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Challenges in the Management of Anaplastic Thyroid Carcinomas: A Report of Three Cases

Henintsoa Murielle Rakotomalala[1], Diora Ronchalde[2*], Tahina Razanadahy[2], Malala Razakanaivo[2], Tovo Harivony[2], Vonjy Angelo Andrianarison[2], Ny Ony Tiana Florence Andrianandrasana[1], Florine Rafaramino[3]

[1]Medical Oncology Department, Joseph Ravoahangy Andrianavalona University Hospital, Antananarivo, Madagascar
[2]Radiotherapy Department, Joseph Ravoahangy Andrianavalona University Hospital, Antananarivo, Madagascar
[3]Faculty of Medicine Antananarivo, Antananarivo, Madagascar
Email: *dronchalde@gmail.com

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Abstract

Anaplastic thyroid carcinomas (ATCs) represent the final dedifferentiated stage of thyroid tumors. This is a severe and potentially lethal malignancy in humans. The clinical presentation is often striking, characterized by a rapidly enlarging, invasive, and compressive cervical mass. The therapeutic strategy involves a multimodal approach that improves local control and survival. We present three cases of anaplastic thyroid carcinoma: two men, aged 71 and 35, and one woman, aged 64, who were treated at the Cobalt Radiotherapy Unit. All three were referred after undergoing thyroidectomy and experienced rapid locoregional progression in the perioperative period. Their subsequent treatment included radiochemotherapy. Our objective is to illustrate the highly invasive nature and poor prognosis of this cancer.

Keywords

Anaplastic Thyroid Carcinoma, Multimodal Treatment, Chemoresistance, Radiotherapy, Madagascar

1. Introduction

Anaplastic thyroid carcinoma (ATC) is the rarest form of thyroid cancer, accounting for less than 2% of cases [1]-[3]. It accounts for approximately 1% - 2% of all primary thyroid cancers and is more commonly found in elderly individuals [4]. Its median survival is restricted to only 4 to 6 months, accompanied by poor quality of life [5] [6]. It is highly aggressive, with a median survival of 3 to 5 months in most cases [7]. The prognosis remains poor, as all ATCs are classified as T4 and

are always staged as IV [8]. Our objective is to provide a clinical illustration of the aggressive behavior of this malignancy through three reported cases.

2. Case Reports

2.1. Case 1

Our first case involved a 71-year-old Canadian man residing in the eastern province of Madagascar. He had no history of alcohol or tobacco use but had a maternal history of cancer. Eight months prior to consultation, he initially experienced cervical pain followed by the rapid and progressive enlargement of a painful cervical mass, complicated by dysphonia. Initial ultrasound revealed an enlarged left thyroid lobe with heterogeneous and hyperechoic contours. In October 2020, he underwent a total thyroidectomy. Histopathological examination showed a 15 × 12 × 5 cm tumor fragment with diffuse microvesicular proliferation of highly atypical spindle and polygonal cells, including giant cells, consistent with an anaplastic carcinoma of the left thyroid lobe infiltrating the right lobe and thyroid capsule. Two weeks postoperatively, he developed a rapidly enlarging tumor recurrence at the surgical site. He was referred to the Oncology Department, where examination revealed infiltration around the surgical scar. A whole-body CT scan showed infiltration of adipose tissue in the thyroid bed, focal thickening of the cervical esophagus, and posterior tracheal wall bulging, with no distant metastases. The treatment plan consisted of hyperfractionated radiotherapy (1.6 Gy twice daily, three days per week, for a total dose of 57 Gy) combined with weekly doxorubicin (10 mg/m^2). Two weeks after radiotherapy, he was hospitalized for acute inspiratory dyspnea with oxygen desaturation (80% on room air), aphonia, fistulation, and diffuse bronchial rales. Emergency management included dexamethasone, atropine, scopolamine, and antibiotics, which provided partial symptom relief. A follow-up CT scan showed a left lateral thoracic abscess extending to the retropharyngeal space and communicating with other collections, a tracheal soft-tissue mass, and new bilateral pulmonary nodules indicative of disease progression. Surgical drainage of the abscess was performed, but the patient declined tracheostomy. He passed away three weeks later.

2.2. Case 2

The second case involved a 61-year-old woman with no significant medical history or prior goiter. She reported consuming non-iodized salt without any specific dietary restrictions. She presented with a rapidly enlarging right-sided cervical mass over two months. Cervical ultrasound revealed a TIRADS VA multinodular goiter, and she underwent a total thyroidectomy in December 2020. Histopathological analysis showed a severely deformed, fragmented right thyroid lobe (5 × 3.5 × 3 cm) with spindle cell proliferation and moderate cytonuclear atypia, infiltrating between normal thyroid follicles, consistent with an undifferentiated carcinoma (spindle cell variant). Two weeks postoperatively, she developed a locoregional recurrence measuring approximately 10 cm in its largest dimension, along

with dysphonia and non-selective dysphagia. She was referred to Oncology after pathology results confirmed anaplastic thyroid carcinoma. Upon evaluation, she was in poor general condition (KPS 3), dyspneic, and had significant difficulty feeding. Due to financial constraints, she could not undergo an extension CT scan; however, a chest X-ray showed no secondary lesions. She underwent emergency placement of a feeding stoma and a tracheostomy on February 16, 2021. Due to her deteriorating condition, she received only one cycle of doxorubicin (20 mg) and two fractions of radiotherapy (1.6 Gy each). She passed away at home on March 3, 2021. (Figure 1)

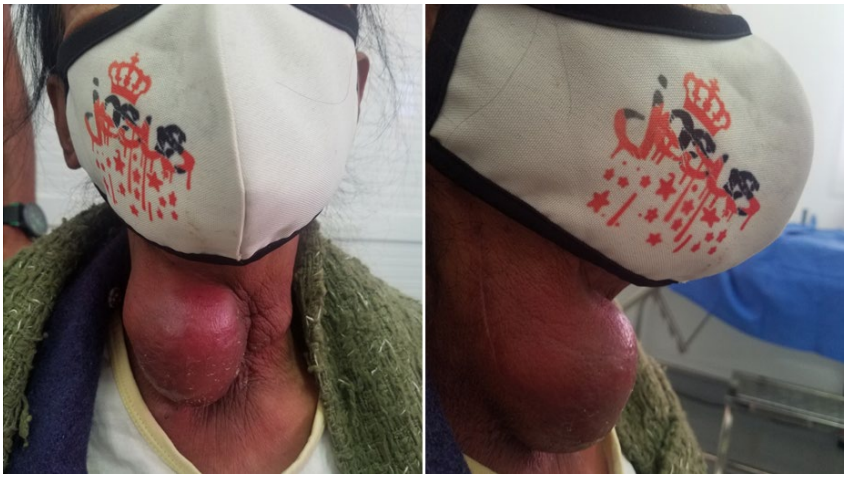

Figure 1. Post operative local recurrence of a right lateralized cervical mass front view and profil view.

2.3. Case 3

The third case involved a 35-year-old man, a smoker (7 pack-years) and occasional alcohol consumer, with a longstanding goiter since age 20. He was referred to the Oncology-Radiotherapy Department in January 2021 after experiencing rapid enlargement of a painful cervical mass over five months. Ultrasound revealed a right TIRADS IVA lesion and a left TIRADS IVC lesion with bilateral metastatic-appearing cervical lymphadenopathy. A cervicothoracic CT scan identified a right thyroid nodule, multiple left thyroid nodules, a right lateral cervical gangliotumoral mass (44 × 41 mm), and multiple supraclavicular, subclavicular, and mediastinal lymph nodes. On November 26, 2020, he underwent total thyroidectomy with lymph node dissection. Pathology revealed a 7 cm right thyroid nodule with papillary carcinoma and an undifferentiated carcinoma with trabecular or coronal architecture, vascular emboli, capsular invasion, and infiltration into surrounding thyroid tissue. The left lobe contained multiple small nodules (2 - 6 mm) with undifferentiated carcinoma infiltration. Fourteen of 17 dissected lymph nodes were metastatic. One month postoperatively, he developed rapidly enlarging right cervical, submental, and right axillary masses. On referral to Oncology, he was in good general condition (KPS 1) but complained of cervical pain, dysphonia, and solid food dysphagia. Examination revealed a firm, fixed, poly lob-

ulated cervical mass, a submental mass, a 10 cm right axillary mass, and a right supraclavicular lymph node. He received one cycle of doxorubicin-cisplatin followed by hyperfractionated cervical radiotherapy including the right axilla, with weekly doxorubicin. After four weeks, tumor volume had significantly decreased, with resolution of the axillary mass. By week 5, he had grade 2 radiation-induced mucositis and secondary skin infection, which improved with supportive care. After completing his first radiotherapy course, he was lost to follow-up one month later.

3. Discussion

Anaplastic thyroid carcinoma (ATC) is a rare tumor, accounting for 1% - 2% of malignant thyroid tumors, with an annual incidence of approximately two per million people [7] [9]. In Morocco, a study by Bouziane *et al.* in an endocrinology department recorded only four cases over seven years [3], whereas in Tunisia, Riahi *et al.* reported 12 cases over 15 years in an ENT department [10]. ATC has a higher prevalence in the sixth and seventh decades of life [10] [11], with a female-to-male ratio of 1.5:1 [12]. A recent large study from the United States including 5359 patients with ATC provides an analysis of the majority of patients were women (58%), with a median age of 70 ± 12 years, a median tumor size of 6.1 cm (range 4.5 - 8 cm), and distant metastases (29%) [13]. However, ATC can also occur in younger individuals, with fewer than 25% of cases reported in this age group [12]. This was the case for our third patient, a young man of 35 years. All our cases presented with a rapidly growing thyroid mass. Bouziane *et al.* and Riahi *et al.* similarly described that the primary reason for consultation was a rapidly enlarging cervical mass, often accompanied by compression symptoms in over half the cases [3] [10] or changes in a longstanding multinodular goiter in over a third of cases [3] [10]. Indeed, ATC should be suspected when a firm cervical mass increases rapidly in size, particularly when associated with hoarseness, cervical pain, dysphagia, and/or dyspnea—prompting urgent evaluation and biopsy [14]. This rapid transformation is often described as "explosive" [9] and is observed in 77% of ATC cases [7]. Approximately 25% of ATC cases are diagnosed in patients with a history of longstanding goiter, which may be linked to endemic iodine deficiency in some regions [7]. Studies by Khaireddine *et al.* reported transformation of multinodular goiter into ATC in 58% of cases [15], which was also observed in our third patient. Cervical pain is reported in 26% of cases [7] and was present in all our patients. In some cases, urgent intervention is required to prevent death by asphyxia [2]. For our second patient, a tracheostomy was essential before any further management. Thyroid ultrasound typically reveals a large, often lobar, thyroid lesion [8]. At diagnosis, the average tumor size is approximately 8 cm [8], whereas in our cases, it averaged 9.1 cm. Histologically, ATC is composed of spindle, polygonal, or giant cells [8]. The spindle cell type is the most common, accounting for 50% of cases [12], consistent with our findings. Carretero *et al.* (2017) reported a case similar to our third patient, where histology revealed a papillary carcinoma component associated with undifferentiated thy-

roid carcinoma [16]. Before initiating systemic treatment, genetic analysis should be performed for all ATC cases [2], though this was unavailable for our patients. Managing ATC requires an urgent and multidisciplinary approach due to the tumor's extremely rapid doubling time [2] [8]. The therapeutic strategy is multimodal, typically involving surgery, external beam radiotherapy, and chemotherapy [2]. However, these approaches often remain insufficient to significantly extend survival [7]. When feasible, total thyroidectomy with lymph node dissection is the first-line curative approach, followed by adjuvant chemoradiotherapy [1] [2] [14] [17]. Accelerated hyperfractionated radiotherapy, delivering 1.25 to 1.6 Gy twice daily to a total dose of 40 - 46 Gy over the cervical and upper mediastinal regions, with possible tumor boost, appears more effective [12] [17]. For our third patient, radiation covered the right subaxillary region due to lymph node involvement. Radiotherapy is often combined with chemotherapy; doxorubicin is used for its radiosensitizing effects [2], as applied in our patients.

ATC is one of the most aggressive human cancers [9]. Some patients have radio- or chemoresistant tumors that progress rapidly despite treatment [7] [9]. Subsequently, other drugs enhancing chemotherapy efficiency have been added. The combination with targeted biological agents such as dabrafenib and trametinib, in cases of mutated BRAF and MEK genes, respectively, may overcome this resistance [18]-[20]. In unmutated cases, novel immunotherapy (anti-PD-1 and anti-PD-L1) has been a recent revolution. Also, the NCCN guideline for thyroid carcinoma recommended that ATC patients with locally resectable disease can be treated with multimodal therapy, and those with actionable mutations (*BRAF*, *NTRK*, *ALK*, *RET*, MSI, dMMR, TMB-H) can be treated with targeted therapy or immunotherapy [21]. According to a study by Wang *et al.* in China, mutations in the multidrug resistance gene in anaplastic thyroid cancers, along with their stem cell differentiation potential, have a significant impact on the effectiveness of chemotherapy and radiotherapy [22]. Although surgery and radiotherapy allow for better local control of anaplastic thyroid cancer, the aggressive nature of the disease often leads to metastatic spread and death [17]. This clinical scenario was observed in our first patient, who experienced rapid local and pulmonary metastatic progression of his disease during treatment. In 2001, a study by Sugitani *et al.* developed prognostic indexes (PI) for anaplastic thyroid carcinomas, identifying four key poor prognostic factors: acute symptomatology, white blood cell count > 10,000/mm^3, tumor size > 5 cm, and the presence of distant metastases [23]. Patients were assigned a PI score ranging from 1 to 4. Those with a PI = 1 had a 62% survival rate at six months, while no patients with a PI = 3 survived beyond six months, and all patients with a PI = 4 died within 3 months [23].

When applied to our patients, these scores were respectively 3, 2, and 3. Additional prognostic factors have been identified, including advanced age (>60 - 70 years), male gender, extrathyroidal invasion, and histology associated with giant or pleomorphic cells [17] [22] [23]. Besides the previously calculated PI score of 3 for Patient 1, all these additional poor prognostic factors were present in this pa-

tient, explaining his extremely short-term survival. However, the coexistence of a well-differentiated papillary carcinoma has been associated with a better prognosis [24]-[26]. In Bouziane's study, all cases had a fatal outcome within 7 months [3], similar to our two patients. Anaplastic thyroid carcinoma accounts for 14% - 50% of thyroid cancer-related deaths [7] and typically leads to death within the first year after diagnosis, with a median survival of 3 months [16].

4. Conclusion

Anaplastic thyroid carcinoma is a highly lethal malignancy with multiple poor prognostic factors in our patients. Although a multimodal approach can improve local control and extend survival, the overall prognosis remains poor.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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