PTC are treated similarly. The standard recommendation has been radioactive Iodine (I-131) ablation for all tumors ≥ 1 cm in diameter, and then thyroid stimulating hormone suppression and close follow-up [1,13,14]. FVPTC is noted as being less aggressive, with a lower incidence of thyroid capsule invasion, extra thyroidal extension, and lymph node metastases [3,15-17]. However, other studies found that FVPTC tended to have a higher rate of distant metastasis compared with conventional PTC [3,18-20], a higher rate of histologic vascular invasion, and during follow-up a higher rate of recurrence [18,21,22]. FVPTC patients with distant metastasis have a relatively poor outcome [23].

Here in, we report a case of FVPTC with several unique features including wide spread metastasis and difficult preoperative diagnosis. We also describe the comprehensive management of this patient.

Case Presentation

In early 2013, a 52-year-old woman presented with first symptoms of persistent shoulder and back pain accompanied by muscular atrophy of the left upper limb and intermittent headache. Magnetic Resonance Imaging (MRI) showed space-occupying lesions in the seventh cervical vertebrae, the first thoracic and left frontal lobe. Bone and brain metastases were considered. In July 2013, the patient underwent resection of the space-occupying lesion in the spinal canal. Postoperative pathology suggested intraspinal metastatic moderately differentiated adenocarcinoma, approximately

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Correspondence:
Yi Fang, Department of Endocrinology, Fifth Medical Center of Chinese PLA General Hospital, Beijing 100071, China,
E-mail: fangyi5zhongxin@163.com

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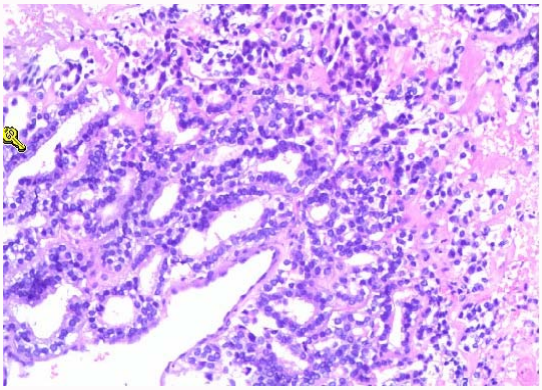

Figure 1: Pathological report showed spinal canal space-occupying, moderately differentiated adenocarcinoma.

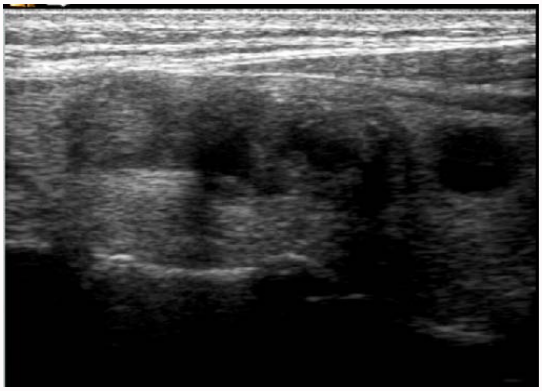

Figure 2: Color Doppler ultrasound of thyroid and cervical lymph nodes revealed: (1) Cystic and solid nodules in the left lobe of thyroid. (2) Hypoechoic nodules in the right lobe of the thyroid.

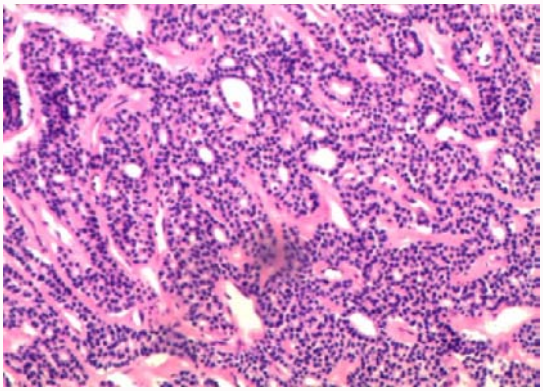

Figure 3: Pathological report showed benign thyroid follicles.

originating from the lung or thyroid (Figure 1). Computed Tomography (CT) scan showed multiple nodules in both lungs. The thyroid ultrasound displayed a hypoechoic nodule in her right lobe and a nodule with cystic and solid components in her left lobe, and no obvious malignant features of the thyroid nodules. Positron Emission Tomography (PET)-CT revealed multiple pulmonary, skeletal, and intracranial metastases from an unknown primary focus. After radiotherapy for cervical spine and brain metastases with a dose of 40G/20F in August 2013, she still suffered intermittent headache. In November 2013, pathology indicated an intraspinal mass and metastatic thyroid carcinoma (follicular subtype).

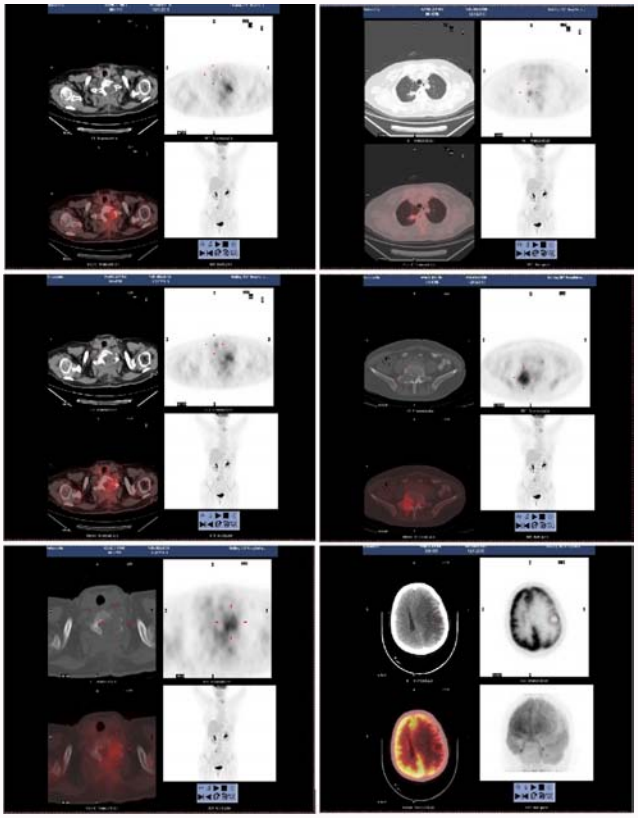

Figure 4: High metabolism of thyroid nodules in the right lobe, multiple metastases in both lungs, multiple bone metastases, and left parietal lobe brain metastases were found on a Fluorodeoxyglucose (FDG)-PET/CT scan.

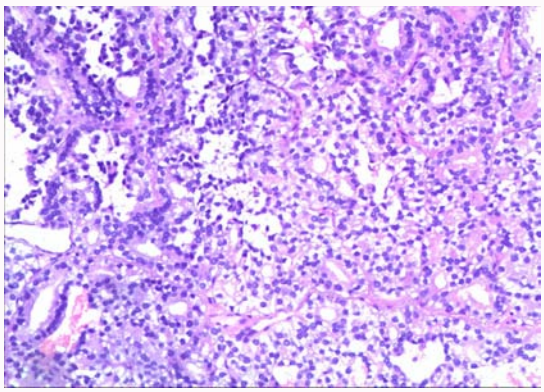

Figure 5: Pathological report was follicular subtype of papillary thyroid carcinoma.

In November 2013 the patient complained of intermittent headache, nausea, and vomiting and was admitted to our hospital. The physical examination found muscle atrophy of the left upper arm, fore arm and left dorsal with muscle strength; volar contracture of the ring finger and with inextensible and normal muscle strength of the lower limbs. The preliminary questionable diagnosis was thyroid cancer, lung cancer, or other malignancy. Thyroid color Doppler ultrasound examination showed a suspicious cystic solid thyroid nodule in the left lobe that might be benign; and a right lobe thyroid hypoechoic nodule that might be cancer (Figure 2).

A lymph node examined by color Doppler ultrasound showed no definite abnormality. Ultrasound-guided core needle biopsies

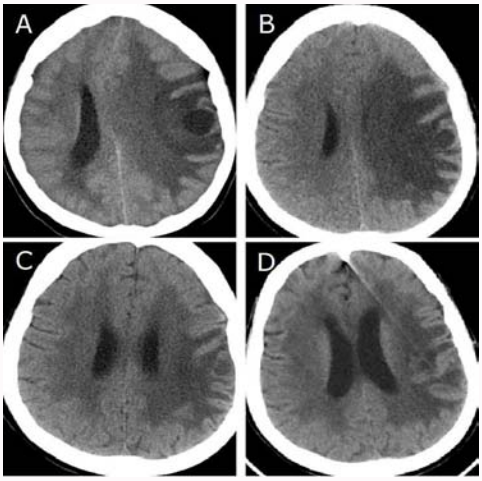

Figure 6: Head CT scans showed brain metastases initially gradually shrank and disappeared. (A) 17 January 2014; (B) 3 July 2014; (C) 15 January 2015; (D) 6 May 2016.

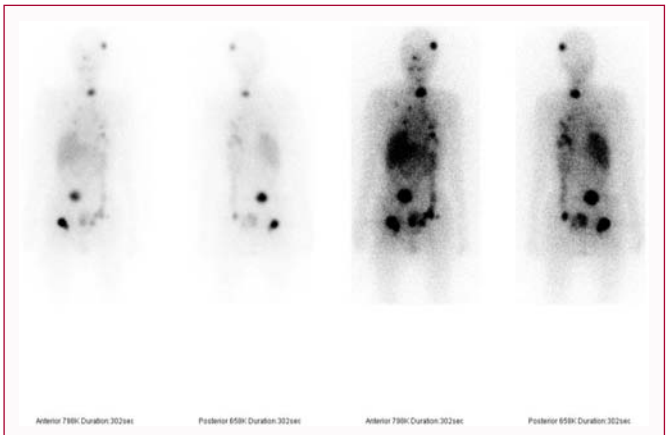

Figure 7: Whole body scan with I-131 sodium iodide with 200 mCi at 48-hour post-administration on November 2nd, 2015 showed thyroid carcinoma complicated with brain, lung, and bone metastases. The range of lung metastasis and right pelvic bone metastasis was enlarged.

of thyroid nodules were performed. The pathological report was benign thyroid follicles and fibro-muscular tissue (Figure 3). This was a clinical contradictory conclusion—the intraspinal metastasis was considered PTC metastasis by the pathological report, but no malignant figures were found in the ultrasonography and biopsy specimen. Laboratory tests revealed normal thyroid function and elevated Thyroglobulin (Tg): Thyroglobulin (Tg) >475 ng/mL (3.5 ng/mL to 77 ng/mL). The PET-CT scan showed high metabolism in the right thyroid lobe, multiple metastases in both sides of the lung, multiple bone metastases, and metastasis in the parietal lobe of the left brain (Figure 4). In December 2013, the patient underwent total thyroidectomy; the pathological report was papillary thyroid carcinoma of the right lobe thyroid, follicular subtype, invasion of capsule, and gross tumor size 1.5 cm × 1.3 cm × 1.2 cm (Figure 5).

In August 2014, the patient was given cervical and cranial radiotherapy. I-131 treatment (200 mCi) was administered 4 times during January 2014 and November 2015. In addition, the patient received the following: Thyroid stimulating hormone inhibition therapy; targeted therapy (oral administration of sorafenib mesylate); surgical treatment for bone metastases; mannitol and hormone for the treatment of brain edema; pain relief; and other supportive treatments. Brain metastases initially gradually shrank and disappeared (Figure 6), and headache and vomiting were alleviated. However, the lung, bone and brain metastases were enlarged at last in November 2015 (Figure 7). She died of malnutrition and cachexia in early June 2016.

Discussion

FVPTC is composed of cells with nuclear features of conventional PTC with a follicular architecture [24-28]. Three clinicopathological entities have been recognized in FVPTC: Encapsulated/Non-Invasive (E/NI)-FVPTC with a more indolent behavior; infiltrative FVPTC, whose behavior is closer to conventional PTC; and a multinodular/diffuse form characterized by aggressive clinical behavior, giving rise to nodal and distant metastases [29,30]. In the present case, the ultrasonic manifestations of thyroid were like that of E/NI-FVPTC, but the biological behaviors were closer to the multinodular/diffuse form of FVPTC with lung, bone, and brain metastases. However, there was no cervical lymph node metastasis in this case. A very large proportion of FVPTCs are histologically difficult to distinguish from benign follicular lesions such as follicular adenoma, especially by fine-needle aspiration biopsy [8,31]. This was also seen in the present case. Tg is an independent predictor of malignancy, and in patients with thyroid nodules, Tg should be determined before surgery, especially when cytology is indeterminate [32,33]. The level of Tg in our patient increased significantly before thyroidectomy, which signaled thyroid malignancy. In addition, immunohistochemical examination combined with genetic tests can improve the diagnostic rate [34].

For the treatment of metastasis, we reviewed the guidelines for radio iodine therapy of differentiated thyroid cancer recommended by the Chinese Society of Nuclear Medicine (2021 edition) [35]. For lung metastases, I-131 treatment is the first choice. Although I-131 treatment may not cure bone metastases with large bone destruction, it can often significantly reduce serum Tg level, relieve pain, improve quality of life, and prolong survival. Brain metastasis is more common in advanced elderly patients, with poor prognosis. Surgical treatment or external beam radiation therapy should be considered first. I-131 treatment is an adjunct to surgery or radiotherapy for brain metastases. In severe cases, brain hernia and other life-threatening reactions may occur. Therefore, I-131 treatment should be accompanied by glucocorticoid therapy, and patients must be closely observed. In the present case, mannitol treatment for high intracranial pressure and dexamethasone for infective brain edema were used before and after I-131. The brain metastases initially gradually shrank and disappeared and the headache and vomiting symptoms were alleviated.

After multiple I-131 treatments, some iodine-uptake metastases still showed disease progression within one year, including gradual growth of the lesions, emergence of new lesions, and continuous increase of Tg in serum, despite maintaining iodine-uptake ability. This is called Radioactive Iodine-Refractory (RAIR)-Differentiated Thyroid Cancer (DTC) [36,37]. Lenvatinib and sorafenib have been approved by the United States Food and Drug Administration, and many other drugs are in trials for the treatment of advanced metastatic RAIR-DTC [38]. Unfortunately, the efficacy of tyrosine kinase inhibitor treatment is limited due to the lack of strong cytotoxic action, fast development of resistance, and side effects [39]. Immunotherapy is also a promising alternative option for RAIR-DTC. The anti-tumor activity of the anti-PDL1 monoclonal antibody pembrolizumab has been evaluated in advanced PD-L1-positive DTC with promising results [40]. However, very few clinical trials have been accomplished.

Conclusion

The available options for patients with metastasizing FVPTC include surgical resection, radio iodine, thyroid stimulating hormone-suppression, locoregional and adjuvant/adjunctive and targeted treatments, immunotherapy, and other novel approaches. None of these are adequate, but the immediate and long-term prospects of individualized targeted therapy look bright.

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