

# Cancer of the Grave: A Rapidly Growing Anaplastic Thyroid Cancer with NRAS and TP53 Mutation: Molecular Understanding and Therapeutic Hopes

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**Abstract** Anaplastic thyroid cancer (ATC) is the rarest form of thyroid cancer known to humans. Among the other thyroid neoplasms, ATC is the deadliest, with unified mortality of almost 100%. With the advances in thyroid ultrasounds and screening protocols, the incidence of ATC increases, which correlates with the increase in papillary thyroid cancer (PTC) that is believed to be the precursor of most ATC. We herein describe a rare case of a 69-year-old Caucasian male with no known past medical or surgical histories who presented with a rapidly growing neck mass that was later confirmed as an undifferentiated anaplastic thyroid carcinoma with a mutation in NRAS and TP53 progressing in two months period into a complete seeding of lungs with metastasis. This case highlights the importance of studying and understanding thyroid oncogenesis's molecular aspects as recently targeted immunotherapy is promising for particular gene mutations by delaying this graving cancer progression.

**Keywords:** Anaplastic thyroid cancer, NRAS, TP53

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## 1. Introduction

Anaplastic thyroid cancer (ATC) is an undifferentiated tumor of the thyroid follicular epithelium. It is a sporadic form of thyroid cancer with a destructive and graving outcome. The annual incidence of anaplastic cancer is around one to two cases per million persons [1]. ATC accounts for less than 1% of all types of thyroid cancers, with a life expectancy of less than a year following diagnosis [2]. The 10-year overall relative survival rate of ATC and other undifferentiated thyroid cancers in the U.S. found to be the smallest 14% [3]. ATC predominates in the elderly, and similarly to other thyroid cancer subtypes, is more common in females, with two-third of the reported cases being women [4,5].

## 2. Case Report

We describe a case of a 69-year-old Caucasian male with only history of former smoking and no other

pertinent past medical, surgical or family histories who presented to our community-based institution with the onset of rapidly growing neck mass mainly in the left side of his neck associated with increasing pain, shortness of breath, hoarseness of voice and difficulty of swallowing. The patient claimed that his neck was flat until a few weeks before the presentation; vitals were stable with patent airway and physical exam with notably bulky anterior neck mass involving mainly the neck's left side. On inspection, no dilated or engorged neck vessels were noticed. Initial blood work was significant for leukocytosis with a white blood cell count of 41,000 mm<sup>3</sup> and a mild decrease in serum albumin, otherwise unremarkable. Computed tomography (CT) of the neck with intravenous contrast showed a sizeable necrotic mass involving the left thyroid lobe with a significant deviation of Trachea (Figure 1), a thrombus in the left jugular vein was also noted with patency of common carotids (Figure 2). CT scan of Chest/Abdomen/Pelvis for staging revealed non-specific mediastinal adenopathy with right pleural based nodules and urinary bladder mass. Histopathology revealed morphology and immunophenotype consistent with undifferentiated thyroid carcinoma (Figure 3 -

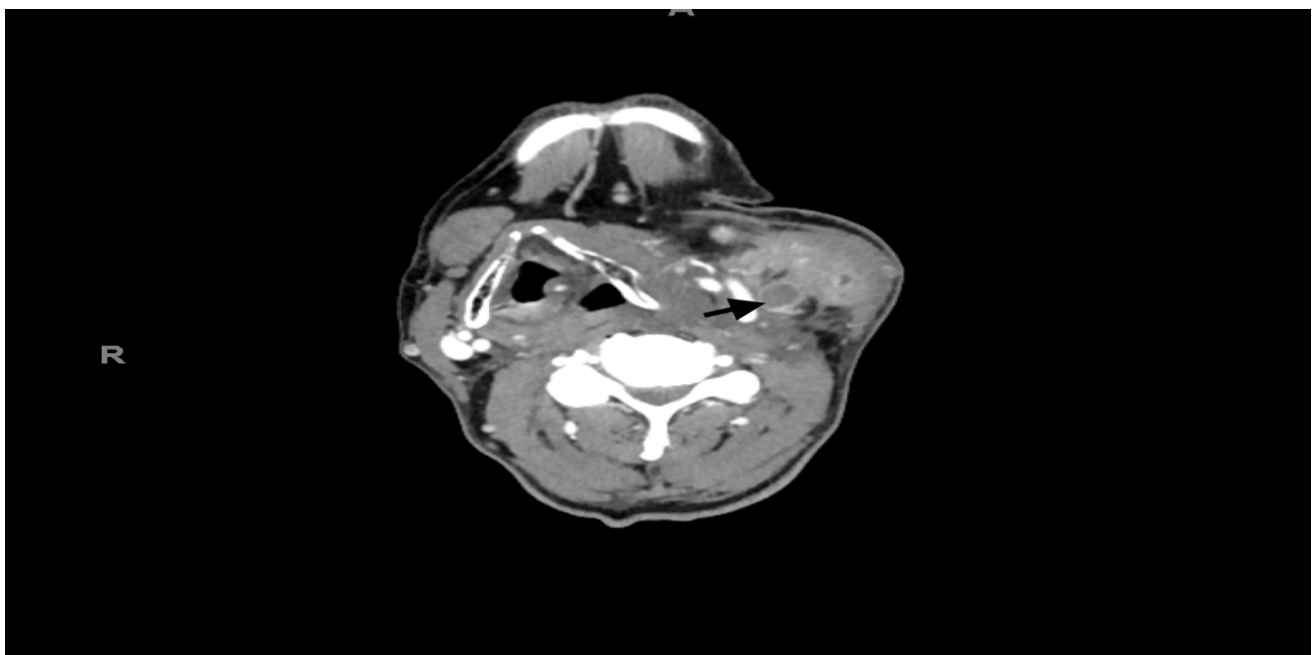
**Figure 6).** further Immunohistochemical staining detected the presence of NRAS and TP53 mutations.

The patient was admitted to the oncology unit under multiple consultants' care, including palliative care, and thereby received chemoradiation therapy with a total of 70 greys (Gy) doses of radiation and seven doses of Cisplatin. For nutritional support, a PEG tube was placed, and the patient was started on Heparin drip later, which was later switched to oral Apixaban for his jugular venous

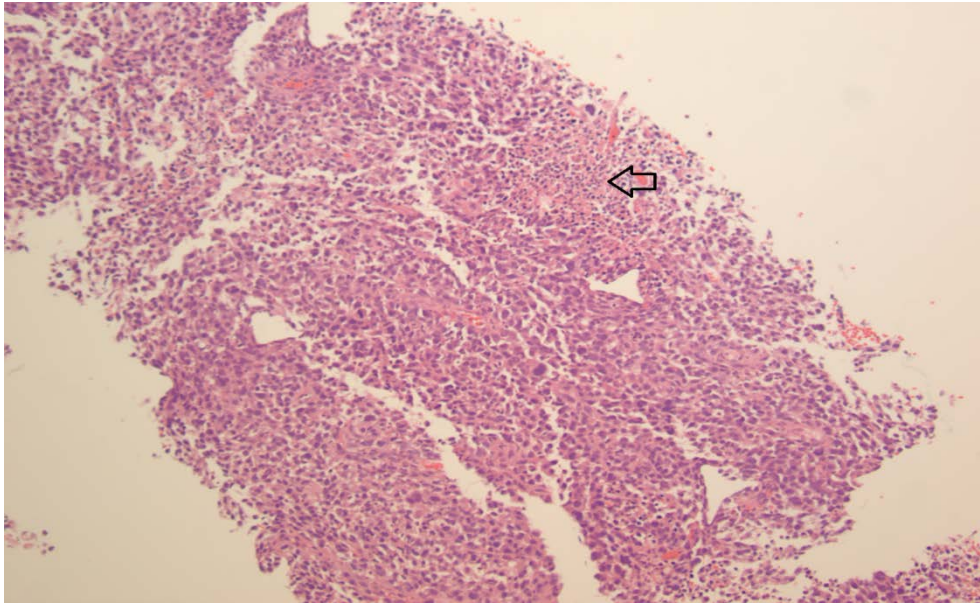
thrombosis. The further diagnostic investigation included thyroid tissue genetic testing by next-generation sequencing that detected mutations in NRAS and TP53. The patient responded initially with a regress in thyroid size and was elected to receive Trametinib therapy but unfortunately, due to rapid change in his cancer's clinical status and fast progression. Care goals were determined to be comfort measures, and subsequently and sadly patient passed away two months following ATC diagnosis.



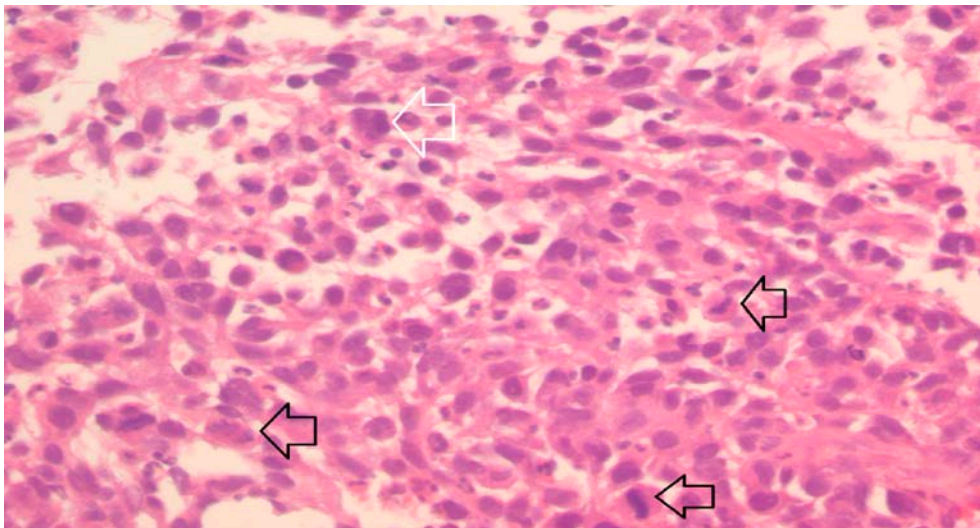
**Figure 1.** Neck CT with contrast showing massive deviation of the trachea to the right and complete encasement of the left common carotid artery. The darker grey background of the mass represents active cancer necrosis



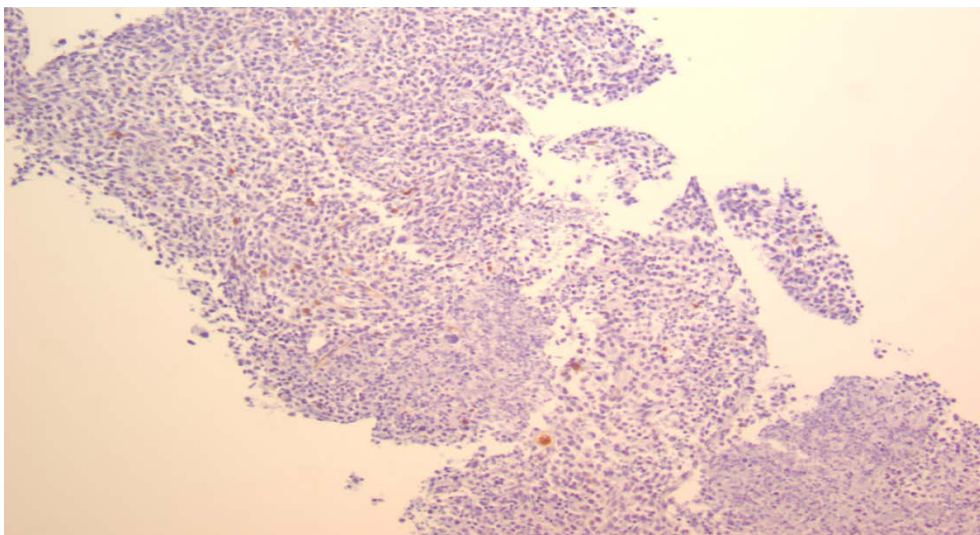
**Figure 2.** Upper cuts of Neck CT showing distal thrombosis of the left internal jugular vein (black arrow).



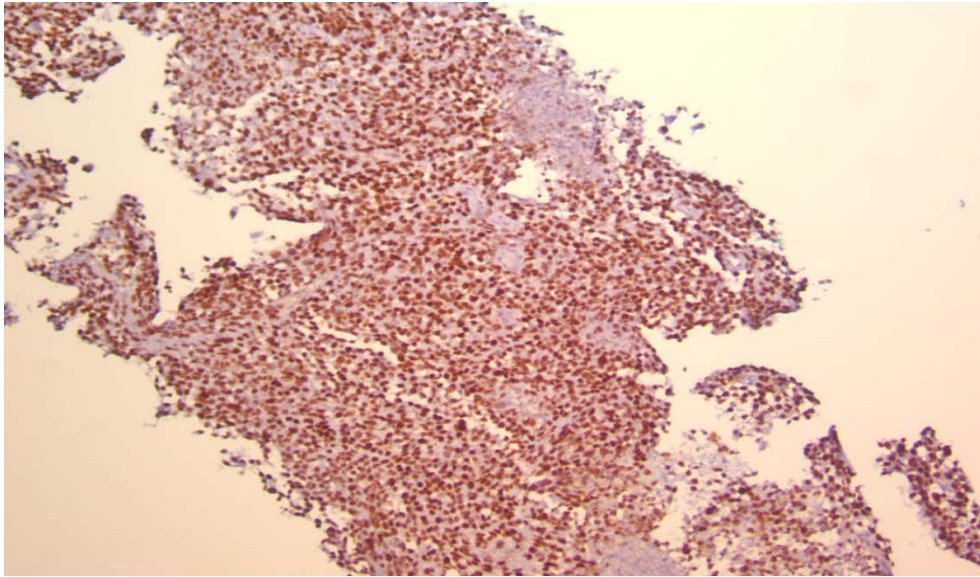
**Figure 3.** Low power (100x) view of a needle core biopsy from the left thyroid lobe showing a high-grade malignant neoplasm with areas of necrosis (black arrow)



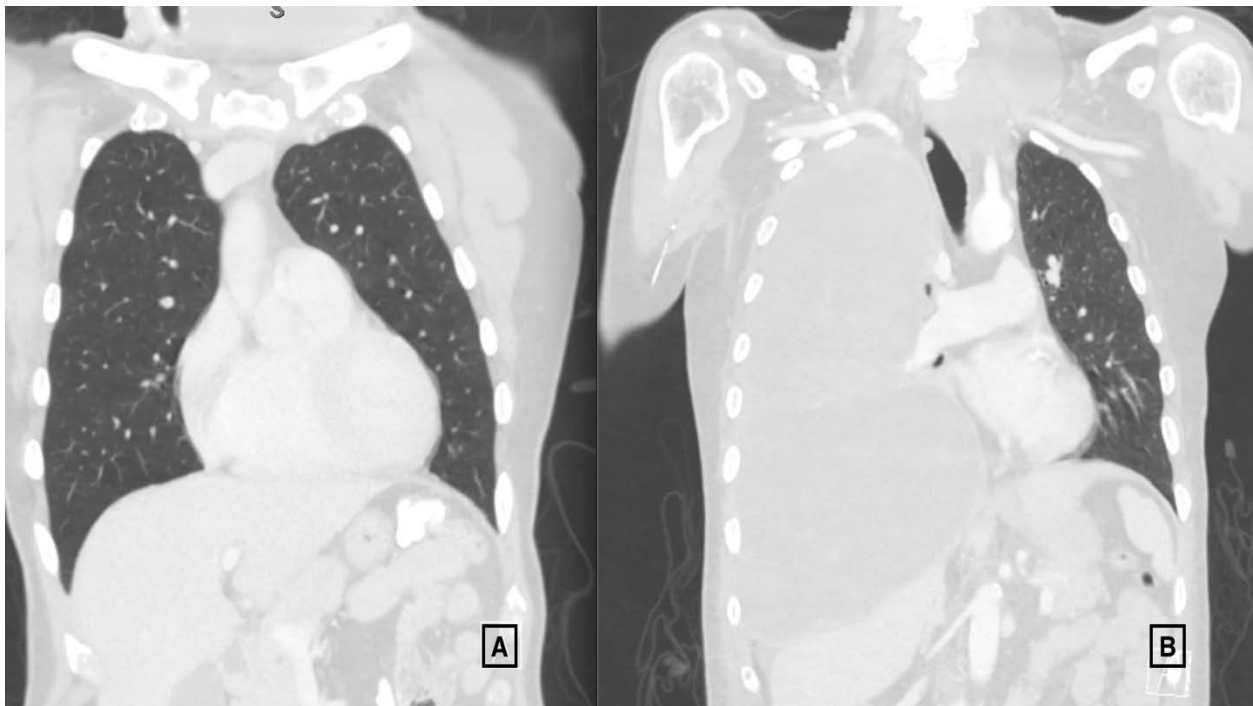
**Figure 4.** high power (400x) the tumor cells display prominent nuclear pleomorphism with bizarre nuclei (white arrow), hyperchromasia, conspicuous nucleoli and brisk mitotic activity (black arrows).



**Figure 5.** Pancytokeratin immunohistochemical stain (100x) showing scattered positive tumor cells with cytoplasmic brown staining.



**Figure 6.** PAX-8 immunohistochemical stain (100x) showing diffuse nuclear positivity, supporting follicular thyroid differentiation.



**Figure 7.** **A.** Initial Contrast CT chest showing probable lung nodules. **B.** Follow up CT chest after 2 months showing seeding of the entire right hemithorax with cancer

### 3. Discussion

Anaplastic thyroid cancer is a rare form of thyroid cancer with inferior outcomes. The mean survival is six months after diagnosis, and the mortality rate is approaching 100% [6,7]. Patients with ATC are usually symptomatic upon diagnosis, unlike other differentiated forms of thyroid cancer that present with a more insidious course manifesting as thyroid nodule and therefore diagnosed with thyroid cancer following tissue sampling with FNA cytology [8]. Almost nearly 90% of patients with ATC present with significant local infiltration and compressive symptoms, with a significant proportion of patients present with distant metastasis at the time of diagnosis [9,10]. Our reported case had both local infiltrations with distant mediastinal, bladder, and lung metastasis. Many

univariate analysis studies have identified several critical prognostic characteristics. The favorable prognostic factors that were associated with lower cause-specific mortality include female gender, age < 60 years, intrathyroidal tumor, external beam radiotherapy, combined radiotherapy, and surgical respectability of the tumor [5]. Moreover, white blood cells count < 10,000 mm<sup>3</sup>; unilateral tumors with a diameter of less than 5 cm, no nodal involvement or invasion to adjacent structures, carry a favorable prognosis as well [11,12]. The reported case was a 69-year-old man who had a bulky neck tumor mass > 5 cm, metastatic disease, and WBCs 41,000 mm<sup>3</sup>, indicating a poor prognosis. Moreover, some authors linked the thyroid anaplastic transformation process to an elevated TSH level, goiter, and radiation exposure; however, further research is needed to understand this malignant transformation [13,14].

The loss of the p53 tumor suppressor gene is involved in the process of transformation from differentiated thyroid cancer (DTC) to an undifferentiated type [15]. The frequency of NRAS mutations in thyroid cancers is rapidly increasing in up to 25% of other thyroid adenocarcinomas, in particular, follicular type [16]. Moreover, the NRAS gene plays an essential signaling role in the Mitogen-activated protein kinase pathway (MAPK), and hence tumors with RAS mutations predict a more aggressive clinical course than tumors without RAS mutations [17]. Different modalities of treatment had been identified depending on the extent of the disease and have shown to improve local control and survival in some patients with regionally confined ATC [18]. However, our patient had a very aggressive metastatic disease with few pleural-based nodules initially, which progressed rapidly within two months into the entire right lung (Figure 7).

An aggressive approach with surgical resection and local radiation compared to a less aggressive strategy, including chemotherapy and genetic mutation analysis, can identify targeted therapy that has been both adopted. Although there are multiple promising modalities of treatment; more recently, the treatment with inhibitors to MAPK pathway such as Trametinib is promising in retarding the progression of this cancer and prolonging the overall survival [19].

## 4. Conclusion

Anaplastic thyroid cancer (ATC) is a cancer of uniformed mortality. Luckily, this cancer incidence is decreasing because of the early detection and better management of other types of differentiated thyroid carcinoma. However, given the fast-evolving pace of ATC, our treatment choices are limited by either following an aggressive multidisciplinary approach to those with early regional cancer or adopting a more palliative strategy that focuses on the goals of care. Large targeted therapy clinical trials are integral to shine more light on this cancer in the hope of mitigating the overall outcomes.

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