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Multifocal Invasive Encapsulated Follicular Variant of Papillary Thyroid Carcinoma with *BRAFK601E* Mutation: Case Report and Literature Review

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Keywords: Invasive encapsulated FVPTC; *BRAF* mutation; *BRAFK601E*.

Abstract

Background: The v-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutation is a genetic disorder that generally associated with Papillary Thyroid Cancer (PTC). The *BRAF*V600E mutation is the most common, while other *BRAF* mutations like *BRAF*K601E accounted for less than 1% of cases. *BRAF*K601E mutation clinically shows less aggressive features but still poses metastasis potential. Newer diagnostic method has been introduced, but the molecular examination offer the possibilities to predict the nature of the tumor's behavior, which might assist in formulating a better treatment strategy and predicting the patients prognosis.

Case description: We report a case of multifocal invasive encapsulated follicular variant of PTC in a 50-year-old woman. The tumors arise in both the right and left thyroid lobes, and both had *BRAF*K601E mutations. Both lesion displaying similar histopathological features. The tumors exhibited a follicular and focal solid pattern, with tumor cell nuclei showing a ground-glass appearance and nuclear grooves, with an overall nuclei score of 2. There was no capsular invasion, extrathyroidal extension, or perineural invasion observed, however, lymphovascular invasion was found in the right thyroid tumor. Further examination revealed that there was no metastases detected in the lymph nodes or other organs.

Conclusion: The *BRAFK601E* mutation is a rare *BRAF* mutation commonly seen in follicular variant of PTC. Our case of multifocal invasive encapsulated follicular variant of PTC

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with the *BRAF*K601E mutation is the first reported case in Indonesia. The behavior of invasive encapsulated FVPTC with *BRAF*K601E mutation is more similar to PTC with rat sarcoma (*RAS*) mutations compared to the *BRAF*V600E mutation. Although the *BRAF*K601E mutation in PTC is commonly associated with less aggressive tumors, other features such as a multinodular lesion nor lymphovascular invasion which rarely seen in *BRAF*K601E should increased awareness for poorer outcomes and further investigations.

Introduction

Thyroid cancer is the most common endocrine neoplasm, with an increasing number of cases over the past three decades due to advances in diagnostic imaging capabilities [1-4]. These improvements have led to more cases being diagnosed, but they often result in overdiagnosis, which can lead to overtreatment, including unnecessary thyroidectomy that might harm the patients. In addition to radiological diagnostics, thyroid cancer can also be diagnosed using Fine Needle Aspiration Cytology (FNAC), histopathology, Immunohistochemistry (IHC), or molecular analysis. Each method has its own strengths and limitations, but newer diagnostic modalities, such as molecular testing, offer the possibility of earlier detection that might help in determining the appropriate therapies.

Molecular analysis provides new techniques to identify the tumor type from cytology or biopsy specimens, which can prevent unnecessary procedures that are commonly performed in hospital settings. Common genetic alterations include Rearranged Transfection (*RET*) rearrangements, *BRAF* point mutations, *RAS* mutations, and Telomerase Reverse Transcriptase (TERT) mutations [5]. The *BRAF* mutation, particularly *BRAF*V600E, is usually seen in patients with PTC and is strongly associated with aggressive features. Another *BRAF* mutation, *BRAF*K601E, has also been reported, but in really small cases. The presence of the *BRAF*K601E mutation should be assessed thoroughly, as it may present with either benign features leading to favorable outcomes or very aggressive features associated with poorer outcomes [6].

Case presentation

A 50-year-old woman presented to the hospital with a growing nodule in the front of her neck. Ultrasonography (USG) revealed nodules in both the left and right thyroid lobes, with maximal diameters of 2 cm and 3 cm, respectively. These findings suggest a score of 4 for the thyroid imaging reporting and data system (TI-RADS). The patient was then suspected of thyroid malignancy, leading to a total thyroidectomy. Gross examination of the specimen revealed a brownish, solid, encapsulated tumor mass with a smooth surface. Histopathological examination showed an encapsulated tumor (Figure 1) with a follicular and focal solid pattern (Figure 2). The tumor cells had nuclei with a ground-glass appearance (orphan annie-eyed nuclei) and nuclear grooves (nuclei score of 2) (Figure 3). There was no evidence of capsular invasion, extrathyroidal extension, or perineural invasion. However, lymphovascular invasion was observed in the right thyroid tumor (Figure 4). The histopathological findings were consistent with the characteristics of an invasive, encapsulated FVPTC.

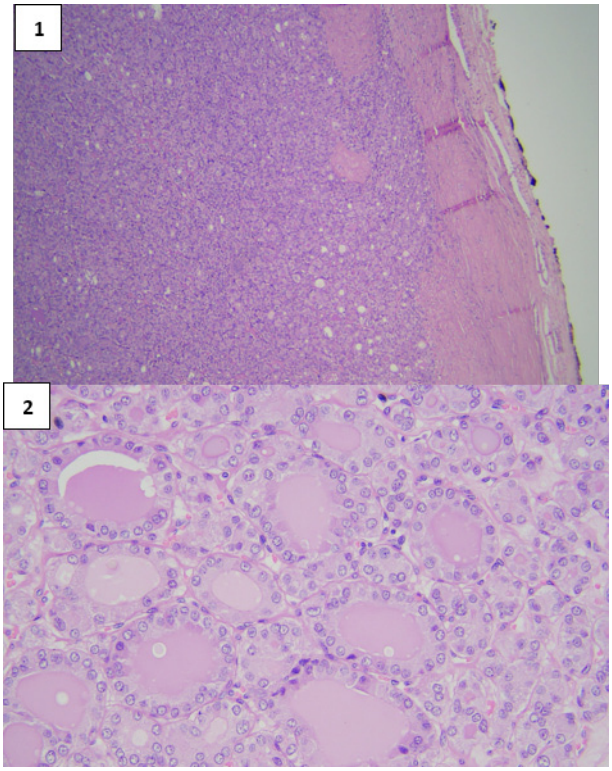

Figure 1: Encapsulated follicular-patterned tumor with thick connective tissue capsule (Haematoxylin eosin (HE), 40X).
Figure 2: Tumor arranged in follicular pattern (HE, 400X).

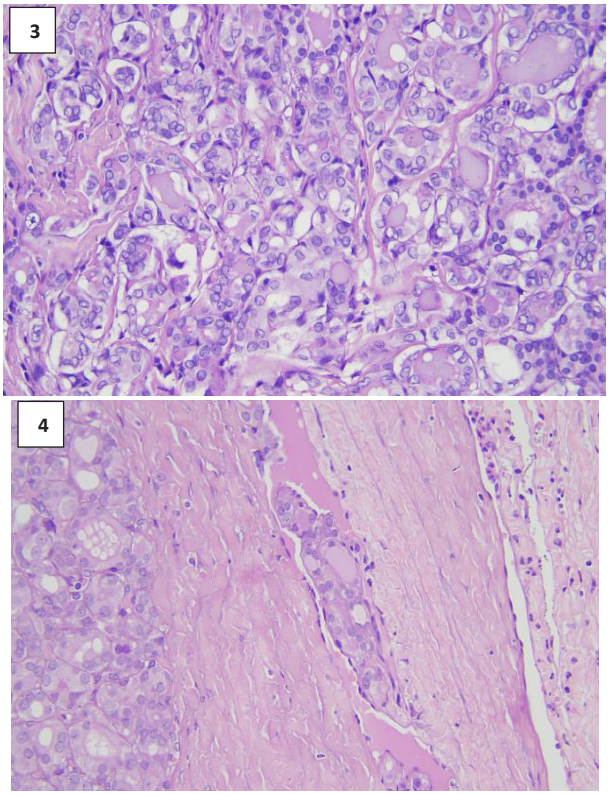

Figure 3: Nuclear groove and ground glass nuclei (HE, 400X).
Figure 4: Lymphovascular invasion (HE, 100X).
The specimen was analyzed using Sanger sequencing, which identified the BRAFK601E mutation in both the left and right thyroid tumors. Further evaluation revealed no metastases of tumor cells to the lymph nodes or other organs.

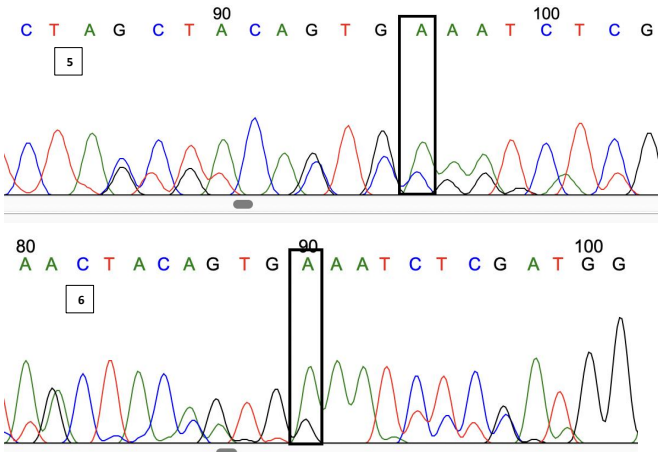

Figure 5,6: Sanger sequencing show mutations at codon 15 of *BRAF* genome at potition 601E.

Disccusion

In 2020, thyroid cancer was the ninth most common cancer worldwide, with a total of 586,000 cases [1,2]. The incidence of thyroid cancer has been increasing as more newly diagnosed cases have been reported [1]. Thyroid cancers originate from the differentiation of the thyroid parenchyma. Based on cell origin, they can be classified into Differentiated Thyroid Cancers (DTCs), which arise from thyroid follicular cells, and Medullary Thyroid Carcinoma (MTC), which arises from parafollicular or supporting cells [2]. DTCs account for 90-95% of all

thyroid malignancies and can be further classified into PTC, follicular thyroid cancer (FTC), and Hurthle cell cancer. PTC has the highest prevalence among these subtypes, followed by FTC [6].

Patients with thyroid cancer typically present with a lump in the neck, often without additional symptoms, unless the tumor has progressed to cause compression or systemic effects [7]. Several factors are considered risks for the development of thyroid cancer, including female gender, a family history of thyroid cancer, radiation exposure (especially during childhood), iodine intake, exposure to external estrogen, obesity, diabetes mellitus, and genetic alterations [6,8]. Thyroid cancers are strongly associated with genetic mutations and translocations in the mitogen-activated protein kinase (*MAPK*) and phosphoinositide 3-kinase/protein kinase B (*PI3K/AKT*) signaling pathways, which regulate cell proliferation, angiogenesis, and migration [9]. Both FTC and PTC can activate the *MAPK* signaling pathway, but to different extents [10]. FTC typically has *RAS*-like mutations, resulting in lower *MAPK* pathway activation, whereas PTC commonly expresses *BRAF*-like mutations, leading to higher *MAPK* pathway activation that is associated with a higher risk of metastasis, a tendency for less likely encapsulation, an infiltrative growth pattern with well-developed nuclear features, and no activation of the *PI3K/AKT* pathway. The differences in molecular expression between FTC and PTC can be attributed to their varying responses to negative feedback mechanisms [13,14].

Due to the nonspecific clinical symptoms, additional examinations such as USG, thyroid function tests, radionuclide scans, FNAC, histopathology, or molecular analysis are usually needed to determine the diagnosis [2]. USG can help distinguish between masses that are more likely to be malignant or benign, but this method may sometimes lead to overdiagnosis and unnecessary thyroidectomy [12]. FNAC is a valuable tool for differentiating tumors, but it cannot evaluate the entire cell and may yield unclear results, particularly for Bethesda classification grades III and IV [2]. Histopathological examination can determine the tumor cell type and origin but can only be performed after thyroidectomy. Additionally, it may pose diagnostic challenges due to overlapping morphological features [14]. Molecular diagnostics are typically recommended for thyroid nodules measuring 1-4 cm, TI-RADS stages 2 and 4 on USG, and Bethesda categories III/IV [11]. The most common mutation in PTC is *BRAF*V600E, which is associated with more aggressive tumors such as the tall-cell variant [15,16]. Other *BRAF* mutations are less common, with an occurrence rate of approximately 0.76%. One of the reported mutations is *BRAF*K601E. The *BRAF*K601E mutation, located at codon K601E in exon 15 of the *BRAF* gene, substitutes lysine (K) with glutamic acid (E) at position 601, leading to increased kinase activity [3]. Studies have shown that the *BRAF*K601E mutation is more likely to exhibit *RAS*-like clinical behavior, has lower oncogenic activity, and a mutation rate 2.5 times lower compared to *BRAF*V600E, which is associated with a better prognosis and treatment response and can often be managed safely with hemithyroidectomy [4,17]. The *BRAF*K601E mutation is commonly reported in follicular adenomas, microPTC, Non-Invasive Follicular Thyroid Neoplasm with Papillary-like nuclear features (NIFTP), and FVPTC, with FVPTC being the most frequently reported [18]. However, some studies have also shown associations between this mutation and more aggressive tumors, potentially influenced by racial, genetic, or geographic factors, so further research is needed to confirm these findings [17].

Our case reports a 50-year-old woman with a growing neck nodule. USG and thyroid scintigraphy suggested the presence of two nodules, presumed to be malignant, so the patient underwent a total thyroidectomy to remove both lesions. Thyroid cancer typically presents as a single solid nodule and rarely presents as multifocal lesions [5]. Histopathological examination revealed a tumor with a follicular and focal solid pattern, with nuclei showing a ground-glass appearance and nuclear grooves (nuclei score 2). There was no capsular invasion, perineural invasion, or extrathyroidal extension, but lymphovascular invasion was observed in the right thyroid tumor. These findings are consistent with the characteristics of invasive encapsulated FVPTC according to the 5th edition of the World Health Organization (WHO) Classification of Tumors of Endocrine Organs. This variant has similar nuclear features to PTC but is arranged in a follicular pattern rather than a papillary pattern [19]. Both gross and microscopic examinations revealed a thick capsule surrounding the tumor, which helps classify it as the invasive encapsulated FVPTC. This variant is associated with *RAS*-like neoplasms, which are less likely to spread and generally have better outcomes compared to the infiltrative FVPTC variant [20]. Although lymphovascular invasion, which is usually associated with a higher risk of recurrence or metastasis, was present in our case, it is more commonly linked with *BRAF*V600E mutations rather than *BRAF*K601E mutations [22]. A nuclear score of 2 or 3 is used to confirm the diagnosis of PTC. A score of 2 is associated with *RAS*-like mutations, while a score of 3 is typically associated with *BRAF*V600E mutations, which are generally more aggressive [14]. Sanger sequencing analysis identified the *BRAF*K601E mutation in both tumors. This finding correlates with the previous results, suggesting a likely favorable outcome with a lower probability of metastasis.

This case was the first reported instance of multifocal invasive encapsulated FVPTC with the *BRAF*K601E mutation in Indonesia. FVPTC is reported in only 20-30% of total PTC cases

[21]. In such cases, thyroid lesions can either present with the same variant or show different variants, which are associated with varying histologic and mutational behaviors. However, the *BRAF*K601E mutation is typically found in less aggressive lesions [18].

Our case is considered unique as both of the lesions exhibited similar histopathological and mutational characteristics, which was invasive encapsulated FVPTC with the *BRAF*K601E mutation. Since we are the first cases reported in Indonesia, we are still lacking additional information about the best strategies for patient management and follow-up. Therefore, we always looked up for other literature that reported similar cases.

Our case aligns with other studies indicating favorable outcomes in patients with the *BRAF*K601E mutation and the possibility for the patient to be treated with hemithyroidectomy. The study reported that four FVPTC cases with the *BRAF*K601E mutation showed less aggressive histological features and were commonly associated with encapsulated FVPTC, consistent with our findings [23]. This study also states that this mutation is proposed to have an excellent prognosis and have less possibility for extracapsular or lymphovascular invasion [16], whereas in our cases, lymphovascular invasion was observed in one lobule. Lymphovascular invasion is associated with metastasis or recurrent potential, but after additional examination, we confirmed that there was no metastasis in our patients. Another study reported that two benign histological features from a total of fourteen cases with *BRAF* cytological mutations were related to *BRAF*K601E mutation [17]. Hence, we recommend that clinicians should perform pre-operative molecular testing, as it may help determine the most appropriate and less aggressive treatment for patients. Although most cases with *BRAF*K601E mutations have favorable outcomes, there are a few reports suggesting that *BRAF*K601E can be associated with poorer outcomes. These instances are usually linked to other tumor types and rarely to FVPTC itself. Therefore, it is essential to correlate molecular results with other clinical and supporting features to determine the best treatment approach and improve patient quality of life.

Conclusions

*BRAF*V600E is the most common *BRAF* mutation found in PTC. Other *BRAF* mutations compromised really small cases with *BRAF*K601E being the most frequently reported among them. *BRAF*K601E can be observed in various thyroid cancer variants, with the FVPTC being the most prevalent. This mutation is typically associated with more favorable outcomes. However, in a few reported cases, it has also been linked to poorer outcomes. Therefore, it is essential to thoroughly assess other clinical, histopathological, and additional features to ensure the best possible quality of life for patients.

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