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Case Report

The diagnostic and therapeutic process of invasive encapsulated follicular variant of papillary thyroid carcinoma with lung metastasis: a case report

Yuling Dong[1], Fuxue Tang[1], Jianxin Hu[2], Jie Zhang[1]

[1]Department of Pathology, Maternal and Child Health Care Hospital of Shandong Province, Jinan 250014, Shandong, China; [2]School of Nursing and Health, Xi'an Innovation College, Yan'an University, Xi'an 710084, Shaanxi, China

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Abstract: The invasive encapsulated follicular variant of papillary thyroid carcinoma (IEFVPTC) is a subtype of papillary thyroid carcinoma (PTC) that is often clinically misdiagnosed as a benign lesion. This case report describes a case of IEFVPTC with lung metastasis, highlighting its pathological features and treatment process to enhance understanding of this disease. A female patient discovered to have a thyroid nodule during a routine physical examination sought evaluation and treatment at our hospital. Fine-needle aspiration of the left thyroid lobe and left cervical lymph node confirmed a diagnosis of the macrofollicular variant of IEFVPTC. Computed Tomography (CT) scans indicated pulmonary metastasis, and the patient underwent tumor excision followed by three courses of radioiodine-131 (I-131) therapy. After treatment, no new lymph node metastases were detected, and both the size and lung metastatic lesions significantly decreased. When thyroid lesions present as nodular hyperplasia, characterized by predominantly large follicles or macrofollicular structures rich in colloid, papillary proliferation of the follicular epithelium and cytological features such as ground-glass nuclei and nuclear grooves, one suspects the possibility of IEFVPTC. Clinical assessment, ultrasound examination, and immunohistochemical staining are often combined to aid in diagnosis, reducing the likelihood of missed cases of IEFVPTC.

Keywords: Macrofollicular, papillary thyroid carcinoma, pulmonary metastasis, diagnostic, therapy

Introduction

The invasive encapsulated papillary thyroid carcinoma (IEFVPTC) follicular variant is a relatively rare papillary thyroid carcinoma (PTC) subtype characterized by predominantly large follicular structures [1]. It typically demonstrates well-differentiated features and lacks the typical nuclear characteristics of classic papillary carcinoma cells [2]. Clinically, it is prone to misdiagnosis as a benign thyroid tumor, such as nodular goiter, large follicular adenoma, follicular neoplasms, or hyperplastic nodules [2]. Misdiagnosing IEFVPTC can undoubtedly lead to delays in patient treatment.

The primary diagnostic methods for most thyroid nodule patients without obvious clinical symptoms include palpation, ultrasound, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), fine-needle aspiration (FNA), serum thyroglobulin testing, and genetic testing [3]. In clinical practice, ultrasound and fine-needle aspiration (FNA) are the primary diagnostic methods for thyroid nodules [4]. Typically, PTC appears on ultrasound as a solid, hypoechoic, or markedly hypoechoic nodules with irregular margins, a longitudinal-to-transverse ratio >1, punctate calcifications, and peripheral vascularity [5]. However, the IEFVPTC variant typically presents as oval-shaped nodules with well-defined boundaries, smooth margins, and homogeneous echogenicity. These nodules resemble benign nodules, and make preoperative ultrasound diagnosis challenging [6]. When FNA reveals tissue with macrofollicular structures or is entirely composed of macro-follicles, it can be challenging for the diagnosing physician to distinguish between lymph node metastasis of thyroid cancer and ectopic thyroid tis-

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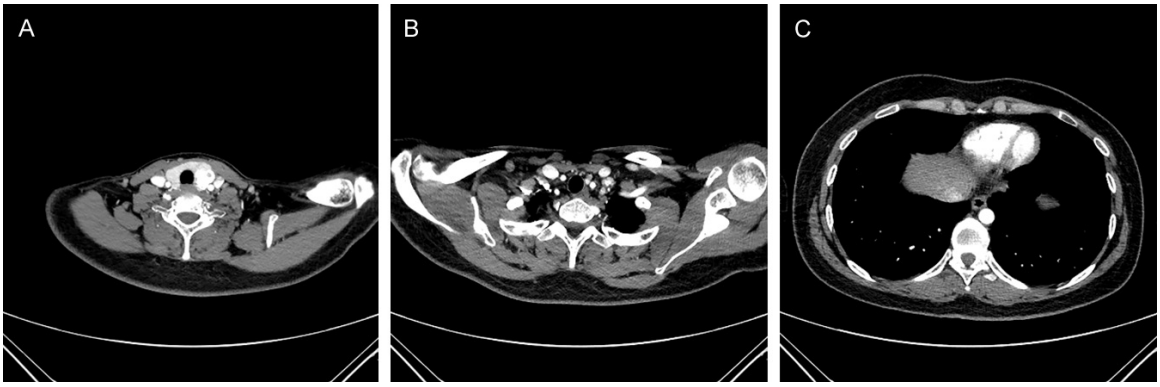

Figure 1. CT imaging showed a thyroid left lobe nodule with irregular calcifications, multiple lymph nodes in the left neck (II-IV regions) with partial calcifications, and multiple solid small nodules in both lungs. A: Thyroid; B: Lymph gland; C: Pulmonary nodule.

sue [7]. Therefore, raising awareness of the diagnosis and differential diagnosis of IEFVPTC is vital for effective patient management.

This case report adheres to the requirements and format of the CARE guidelines [8]. This study analyzes the diagnostic and treatment process of a female patient with IEFVPTC, aiming to provide clinical and pathological physicians with more insights into this disease. This study was approved by the hospital's Ethics Committee, where we worked. The patient provided informed consent for using her treatment information in scientific reporting, ensuring that her details remained confidential.

Case presentation

History of present illness

A female patient in her 30's was referred to our hospital after a nodule was found on the left side of her thyroid. Physical examination revealed a palpable mass in the left lobe and isthmus of the thyroid, characterized by firm texture and well-defined boundaries. Thyroid color Doppler ultrasound showed a mixed echo in the central part of the left lobe (3.9×2.2×1.7 cm), with an irregular shape, unclear margins, and a shell-like strong echo phenomenon (2.7×1×0.3 cm). Several enlarged lymph nodes were detected in the patient's left neck. A node in region II (2.0×0.5 cm) showed cortical thickening with a slightly hyperechoic mass, while another in region IV (1.2×0.4 cm) contained a hyperechoic mass.

A biopsy of the thyroid's left lobe and fine-needle aspiration of the left cervical lymph nodes revealed cancer cells but no BRAF gene mutation. Positron emission tomography/computed tomography (PET/CT) imaging revealed a nodule with irregular calcifications in the left lobe of the thyroid, multiple lymph nodes in the left neck (regions II-IV) with partial calcifications, and several small solid nodules in both lungs (**Figure 1**). Considering the comprehensive pathological diagnosis and clinical findings, thyroid cancer with multiple neck lymph nodes and lung metastases was suspected. Laboratory results for various serum indicators were within the normal range, including thyroglobulin (TG) at 65.41 ng/ml, calcitonin at 2.02 pg/ml, anti-thyroglobulin antibody at 20.82 IU/ml, anti-thyroid peroxidase antibody at 13.91 IU/ml, thyroid-stimulating hormone (TSH) at 1.47 μIU/ml, free thyroxine (FT4) at 16.19 pmol/L, free triiodothyronine (FT3) at 4.99 pmol/L, and parathyroid hormone at 4.66 pmol/L.

Pathological diagnosis

The frozen sections reveal prominent calcification within the tumor tissue, surrounded by follicles of varying sizes. The follicular epithelial cells exhibit mild proliferation with round nuclei arranged loosely and lacking malignant features such as invasive growth, stromal reaction, and structural heterogeneity (**Figure 2**). Based on these findings, it was clinically recommended to proceed with further diagnostic procedures.

The H&E staining of the tissue section shows follicle nodules of varying sizes, surrounded by

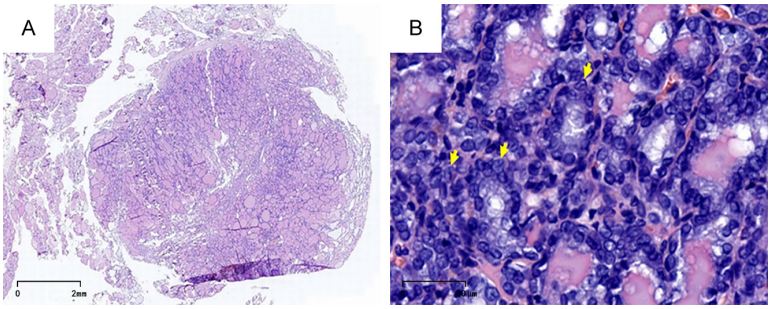

Figure 2. Microscopic examination of H&E staining of IEFVPTC tissue. A: The follicles appear as nodules of varying sizes, surrounded by a fibrous capsule of uneven thickness. Within the nodules, follicles of different sizes rich in colloids can be observed. Larger follicles have diameters exceeding 200 μm, and resorption vacuoles can be seen in some more actively proliferating follicles (10×). B: The follicular epithelial cells are mostly flat or low columnar, with some translucent nuclei. However, unlike the "ground-glass" nuclei characteristic of PTC, nuclear grooves and intranuclear pseudo inclusions are not observed (yellow arrow, 200×).

fibrous capsules of differing thicknesses. Within the nodules, there are follicles rich in colloid. Larger follicles have a diameter of >200 μm, and some actively proliferating follicles contain absorptive vacuoles. The follicular epithelial cells differ from typical PTC cells, appearing mostly flattened or short columnar. Some cell nuclei are translucent, but unlike PTC's "ground-glass" nuclei, they do not have nuclear grooves or intranuclear pseudoinclusions. In some actively proliferating small follicles, the cytoplasm is clear, and no papillary structures are observed. Cancer metastases were identified in multiple lymph nodes in the neck, displaying a morphology similar to the primary lesion, with several of these lymph nodes also showing prominent calcifications.

Immunohistochemical staining revealed positive expression of CK19 (60%+) and HBME1 (70%+) in some actively proliferating follicles, while CD56 expression was negative (-). The immunohistochemical staining of the lymph nodes was similar to those of the primary lesion (**Figure 3**).

Treatment and prognosis

With the patient's informed consent, the clinical physician performed a left thyroid lobectomy. Following surgery, the patient was prescribed levothyroxine tablets to maintain thyroid function. Since lung metastases were already present, postoperative radioactive iodine (I-131) therapy, consisting of three sessions, was administered. After radiotherapy, CT scans revealed a significant reduction in the size and number of lung metastatic lesions, without new metastatic foci observed (**Figure 4**). After thorough communication with the patient and obtaining her consent, with personal information concealed, her diagnostic and treatment process are herein utilized for academic reporting.

Discussion

IEFVPTC is a relatively rare subtype of PTC, accounting for 2.6% of cases [9]. Due to its atypical cancer cell characteristics, this subtype is prone to misdiagnosis as a benign lesion. Even in the presence of clear metastatic cancer, there is still controversy among pathologists regarding its classification. In this IEFVPTC patient, ultrasound examination revealed mixed echogenicity in the left thyroid, irregularly shaped and poorly defined shadows, and shell-like strong echoes. The patient also had several enlarged lymph nodes in the left neck, showing cortical thickening and an echogenic mass. CT scans revealed a nodule with irregular calcifications in the left lobe of the thyroid, multiple lymph nodes with partial calcifications in various areas of the left neck, and several small solid nodules in both lungs.

Subsequently, we performed fine-needle aspiration of the left thyroid lobe and left neck lymph nodes. In this study, the aspirated tissue tested negative for BRAF gene mutation, an essential diagnostic reference for PTC. This is consistent with findings by Yeo M et al., who also reported negative BRAF mutations in two cases of IEFVPTC [10]. The possibility of IEFVPTC cannot be ruled out even when BRAF gene mutation testing is negative. A frozen section biopsy and laboratory tests, including TG, CT, TSH, FT3, and FT4, showed no abnormalities. Therefore, this study concludes that these markers have limited utility in the differential diagnosis of IEFVPTC.

We performed further H&E staining on the surgically excised tumor tissue. The results

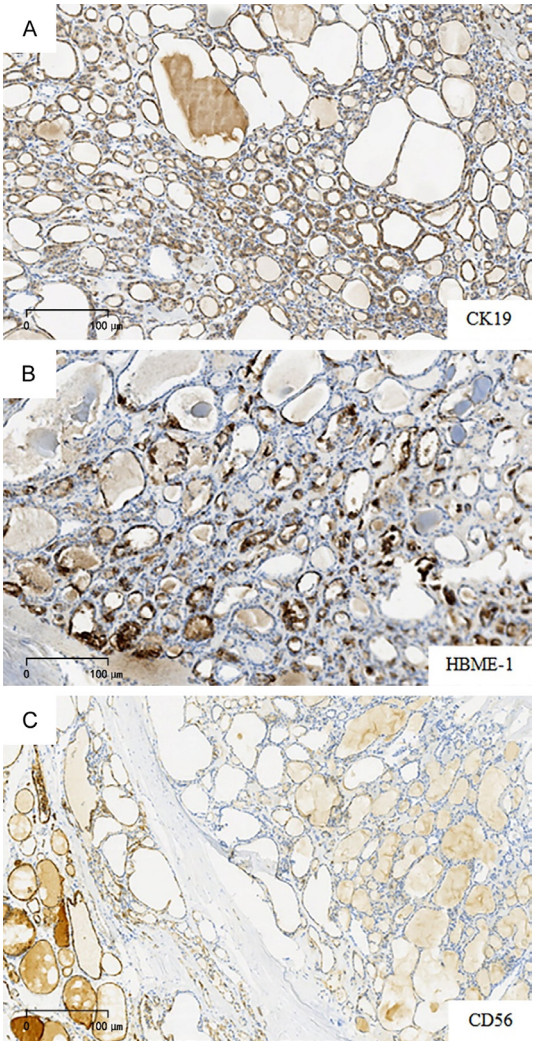

Figure 3. Immunohistochemical results of the factors. A: More than 60% of the cells show positive CK19 staining; B: More than 70% of the cells show positive HBME-1 expression; C: CD56 shows negative expression.

revealed that the follicles within the mass formed nodules of varying sizes, externally surrounded by fibrous capsules of variable thickness. The follicles were enlarged and filled with colloids. Unlike typical PTC cells, the follicular epithelial cells were predominantly flattened or short columnar, with some nuclei appearing translucent. Notably, the tumor cells in this patient did not show nuclear grooves or intranuclear pseudoinclusions. The cytoplasm of some actively proliferating small follicles appeared clear, and no papillary structures were observed in any of the sections. Metastatic cancer was identified in multiple lymph node groups in the neck, exhibiting a morphology similar to the primary lesion, with several lymph nodes displaying prominent calcifications. In immunohistochemical staining of PTC, CK19 is typically diffusely positive [11]. In contrast, CK19 is either negative or only focally positive in normal thyroid tissue, thyroid adenomas, and nodular goiters, with significantly weaker expression than PTC. Research indicates that HBME-1 exhibits high sensitivity and specificity in diagnosing IEFVPTC [12]. Additionally, the overexpression of Galectin-3 is strongly associated with PTC's occurrence, development, and even metastasis [12]. Although Galectin-3 demonstrates high diagnostic accuracy in distinguishing papillary carcinoma from benign lesions, its positive expression alone cannot serve as definitive diagnostic criterion. CD56, a cell surface sialoglycoprotein, has been shown in recent studies to exhibit high sensitivity and specificity in diagnosing PTC [13]. In this study, CK19 and HBME1 were positively expressed in some actively proliferating follicles, whereas Galectin-3 and CD56 showed no positive expression. Based on pathological findings, the patient was ultimately diagnosed with IEFVPTC. Consequently, additional testing for the epithelial marker TROP-2, thyroid microvascular endothelial marker HBME-1, cell proliferation marker p53, and tumor suppressor marker Ki-67 was not pursued, representing a limitation of this study.

Due to the sizeable follicular structure and subtle or patchy nuclear features, IEFVPTC is often difficult to distinguish from other PTC subtypes using cytology and fine-needle biopsy alone. This diagnostic challenge increases the risk of misclassification in clinical practice, necessitating further pathological analysis to enhance accuracy. When thyroid lesions exhibit nodular growth predominantly composed of large follicles or macrofollicular structures rich in colloid, with follicular epithelium forming small papillary or fan-shaped protrusions extending into the follicular lumen, along with absorptive vacuole changes and hemorrhage around the colloid, suspicion of IEFVPTC may be considered. Additionally, papillary growth of the follicular epithelium, ground-glass nuclei, and nuclear grooves further supports the possibility. A comprehensive approach integrating clinical assessment, ultrasound imaging, and immunohistochemical staining is essential to improve diagnostic accuracy and minimize the risk of overlooking IEFVPTC.

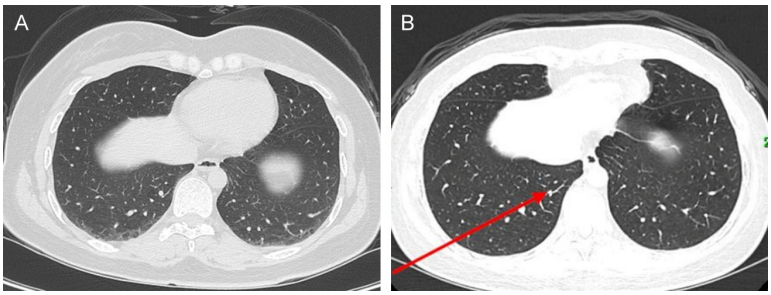

Figure 4. CT scans before and after radiotherapy assess changes in the size of pulmonary metastatic lesions. A: Before radiotherapy; B: After radiotherapy.

Disclosure of conflict of interest

None.

Abbreviations

IEFVPTC, Invasive Encapsulated Follicular Variant of Papillary Thyroid Carcinoma; CT, Computed Tomography; I-131, radioiodine-131 therapy.

Address correspondence to: Jie Zhang, Department of Pathology, Maternal and Child Health Care Hospital of Shandong Province, Jinan 250014, Shandong, China. E-mail: 18754193800@163.com

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