Endokrynologia Polska
DOI: 10.5603/EP.a2018.0010
Tom/Volume 69; Numer/Number 1/2018
ISSN 0423–104X

Anaplastic thyroid carcinoma with rapid thyrotoxicosis — a case report and the literature review

Anaplastyczny rak tarczycy z gwałtowną tyreotoksykozą — opis przypadku i przegląd literatury

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Abstract

Introduction: Anaplastic thyroid carcinoma (ATC) is one of the most aggressive human malignancies and constitutes approximately 1.6–5% of the malignant neoplasms of the thyroid gland. ATC usually manifests itself with the local symptoms due to a rapidly enlarging thyroid mass, and as other thyroid cancers, has only seldom been reported to cause thyrotoxicosis. Up to now only 9 cases of ATC with concomitant thyrotoxicosis have been described.

Case report: We report a rare case of a 66-year-old woman, who had had the preexisting large, euthyroid multinodular goiter for almost 50 years. She was consulted by a doctor because of a 4-week history of thyrotoxicosis, symptoms of the congestive heart failure and a rapid increase in the size of the goiter. Thyroid hormone levels were consistent with a hyperthyroid state. The fine-needle aspiration biopsy confirmed a diagnosis of the anaplastic thyroid carcinoma, the small cells variant. The 99m Tc-pertechnetate scintigraphy visualized non-homogenous tracer distribution with hot nodules.

She was given a doxorubicin (20 mg/week) and required the continuous antithyroid treatment. The patient died a one year after the first symptoms of the disease occurred.

Discussion: The association between ATC and a thyrotoxic state is very rare. In most cases, thyrotoxicosis concomitant with ATC was thought to be a result of the destruction of the thyroid follicles by the rapid infiltration with malignant cells, resulting in the leakage of preformed hormones to the circulation. In that case the most probable cause of thyrotoxicosis was the multinodular goiter coexisting with ATC. A simultaneous onset of tumor growth, thyrotoxicosis and a relatively long survival time of our patient is worth to notice and discuss. **(Endokrynol Pol 2018; 69 (1): 28–31)**

Key words: *anaplastic thyroid carcinoma, thyrotoxicosis*

Streszczenie

Wstęp: Anaplastyczny rak tarczycy (ATC) jest jednym z najagresywniejszych nowotworów w patologii ludzkiej i stanowi około 1,6–5% złośliwych nowotworów tarczycy. Rozpoczyna się zwykle objawami miejscowymi wtórnymi do szybkiego wzrostu guza i, podobnie jak w przypadków innych typów raka tarczycy, jedynie sporadycznie jest on skojarzony z nadczynnością tarczycy. Dotychczas opisano 9 przypadków ATC ze współistniejącą tyreotoksykozą.

Opis przypadku: Autorzy prezentują rzadki przypadek 66-letniej kobiety ze stwierdzanym od blisko 50 lat ogromnym wolem guzowatym, wcześniej w stanie eutyreozy. Pacjentka zgłosiła się do lekarza z powodu utrzymujących się od 4 tygodni objawów nadczynności tarczycy, zastoinowej niewydolności krążenia oraz gwałtownego wzrostu objętości wola. Wyniki badań hormonalnych były typowe dla pierwotnej nadczynności tarczycy. W biopsji cienkoigłowej potwierdzono rozpoznanie raka anaplastycznego z małych komórek. Scyntygrafia technetowa wykazała niejednorodne gromadzenie znacznika oraz kilka gorących guzków. Pacjentka była leczona doksorubicyną w dawce 20 mg/tydzień, wymagała także stałego podawania tyreostatyku. Zmarła po roku od wystąpienia pierwszych objawów choroby.

Dyskusja: Skojarzenie ATC z tyreotoksykozą jest niezwykle rzadkie. W większości przypadków nadczynność tarczycy współistniejąca z ATC wynika z uwalniania do krążenia hormonów z nabłonka tarczycy niszczonego przez naciek nowotworowy. W prezentowanym przypadku najbardziej prawdopodobną przyczyną nadczynności tarczycy było współistnienie wola guzowatego toksycznego. Warto zwrócić uwagę na jednoczesne wystąpienie gwałtownego wzrostu wola i tyreotoksykozy oraz na względnie długie przeżycie pacjentki. **(Endokrynol Pol 2018; 69 (1): 28–31)**

Słowa kluczowe: *anaplastyczny rak tarczycy, tyreotoksykoza*

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Introduction

Anaplastic thyroid carcinoma (ATC) derives from the well-differentiated thyroid follicular epithelial cells and in different geographical regions constitutes approximately from 1.3% to 9.8% of all thyroid malignant neoplasms [1]. It is one of the most aggressive human malignancies, with a total disease-specific mortality of at least 90% [2]. ATC usually manifests itself with the local symptoms due to a rapidly enlarging thyroid mass and, as other thyroid cancers, has only seldom been reported to cause thyrotoxicosis.

Case report

We report a case of a 66-year-old woman, who had had the preexisting large, euthyroid multinodular goiter for almost 50 years. She contacted a doctor with a history of 4-week of unintentional 10 kg weight loss, palpitations, dyspnoea, shortness of breath, insomnia, tremor and a rapid increase in the size of the goiter. Physical examination revealed a large, firm, nontender multinodular goiter. There were some bilaterally palpable lymph nodes in the angles of mandible regions. Her heart rate was totally irregular, 120 beats per minute, blood pressure was 150/80 mm Hg. She had bilateral ankle oedema. No signs of orbitopathy were present and she did not have any symptoms suggesting an airway compression. Thyroid hormone levels were consistent with a hyperthyroid state and were as follows: suppressed serum level of thyrotropin (TSH) < 0.005 uIU/ml, free thyroxine (fT4) = 64.2 pmol/l (range 10–20 pmol/l) and free triiodothyronine (fT3) = 14.3 pmol/l (range 3.1–6.5 pmol/l). ECG revealed atrial fibrillation. At that moment, the patient firmly refused hospitalization and extending the diagnostic tests with biopsy for family reasons. The thyrotoxicosis was treated with thiamazole in a daily dose of 60 mg and a beta-blocker (bisoprolol 10 mg/day). Hydrochlorothiazide (in the dose of 12.5 mg/day) and acenocoumarol were also administered.

Within two weeks of the treatment, patient's general condition much improved. Moreover palpitation, tremor and oedema disappeared. The heart rate was 80 per minute, but the atrial fibrillation was still recorded. Thyroid function tests revealed the following: fT4 = 34.2 pmol/ml, anti-thyroid peroxidase antibodies (anti-TPO) = 0.11 IU/ml (range 0–100 IU/ml), thyroglobulin = 120 ng/ml (range 0–60 ng/ml), anti-thyroglobulin antibodies = 28 IU/ml (standard < 40 IU/ml), thyrotropin receptor antibody (TRAb) = 0.8 IU/l (range 0.0–1.5 IU/l). Carcinoembryonic antigen, alpha-fetoprotein levels and other tumor markers (CA-125, CA 19-9, CA 15-3) were in the normal levels. The dose of thiamazole was consistently reduced to a maintenance dose, 5 mg per day. The euthyroidism was achieved following 8 weeks of antithyroid drugs therapy. Repeated thyroid function test showed: fT4 = 18.5 pmol/l, fT3 = 7.3 pmol/l. After the next 3 months of treatment, the goiter had become more firm and the patient started to complain about choking sensations. At that moment she agreed to be hospitalized and she was referred to the Department of Endocrinology, Diabetes and Isotope Therapy to undergo more advanced examinations because of the suspicion of ATC.

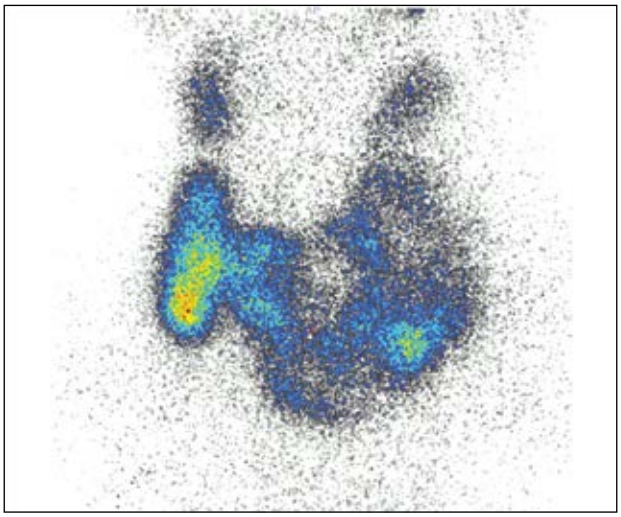

Figure 1. *Thyroid ^{99m}Tc-pertechnetate scintigraphy: foci with excessive accumulation of the tracer*

Rycina 1. *Scyntygrafia tarczycy ^{99m}Tc z widocznymi ogniskami wzmożonego wychwytu znacznika*

The thyroid ultrasound examination revealed a large mass with a heterogeneous echogenicity, which extended below the sternum, especially on the left side. There were multiple focal lesions in the thyroid gland with a hypoechogenic and hypervascular structure in the left lobe. The chest X-ray picture showed an enlargement of the superior mediastinum, a deviation of trachea to the right with its constriction and bilateral metastatic lesions in the lungs. ECG confirmed a persistent atrial fibrillation with a ventricular mean rate 78/min. The 99m Tc-pertechnetate scintigraphy visualized a non-homogenous tracer distribution with a high uptake within the hyperfunctioning nodules (hot nodules) (Figure 1). A thyroid radioiodine uptake was 16% after 24 hours.

A fine-needle aspiration biopsy of the thyroid confirmed the diagnosis of anaplastic thyroid carcinoma, the small cells type with a positive thyroglobulin reaction (Figure 2).

The tumor was considered unresectable because of its advanced stage and the presence of lung metastases. Due

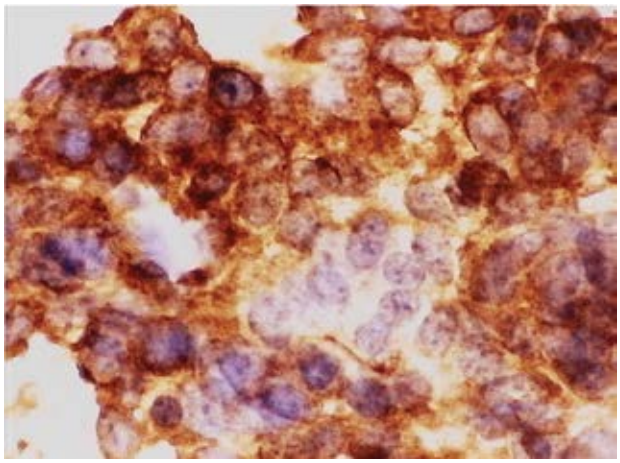

Figure 2. *FNA thyroid biopsy: anaplastic carcinoma of small cells with positive stainig of thyroglobulin (×200)*

Rycina 2. *BAC tarczycy. Rak anaplastyczny z małych komórek z dodatnią reakcja na tyreoglobulinę (×200)*

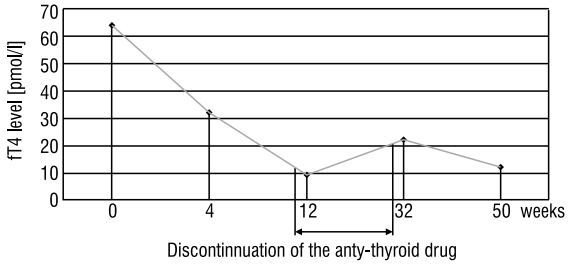

Figure 3. *Thyroid function during the treatment: transient post thiamasole hipothyroidism and relapse of hyperthyroidism after discontinuation of the medication*

Rycina 3. *Funkcja tarczycy w trakcie leczenia: przejściowa polekowa niedoczynność i nawrót nadczynności tarczycy po zaprzestaniu leczenia*

to the rise of fT4 to 23 pmol/l after the antithyroid medication withdrawal, the continuous treatment with thiamazole was restored in a dose of 10 mg and kept till the end of the follow-up (Figure 3). The patient had a treatment of chemotherapy based on doxorubicin (20 mg/week) and she died a year after the first medical consultation.

Discussion

Anaplastic carcinoma of the thyroid is one of the most aggressive cancers, with a median survival time reported from 1.2 to 10 months after the diagnosis [3]. It is worth noting, that although this type of cancer is a rare neoplasm, the mortality rate is above 90% and it is the cause of 14–39% deaths of patients with the thyroid cancer [4]. One-year and 5-year relative survival rates are estimated to be 10–20% and 4.6–5.4% respectively [3, 5]. All patients diagnosed with ATC are classified as stage IV according to the American Joint Committee on Cancer TNM system [6].

The clinical manifestation of ATC reflects the local invasion and mass effect caused by the thyroid tumor growth. Nearly all patients have the symptoms of an enlarging primary tumor of the neck and dysphagia. Moreover, also a change of voice or stridor occurs [5]. However, the history of our patient's illness was different. The symptoms of thyrotoxicosis and the heart failure were the reasons to seek a medical attention. She initially refused to be hospitalized and that decision caused a delay in the diagnosis.

The association between ATC and a thyrotoxic state is very rare. To our knowledge, only nine other cases have been described in the literature [7–15].

The rapid growth of the primary tumor may rarely cause a nonspecific thyroiditis with symptoms of thyrotoxicosis. One of the possibilities of that state is the follicular disruption and a release of the thyroid hormones from the preformed pool. Phillips et al. suggested that the thyroid hormones level may be elevated due to an alternative mechanism, one of the hypothesis is a hormone production from metastases [12, 16]. However, in that case the unusual symptoms of the disease was probably caused by the multinodular goiter coexisting with ATC. Low concentration of the TSH-receptor binding antibodies and the anti-TPO antibodies excluded the Graves' disease or an autoimmune thyroiditis as potential causes of the thyrotoxicosis. It should be noted that active thyroid nodules were seen in the scintigraphy, even after several weeks of the antithyroid treatment. Moreover, we observe the recurrence of the hyperthyroidism during the short break in the thiamazole therapy. It is also relevant that this treatment was very effective to control symptoms of the congestive heart failure and it was necessary to continue the therapy within the whole period of the follow-up. In the literature, we found only one case report of a patient who had ATC and coexisting thyrotoxicosis most likely caused by the multinodular goiter [9].

Various prognostic factors, such as age, gender, size of the tumor and the presence of the metastases are considered as important in a prognosis of patients' outcome. Due to the rare occurrence of the ATC and its fast, aggressive course, there are not many randomized trials with an assessment how that factors determine the survival.

Kebebew et al. analyzed data from the SEER database and they estimated that the age under 60 and the intrathyroidal ATC location are the two main factors for expecting longer survival [4]. Our patient was a 66-year-old woman and there have been found metastases in the lungs, what indicated a poor progno-

sis. On the other hand, she lived longer than median survival of anaplastic cancer patients. It is also worth to emphasize and discuss a simultaneous onset of tumor growth and thyrotoxicosis with a relatively long survival time in the presented case report. Because it is an extremely rare state, there is no data in the literature comparing the influence of the hyperthyroidism to the better outcome in the ATC. The longer survival of our patient due to the presence of the multinodular goiter is only one of the possible hypothesis. Also in the literature there are studies suggesting that thyroid disease co-morbid with ATC may have an influence on the outcome [4, 17].

The standards of the ATC treatment have not been established yet. There are only few options and unfortunately, the survival benefits are still limited. Multidisciplinary therapy, including neoplasm resection, radiotherapy and chemotherapy, may prolong the survival in some groups of patients; a better prognosis is expected for patients without tumor residues (R0) [2, 5]. In chemotherapy, doxorubicin is the most common drug, but the response rate is estimated to be only about 22%. To improve the outcome, clinical trials were conducted, in which drug combinations, such as doxorubicin, cisplatin and taxanes or docetaxel and cisplatin were used, but the response rate was about 50%. What is more, there are a few new drugs tested for the ATC treatment. One of them is sorafenib, approved by the FDA for patients with the metastatic thyroid cancer, however it has a limited efficacy in the anaplastic carcinoma [18].

Summarizing, the anaplastic thyroid carcinoma is a rare type of the neoplasm, but it is associated with high mortality. It usually occurs with a normal level of thyroid hormones and only a few cases of ATC with a concomitant thyrotoxicosis have been reported. In most cases thyrotoxicosis was caused by the hormones released from the destroyed follicles, but in our patient it was most likely secondary to the presence of the multinodular goiter.

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