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RESEARCH ARTICLE

Anaplastic thyroid carcinoma case series

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ABSTRACT

Aim: Among the endocrine malignancies, thyroid carcinoma (TC) is the most common. However, anaplastic TC accounts for 1-2% of these cancers. The aim of this study was to evaluate the demographic and pathologic features, treatments, and survival of patients with anaplastic TC.

Methods: Anaplastic TC patients who applied to our medical oncology clinics between 01.01.2012 -01.12.2018 were retrospectively evaluated.

Results: A total of 8 patients were included in the study. There were 4 female and 4 male patients with a median age of 68 (minimum 61-maximum 83) years. The initial complaint of all patients was a fast-growing swelling in the neck. Six patients had total thyroidectomy. Two patients had anaplastic TC with a differential TC. Six patients were at stage 4C. The most common site of metastasis was the lung (75%). Five patients had received a median of 3 (1-6) cycles of chemotherapy. Radiotherapy was applied to 7 patients. All patients except one died during the follow-up period. The median survival time of the patients was 3 (2-15) months.

Conclusion: Anaplastic TC, an aggressive tumor with high metastasic potential, has no effective treatment at present. Effective treatments are needed for this rare and aggressive disease. Developments in the molecular field are promising for the treatment of ATC.

Keywords: anaplastic thyroid carcinoma, overall survival, thyroid

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INTRODUCTION

Thyroid cancers (TCs) are the most common endocrine malignancies, although they constitute 3-4% of all cancers annually (1). The incidence of TCs has increased dramatically in recent decades, due in large part to the identification of subclinical disease. Increase in the occurrence of TCs may be due to the widespread use of diagnostic methods, such as ultrasound, computed tomography, and fine needle aspiration biopsy (FNAB), which incidentally detect subclinical TCs (2).

TCs are classified into three main histological types. Differentiated TCs divided into papillary and follicular types constitute more than 90% of thyroid malignancies. Dedifferentiated TCs comprise poorly differentiated TCs and anaplastic TCs are rare (5 and 1%, respectively). In contrast, medullary TCs, which represent 5% of TCs, arise from parafollicular C cells (3).

Subclinical TCs have little negative effect on the overall survival of patients, but anaplastic TCs are very rare and also have unfavorable prognoses because of iodine/radioiodine refractoriness and high metastatic potential. The clinical management of anaplastic TC requires a multidisciplinary approach in which surgery, radiotherapy, and/or chemotherapy should be considered (4). Unfortunately, there is no effective treatment for this disease (5). This disease has an average survival time of 3–6 months from the time of diagnosis and is responsible for 50% of cancer deaths in patients with TC (6).

In this study, it was aimed to evaluate the demographic and pathological features of the patients diagnosed with anaplastic TC, the treatment protocols applied to the patients, and their survival.

METHODS

Patients with histologically confirmed anaplastic TC who applied to Bolu Abant Izzet Baysal Univercity and Başkent Univercity, Departments of Medical Oncology between 01.01.2012 -01.12.2018 were retrospectively evaluated. Inclusion criteria were age ≥18 years and evidence of anaplastic TC on histopathological examination of the primary tumor, lymph nodes, or distant metastases. Poorly differentiated TCs were excluded. Data regarding the symptoms, surgical procedures, histopathological findings, and other treatment methods of anaplastic TC cases were recorded. Tumor staging was determined according to the Tumor, Node, Metastasis (TNM) classification proposed by the American Joint Committee on Cancer (7). The data were analyzed using SPSS for Windows, version 15.0.

RESULTS

A total of 8 patients' data were reviewed during the study period. There were 4 female and 4 male patients with a median age of 68 (minimum 61-maximum 83) years. The clinical characteristics of the patients are shown in Table 1.

All patients initially had a firm palpable swelling in the neck, 87.5% of patients had pain, 50% of patients had dyspnea, and 25% of patients had dysphagia due to a tumor or compression or infiltration, respectively. A very small number of patients had accompanying symptoms such as weight loss, fatigue, and night sweats.

There was a history of thyroid nodules in 75% of our patients, 37.5% of whom had FNAB from thyroid nodules. Seventy-five percent of our patients had undergone total thyroidectomy operation.

In the pathology reports, 25% of them had anaplastic TC combined with differentiated TC, while 75% of them had only anaplastic TC. The median diameter of tumors was 7 (range 1.6-8) cm in the pathology reports. Three of the patients were giant cells and spindle cells in the tumor and also one of them was had wide necrosis areas and atypical mitosis (Figure 1). Thyroglobulin was positive in 25% of the patients. Thyroglobulin positivity was observed in anaplastic TC which was developed from papillary TC. Others were thyroglobulin-negative staining (Figure 2). Two patients had tumors limited to the thyroid gland at diagnosis and were classified as stage IVA. Six patients had distant metastases and were in stage IVC at the time of diagnosis. These patients with stage 4C had metastasis in the lung, and one of them (16.6%) had metastases in the sacral bone.

Table 1. The clinical characteristics of patients.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age	61	65	83	66	82	70	62	72
Gender	Male	Female	Female	Female	Male	Female	Male	Male
Co-morbidity	CAD, HT	HT, DM	HT	HF	CAD, DM, HT	HT, DM	HT, DM, ESRD	BPH
Noduler goiter	No	Yes	Yes	Yes	Yes	Yes	No	Yes
FNAB	No	Yes	No	No	Yes	Yes	No	No
Initial compliants	Swelling, Pain, Dyspnea	Swelling, Dyspnea	Swelling, Pain	Swelling, Pain	Swelling, Pain, Dyspnea	Swelling, Pain, Dysphagia	Swelling, Pain, Dyspnea	Swelling, Pain, Dysphagia
Operation	Total thyroidectomy	No	Total thyroidectomy	Total thyroidectomy	No	Total thyroidectomy	Total thyroidectomy	Total thyroidectomy
Pathology	Anaplastic TC	Anaplastic TC	Anaplastic TC	Anaplastic TC+ Differentiated TC	Anaplastic TC	Anaplastic TC+ Differentiated TC	Anaplastic TC	Anaplastic TC
Tumor diameter	1,6 cm	2.2 cm	7 cm	8 cm	8 cm	7.5cm	7 cm	5 cm
Thyroglobulin	Negative	Negative	Negative	Positive	-	Positive	-	-
Morphology	Giant cell	-	-	-	-	Spindle cell	Giant cell	-
Stage	4A	4C	4C	4C	4C	4C	4C	4A
Metastasis	No	Lung	Lung	Lung+ sacral bone	Lung	Lung	Lung	No
Chemotherapy	CisEp	-	-	CaP	-	CisDx	CaP	Dx
Number of cycles	4	-	-	2	-	3	1	6
Palliative radiotherapy	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Palliative Supportive Treatment	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
OS (months)	6	2	3	3	2	6	2	15
Last status	Exitus	Exitus	Exitus	Exitus	Exitus	Exitus	Exitus	Alive

CAD: Coronary Artery Disease HT: Hypertension DM: Diabetes Mellitus ESRD: End Stage Renal Disease, BPH: Benign Prostatic Hypertrophy, HF: Heart Failure, FNAB: Fine needle aspiration biopsy, AnaplasticTC: Anaplastic thyroid carcinoma, Differentiated TC: Differentiated thyroid carcinoma, CisEp: Cisplatin Epirubicin, CaP: Carboplatin Paclitaxel, CisDx: Cisplatin Doxorubicin, Dx: doxorubicin, OS: Overall survival

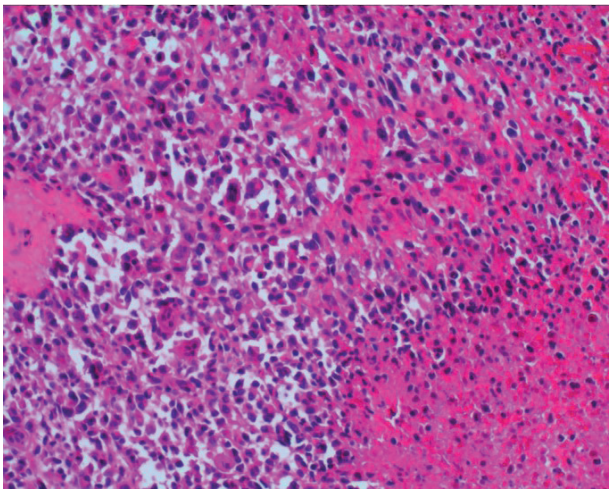

Figure 1. Pathological sign of multinuclear giant cells and necrosis of ATC.

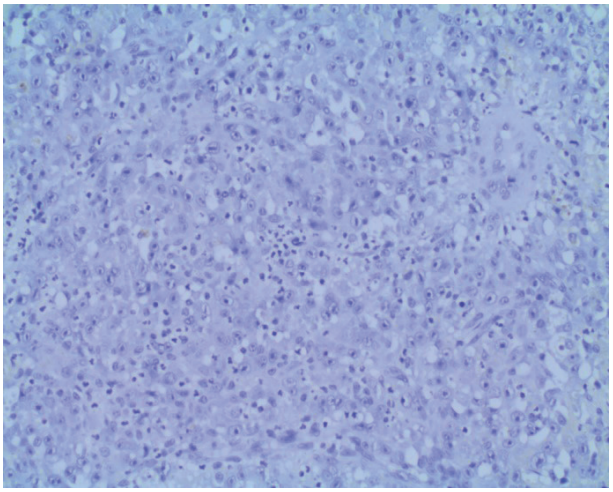

Figure 2. Thyroglobulin negative staining of ATC.

Two patients with stage IVA had taken cisplatin epirubicin (CisEp) and doxorubicin (Dx), 2 patients with stage IVC, 2 patients had taken Carboplatin Paclitaxel (CaP), 1 patient had taken CisDx, and 3 patients had not received chemotherapy. 87.5% of the patients had received palliative radiotherapy. All patients received palliative supportive care. 7 patients (87.5%) died during the study period. Contrary to expectations, one patient was alive. The median survival time of the patients was 3 (2-15) months.

DISCUSSION

The incidence of anaplastic TC typically peaks in the 6-7th decade of life, with a higher occurrence in women compared to men. This gender disparity may be attributed to the inherent biological characteristics of the cancer (5,8,9). In our study, all cases were over 60 years old, but the proportion of men and women was equal.

Although the complaints of the patients vary depending on the state of the in anaplastic TC, mass on the neck, neck pain, dispnea, dysphagia, and hoarseness due to rapidly growing mass in the thyroid are the most common complaints (8-10). The primary complaints of our patients were a rapidly growing neck mass and pain due to this swelling, and the other symptoms were also seen.

Although differentiated TC is diagnosed by FNAB from thyroid nodules, the diagnosis of anaplastic TC is based on typical clinical symptoms and is confirmed pathologically via surgical biopsy. The pathological appearance of anaplastic TC varies. Examining various sections by obtaining multiple slices from the tumor and employing immuno-histochemical (IHC) staining methods is recommended. Pathologically, the most common morphology of anaplastic TC is biphasic spindle and giant cells. Anaplastic TC has wide necrotic areas, surrounding invasion, angiotropism, high mitotic activity, and atypical mitosis (11,12). Sometimes it may be difficult to distinguish anaplastic TC from medullary TC, thyroid lymphoma, and other tumors that metastasize to the thyroid gland (13). IHC staining should be performed to make this distinction. We performed IHC staining to differentiate anaplastic TC from papillary TC, medullary TC, lymphoma, and malignant melanoma for our cases. Negative staining for thyroglobulin is expected in anaplastic TC, while differentiated TC is stained positive for thyroglobulin. However, thyroglobulin may stain positive in anaplastic TC which is developing from differentiated TC (14).

Coexisting thyroid diseases such as multinodular goiter and differentiated TC may be the risk factor for anaplastic TC (8,15,16). Iodine deficiency has also been involved in the etiology of anaplastic TC (17). Anaplastic TC develops from more differentiated TC

as a result of one or more dedifferentiating steps, particularly loss of the p53 tumor suppressor gene. The mechanisms leading to the anaplastic transformation of differentiated TC are uncertain (18,19). There are studies that emphasize that anaplastic TC is seen more common in areas where endemic goiter is common. In a study conducted by Demeter et al, it was found that 76% of anaplastic TCs were found to have a history of thyroid disease, such as primary benign goiter or differentiated TC, and among these patients, 46% had a history of papillary TC (46%) (20). Eighty percent of anaplastic TC patients have a goiter history. As we mentioned above; in our patients as a rate of 75% of them had thyroid nodules and 25% of them anaplastic TC development was present on the ground of papillary TC. All anaplastic TCs are considered as stage IV. Stage IVA only in the thyroid, extrathoracic, and cervical lymphadenopathy in stage 4B and distant metastasis in stage IVC (7,21,22).

Anaplastic thyroid cancers (TCs) are frequently diagnosed at an advanced stage, posing challenges in identification during stages IVA and IVB due to their aggressive nature. Characterized by rapid growth, local invasiveness, and metastatic potential, anaplastic TC exhibits aggressive behavior with a substantial 90% local spread upon initial presentation. This local spread typically involves adjacent structures such as muscle and fat tissue around the thyroid, as well as the lymph nodes, larynx, trachea, esophagus, tonsils, large vessels, and mediastinum. Distant metastases are found in 15 to 50 percent of patients at the time of the diagnosis, and with a rate of 90%, the most common distant metastasis is the lung. In anaplastic TC, 5 to 15% of patients have bone metastasis (11). Similar to the literature, 75% of our patients had the most common metastasis in the lung and one of them had a metastasis in the sacral bone with lung metastasis.

Anaplastic TC is one of the most aggressive diseases (23). Death is due to complications of local and distant disease and/or therapy. Age, sex, tumor size, resectability, and tumor spread are important factors affecting the prognosis (23,24).

Despite multimodality therapies such as surgery, external beam radiation and systemic chemotherapy, in anaplastic TC, response rates to these therapies are <15% and long-term outcomes remain dismal, with no curative options for patients who have exhausted conventional therapies (25). Active surgical treatment is beneficial for patients with anaplastic TC, but the benefits of extensive surgery are limited. Locoregional resection may be necessary for the palliation of the airway or esophagial obstruction (26,27). 75% of our patients had palliative total thyroidectomy.

External beam radiotherapy (EBRT) or intensity modulated radiation therapy (IMRT) can be used as radiotherapy may increase survival in some patients (28,29). IMRT can also be used to reduce toxicity. External irradiation should be considered for skeletal metastases or brain lesions (3,10). In our study, radiotherapy was applied to the neck area of 7 patients by IMRT technique. One patient who had sacral bone metastasis was applied additional EBRT for bone metastasis and one patient could not receive radiotherapy. Unfortunately, systemic chemotherapy is unable to prolong the survival of patients with anaplastic TC; however, in certain cases, conventional treatments might improve symptoms and quality of life (4). Chemotherapy can be started in anaplastic TC after surgery and radiotherapy or if these treatments are not possible. Taxanes (paclitaxel or docetaxel) and/or anthracyclines (doxorubicin) and/or platins (cisplatin or carboplatin) are recommended (4).

Systematic treatments are consistently under exploration for anaplastic TC. In a study, a response rate of 29 percent was observed in patients with BRAF-mutant anaplastic TC who received treatment with the BRAF inhibitor vemurafenib (29). Another study focused on patients with rare malignancies, including anaplastic TC, characterized by BRAF V600E mutations. In this study, the BRAF inhibitor dabrafenib (150 mg twice daily) was administered in combination with the MEK inhibitor trametinib (2 mg once daily). These data indicate that tumor mutation screening should be performed in patients with anaplastic TC as it has the potential to transform the outcome for these patients (25). Larotrectinib may be another option in neurotrophic receptor tyrosine kinase (NTRK) gene fusion-positive anaplastic TC patients regardless of their age or the tumor type (30). Unfortunately, we were unable to implement these treatments. However, we think that these treatments based on genetic mutations could be considered for future patients.

Anaplastic TCs are rare, highly aggressive, undifferentiated tumors, and the median survival of these patients is 5 to 12 months and the 1-year overall survival rate is 20% to 40%. (27). In our study, the median survival of the patients was 3 months, except for one patient who had a survival of 15 months. The biopsy material from this patient with extended overall survival was attempted to be re-evaluated, but the pathology material couldn't be accessed as the pathology blocks were stored at a different hospital.

CONCLUSION

Treatment response rates and overall survival in ATC are poor, and there are very limited treatment options for patients who have exhausted standard multimodality treatments such as surgery, IMRT, and systemic chemotherapy. The effect of cytotoxic chemotherapy on survival and quality of life in ATC patients is limited. Effective treatments are needed for this rare and aggressive disease. Developments in the molecular field are promising for the treatment of ATC.

Ethical approval

This study has been approved by the Bolu İzzet Baysal University, Faculty of Medicine, Clinical Researches Ethics Commite (approval date 04/07/2023, number 2023/235). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: ÜÜ, NK; Concept: ÜÜ, NK, TTD; Design: ÜÜ, NK; Data Collection or Processing: NK, SED, SR; Analysis or Interpretation: TTD; Literature Search: ÜÜ, NK; Writing: ÜÜ, TTD. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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