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CASE REPORT

Comprehensive Treatment of Anaplastic Thyroid Cancer: A Case Report

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Background: Anaplastic thyroid cancer (ATC) is a rare, highly aggressive malignancy that accounts for less than 2% of thyroid cancers but contributes significantly to morbidity and mortality. Despite its rapid progression and poor prognosis, recent advances in targeted therapies and immunotherapies offer some hope for treatment.

Case Presentation: A 55-year-old female with no prior thyroid disease was diagnosed with advanced ATC after a routine check-up revealed a neck mass. She presented with a tumor compressing the trachea, recurrent laryngeal nerve, and carotid sinus, accompanied by Horner's syndrome. Fine-needle aspiration confirmed anaplastic sarcoma. After a multidisciplinary consultation, the patient was treated with anlotinib, tislelizumab, and albumin-bound paclitaxel, resulting in significant tumor shrinkage and symptomatic relief. However, due to financial constraints, treatment was discontinued. One month later, the tumor rapidly progressed, leading to tracheal compression and asphyxiation, causing her death.

Conclusion: This case highlights the potential benefits of combination therapy for advanced ATC, demonstrating significant temporary improvements. However, the discontinuation of treatment due to financial limitations led to rapid disease progression, underscoring the importance of continuous, accessible care. This case also emphasizes the impact of socio-economic factors on patient outcomes and survival in aggressive cancers.

Keywords: ATC, combination treatment, chemotherapy, immunotherapy, targeted therapy

Introduction

Anaplastic thyroid cancer (ATC) represents one of the most lethal forms of thyroid malignancy, accounting for less than 2% of thyroid cancer cases, but responsible for a significant proportion of the morbidity and mortality associated with thyroid cancer. Characterized by rapid growth and an aggressive clinical course, ATC typically presents in advanced stages with extensive local invasion and distant metastases. Treatment for ATC has been largely palliative, focusing on improving quality of life and extending survival through a combination of surgery, radiation therapy, and chemotherapy. However, these interventions rarely achieve long-term control of the disease. In recent years, targeted therapies and immunotherapies have begun to be explored, with some promising results in selected patients, though the overall prognosis remains dismal, with a median survival time of less than a year from diagnosis. We report a case of advanced anaplastic thyroid cancer with extensive bilateral pulmonary metastases. Following a multidisciplinary team consultation, the patient was treated with anlotinib, tislelizumab, and albumin-bound paclitaxel, resulting in significant tumor reduction and symptomatic improvement. Due to financial constraints, the patient was forced to discontinue treatment. The tumor progressed rapidly, and one month after treatment cessation, the patient succumbed to tracheal compression caused by the tumor, leading to asphyxiation.

Case Presentation

A 55-year-old female presented on October 17, 2021, with a one-month history of an incidental finding of a left-sided thyroid mass. She reported being previously healthy with no family history of thyroid disease. The patient noted local

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pain, hoarseness, coughing while drinking, difficulty breathing, and dysphagia. Additionally, she experienced swelling on the left side of her face, ptosis of the upper eyelid, but no fever, weight loss, tremors, or limb numbness were reported. A significant drop in heart rate and blood pressure was noted upon turning her head to the left. On examination, there was noticeable asymmetry of the neck with tracheal deviation to the right. A firm, tender mass approximately 8×8 cm in size was palpable in the left thyroid region, with irregular borders and a non-smooth surface. The mass was immobile during swallowing. No enlarged lymph nodes were palpated in the anterior or lateral cervical regions, and no vascular bruits were detected. The patient underwent a series of comprehensive diagnostic evaluations, including a thyroid ultrasound (Figure 1), enhanced CT of the neck (Figure 2), PET-CT (Figure 3), and a fine needle aspiration biopsy of the thyroid mass (Figure 4). These assessments led to the diagnosis of undifferentiated thyroid cancer with bilateral pulmonary metastases.

Following a multidisciplinary team evaluation, the patient was prescribed the following treatment regimen: anlotinib 8 mg orally, to be taken continuously for two weeks, followed by a one-week break; albumin-bound paclitaxel 400 mg, administered via intravenous infusion every three weeks; lobaplatin 20 mg, delivered intravenously over five consecutive days, with a 15-day interval before the next cycle; and tislelizumab 200 mg, administered intravenously every three weeks.

After one treatment cycle, a follow-up thyroid ultrasound indicated a noticeable enlargement of the left lobe with an internal hypoechoic mass measuring approximately 94×59×56 mm, which had slightly decreased in size compared to previous assessments. After three treatment cycles, a chest CT scan showed multiple nodules of varying sizes across both lungs, with the largest measuring approximately 2.7 cm × 1.9 cm in the dorsal segment of the right lower lobe, also slightly smaller than before. Post-treatment, after three cycles, there was a significant reduction in the neck mass (Figure 5), marked alleviation of dysphagia, substantial improvement in respiratory distress, resolution of symptoms associated with carotid sinus pressure when turning the head, and disappearance of Horner's syndrome symptoms.

Discussion

Anaplastic thyroid carcinoma (ATC) is a rare, aggressive tumor, making up 1.3% to 9.8% (median = 3.6%) of thyroid cancers.[1–3] All ATCs are stage IV (AJCC 8th Edition). Stage IVA is confined to the thyroid without lymph node or

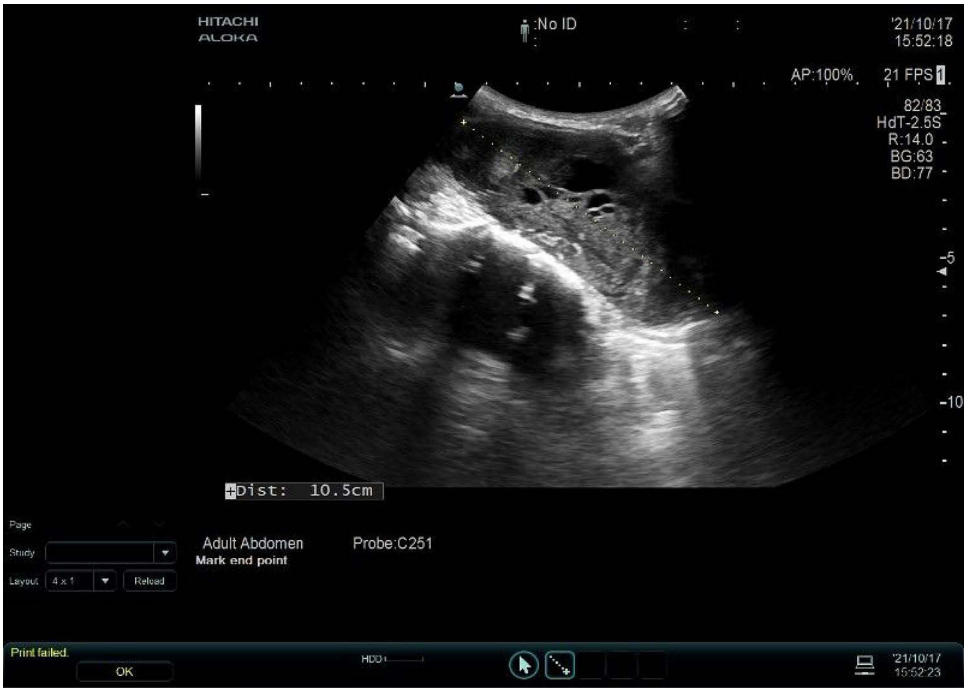

Figure 1 The left thyroid lobe is enlarged with a hypoechoic nodule (105 × 67×40 mm). The nodule's inferior margin extends posteriorly to the clavicle, while the superior margin is well-defined. Internal echogenicity is uneven, with a cystic-solid appearance. Color Doppler shows minimal blood flow signals. The trachea is displaced to the right. No significant lymph node enlargement is observed. Conclusion: Left thyroid lobe nodule, TI-RADS category 4a.

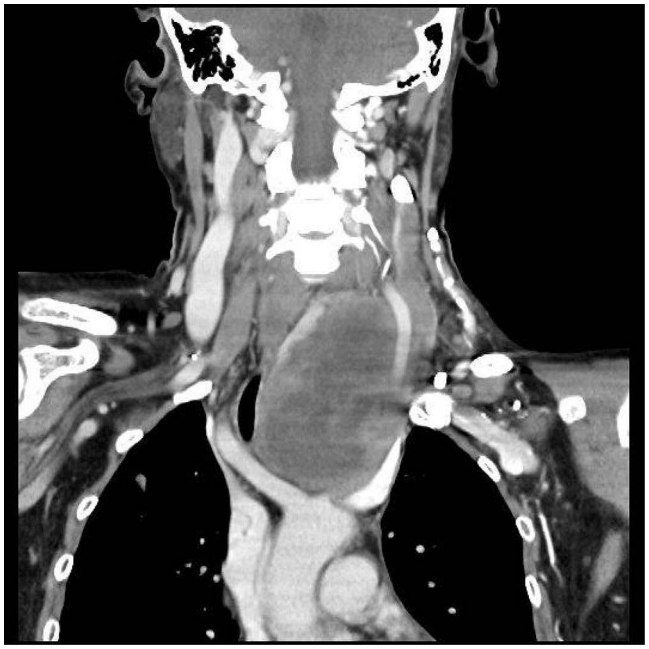

Figure 2 A large soft tissue mass (6.3 × 5.9×9.8 cm) extends from the left neck to the upper mediastinum, displacing adjacent blood vessels and compressing the trachea, main bronchus, and esophagus. The left thyroid lobe is indistinct, with progressive, uneven contrast enhancement. A low-density filling defect in the left internal jugular vein suggests a thrombus. No significant lymph node enlargement is seen. Multiple pulmonary nodules and bilateral maxillary sinusitis are present. Conclusion: Likely thyroid-origin malignancy, with possible aggressive thymoma; clinical correlation and further investigations recommended. Possible thrombus in the left internal jugular vein.

distant metastasis (T1-T3a, N0, M0). Stage IVB involves thyroid capsule invasion or regional lymph nodes (≥N1), while Stage IVC has distant metastasis (M1).The 1-year survival rates for Stage IVA, IVB, and IVC ATC are 72.7%, 24.8%, and 8.2%, respectively,[4] with median survival of only 3 months for distant metastasis.[5,6] ATCs grow rapidly, invade aggressively, and lack typical follicular cell functions like iodine uptake and thyroglobulin production. This allows fast spread to surrounding tissues and distant organs, leading to late-stage diagnoses.

Therapies for ATC include surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapy. While effective in other thyroid cancers, their use in ATC remains uncertain. Exploring new treatments is vital to improving outcomes in this aggressive cancer.

Thyroid anaplastic sarcoma, specifically histiocytic sarcoma of the thyroid, is an extremely rare and aggressive malignancy. This tumor is characterized by its rapid progression and poor prognosis. The diagnosis of thyroid anaplastic sarcoma is challenging due to its non-specific cytomorphological features, which often mimic other thyroid malignancies such as ATC and medullary carcinoma of the thyroid. Given the extremely low incidence of thyroid anaplastic sarcoma, there is a lack of literature on drug treatments for advanced cases. Therefore, after an MDT (multidisciplinary team) discussion, we decided to base our treatment plan on the protocols used for ATC.

Surgical Treatment of ATC

ATC can invade through direct extension into the neck and mediastinal structures or via lymphatic spread, necessitating careful evaluation of the tumor's resectability. Therefore, all patients should undergo routine imaging studies preoperatively to assess the extent of local disease and exclude the presence of distant metastases. For patients with resectable Stage IVA and IVB disease, surgical intervention is recommended, followed by prompt adjuvant radiochemotherapy. The specific surgical approaches include total thyroidectomy, near-total thyroidectomy, or completion thyroidectomy (if discovered incidentally post-operatively), combined with therapeutic cervical lymph node dissection (R0 or R1 resection). For patients with unresectable or R2-resected tumors, radiotherapy combined with chemotherapy is advised, with targeted drugs selected based on molecular testing results, and surgical opportunities reassessed appropriately. Patients in

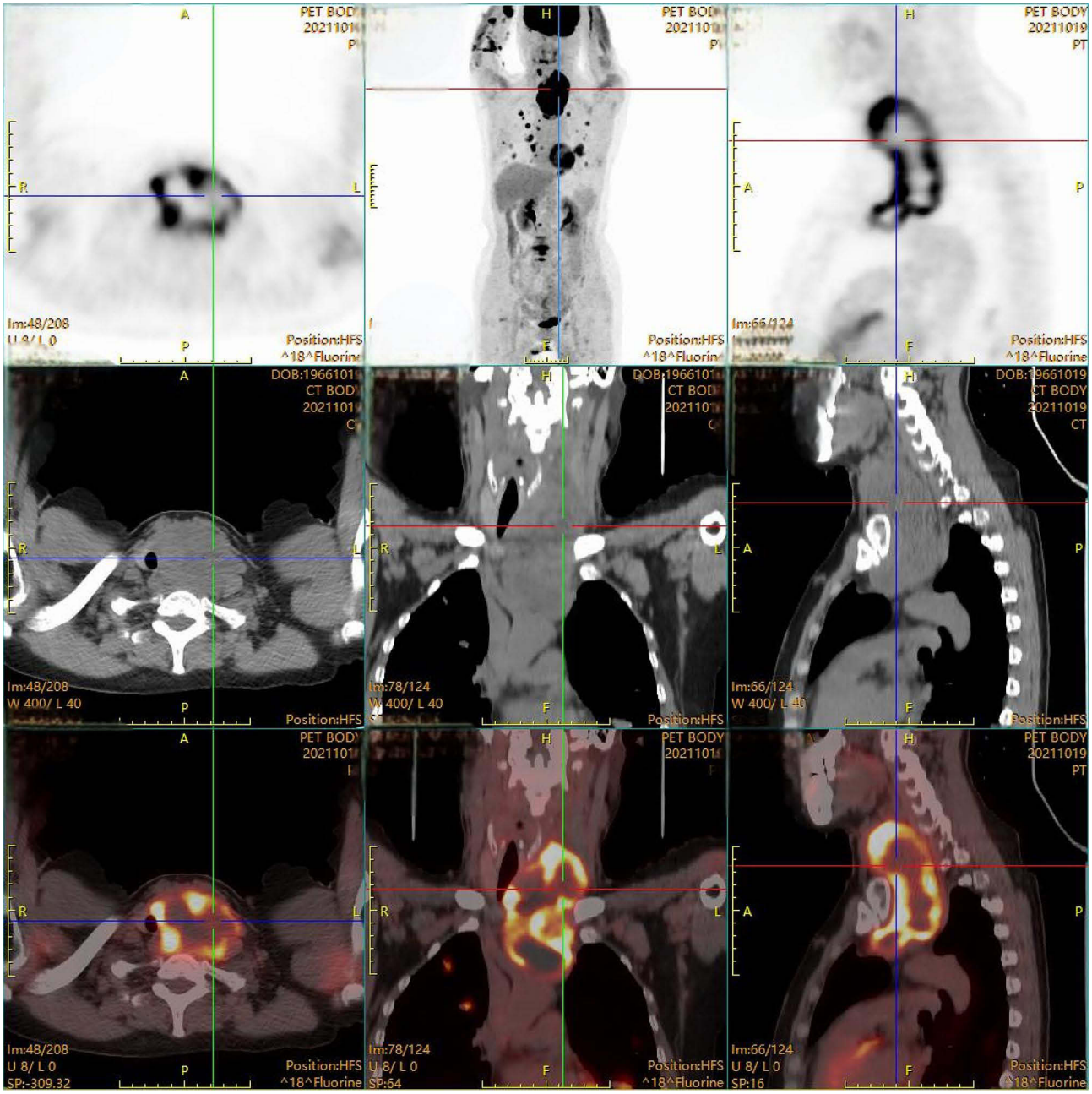

Figure 3 A large, heterogeneously dense soft tissue mass extends from the hyoid bone to T5, with central necrosis and solid components, showing markedly increased FDG uptake, suggestive of a malignant thyroid tumor.Scattered solid nodules of varying sizes near the hilum in both lung fields show increased FDG uptake, suggesting metastatic thyroid involvement.

Stage IVC often undergo palliative surgery to manage disease-related symptoms, such as preventing airway or esophageal obstruction.[7]

Chemotherapy for ATC

ATC is poorly responsive to chemotherapy, but it can complement surgery and radiotherapy. Common agents include doxorubicin, taxanes, bleomycin, and mitoxantrone, with doxorubicin often combined with cisplatin.[8] Lowe et al found that adding doxorubicin and cisplatin to radiotherapy extended median survival by 220 days compared to surgery and radiotherapy alone,[9] highlighting chemotherapy's role in enhancing other treatments.

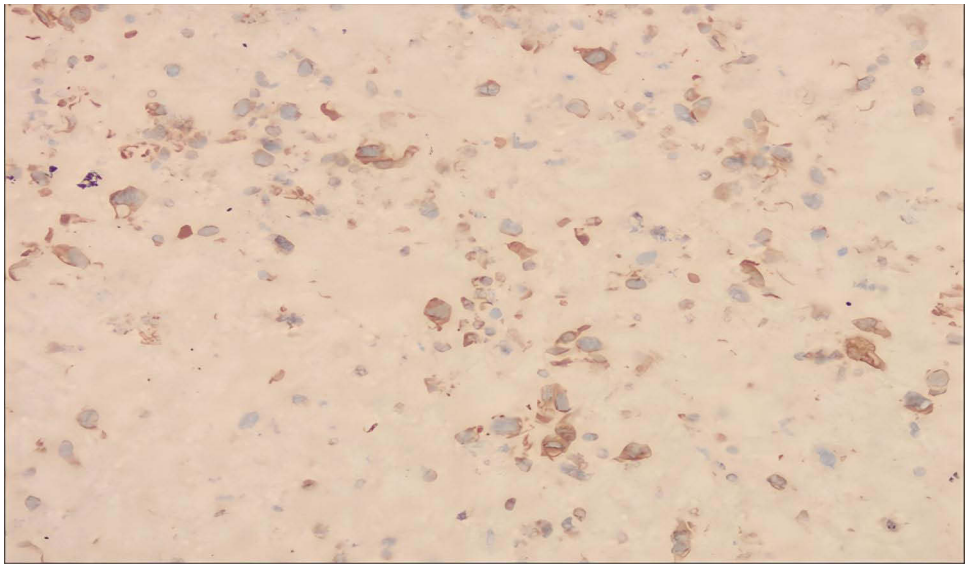

Figure 4 Reveals clusters of irregular and spindle-shaped atypical cells. The immunohistochemical profile is suggestive of a pleomorphic undifferentiated sarcoma. The immunohistochemistry results are as follows: Vimentin positive (+); Smooth Muscle Actin (SMA) positive (+); CD56 focally positive (+); Galectin-3 focally positive (+); cytokeratins AE1/AE3 negative (-); CK7 negative (-); CK8/18 negative (-); CK19 negative (-); Desmin negative (-); Thyroid Transcription Factor-1 (TTF-1) negative (-); Neuron-Specific Enolase (NSE) negative (-); Chromogranin A (CgA) negative (-); Synaptophysin (Syn) negative (-); Thyroglobulin (TG) negative (-); Calcitonin (CT) negative (-); Parathyroid Hormone (PTH) negative (-); CD68 negative (-); PAX-8 negative (-); P53 negative (-); and Ki-67 positive (+) with a proliferation index of 40%. BRCA1/2 genes are wild-type.

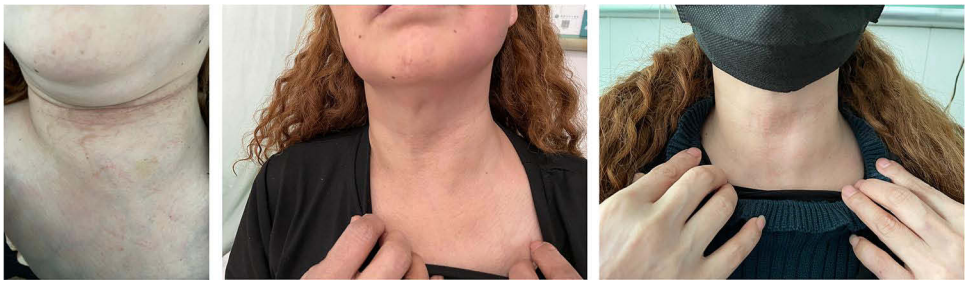

Figure 5 After six cycles of treatment, the patient's tumor was visibly reduced in size.

Targeted Therapy for ATC

Targeted therapy for ATC aims to inhibit tumor growth, proliferation, and metastasis by disrupting key molecular pathways and signaling mechanisms. Several common genetic mutations, such as BRAF, RAS, and P53, have been identified in ATC, enabling the targeting of specific pathways like the RAS/RAF/ERK and PI3K/AKT/mTOR pathways. The advent of targeted drugs, including tyrosine kinase inhibitors, BRAF inhibitors, and PI3K/mTOR pathway inhibitors, has significantly improved the survival rates of patients with undifferentiated thyroid carcinoma.[10,11]

Tyrosine Kinase Inhibitors (TKIs) for ATC

TKIs target the MAPK pathway, regulating tumor cell proliferation, differentiation, and apoptosis. Key inhibitors, including lenvatinib, sorafenib, and vandetanib, show promise in treating ATC. Lenvatinib combined with vinorelbine significantly reduced tumor growth in a xenograft model of ATC.[12] Additionally, docetaxel combined with imatinib enhanced antitumor activity by up to 69.9%.[13] Anlotinib inhibits ATC cell proliferation and migration, induces ferroptosis, and activates autophagy, with combination strategies showing improved therapeutic effects.[14] A study by Zheng et al found that anlotinib resulted in a 60% response rate in advanced thyroid cancer, with an acceptable safety profile.[15]

BRAF Inhibitors in ATC

BRAF V600E mutations activate the MAPK pathway, promoting tumor proliferation. BRAF inhibitors, such as dabrafenib and vemurafenib, block this signaling. Dabrafenib combined with trametinib (DT regimen) was FDA-approved for ATC with BRAF V600E mutations. A Phase II trial of 16 ATC patients showed a 69% overall response rate, with one complete response.[16] Vemurafenib treatment in a BRAF-mutant ATC patient showed early effects but disease progression after two months.[17]

PI3K/mTOR Signaling Pathway in ATC

The PI3K/AKT/mTOR pathway regulates cell proliferation and is activated by mutations in tumor suppressor genes. Inhibitors like everolimus target mTOR phosphorylation to inhibit tumor growth. A study of five ATC patients treated with everolimus reported a median overall survival of 7.4 months, with one partial response lasting 27.9 months.[18] In a metastatic ATC case, everolimus reduced tumor size by 63% and continued to show effects for 18 months.[19]

Additional Therapies

Further research is needed on targeted drugs such as the proteasome inhibitors bortezomib[20] and carfilzomib,[21] the CDK inhibitor dinaciclib,[22] the peroxisome proliferator-activated receptor gamma agonist,[23] and the angiogenesis inhibitor fotibastatin.[24] These agents represent promising avenues for future investigations in the management of ATC.

Immunotherapy

Immunotherapy for ATC primarily focuses on modulating tumor-associated macrophages (TAMs) and immune cells like T lymphocytes and NK cells, targeting immune escape checkpoints. Inhibiting PD-1/PD-L1 pathways has shown early promise, especially when combined with targeted molecular inhibitors. A Phase II trial combining pembrolizumab (PD-1 inhibitor) with lenvatinib extended overall survival (OS) to 18.5 months in ATC patients.[25] Another study found that pembrolizumab added to dabrafenib and trametinib increased OS by 3.8 months (7.4 to 11.2 months), while the addition of pembrolizumab to lenvatinib extended OS by 8.25 months (10.4 to 18.65 months).[26]

Given ATC's heterogeneity, ongoing research into next-generation immune checkpoint inhibitors and combination therapies is vital. A case report by Yurou Xing et al demonstrated that radiotherapy combined with tislelizumab immunotherapy resulted in significant tumor reduction and was well tolerated, offering a promising strategy for ATC.[27]

Radiotherapy for ATC

Radiotherapy plays a critical role in reducing local recurrence and metastases in ATC, particularly when tumors cannot be fully resected. It also aids in reducing residual cancer cells after surgery. A retrospective study of 1,147 ATC patients across 17 projects found that radiotherapy improved survival rates.[28] Research suggests that a cumulative radiation dose of 50 Gy or higher is associated with better outcomes.[29,30]

Patient Case Discussion

Since targeted therapy might change the course of the disease, in anaplastic thyroid carcinoma (ATC), it is recommended to perform BRAF assessment (both immunohistochemistry (IHC) and molecular testing) and other parallel genetic testing (ALK, NTRK, or RET fusions) as soon as possible.[3] In addition, testing for other key genetic alterations such as RAS, TERT, PIK3CA, TP53 should also be considered. These genes have been shown to play significant roles in thyroid carcinogenesis, and their mutations or fusions can be potential targets for personalized therapy.[3,31,32] Although some targeted drugs and genes still lack clinical research in ATC, they provide a new therapeutic approach, offering new attempts and explorations for patients with advanced ATC. In this case, due to the limited availability of targeted gene therapies in Zibo city, China, at that time and the high cost of these therapies, the patient's biopsy pathology only included testing for the BRAF gene. Other gene tests, such as TERT, P53, RET, RAS, and other targeted gene inhibitors, were not conducted.

In this patient, a combination of chemotherapy, targeted therapy, and immunotherapy was employed, achieving notable results within three months. However, due to severe thrombocytopenia reaching grade IV myelosuppression and the high costs involved, the patient and their family decided to discontinue treatment. Compared to other studies, reports on ATC treatment, especially regarding immunotherapy and targeted therapy, are scarce. Most research focuses on singular treatment methods rather than combination therapies. Thus, the data provided in this case fills a gap in the literature, showcasing the potential value of combination treatment strategies in ATC management.

Challenges and Unresolved Issues

Despite the encouraging treatment outcomes reported, several challenges persist in the treatment of ATC. Identifying which patients are most likely to benefit from combination therapies remains crucial. Additionally, managing and mitigating treatment-related side effects is key to optimizing therapeutic strategies. More research is needed to explore the best combinations of treatments and how to tailor these strategies to individual patient variations.

Future Directions

Future studies should focus on validating the treatment effects observed in this case through clinical trials and exploring new targets and immunotherapy strategies. Additionally, research should aim to develop more precise biomarkers to guide treatment decisions and monitor responses. Through these efforts, we can anticipate greater advancements in the treatment of ATC.

Conclusion

This case report demonstrates the potential effectiveness of a combined approach of chemotherapy, immunotherapy, and targeted therapy in patients with anaplastic thyroid carcinoma. Although positive initial results were achieved, further research is required to validate these findings and optimize treatment strategies. With ongoing exploration and innovation, there is hope for improving treatment outcomes and the quality of life for these patients.

Abbreviations

ATC, Anaplastic thyroid cancer.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics Statement

We have clarified in the manuscript that the study was approved by Ethics Committee of Zibo Central Hospital. Written informed consent was obtained from the patient for publication of this report.

Consent to Publish Declaration

We had previously obtained the patient's consent for publication and there is no personal information regarding the patient in this case report.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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