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Introduction

Anaplastic thyroid carcinoma (ATC) is one of the most lethal neoplasms affecting humans. Although ATC constitutes only about 1–5% of primary thyroid malignancies, it accounts for more than half of the thyroid cancer deaths. A diagnosis of ATC is almost inevitably fatal and most patients die within a year of diagnosis. ATC usually affects the elderly and majority of the patients exhibit advanced disease with extensive local invasion, regional and distant metastasis at presentation. Owing to the rarity and aggressiveness of the disease there is no explicit consensus regarding the treatment protocol. Increased age at presentation, rapid progression and poor general conditions of the patients often make treatment decision difficult. However multimodality treatment has been known to produce improved outcome. Complete surgical resection whenever feasible along with adjuvant chemotherapy or radiotherapy is the best treatment strategy. Understanding the behaviour of the disease is essential in identification of the group of patients who would benefit from optimal treatment. Fine needle aspiration cytology serves as a reliable tool in the early detection of the disease. Through this study, we aim to retrospect the clinical, cytological and histopathological features as well as the management and survival of ATC cases reported in our institution.

Abstract

Background: Anaplastic thyroid carcinoma (ATC) is one of the most aggressive and lethal solid tumors known to affect humans. Although ATC accounts for only 1% to 5% of all thyroid tumors, it portends a dismal prognosis with a median survival of 4 to 12 months from the time of diagnosis. In this retrospective review we aim to study the clinical, cytological and histopathological features and management of ATC cases reported in our institution.

Materials and methods: Twenty-two patients with ATC were identified from institutional database between January 2012 and December 2016. Clinicopathologic data and survival data was obtained from the medical records. Fine needle aspiration cytology (FNAC) slides and histological slides were reassessed for the predominant morphologic findings.

Results: Of the 22 patients, 8 were male and 14 were female. The median age at presentation was 70 years (range 50–85 years) with a median survival of 3 months. A history of pre-existing thyroid disease was present in 32% of the patients. Distant metastases were seen in 41% of patients. FNAC findings noted were pleomorphic vesicular nuclei, multinucleated giant cells, necrotic background, atypical squamoid cells, spindle cells and atypical mitosis. Majority of the patients (59%) received palliative radiotherapy as treatment. 14% underwent total thyroidectomy and remaining 27% received best supportive care.

Conclusion: ATC remains a highly lethal disease with limited survival. FNAC can serve as a reliable tool in the early diagnosis. With several drugs in clinical trial, the therapeutic scenario of ATC might improve in future.

Keywords: ATC, FNAC, Multinucleated giant cell, Retrospective, Survival.
Materials and Methods

Following the institutional review board approval, a retrospective review of the database was performed to identify patients with ATC who reported to the institution from January 2012 to December 2016. Clinical variables like age, sex, presenting complaints, nodal status, pre-existing thyroid disease, presence of metastatic disease and treatment received were obtained from the medical records. The FNAC slides and histopathological slides were retrieved from the archival files of the Oncopathology department and reviewed. FNAC slides were assessed for features like multinucleate bizarre giant cells and/or spindle/squamoid cells with marked atypia, abnormal mitoses and necrotic background. The H&E sections were re-evaluated and the diagnosis was confirmed.

Follow up data of all the patients were obtained from the medical records. A telephonic survey determined the status of patients who were lost to follow up. Death was attributed to ATC if there was evidence of progressive disease and no other proximate cause of death was identified. Overall survival curve was obtained using Kaplan–Meier estimate.

Results

A total of 22 patients were diagnosed with ATC from 2012 to 2016. It accounted for 3.5% of the total thyroid malignancies reported in our institution. Of the 22 cases, 8(36%) were males and 14(64%) females. The median age at presentation was 70 years (range 50–85 years). The most common presenting complaint was rapidly enlarging mass in the neck (68%) followed by dysphagia (41%) and hoarseness (36%). Other symptoms were pain...
(27%) and dyspnoea (26%). At the time of diagnosis, clinical evidence of nodal disease was present in 55% and distant metastasis in 41% of the cases. The most common site of distant metastasis was lung. A history of pre-existing thyroid disease was present in 32% of the patients. However no data was available regarding the type of lesion present.

FNAC slides were available only for 20 patients as only these patients underwent FNAC from our institution. Three patients had surgical intervention and H&E slides of these cases were retrieved. Predominant FNAC finding was sheets and clusters of cells with pleomorphic vesicular nuclei followed by presence of multinucleated giant cells and necrotic background. Other findings included atypical squamoid cells, spindle cells and atypical mitoses (Figures 1, 2). Histopathologic slides when assessed showed that 2 cases were spindle cell type and one was a rhabdoid variant (Figure 3 G–H).

Palliative radiotherapy was the treatment received by 59% patients. Three patients had undergone total thyroidectomy (14%) of which one was operated in our institution and two operated outside. The remaining (27%) were provided with best supportive care. Tracheostomy was performed in four patients for impending airway compromise. Follow up data of the patients revealed that the median survival in this cohort was 3.0 months (95% confidence interval with lower bound 1.870 and upper bound 4.130) (Figure 4). All the 22 patients succumbed to the disease with a maximum survival of 7 months.
Discussion

ATC is defined by the WHO as a highly malignant tumor wholly or partially composed of undifferentiated cells that retain features indicative of an epithelial origin on immunohistochemical or ultrastructural ground. ATC is a rare disease with reported incidence varying from 1–3% in different studies. In the current study, the incidence of ATC was 3.5% which is higher than the values reported in literature. A comparatively higher frequency of ATC in our study may be due to the selection bias as the data was collected from the archival files of an Oncology centre. ATC most often afflicts the elderly. The median age at presentation in our study group was 70 years. The youngest patient in the series was 50 years old. A male: female ratio of 1:1.7 was noted. Female preponderance and occurrence in the elderly as noted in the current study is in accordance with the literature.

Being an aggressive lesion, ATC commonly presents with a rapidly evolving central neck mass. Dysphagia, hoarseness, pain and dyspnoea are other symptoms. Our series also presented with similar symptoms. Duration of less than 2 weeks was reported by most of the patients. Lymph node metastasis and distant metastasis at presentation is a common finding in ATC cases. The usual sites of distant metastasis are lungs and bones. 41% of patients had lung metastasis at presentation. Two patients had metastasis to the ribs.

It has been hypothesized that anaplastic carcinoma may represent a dedifferentiation of either a benign lesion or a well–differentiated carcinoma. This is validated by the fact that majority of ATC patients are elderly, may present with positive history of previous thyroid disease, and show ‘transforming areas’ on light microscopy. In their series of ATC, Mc Iver et al observed that 23% of the patients had evidence of pre–existing or co existing differentiated thyroid cancer and 20% patients had thyroid nodule or goiter. In the present study, 32% of the patients had a history of long standing thyroid disease. However none of them had sought any treatment in the past: thence the pathology could not be identified.

The concurrent occurrence of ATC and foci of well differentiated thyroid cancer has been well documented in literature and corroborates the notion that ATC arises due to transformation of a differentiated thyroid cancer. Also lending support to this hypothesis are the evidences from the genetic and molecular studies. About 70% of the ATC cases show loss of expression of the tumor suppressor gene p53. Lesser proportion of well differentiated thyroid cancers exhibits this phenomenon. It has been proposed that TP53 plays an important role in the transformation of well differentiated thyroid cancers to ATC. RAS mutation, BRAF mutation or RET/PTC fusion which are commonly seen in differentiated thyroid cancers, have been identified in a proportion of ATC cases. PIK3CA and PTEN gene mutations also occur in both differentiated thyroid cancer and ATC. These findings also lend support to the belief that undifferentiated carcinomas arise by progression of differentiated thyroid carcinomas.

Fine needle aspiration cytology is regarded as the gold standard for initial investigation in the diagnosis of thyroid swellings. The technique is safe, simple and quick with a low complication rate. On FNAC, the undifferentiated tumours yield a highly cellular aspirate with markedly pleomorphic nuclei. Giant cells, characterized by extreme pleomorphism, with bizarre multiple hyperchromatic nuclei and abundant eosinophilic cytoplasm are often present. The background is dirty with necrotic debris and a few inflammatory cells. Atypical squamoid cells and spindled cells also form prominent components of the cytological smear. Chromatin clumping, prominent irregular nucleoli and atypical mitoses can also be appreciated.

On cytology, poorly differentiated thyroid carcinoma has to be considered in the differential diagnosis. They are characterized by trabecular or nested architecture with a uniform population of follicular cells exhibiting a high nuclear cytoplasmic ratio and variable nuclear atypia. Apoptosis, mitosis and necrosis can be seen. However compared to ATC they exhibit a lesser degree of nuclear atypia with a strikingly monotonous appearance and lack of spindle cells and giant cells. In the current series, one of the cases was given a diagnosis of poorly differentiated carcinoma on FNAC, which following histopathologic examination turned out to be ATC. On reviewing the slide we found that the smear showed clusters of cells with high nuclear cytoplasmic ratio and nuclear atypia. However there was lack of spindle cells, giant cells, atypical mitosis or necrosis. The possible justification for an erroneous diagnosis is that the FNAC might have been from a more differentiated area of the tumour. Nevertheless bizarre tumour cells with multi nucleation and necrotic background along with a clinical presentation of rapidly evolving central neck mass allows for a facile diagnosis.

Other differential diagnosis which has to be contemplated is primary squamous cell carcinoma of thyroid. However squamous cell carcinoma of thyroid is an extremely rare entity. Cytologic samples are composed almost exclusively of large, pleomorphic keratinized cells. Metastatic carcinomas should also be considered in the setting of a known primary.

Several morphological variants of anaplastic thyroid carcinoma have been described which include spindle cell variant, giant cell variant, rhabdoid variant, angiomatoid
variant and paucicellular variant. The spindle cell variant show tumour cells arranged in fascicles and resemble sarcoma. The rhabdoid variant features ovoid cells with eccentric nuclei. ATC at presentation are often inoperable; hence the current series had only three cases for histopathologic review. Two slides were of spindle cell type and one rhabdoid variant. Although several morphologic variants are described such categorisation doesn’t imply any prognostic significance.

ATCs exhibit a variable immunophenotype. CK is positive in 40–100% of the cases. Vimentin immunexpression is frequent. However differentiated thyroid markers like TTF1 and thyroglobulin are usually negative. PAX 8 expression is retained and thus, an important diagnostic tool.

All ATCs are considered stage IV by the International Union Against Cancer (UICC)—TNM staging and American Joint Commission on Cancer (AJCC) system. Multimodality treatment ie, surgery combined with radiation and chemotherapy is recommended for the management of ATC. The role of radical surgery in the treatment is questionable as resection is not known to alter the course of the disease. Often the tumour is so widely invasive at presentation that it is beyond the bounds of any meaningful resection. Howbeit as per NCCN guidelines if the patient appears to have a resectable disease, an attempt at total thyroidectomy with complete gross tumour resection should be made, with selective resection of all involved local or regional structures and nodes. Several studies report a survival benefit following radical resection. In a large series of 329 patients by Seung–Kuk Baek et al, gross surgical resection was one of the significant predictors of improved outcome. A. Mohebati et al also reported a similar result. Nevertheless as per the treatment guidelines of our institution, surgery is considered only if the lesion is small and limited to thyroid gland.

Radiation therapy is known to reduce the morbidity and mortality from loco regional complications of ATC. Role of radiotherapy varies from palliation to definitive treatment to prolong the survival of the patient. External beam radiotherapy can be given as adjuvant post–surgery following R1/R0 resection. It can also be tried in R2 resection and unresectable disease. Doses and fractionation can vary. In the current series, majority of the patients received palliative radiotherapy. The dose ranged from 20 Gy in 5 fractions to 30 Gy in 10 fractions.

Treatment with single agent chemotherapy is not very effective although some patients may show disease response or can have stable disease. Recommended regimens include paclitaxel and carboplatin combinations, docetaxel and doxorubicin combinations, paclitaxel alone, or doxorubicin alone. Chemotherapy alone can be considered for patients with unresectable or metastatic disease. Single–agent doxorubicin is the only agent that is approved by the FDA for ATC. Novel multitargeted therapies including bevacizumab with doxorubicin, sorafenib, sunitinib, imatinib, pazopanib, osbretabulin, crolibulin and efatutuzone have all been tried in clinical trials. The two small–molecule tyrosine–kinase inhibitors imatinib mesylate and sorafenib are in the midst of Phase II clinical trials. These clinical trials might improve the therapeutic scenario in the future.

**Conclusion**

ATC represents a highly aggressive neoplasm with dismal prognosis. In our study we found that the incidence of ATC was 3.5% which is higher than the reported values elsewhere. However this value might not represent the true picture as the cases were retrieved from an oncology centre. Similar studies from other parts of the world may yield further information about this rare tumour. FNAC is a simple and cost effective diagnostic tool in making rapid diagnosis of ATC for early patient management. Molecular based research for a better understanding of tumour biology may open pathways for targeted therapy, which can improve the prognosis of this extremely fatal disease.

**References**


