

Case Report

Metastatic BRAF V600E-Mutated Thyroid Carcinoma: Molecular/Genetic Profiling Brings a New Therapeutic Option

Joana S. Reis Inês Costa Mariana Costa Ana Carmo Valente
Marta Baptista Freitas Catarina Lopes Almeida Marina Gonçalves
Carina Teixeira Maria Ribeiro Cláudia Caeiro Catarina Fernandes
Miguel Barbosa

Centro Hospitalar Universitário de São João, E.P.E. Porto, Porto, Portugal

Keywords

BRAF mutation · Metastatic thyroid cancer · BRAF inhibitors · Lenvatinib intolerance · Precision oncology

Abstract

We describe a case of a 46-year-old woman diagnosed with localized PTC 20 years ago, having already undergone several treatments with iodine-131 and then treatment with lenvatinib for metastatic disease, to which she developed intolerance. In 2020, in addition to pleural, thoracic, and abdominal lymph node metastasis, progression with symptomatic vertebral bone metastasis was detected, which led to the equation of new therapeutic options. In this context, a genetic/molecular test was carried out, which identified the BRAF V600E mutation and enabled the start of treatment with dabrafenib/trametinib since June 2020. This treatment allowed functional gain, symptomatic relief, and stabilization of the disease. It demonstrates how, in rare tumors, the personalized medicine approach can bring new treatment possibilities.

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Introduction

Papillary thyroid carcinoma (PTC) is the most common histologic type of thyroid cancer; however, distant metastasis is rare, occurring in 1–4% of patients and reducing the survival rates [1]. Genetic/molecular profiling is a developing tool in the approach to cancer disease. Emerging data suggest that broad genetic analysis will play an important role in risk stratification and therapeutic approach in PTC. BRAF mutations have been previously identified as oncogenic drivers in several cancer subtypes [2]. In PTC patients, BRAF V600E mutation has already been shown to be a potential predictor of disease persistence and worse prognosis. It may involve a poor response to standard therapies, more frequent extrathyroid extension, lymph nodes, and distant metastasis. However, it allows the use of specific target therapies [3–6]. Patients with BRAFV600E mutation are also known to be poor responders or refractory to iodine-131 due to acquired mutations that compromise their cellular uptake. In the iodine-131 resistance setting, the recommended systemic treatments are very limited; lenvatinib, a multitargeted tyrosine kinase inhibitor, is the most relevant agent. Following failure or intolerance to lenvatinib, there are no robust data to support a second line of treatment. In 2018, the use of a BRAF inhibitor, dabrafenib, with a MEK inhibitor, trametinib, was approved for the treatment of metastatic anaplastic thyroid carcinoma in patients with BRAF V600E mutation [7, 8]. This combination has already been approved and widely used for the treatment of other BRAF mutated cancers [8, 9].

Case Presentation

A 46-year-old woman, with Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 0, after total thyroidectomy in 1997, was diagnosed with early multifocal PTC. She underwent three treatments with iodine-131 over the next 20 years (total dose 400 mCi). In December 2017, she was detected with malignant pleural effusion and scattered pleural implants. She underwent another treatment with iodine-131 during 2018 (dose 200 mCi). The positron emission tomography with fluorodeoxyglucose integrated with computed tomography (18F-FDG-PET/CT) scan of March 2019 described pleural, thoracic, and abdominal lymph node metastasization (Fig. 1).

She started treatment with lenvatinib 24 mg/id in May 2019, with the need for a progressive dose reduction up to 10 mg/id due to grade 2 mucositis. After several deferrals, lenvatinib was discontinued in January 2020 due to grade 3 asthenia. At this time, ECOG-PS was 1, mostly due to the adverse effects of the treatment.

In May 2020, she developed new neurological symptoms and back pain. Lumbar CT was performed, which identified multiple bone metastases with canal stenosis and radicular compression. One month later, she had clinical worsening and CT showed an increase in the number and size of lymph node and bone metastasis. The pain was difficult to control with opioid analgesia. At that time, ECOG-PS was 3 due to intense pain. Zoledronic acid was started. In June 2020, FoundationOne CDx test was performed, for genetic/molecular study, and the BRAF V600E mutation was identified (mutant allele frequency 0.16%). There was no other biomarker or genomic findings. After approval from the Ethics Committee and the Pharmacy and Therapeutics Committee, she started off-label treatment with dabrafenib/trametinib doublet in July 2020. This combination may be associated with cardiotoxicity, notably with cardiomyopathy. To assess baseline cardiac function, the patient was assessed in a cardioncology consultation before the start of treatment. She then maintained echocardiographic monitoring every 3 months.

After 3 months of treatment, she presented significant pain improvement, reduced opioid dose, recovery of the previous functional state, and no adverse effects from dabrafenib/trametinib therapy. The October 2020 CT image showed a significant reduction in thoracic and abdominal

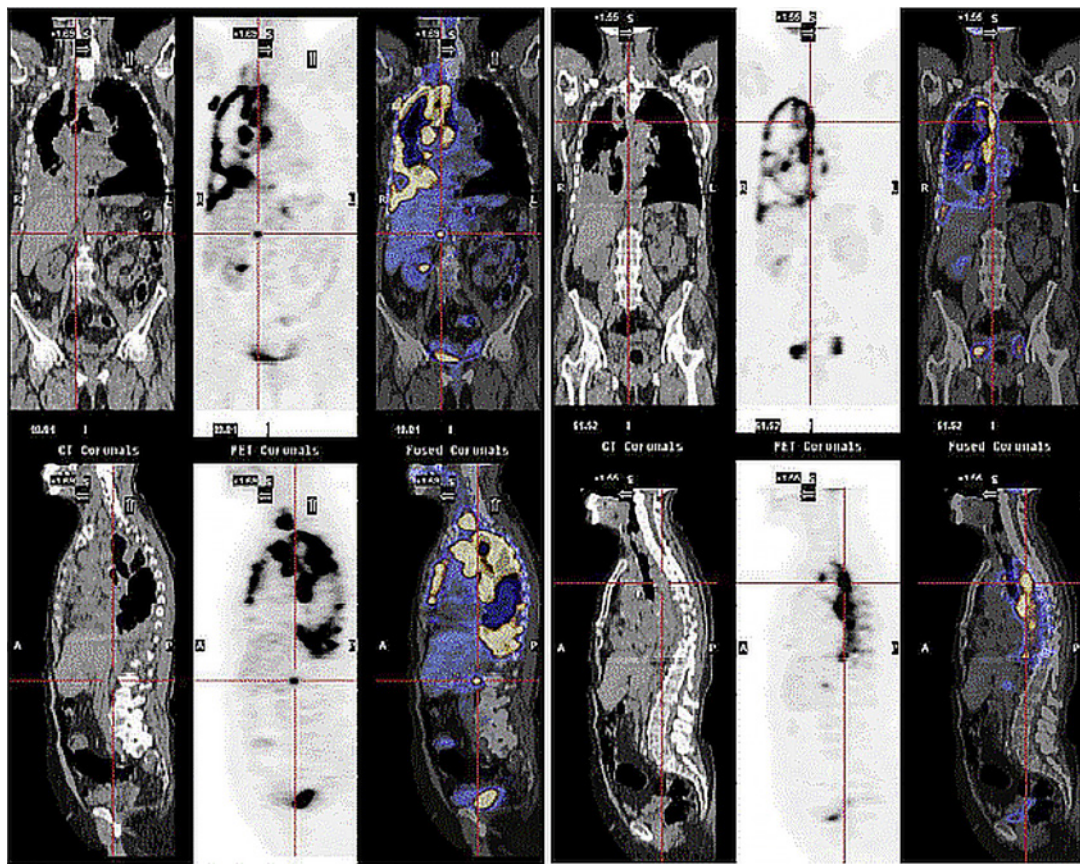


Fig. 1. 18F-FDG-PET/CT scan from March 2019.

lymph nodes, stable pleural disease, and response of bone lesions. Cardiac surveillance was maintained with electrocardiogram every 3 months (Fig. 2).

Currently, she maintains treatment with good tolerance. Performance status remains stable (ECOG-PS 1), and pain is well controlled. Over these 22 months on dabrafenib/trametinib, successive CT imaging shows a slight gradual growth of lymph node metastasis but with stability of bone and pleural disease (Fig. 3).

Discussion

The BRAF V600E genotype in PTC is generally associated with aggressive clinical phenotypes and worse survival outcomes compared to BRAF wild type. In the literature, the prevalence of this mutation is described with disparate percentages ranging from 25.4% to 89.0%.

We know that in metastatic PTC, once refractory iodine-131 status is reached, a parallel phenomenon of cellular dedifferentiation takes place. Reversing this process is the basic concept for the approval of tyrosine kinase inhibitors (TKIs), and the focus of the most recent research activity that seeks to reverse this dedifferentiation by interfering with various pathways (with emphasis on the mitogen-activated protein kinase [MAPK] pathway). To date, several combinations have shown benefit in preclinical studies and there is already a possible role for immunotherapy in the approach to metastatic PCT refractory to iodine-131.

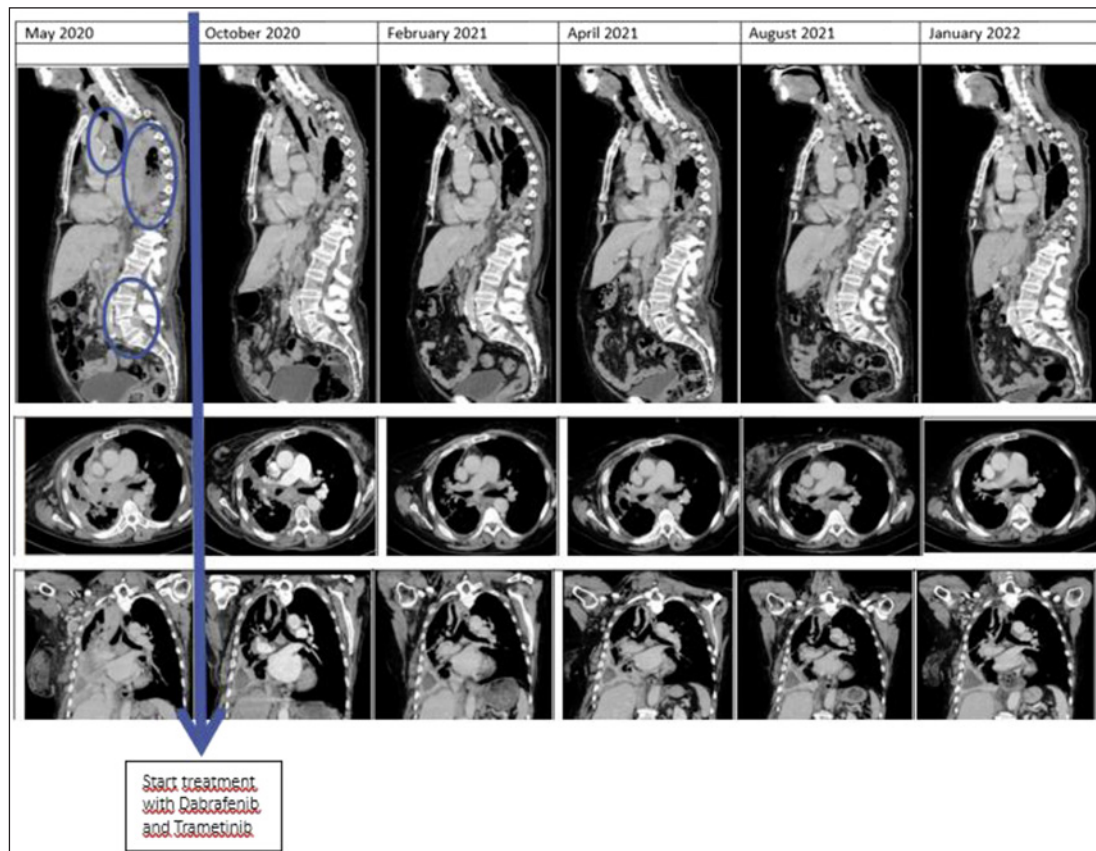


Fig. 2. Temporal evolution in CT imaging.

Despite this, the acquisition of resistance to MAPK pathway inhibition may be a concern and therefore, drugs with alternative targets remain under investigation.

All these concepts are based on a genetic and molecular perspective of PTC. A more standardized use of detection/sequencing tools could help clarify these possible treatment targets. The accessibility of these tools is a pertinent issue, being available only in large centers and often with broad-spectrum and therefore very expensive tests.

The clinical case described is intended as a reflection on all these concepts. This real life case in which an important clinical gain was achieved by the accessibility of a molecular and genetic assessment tool. The identification of a therapeutic target, for which there is an approved drug combination, and whose toxicity is perfectly manageable, is a major benefit from the perspective of the patient and the accompanying clinician. The results show how, in iodine-131 refractory and TKI intolerant settings, inhibition of the BRAF/MEK pathways is effective in reversing exuberant symptoms. BRAF/MEK inhibition can be considered one of the pathways to reverse dedifferentiation and has, in this case, a sustained effect for almost 2 years now. Lenvatinib was discontinued not due to therapeutic failure but due to intolerance to side effects. Tolerance should be a primary consideration when choosing treatment and investigating new agents.

Knowing this, should we do genetic and molecular testing of all patients with metastatic PTC? If so, would it be beneficial to do it before or after the iodine-131 refractory setting?

There are several ongoing studies with targeted therapies and immunotherapy, in monotherapy or combinations. The next few years will certainly bring exciting new developments in the approach to metastatic PTC.

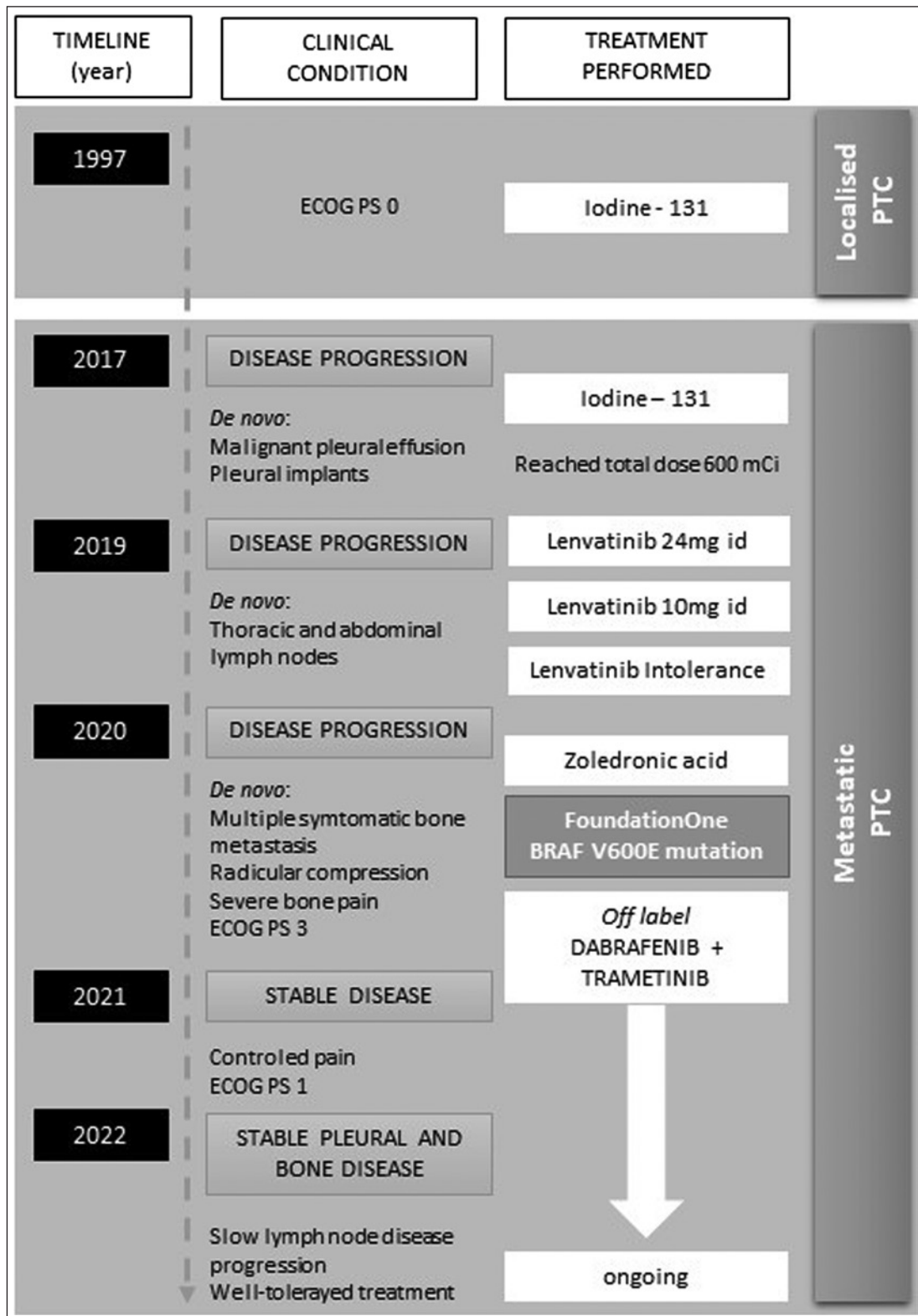


Fig. 3. Treatment approach timeline.

Conclusion

We demonstrate how, in rare tumors, it is important to study the genetic/molecular profile in order to personalize treatment and increase therapeutic options.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for the publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Joana S Reis: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Inês Costa; Mariana Costa; Ana Carmo Valente; Marta Baptista Freitas; Catarina Lopes Almeida; Marina Gonçalves; Carina Teixeira: drafting the work or revising it critically for important intellectual content. Catarina Fernandes: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content. Cláudia Caeiro; Maria Ribeiro; Miguel Barbosa: final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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