

Incidental anaplastic thyroid carcinoma: A case report

İnsidental anaplastik tiroid karsinomu: Olgu sunumu

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ABSTRACT

Anaplastic thyroid carcinoma is one of the most aggressive of all human malignant diseases. It has an unfavorable prognosis and responsible for most of the mortality and morbidity rates due to thyroid carcinomas. We present a case of incidental anaplastic thyroid carcinoma and discuss the epidemiology, biology, risk factors, prognostic factors of the disease and the approach to treatment, in the light of the current medical literature. The prognosis is much better in cases with incidental carcinoma compared to the classical type and surgical excision of the tumor has a favorable effect on the results. Our case was followed-up for 1.5 years with no evidence of recurrence or metastasis.

Key words: Thyroid, anaplastic, carcinoma, incidental, immunohistochemistry

ÖZET

Anaplastik tiroid karsinomu; insan maligniteleri içinde en agresif olan tümörlerden biridir. Kötü prognozudur ve tiroid karsinomlarına bağlı mortalite ve morbiditenin önemli kısmını oluşturmaktadır. Biz bu makalede anaplastik tiroid karsinomlu bir olgu rapor ederek epidemiyoloji, biyoloji, risk faktörleri ve prognostik faktörleri, tedavi yaklaşımlarını literatür bilgileri eşliğinde tartıştık. İnsidental karsinomlu olgularda prognoz klasik tipe göre daha iyidir ve tümörün cerrahi olarak çıkarılması, sonuçları olumlu etkilemektedir. Olgumuz tanı sonrası 1.5 yıl takip edilmiş olup, nüks veya metastaz saptanmamıştır.

Anahtar sözcükler: Tiroid, anaplastik, karsinom, insidental, immünhistokimya

INTRODUCTION

Well-differentiated thyroid carcinomas are usually slowly growing asymptomatic tumors that carry an excellent prognosis when treated properly. Anaplastic thyroid carcinomas (ATC) are aggressive undifferentiated tumors with a very high mortality rates. They usually infiltrate into surrounding tissues at the time of diagnosis, and have unfavorable prognosis. Among thyroid carcinomas, ATC is the third in frequency at a rate of 1.6% after papillary and follicular carcinomas (1,2,3). The average survival is 6-12

months with a 10-year survival of approximately 3 percent (4). Most patients have local symptoms such as dysphagia, dysphonia, stridor and neck pain. Although some series report a few cases of incidental ATC in thyroid nodules, ATC frequently appears as a rapidly growing mass in the neck. About 40% of the cases have cervical lymph node metastases, 90% directly invade the surrounding soft tissues and organs such as trachea and larynx and 75% have distant metastases. Metastases are seen most commonly in the lungs and the brain (1,2,5).

CASE REPORT

A 50-year-old female patient had undergone diagnostic fine needle aspiration biopsy (FNAB) of a nodule 1 cm in diameter localized

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within the right lobe of the thyroid gland which was found to be radiologically suspicious 8 months ago. FNAB had shown thyrocytes that formed single-layer cohesive groups and colloidal material in the background, interpreted as a "benign colloidal nodule". She underwent bilateral subtotal thyroidectomy 8 months later as her clinical symptoms persisted. On macroscopic examination, the gland was encapsulated except for one side and measured 7x5x3 cm. There was one nodule with a cross-section rich in colloid in the right lobe where the FNAB was performed while there was another nodule 2 cm in diameter which was separated from the surrounding thyroid tissue with a thick fibrous capsule. Other areas were normal. Four micron thick HE stained sections obtained from routine paraffin blocks showed an adenomatous nodule consisting of multi-sized follicles filled with colloidal material detected on the microscopic examination of the right lobe nodule. Microscopic examination of the 2 cm nodule in the left lobe showed a tumor where pleomorphic cells proliferated with a solid pattern around large areas of necrosis surrounded by a thick fibrous capsule (Figure 1a-b). Tumor cells consisted of atypical cells containing a few nucleoli, with amphophilic cytoplasm, a bizarre nucleus and a coarse chromatin pattern in some areas and contained osteoclast-type multinuclear giant cells while other areas had squamoid characteristics. The component with squamoid characteristics did not have tumor cells forming trabeculae, fol-

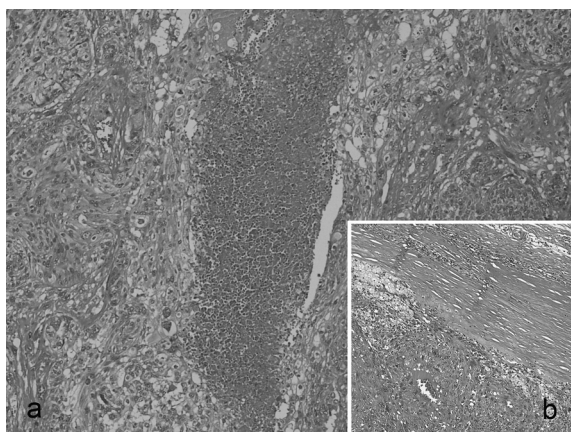


Figure 1a. Pleomorphic cells proliferated with a solid and storiform pattern around large areas of necrosis (HE x200). **b.** The tumor was surrounded by a thick fibrous capsule (HE x100).

licles\ nests or papillary structures, but there were morphological characteristics of epithelial differentiation. There were spindle and giant cells forming a fascicular and storiform pattern in the sarcomatoid areas. All nodule was sampled to find any concurrent well-differentiated carcinoma focus. There were no findings of differentiated thyroid carcinoma or extracapsular invasion. The histopathological differential diagnosis was between ATC, primary and metastatic sarcomas, insular carcinoma and metastatic carcinomas. The palisading encirclement of the large central necrosis area by tumor cells and the sarcomatous component of spindle and multinuclear giant cells accompanied by undifferentiated epithelial areas made a diagnosis of anaplastic thyroid carcinoma likely. We used primary antibodies pancytokeratin (Neomarkers/Biogen1/100-200), Epithelial membrane antigen (EMA) (Neomarkers/Biogen ready to use), Thyroglobulin (Neomarkers/Biogen ready to use) and Carcinoembryonic antigen (CEA) (Dako 1/25) for the immunohistochemical study (streptavidine-biotin immunoperoxidase technique, AEC chromogen) to determine the nature of the cells. There was strong staining with pancytokeratin and focal positive staining with EMA and CEA that excluded the possibility of primary and metastatic sarcomas (Figure 2). We used thyroglobulin staining for the insular carcinoma and calcitonin for the medullary carcinoma possibilities considered in the differential diagnosis. Neither results were positive, excluding insular and medullary carcinomas. Pancytokeratin is the most important marker in the immuno-

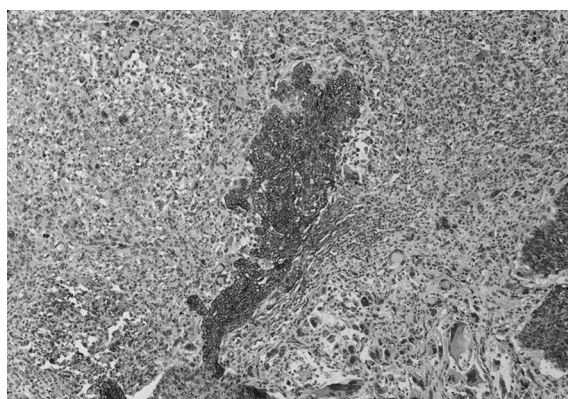


Figure 2. Anaplastic carcinoma showing positive reaction for keratin in squamoid areas of the tumor (x200).

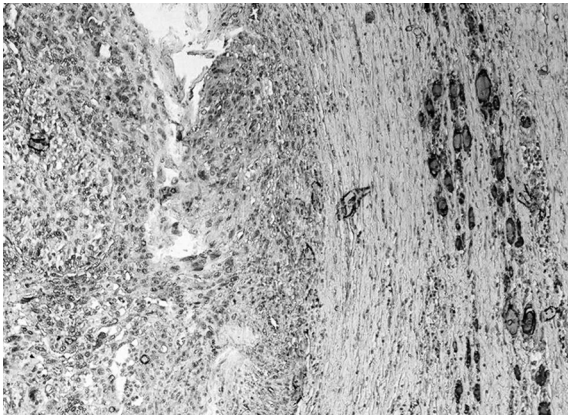


Figure 3. There was no immunostaining with thyroglobulin in tumour cells (x100).

histochemical differential diagnosis of ATC with a staining rate of 50-100%. Thyroglobulin staining has (8%) been rarely reported (6). However, there was no staining in our case (Figure 3). We looked for a primary focus with radiological, clinical and biochemical tests to eliminate the possibility of a metastatic carcinoma and found no primary neoplastic foci. The case was diagnosed as an incidental anaplastic thyroid carcinoma after evaluation of the histopathological, immunohistochemical and clinical findings. Subsequent total thyroidectomy, radiotherapy and chemotherapy were performed for treatment. The patient was alive 1.5 years later.

DISCUSSION

Anaplastic thyroid carcinoma is seen at a rate of 1.6% in endemic goiter regions, third in frequency following papillary and follicular carcinoma. The incidence has decreased from 5-14% in 1990s to 1.7-2% in 2000s (1,2,7,8,9). Agrawal et al (10) have reported the ATC incidence as 7.7% between 1969 and 1973 and 4.2% between 1989 and 1993. Lampertico et al (11) have reported a decrease from 11% to 5% from 1979 to 1993. On the contrary, the rate of well differentiated papillary carcinomas has meanwhile increased about 3.5% during this period (10,12).

The decreased ATC incidence has been explained in many ways. When the hypothesis of de-differentiation of benign or malignant thyroid diseases for the etiopathogenesis of

ATC is taken into account, many benign and malignant thyroid diseases that are risk factors for ATC development are now treated at an early stage with effective surgery. It is reported that ATC is seen twofold in frequency in areas of endemic goiter (13). The use of prophylactic iodine in endemic areas in recent years seems to have eliminated another important risk factor (13,14). Another factor that may explain the decreased incidence of ATC is that many tumors are now correctly being diagnosed as lymphoma, undifferentiated insular carcinoma or medullary carcinoma with the increased availability of immunohistochemical studies (15). It is therefore easy to explain the decreased incidence in recent years.

ATC is seen frequently in women in their 6th or 7th decades. The female/male ratio is 3/1-1.2/1. The most comprehensive study on the subject is the 134-case series of McIver et al (16) that states that the first clinical symptom is a rapidly growing mass in up to 97% of the patients. Hemorrhage into the mass may cause pain and dysphagia. About 50% of the cases have distant metastases at the time of diagnosis (3,13,14,17).

"Incidentaloma" can be defined as an asymptomatic tumor found incidentally during an unrelated procedure (18). The rate of small occult tumors found incidentally during an autopsy or surgical series has been reported as 0.5-13% in various articles. The rate of incidental tumors is now increasing rapidly with the extensive use of ultrasound and other imaging studies (13,18). Most incidental tumors are papillary microcarcinomas. ATCs are rarely found incidentally in thyroid nodules (13,18). Incidental ATC is defined as an ATC focus in a differentiated tumor focus (5). This definition is closely related to the etiopathogenesis. Nishiyama et al (19) have reported that when multiple sampling is performed on an ATC cases, a focus of a well-differentiated cancer is always found. Ibanez et al (11) have sampled the thyroid in 42 cases and found a well-differentiated tumor focus in each case. When a well-differentiated tumor cannot be found, it is thought that this is due to inadequate sampling or ATC growing to a size that destroys all well-differentiated tumor (11). Sa-

bin et al (20) have found a concurrent well-differentiated carcinoma in 21-79% of ATC cases. We did not find a well-differentiated focus in our case although all nodule was sampled.

There are two etiopathogenetic theories on ATC development. One is the development due to anaplastic transformation of an accompanying well-differentiated tumor and the other one is the *de novo* development theory (1,7,17,21). The presence of a previous or concurrent well-differentiated carcinoma is 24-89% for ATC (21). Its incidence in the elderly and in long-term tumors that have not been adequately treated supports the anaplastic transformation theory. A study has found insular carcinoma in 27% and anaplastic carcinoma in 24% of women with goiter of more than 10 years duration (2). Demeter et al (22) have reported previous benign or malignant thyroid pathology in up to 76% of ATC cases and that 46% of these cases had previous or concurrent papillary thyroid carcinoma.

Genetic studies to understand the pathogenesis, progress and kinetics of tumors have increased recently and provided some insight into the development of the incidental ATC (23). The loss of tumor suppressor gene p53 has been shown in colon, lung and breast tumors and also thyroid tumors (24). The dedifferentiation from a well-differentiated thyroid carcinoma into undifferentiated or anaplastic thyroid carcinoma is associated with a p53 mutation. ATC cases show a higher incidence of p53 mutation than differentiated thyroid carcinomas (25). Sniezek et al (24) showed loss of p21 gene expression in anaplastic and insular carcinomas. The BRAF mutation is the most common mutation in papillary carcinomas as shown in many recent genetic studies and it has been found more frequently in cases with dedifferentiation from well-differentiated carcinoma (4,20,23,26). The rate of a BRAF mutation in a study by Nikiforova et al (20) has been found to be 38% in papillary thyroid carcinoma, 0% in follicular and Hurtle cell carcinoma, 13% in well-differentiated carcinoma, 10% in anaplastic carcinoma, and 0% in medullary carcinoma, Hurtle cell adenoma and hyperplastic nodules.

The prognosis of anaplastic thyroid carci-

noma depends on many factors such as age, gender, tumor size and resectability. Guiffride et al (27) have reported the patient's age and the extent of the disease at the time of diagnosis as the most important prognostic factors. Sugino et al (13) studied 47 cases and listed the important prognostic factors as the presence of acute symptoms, a tumor diameter more than 5 cm, distant metastases and leucocyte counts over 10.000/ml. Another study by Venkatech et al (7) reported the mean survival as 8 months for localized and 3 months for metastatic disease. When incidental ATC and classical ATC are compared, there is inadequate data about better prognosis (13,17). Pierie et al (5) have reported a 1-3 year survival rate of 90% for incidental ATC. However, the number of incidental ATC cases in this series is not adequate to reach statistically significant conclusions (5).

It is important to understand carcinogenesis to define treatment strategies. Treatment of ATC varies as it is rare and presents at various stages at the time of diagnosis (13). ATC is seen more often in the elderly of poor general health status. Since it is difficult to diagnose and there is no effective treatment, it is still one of the most fatal tumors (14). The current treatment options are surgery, radiotherapy and chemotherapy. Combined treatment options are used when there is widespread metastasis with poor prognosis, likely to be fatal within a few months. The primary treatment is the surgical removal of the tumor. The surgical treatment for ATC has changed from tracheostomy for palliative reasons to curative resection, if possible (17). Chemotherapy or radiotherapy is used following surgical treatment. Pre- and postoperative radiotherapy can also be used for cases scheduled for surgery. There are many few patients with long-term survivals and the mortality rate is reported as 70-95% (17). Sugino et al (13) have suggested adding radiotherapy to surgical treatment for control of local disease and found a much better prognosis for incidental ATC than the classical type even if incidental ATC foci are thought to be life-threatening. However, other series have reported differences between the incidental type and the classical type and stated that radiotherapy does not change 1-year survi-

val or cumulative survival in ATC cases. Ojeda et al (21) reported a statistically favorable survival times in cases with focal ATC in a differentiated tumor or ATC limited to a single thyroid lobe in their 30-case series. The mean survival period of 5 such cases was 24 months. This study emphasizes that the prognosis of ATC accompanying a well-differentiated tumor is not different from pure ATC but the prognosis is better when a single focus is present (21). Our case had ATC within a nodule limited to a single lobe and survived for 1.5 years, consistent with this study. In conclusion, a combination of radiotherapy, chemotherapy and in resectable cases aggressive surgery may be beneficial until treatment options with proven efficacy are found.

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