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Case Report

Visceral Perforation Complicating BRAF/MEK Targeted Therapy of Papillary Thyroid Carcinoma with Anaplastic Areas

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Simple Summary: Anaplastic thyroid cancer is an aggressive type of thyroid cancer. In recent years, treatments have been developed which target mutations in the BRAF/MEK pathway seen in some cases of anaplastic thyroid cancer. This case report describes a patient with anaplastic thyroid cancer who had a such a rapid and successful response to this targeted therapy that they experienced life threatening complications.

Abstract: Anaplastic thyroid cancer (ATC) is considered to be one of the most virulent, treatment-refractory malignancies. Recent molecular insights into the biology of thyroid cancer have transformed ATC management, and BRAF/MEK targeted therapy is now incorporated into guideline-based multidisciplinary care. We report visceral perforation in the setting of an extreme response to such therapy in a patient with ATC. Molecularly targeted therapy afforded a dramatic but life-threatening response to treatment. This report highlights the complexities of care for the patient and treating clinicians.

Keywords: anaplastic thyroid carcinoma; targeted therapy; perforation; complications

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1. Introduction

Historically, a diagnosis of anaplastic thyroid cancer (ATC) carried a median overall survival of 3–6 months with a 1-year survival rate of 20% [1,2]. This prognosis was related to its invasive potential with local infiltration of vital neck structures and the rapid development of distant metastases. These characteristics were compounded by the refractoriness of ATCs to standard chemotherapy agents and radiotherapy [3].

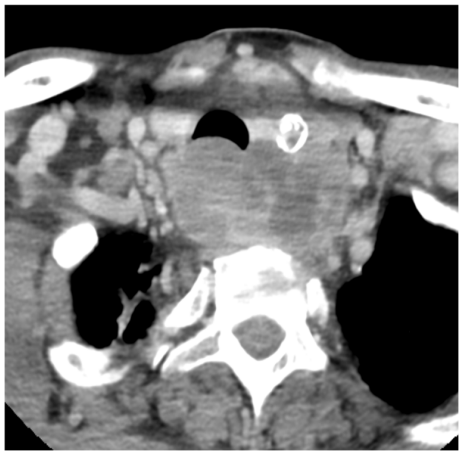
The V600E mutation in the BRAF (V-Raf murine sarcoma viral oncogene homolog B1) oncogene has been identified in melanoma and other solid tumor malignancies such as thyroid cancers. The mutation is reportedly found in 10–50% of ATCs [4,5]. Initial successful use of BRAF V600E targeted therapies in melanoma has been followed by their combination with MEK (mitogen-activated protein kinase) inhibitors, and subsequent extension of their use in other cancer types, including rare tumors [6]. The use of BRAF-

and MEK-targeting drugs in ATC is described in several basket studies, small single-arm studies, and case reports [7–10].

These reports of activity in previously treated patients have led to guideline integration into first-line treatment of suitably selected patients, including as a bridging strategy in potentially resectable disease [11]. Cohort studies have demonstrated improved survival with such strategies [12]. In this report we review life-threatening complications of targeted therapy in a patient with newly diagnosed ATC. This is a rare complication of a rare malignancy, and, at present, there is very limited available data detailing such a presentation.

2. Case Report

As outlined by the accompanying patient testimony, a 65-year-old gentleman presented with a 6-week history of dysphagia. Computed tomography (CT) imaging of the thorax, abdomen, and pelvis, and magnetic resonance imaging (MRI) of the neck revealed a 7.2 centimeter (cm) mass centered in the left lobe of the thyroid. The mass involved the cervical esophagus and posterior tracheal wall, leading to moderate cervical tracheal airway narrowing and invasion of both the prevertebral fascia and the posterior arch of the cricoid with metastatic right level 2, bilateral level 3, and bilateral level 4 neck nodes (shown in Figures 1 and 2). A 12 millimeter (mm) right hilar node and right paratracheal and subcarinal nodes of less than 10 mm were suspicious for malignant involvement (Stage IVC) [13].



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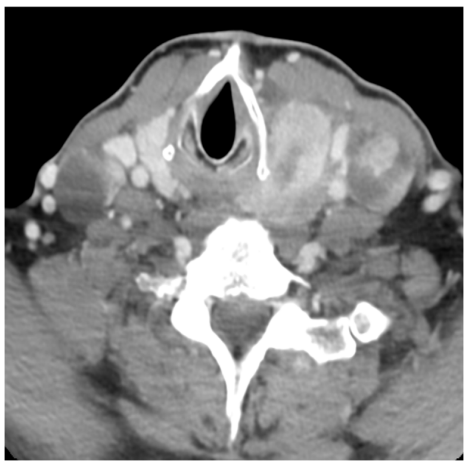

(**B**)

Figure 1. Pre-treatment CT imaging demonstrated a heterogeneous mass centered in the left thyroid with enhancing, calcified, and hypo-enhancing components invading the esophagus and trachea with enhancing neck adenopathy (**A**,**B**). (**A**) Axial image at the level of the second thoracic vertebra. (**B**) Axial image at the level of the sixth cervical vertebra.

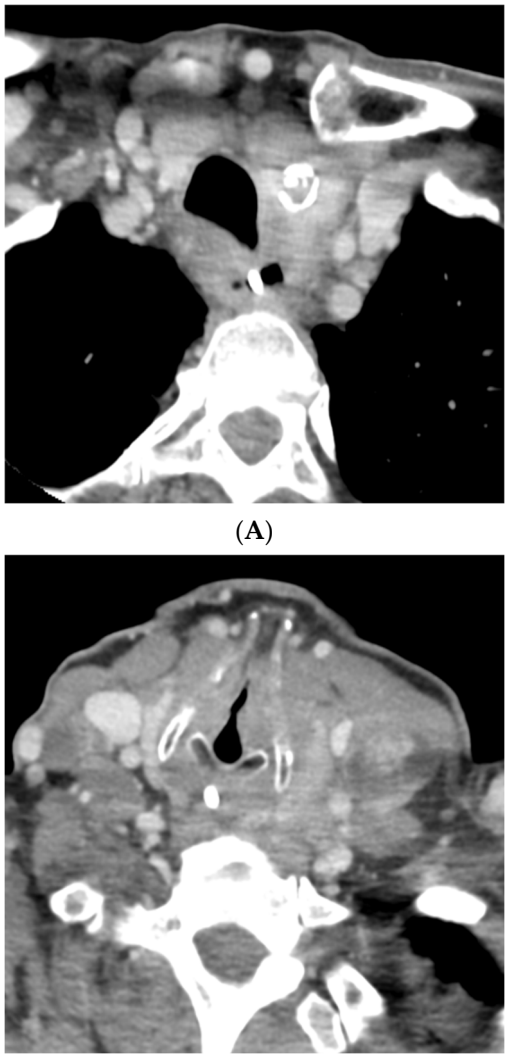

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Figure 2. A follow-up CT of the neck and thorax performed 12 days later demonstrated a significant decrease in the hypo-enhancing (likely anaplastic) component of the mass with residual enhancing mass and adenopathy (likely papillary component) (**A**,**B**). (**A**) Axial image at the level of the second thoracic vertebra. (**B**) Axial image at the level of the sixth cervical vertebra.

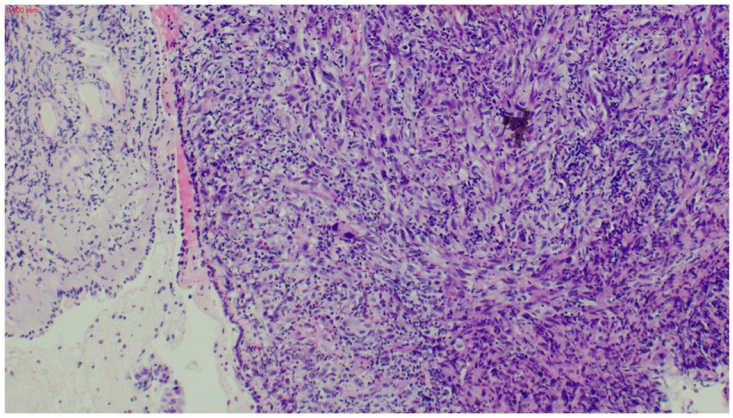
Fine needle aspiration of bilateral level III neck masses in addition to a biopsy of the thyroid mass demonstrated malignant cytology, consistent with papillary thyroid carcinoma (PTC).

Further sectioning of a cell block found a small quantity of tumor (10%) demonstrating a BRAF V600E mutation. NRAS mutations were not detected. The patient underwent pan-endoscopy with rigid esophagoscopy. A left tracheal biopsy demonstrated respiratory-type mucosa with an underlying infiltrative tumor, which appeared highly pleomorphic, consistent with a poorly differentiated carcinoma and consistent with ATC (shown in Figure 3). An upper esophageal biopsy showed clusters of malignant cells with similar appearances to the tracheal biopsy. An incidental pulmonary embolism was detected and anticoagulation was initiated.

The case was discussed at the regional Head and Neck multidisciplinary team meeting (MDM), which advised of the presence of locally advanced PTC and ATC. The case was not amenable to surgery due to esophageal involvement and unreconstructable tracheal involvement. The patient commenced encorafenib 450 milligram (mg) once daily and binimetinib 45 mg twice daily (EB) in a neoadjuvant approach [14]. Encorafenib inhibits the

BRAF gene, which encodes for B-raf protein, which is a proto-oncogene. Binimetinib is a mitogen-activated protein kinase 1/2 (MEK 1/2) inhibitor. A clinical response was noted by day 3 with improving dysphagia. On day 5 of EB treatment, while attending hospital, the patient collapsed with a large volume hematemesis. Gastroscopy (shown in Figure 4) and bronchoscopy revealed erosion of the esophagus with resultant hemorrhage and the presence of a tracheo-esophageal fistula. CT imaging 12 days following initiation of EB therapy confirmed treatment response with a decreasing left thyroid mass but unchanged neck and mediastinal lymphadenopathy. Nasogastric feeding was implemented. The fistula was managed conservatively and following demonstration of clinical closure using barium swallow testing, a light oral diet was resumed. Due to concerns regarding tumor flare, a decision was made to administer EB treatment orally with small mouthfuls of yogurt from day 12 after the episode of hematemesis [10]. This was tolerated by the patient without aspiration into the airway. Crushing the binimetinib and opening the encorafenib capsules were considered, but the manufacturing company advised that there was insufficient evidence for its use in this manner at the time [15]. Subsequently, the patient underwent percutaneous gastrostomy tube (PEG) insertion. Repeat endoscopy at the time of PEG insertion demonstrated fistula resolution.

MRI 4 weeks later demonstrated a sustained treatment response. Three weeks later, FDG-Positron Emission Tomography (PET) CT demonstrated uptake in the left lobe of the thyroid gland, bilateral cervical lymph nodes, and superior mediastinal lymph nodes (shown in Figure 5). Subsequent MDM discussion recommended radical thyroidectomy based on data from cohort studies showing improved outcomes [16,17].



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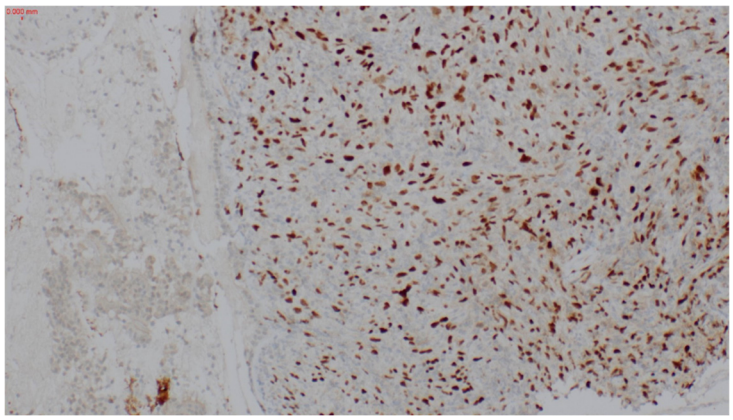

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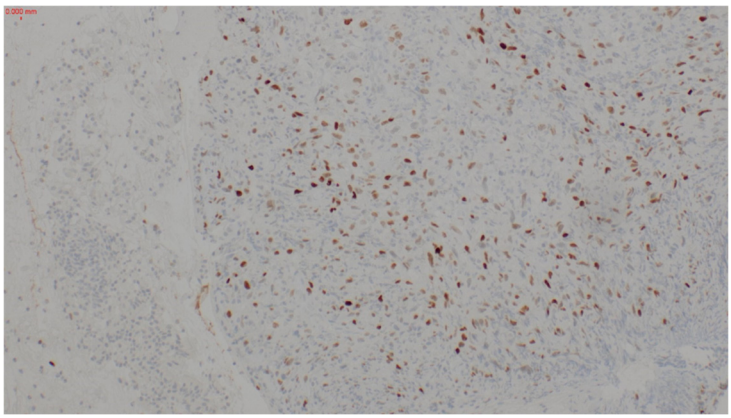

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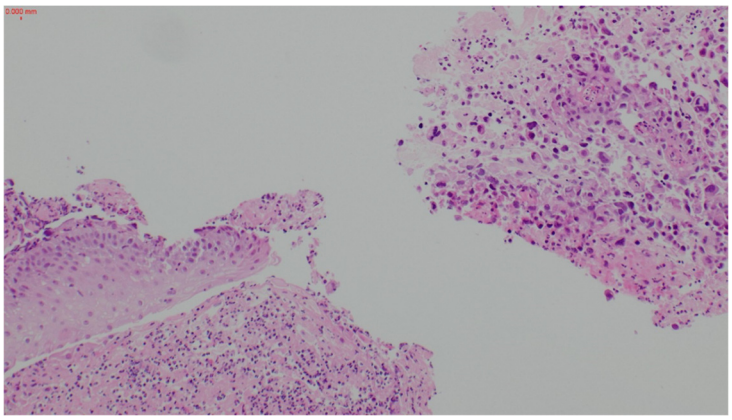
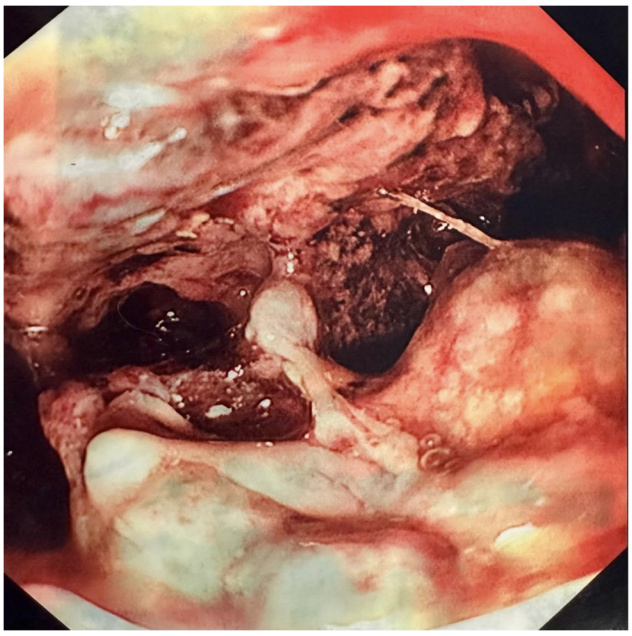


(**D**)

Figure 3. Hematoxylin and Eosin (H&E) stain shows anaplastic thyroid carcinoma involving the trachea, with respiratory epithelium on the surface (10× magnification) (**A**). PAX8 (**B**) and TTF1 (**C**) immunohistochemical stains support the thyroid origin of the anaplastic tumor (10× magnification). H&E stain of the esophageal biopsy demonstrates a superficial fragment of squamous mucosa with necro-inflammatory debris and a separate fragment of tumor (10× magnification) (**D**).



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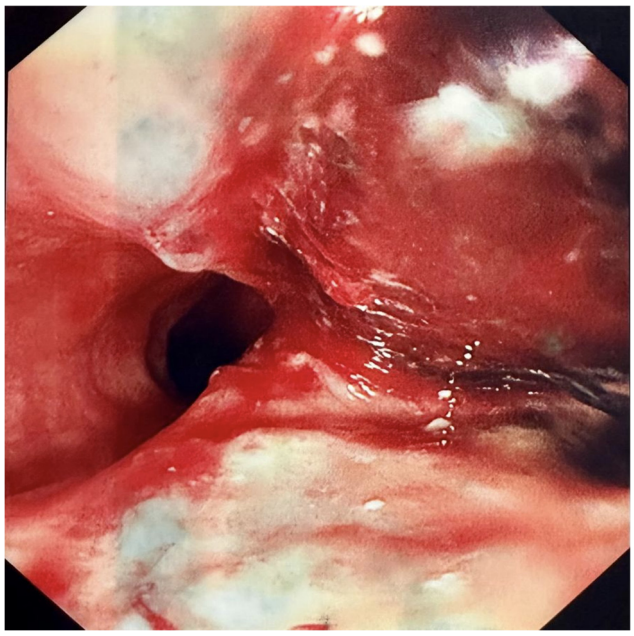

(**B**)

Figure 4. Gastroscopy demonstrated necrotic debris at the site of fistulation with an overlying clot (**A**). The clot was removed using suction. Fistulation was confirmed by passing an endotracheal tube and passing air bubbles via gastroscopy (not pictured). Bubbling was then noted on bronchoscopy, thus demonstrating the passage between the two viscera. Bronchoscopy demonstrated an adherent clot over the site of fistulation (**B**).

Total thyroidectomy, bilateral comprehensive neck dissection, and central and superior mediastinal nodal dissection were performed, with a surgical impression of complete removal of all gross tumor and abnormal lymph nodes.

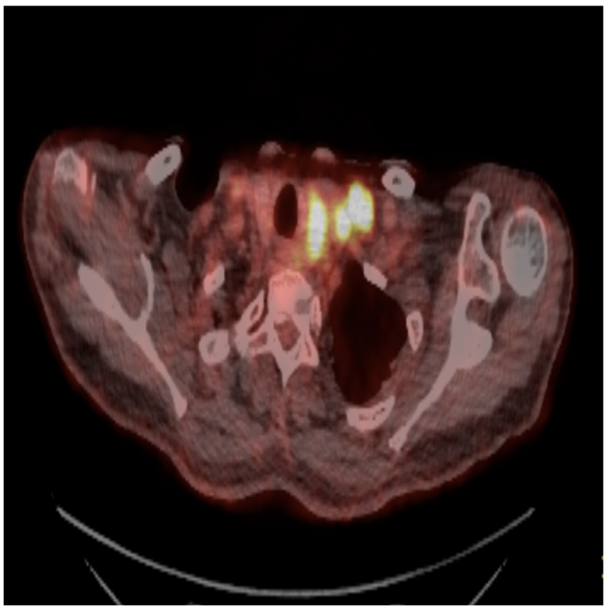

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Figure 5. *Cont.*

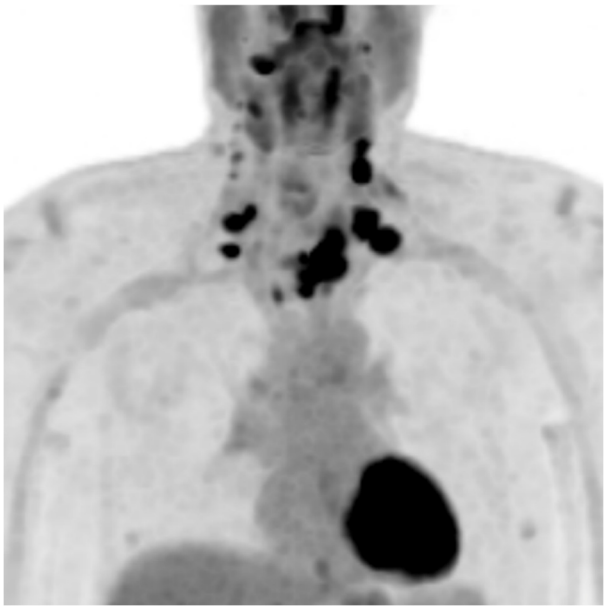

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Figure 5. (**A**,**B**): Pre-operative PET CT demonstrated uptake within the residual component of the left thyroid mass and the bilateral neck adenopathy but no distant metastatic disease.

Pathological investigation demonstrated a 4.5 cm papillary thyroid cancer with extrathyroidal extension and metastatic PTC in 36 of 100 resected lymph nodes with multilevel extranodal extension. A separate fibrotic plaque removed from the esophagus and trachea, corresponding with the area of previously grossly invasive cancer, was negative for tumor. There was no evidence of ATC within the resected tissue. Immunohistochemistry for BRAF V600E demonstrated positive staining, confirming the presence of BRAF mutation in the well-differentiated PTC component (shown in Figure 6).

Following further discussion at both regional and national MDMs, indefinite BRAF/MEK inhibition therapy was recommended in conjunction with radioactive iodine (RAI) adjuvant therapy at a dose of 5.5 GBq (giga-becquerel). Unstimulated thyroglobulin levels were 222 mcg/L pre-therapy, and anti-thyroglobulin levels were <3 mU/L, with levels rising to 316 mcg/L with associated TSH levels of 192 mU/L due to the administration of recombinant human thyroid-stimulating hormone. The nuclear medicine RAI isotope was 131. External beam radiotherapy was not recommended. A post-therapeutic single-photon emission computerized tomography (SPECT) scan was clear of any residual disease. Ten months after initial therapy initiation, the patient remains in remission with no evidence of relapsed disease on surveillance CT imaging.

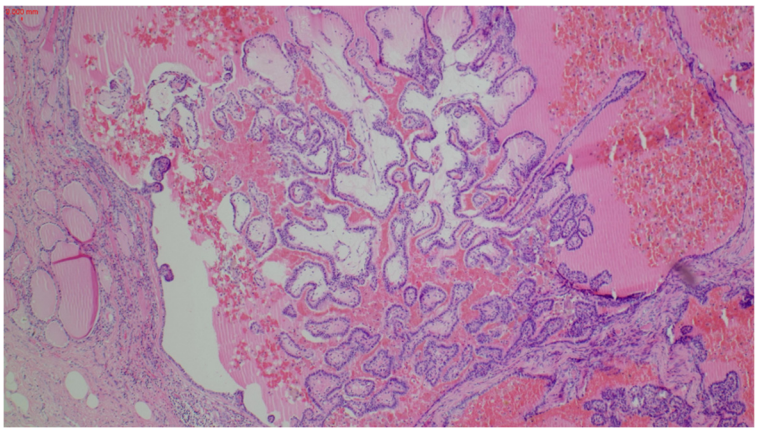
The patient provided the following written testimony regarding his experience:

"I first became aware of the cancer in mid-March 2023, when I found swallowing difficult. Within two to three weeks, I was no longer able to eat meat or hard foods. By early May, scans had revealed I was inoperable due to the extent of the spread of the tumor. I had lost my voice and even eating sloppy porridge was proving difficult. At this point I was put on the targeted therapy, and fortunately, was able to swallow the large pills by taking them gradually during the day. At no stage were there any noticeable side effects to taking the pills.

On the third day of taking the pills I noticed a small easing in swallowing. This had increased by the fourth day. On the fifth day, I travelled to hospital for a biopsy but collapsed hemorrhaging as the tumor had shrunk so rapidly that it ruptured the esophagus. I do not remember this. I was not expected to survive the day, but I did. I was then not expected to survive the week, but I did. All thanks to the amazing hospital staff.

Within four days I was back on the targeted therapy. My voice had returned a little. Soon the tumor, that had been visible externally, was much diminished. By the time I left

hospital, I was allowed to eat yogurts, but soon was able to consume more diverse foods. This time the restriction on foods was related to the damage to the esophagus, as I no longer felt the intense restriction on swallowing.



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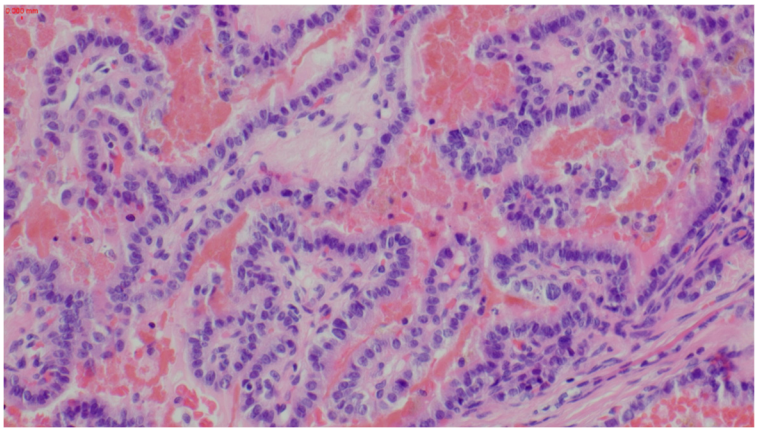

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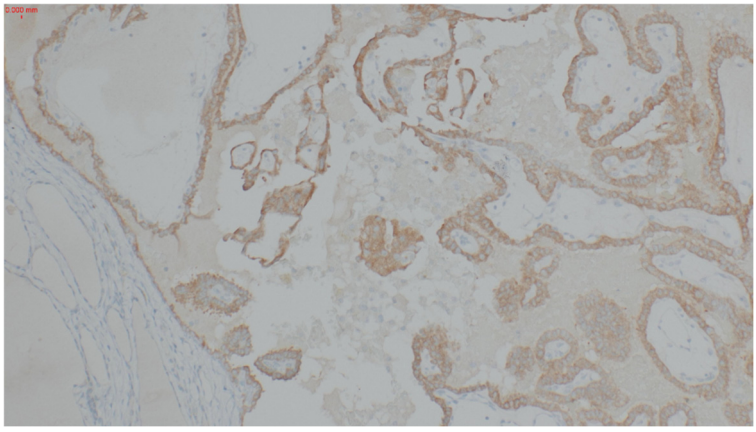

(**C**)

Figure 6. (**A**–**C**): Hematoxylin and Eosin (H&E) stain of the resected papillary thyroid carcinoma ((**A**) = H&E at 4× magnification; (**B**) = H&E at 20× magnification; (**C**) = BRAF immunostain at 10× magnification).

The treatment did not have any negative effect on my daily life, and I was able to build up the strength to return to basic activities. Taking the pills is now just part of my daily routine. The pills gave me hope when I had none and saved my life".

3. Discussion

This case describes an incidence of extreme response to targeted therapy with life-threatening visceral perforation. The perforation was associated with a pathological complete response to targeted therapy in that ATC, which had initially infiltrated tissues concordant with its clinical notoriety, and was not detected in subsequent thyroidectomy and nodal dissection.

Treatment-related perforations are commonly associated with some malignancies such as lymphoma but are rarely reported in solid tumor malignancies [18,19]. When present, perforations develop in the treatment of lymphoma at a median of 46 days (range 2–298 days) after commencing systemic therapy, with 44% occurring within 4 weeks as in the present case [18].

Local complications following the use of targeted therapy in ATC have been documented. One case report describes the use of lenvatinib, which is a multiple receptor tyrosine kinase inhibitor, in recurrent ATC, after surgical resection of stage IVC disease in which the patient suffered a carotid artery aneurysmal rupture 19 days after commencing treatment [20].

Staub and colleagues published a retrospective study analyzing the use of lenvatinib in patients with thyroid cancer [21]. Sixteen patients, including nine with PTC and three with ATC, were included. Most patients had previous curative surgical resections (13/16) or radio-iodine therapy (9/16), and some had previous external beam radiotherapy (6/16). Three patients suffered fistulae or a tumor bleed in response to treatment with lenvatinib; two of these cases occurred in patients with ATC. Statistical analysis determined that ATC was a risk factor for developing such a complication (Odds Ratio 3.19; 95% CI: 1.61–1.98; $p < 0.033$).

In the present case, the rapid onset of perforation was concordant with a response to therapy within days of starting treatment. To our knowledge, such a response is unique and has not been observed in case reports, case series, or cohort studies reviewed for this manuscript [7,10,15,16,19,20]. Our patient was fortunately attending hospital for a routine follow-up visit when he collapsed due to hemorrhage and associated perforation.

ATC derives from well-differentiated thyroid carcinomas (WDTCs) such as papillary and follicular carcinomas [22,23]. Nikiforova and colleagues analyzed 320 thyroid tumors and nodules for BRAF mutations. They concluded that BRAF mutations arose only in PTC and poorly differentiated and anaplastic carcinomas deriving from BRAF mutant PTC [24]. This is now widely recognized to be the case [25,26]. In contrast to the pathological complete response observed in the ATC component in the present case, the PTC component showed little radiological or pathological response, despite harboring an identical BRAF-sensitizing mutation. Other studies have demonstrated poor response rates to BRAF/MEK targeted therapies in PTC as in the present case [27,28]. Several investigators have demonstrated the accumulation of additional genetic abnormalities as PTC transforms to ATC. These include the development of "katageis" with focal hypermutability, and alterations in cyclin kinase genes regulating the cell cycle [3,29,30]. It is possible that such changes sensitize the cell to targeted therapy. Comprehensive evaluation with a whole genomic outlook and RNA sequencing, as was performed by these investigators, has not been performed in the present case.

The paradigm for the management of thyroid malignancies has evolved significantly in the past two decades. Food and Drug Administration approval for the use of BRAF/MEK inhibitor combinations in ATC was obtained based on the results of an open-label, phase 2 clinical trial, which enrolled 100 patients with BRAF V600E-mutated malignancies to receive dabrafenib and trametinib (DT) [7]. The overall response rate amongst the 16 ATC patients enrolled was 69% (11/16 patients; 95% CI: 41–89%) with 7 ongoing responses at the time of data cut-off. Although median progression-free and overall survival rates were not reached at time of data cut-off, the 12-month estimates were 79% and 80%. Such figures contrast sharply with historical data [1,2]. Consequently, National Comprehensive Cancer Network (NCCN) guidelines for management of ATC recommend molecular testing to inform systemic therapy options and available clinical trials [31]. When systemic therapy is indicated, the NCCN recommends the use of targeted therapies. Systemic therapy

options include larotrectinib or entrectinib for NTRK (Neurotrophic Tyrosine Receptor Kinase) gene-fusion-positive tumors, selpercatinib for *RET* (Rearranged during transfection) gene-fusion-positive tumors, and pembrolizumab (a humanized monoclonal antibody against programmed death 1 [PD-1] ligand) for tumors with a high tumor mutational burden ($\geq$10 mut/Mb) and *BRAF*-targeted therapies [32–36]. In the present case, EB was prescribed as a therapy based on its favorable toxicity profile and favorable prior institutional experience.

Current guidelines highlight the need for a multimodality approach to the management of ATC [31,37]. In recent years, clinicians have trialed short periods of targeted therapy in a neoadjuvant setting for ATC to minimize the extent of surgery or to achieve resectability in initially unresectable disease [12,38]. One case series described complete surgical resection following neoadjuvant DT in six patients with initially unresectable, BRAF V600E-mutated ATC [36]. Three of the patients also received perioperative pembrolizumab. A complete surgical resection was achieved in all cases. OS at 6 months was 100% and OS at 1 year was 83% (5/6 patients). Pathological assessment of resected samples detected $\leq$5% tumor viability in 83% of resected tumors [38]. This case series represented the first prospective demonstration of the feasibility and effectiveness of a neoadjuvant approach using DT in patients with initially unresectable BRAF-mutated ATC. Subsequently, Maniakas and colleagues reported their 20-year experience in the treatment of 479 patients with ATC [12]. In this cohort of 479 patients, 23 received surgery following neoadjuvant treatment; 20 of these were BRAF-targeted therapies; the other three patients received chemotherapy or a checkpoint/MEK-inhibitor combination. The 1-year survival rate of the 20 patients (8 of whom had presented with stage IVC disease) treated with neoadjuvant BRAF-directed therapies followed by surgery was 94%, compared to 52% in 35 patients treated with a BRAF/MEK-inhibitor combination without tumor resection. A recently published case series described the use of BRAF and MEK inhibitors in two cases of ATC previously adjudged to be unresectable. This resulted in a partial response in each case and conversion to resectability in one of the cases [39]. These studies formed the basis for the decision to proceed to thyroidectomy in the present case.

Radioiodine (Iodine –131) therapy is the treatment of choice following resection of intermediate- and high-risk WDTC [31]. BRAF mutant PTC and poorly differentiated thyroid carcinomas demonstrate poor response rates to standard radioiodine treatment [40]. The absorption of radioactive iodine by cells is associated with a sodium-iodine symporter. There is reduced expression of this symporter in poorly differentiated thyroid cells, thus impacting the efficacy of RAI in these patients [40]. However, it has been demonstrated that BRAF/MEK inhibitor treatment can stimulate radioiodine uptake in these cancer cells and restore the therapeutic benefit of radioiodine therapy [41].

4. Conclusions

Anaplastic thyroid cancer (ATC) is considered to be one of the most virulent, treatment-refractory malignancies. Recent molecular insights into the biology of thyroid cancer have transformed ATC management, and targeted therapy is now incorporated into guideline-based multidisciplinary care. This case report contributes to limited published data demonstrating life-threatening complications following response to targeted therapy in ATCs. The patient's subsequent favorable outcome has been transformative as he outlines in his testimony. This report highlights the complexities of care for the patient and treating clinicians. Further studies are needed to discern treatment paradigms for patients with BRAF/MEK-refractory or unresponsive disease in order to extend the benefits of this transformative therapy to all patients with ATC.

Author Contributions: Concept: S.L.B. and S.O.; data collection: all authors; manuscript writing: all authors. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Independent ethical committee approval was not required given the nature of this single-patient case report.

Informed Consent Statement: Written informed consent has been obtained from the patient for publication of the case report and accompanying images.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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Conflicts of Interest: The authors declare no conflict of interest.

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