Chapter 43
A Patient with *BRAF*V600E-Mutated Anaplastic Thyroid Cancer with Metastatic Disease

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Anaplastic thyroid cancer (ATC) is a deadly disease, and, until recently, little progress had been made to change the outcomes of these patients. In 2018, the US Food and Drug Administration (FDA) approved a BRAF/MEK inhibitor combination, dabrafenib/trametinib, for *BRAF*V600E-mutated ATC. These drugs are highly efficacious in this ATC subtype, and therefore, *BRAF*V600E status is now part of the initial evaluation for all ATC patients. Dabrafenib/trametinib is now the standard of care for BRAFV600E-mutated ATC patients in the USA.

Case Presentation

A 72-year-old woman presented to the local emergency room with dyspnea and palpitations. She was found to have a right-sided neck mass, a pulmonary embolism, and a large pleural effusion. Thoracentesis was performed, revealing metastatic adenocarcinoma, positive for PAX8 (diffuse) and TTF-1 (weak) and negative for thyroglobulin and estrogen receptor, compatible with a thyroid primary. Ultrasound of the neck revealed a 5.5 cm partially cystic mass in the right supraclavicular region and multiple thyroid nodules. CT scan of the neck and chest revealed

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similar findings as well as mediastinal adenopathy. Taken together, the clinical picture was consistent with stage IVC ATC. The patient subsequently underwent biopsy of the supraclavicular mass, which showed poorly differentiated carcinoma. The patient was referred to an academic cancer center.

On initial staging FDG-PET/CT, shown in Fig. 43.1, (panel a), a large right necrotic mass adjacent to right thyroid hypermetabolic nodule was identified. Additional sites of disease included bilateral cervical lymph nodes, bilateral pulmonary nodules, a left sternal bone metastasis, and paracaval lymph nodes. An MRI of the brain showed no evidence of metastatic disease.

Fine-needle aspiration with cell block preparation of the supraclavicular lesion was performed in order to obtain immunohistochemistry staining for *BRAF*V600E. The biopsy showed high-grade, poorly differentiated carcinoma with squamoid features, positive for PAX-8, TTF-1, and *BRAF*V600E. She was started on dabrafenib 150mg twice a day and trametinib 2mg once daily by mouth. The patient noticed a rapid reduction in her neck mass. Restaging FDG-PET scan performed 2 months after starting dabrafenib/trametinib (Fig. 43.1, panel b) showed significant reductions in size and FDG avidity within the right supraclavicular mass, right thyroid nodule, sternal metastasis, bilateral lung, pleural, and nodal disease in the chest and abdomen. The patient's disease has remained stable on dabrafenib/trametinib.

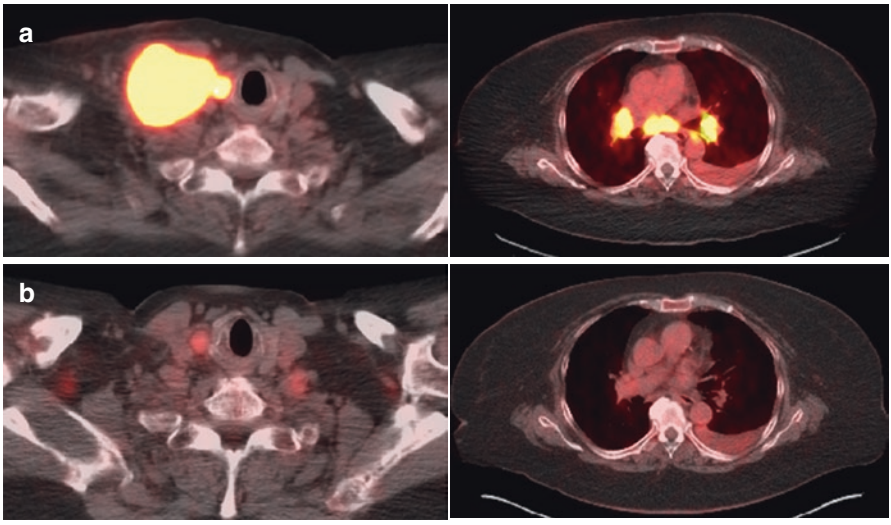

Fig. 43.1 Pre- and post-treatment FDG-PET/CT imaging. (**a**) Baseline FDG-PET/CT imaging showing a right supraclavicular mass with an SUV of 32, a small right-sided thyroid nodule in the neck (left panel), and multiple mediastinal adenopathy and left pleural effusion (right panel). (**b**) FDG-PET/CT was performed after treatment with dabrafenib/trametinib for 2 months, showing near resolution of metastatic lymphadenopathy in the neck and lungs. The right thyroid nodule shows significantly less metabolic activity

Assessment and Literature Review

ATC is a rare form of thyroid cancer and the most aggressive. The clinical picture is of a rapidly growing neck mass causing dyspnea, stridor, hoarseness, and/or dysphagia. Because ATC is often derived from well-differentiated thyroid cancer ("anaplastic transformation"), patients may report a history of prior thyroid cancer. The diagnosis of ATC can be made via fine-needle (FNA), core, or incisional biopsy. Core biopsy or FNA with a cell block preparation is preferred, to allow for immunohistochemical staining for BRAFV600E and molecular testing. Image guidance is helpful to avoid tumor areas with significant necrosis to increase diagnostic yield.

*BRAF*V600*E* is the most common actionable mutation in ATC and influences initial treatment. Thus it must be assessed at diagnosis in all ATC patients. Although next-generation sequencing (NGS) of tumor is the gold standard for molecular testing, results can take several weeks to obtain. Therefore, rapid methods are used as an adjunct to NGS. The most rapid method is immunohistochemistry (IHC) staining for BRAFV600E protein [1]. This test should only be performed on FNA cell blocks or core/surgical specimens to maximize accuracy. The second test is cell-free DNA (cfDNA) on peripheral blood specimens [2, 3]. The pathologic diagnosis is at times difficult to make, as this is a rare tumor and there are many pathologic morphologies, some of which can mimic other cancers. For example, the squamous morphology is often confused with squamous cell carcinoma of the head and neck or lung.

Assessment of the airway, staging, and *BRAF*V600E status should be performed quickly and in tandem, in order to initiate treatment as soon as possible. The first step is to ensure that the airway is secure. The airway may be threatened by vocal cord paralysis, laryngeal edema, external compression, and/or direct invasion by disease. Laryngoscopy should be performed on all patients with a new diagnosis of ATC. Tracheostomy may be necessary to secure the airway in patients presenting with significant respiratory distress. Patients without respiratory distress or concerning physical exam findings may not require upfront prophylactic tracheostomy. Imaging of the neck and chest with contrast is necessary for staging and determination of resectability. Cross-sectional imaging with CT or MRI of the body and brain is also necessary to determine the extent of disease at other sites, as 50% of patients have distant metastases at diagnosis. FDG-PET/CT is very helpful with identifying areas of metastasis that may be difficult to evaluate with cross-sectional imaging alone.

Once staging is complete and *BRAF*V600E status has been determined, further treatment planning can start. Surgery can be considered as the primary treatment for stage IVA patients who are fit for surgery and can undergo resection without significant morbidity. Stage IVB patients (nodal metastasis or disease extending outside the thyroid without distant metastasis) with resectable disease may also be considered for upfront surgery on a case-by-case basis with goals of achieving complete resection. Surgery that leaves behind gross disease (R2) is not beneficial to patients and should not be performed. Furthermore, radical surgery such as laryngectomy

and/or esophagectomy is not recommended in ATC patients. Stage IVB patients who do not have a *BRAF*V600E mutation and cannot be treated with surgical resection should receive external beam radiation to the neck with concomitant chemotherapy. Those who do have *BRAF*V600E-mutated stage IVB ATC may also undergo upfront chemoradiation. However, a newer approach to these patients is to start neoadjuvant dabrafenib plus trametinib and later undergo surgical resection followed by chemoradiation [4]. Ongoing clinical trials are evaluating whether this approach leads to improved survival.

Until recently, there were no effective systemic therapies for patients with stage IVC disease (distant metastasis). Targeted therapy against *BRAF*V600E with dabrafenib plus trametinib has shown high response rates (69%) and improved survival [5]. The median progression-free and overall survival were 14 and 20 months in clinical trial, respectively [6]. The BRAF/MEK inhibitor combination, dabrafenib/trametinib, is now approved in the USA and considered the standard of care for patients with tumors harboring a *BRAF*V600E mutation. It should be recognized, however, that the clinical trial that led to the approval enrolled only patients able to swallow whole pills. This likely biased the patient population. Others have reported shorter median overall survival [7, 8] and treatment resistance [9]. Thus, newer approaches to deter resistance, such as the addition of immunotherapy to the BRAF/MEK inhibitor combination [10], are being studied at this time.

In addition to *BRAF*V600E, gene fusions, particularly *NTRK* and *RET* fusions, are also potentially actionable in patients with ATC. There are currently selective NTRK and RET inhibitors approved for solid tumors harboring these fusions [11–14]. However, these alterations are rare in ATC, and response rates have not been established in a larger population of ATC patients.

Patients without an actionable mutation or fusion still lack effective therapies. Thus, patients with stage IVC without a *BRAF*V600E mutation should be referred for clinical trials. Emerging research suggests that the anti-PD1 checkpoint inhibitor, spartalizumab, may have efficacy in ATC patients with high PD-L1 expression and in those without a *BRAF*V600E mutation [15]. Combinations of checkpoint inhibitors [16] or checkpoint inhibitors plus targeted therapy [10] have also been studied in ATC and appear promising.

Clinical Pearls/Pitfalls

- *BRAF*V600E mutation status is now part of the initial evaluation of ATC patients.
- Rapid BRAF testing should be performed by immunohistochemistry on tumor biopsy specimens and/or assessment of cell-free DNA in peripheral blood.
- Dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) are effective for ATC patients with *BRAF*V600E mutation and now the standard of care.
- Stage IVC ATC patients without a *BRAF*V600E mutation should be treated within the context of a clinical trial, as there are still no effective therapies for these patients.

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