

Case report

Collision tumor of the thyroid – a challenge during the COVID-19 pandemic

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Abstract

Some of the patients with anaplastic thyroid carcinomas have a coexistent differentiated thyroid cancer, sustaining the hypothesis that this cancer may develop from more differentiated tumors. We describe a case with a collision tumor of the thyroid, defined as a neoplastic lesion composed of two distinct cell populations, with distinct borders. The patient presented during the COVID-19 pandemic with dysphonia, dyspnea, multinodular goiter and a painless, rapidly enlarging, left cervical swelling. She had been first time diagnosed with left nodular goiter in 2007, with an indication for surgery, which she declined. After partial excision of the left latero-cervical adenopathy, the pathological analysis showed massive lymph node metastasis from anaplastic thyroid cancer. A total thyroidectomy was done; the postoperative pathological exam identified a papillary thyroid microcarcinoma in the right lobe and an anaplastic thyroid cancer in the left lobe. Postoperatively, levothyroxine treatment was started and the patient was referred to radiotherapy. This case highlights the importance of urgent management of some cases with compressive multinodular goiter, even during the COVID-19 pandemic.

Keywords: collision tumor; anaplastic thyroid cancer; papillary thyroid microcarcinoma; dedifferentiation

Introduction

Anaplastic thyroid cancer, also known as undifferentiated thyroid cancer, accounts for less than 2% of all thyroid cancers, being the most aggressive malignancy of the thyroid gland. It is a rare tumor, but it accounts for more than 50% of all thyroid cancer deaths [1]. The recently updated analysis of the SEER database (SEER database - Surveillance,

Epidemiology and End Results database - the authoritative source for cancer statistics in the United States), populated with data compiled from 1986 to 2015, described a mean overall survival (OS) at 6 months of 35%, with the mortality rate from anaplastic thyroid approaching 100% at 2 years [2]. Data from the SEER database point to the fact that the incidence of this type of cancer continues to increase; there could be a valid explanation for this increase, as the SEER database is constantly enlarging [3]. The incidence rate standardized by age per 1,000,000 persons in America is showing an upward trend. According to the scientific literature, the average age of patients with anaplastic tumor of the thyroid gland ranges between 65 and 72

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years [4, 5]. This form of thyroid tumor is more frequent in women (60-70% of the cases with anaplastic thyroid tumors are women) [6].

Almost all patients with anaplastic thyroid tumors present with a rapidly enlarging, firm, palpable cervical mass. At diagnosis, in 90% of all cases the tumoral cells have already migrated regionally or to distant organs [5, 7]. Distant spread at diagnosis is found in 15-50% of all patients [5, 8-9]. Because of their aggressive behavior, The American Joint Committee on Cancer (AJCC) classifies all anaplastic thyroid cancers as stage IV: anaplastic tumors confined to the thyroid are classified as stage IVA, anaplastic tumors that extend beyond the thyroid are stage IVB and patients with distant metastases are classified as stage IVC. As opposed to well-differentiated thyroid cancers, tumor cells of anaplastic thyroid carcinoma do not produce thyroglobulin, meaning that these tumors have no tumor marker for their diagnosis. Anaplastic tumor cells do not uptake iodine, making radioiodine therapy ineffective, and these tumors do not respond to thyroid-stimulating hormone suppressive therapy.

Based on postoperative histopathological analysis, 20-30% of patients with anaplastic thyroid carcinoma have a coexistent differentiated thyroid cancer. The majority of these coexistent thyroid tumors are papillary thyroid cancers, but there are reports in the literature of coexistent follicular thyroid cancer, too. These observations sustain the hypothesis that anaplastic thyroid carcinoma may develop from more differentiated tumors, which undergo one or more dedifferentiating steps [10].

This presentation will describe a case with a collision tumor of the thyroid diagnosed and treated during the difficult time of COVID-19 pandemic. A collision tumor is defined as a neoplastic lesion composed of two or more distinct cell populations that have distinct borders.

Case report

A 56-year-old female patient was admitted into the Department of Endocrinology of the Emergency County Hospital Timisoara, in

August 2020, complaining of dysphonia, fatigue, inspiratory dyspnea and a painless left latero-cervical swelling, which was described as rapidly growing over the previous 4 weeks. The personal history of the patient pointed to a diagnosis of left nodular goiter, detected in 2007, with an indication for surgery since then. The patient declined the recommended treatment and didn't show up for follow-up a long period of time. At the beginning of 2020, a diagnosis of chronic autoimmune thyroiditis was established.

At admission, the clinical examination of the anterior cervical region revealed a palpable painless nodule of approximately 4 cm, hard in consistency, adherent to the skin. Next to it, we noticed a left latero-cervical adenopathy of approximately 5 cm, fixed to underlying tissues, hard in consistency and painless, that appeared for the first time, affirmatively, in June 2020. The patient noticed a rapid growth of this lesion in the last 4 weeks. The thyroid ultrasound detected a small solid nodule in the right lobe, markedly hypoechoic, measuring 6/7.5/7mm, with a thin hypoechoic halo, showing an ultrasound (US) aspect "taller than wide" and increased internal vascularization. The thyroid nodule was classified according to ACR-TIRADS classification [11], based on the nodule's ultrasound features, as TIRADS 5 (Figures 1a and 1b). In the left lobe, the thyroid ultrasound revealed a large solid, marked hypoechoic nodule, occupying almost the entire lobe; this nodule measured 27.7/42.6/26.6 mm, had ill-defined margins, microcalcifications and no halo. The nodule had mild peripheral and no internal blood flow; it was classified as ACR-TIRADS 5 (Figure 2). On ultrasound, the left latero-cervical lymphadenopathy appeared round, hypoechoic, inhomogeneous, with mild internal vascularity and loss of hilar architecture. It measured 51/45.7/40 mm (Figure 3).

A computed tomography (CT) scan of the cervical area and thorax was performed, which showed a right thyroid lobe of normal size, with an infra-centimetric nodule and a left thyroid lobe with increased dimensions, having a length of 43/50 mm, and displacing anteriorly the sternocleidomastoid muscle, without a clear separation plan. The latero-cervical left



adenopathy measured 54/52/50 mm and was in close contact with the left thyroid lobe, displacing anteriorly the left jugular vein. The CT scan of the thorax showed a solitary infra-centimetric pulmonary nodule in the apex of the right lung that was not clearly described as a metastasis.

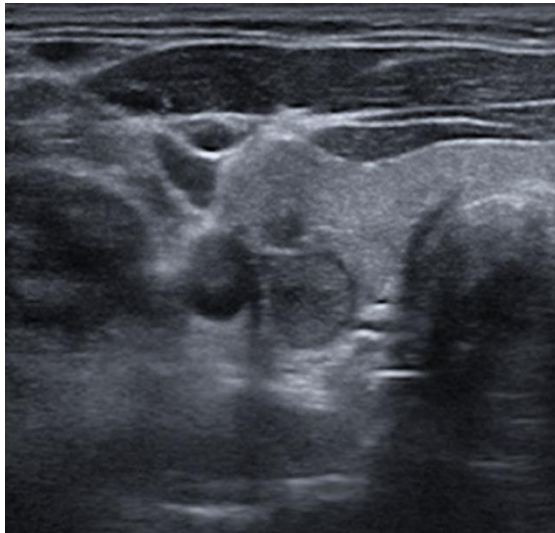


Fig. 1a. Right lobe of the thyroid, showing a small solid nodule, markedly hypoechoic, of 6/7.5/7mm, with a thin hypoechoic halo, “taller than wide” (ACR-TIRADS 5)

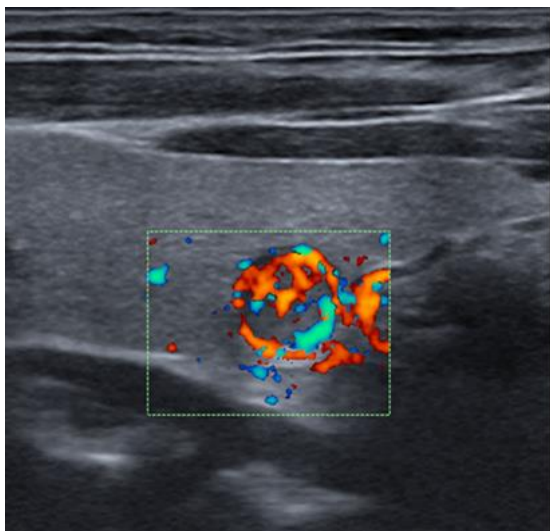


Fig. 1b. The same nodule in the right lobe of the thyroid, showing increased vascular flow on colour Doppler sonography

The laboratory examination revealed euthyroid status, with increased levels of anti-thyroid peroxidase (509 U/L, normal values < 60 U/L) and anti-thyroglobulin antibodies (481

U/L, normal values <60 U/L), confirming the diagnosis of chronic autoimmune thyroiditis.

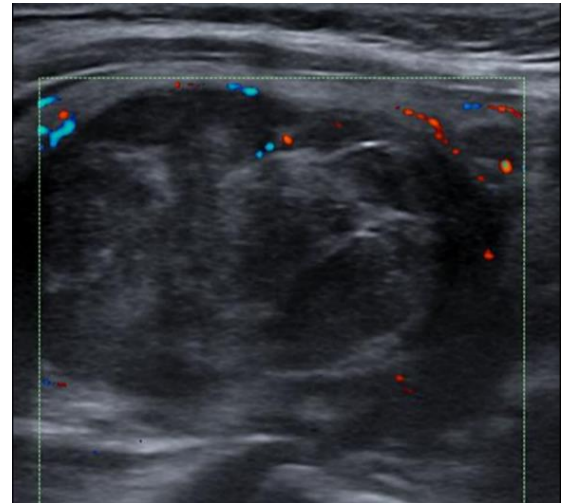


Fig. 2. The left lobe of the thyroid with a large solid nodule, occupying the entire lobe, measuring 27.7/42.6/26.6 mm. The nodule has ill-defined margins, microcalcifications and no halo, mild peripheral and no internal blood flow

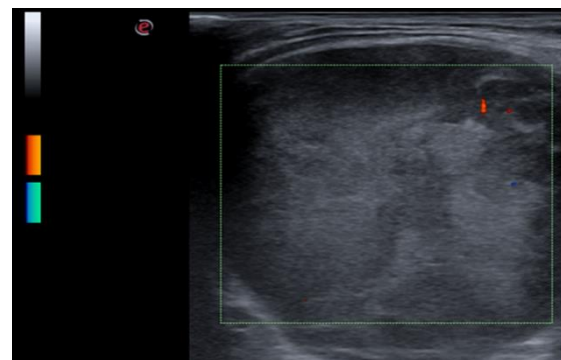


Fig. 3. Left laterocervical lymphadenopathy appearing as a round, hypoechoic, inhomogeneous mass, with mild internal vascularity and loss of hilar architecture

The blood analysis also showed a slightly high white blood cell count (10,400/ μ L, normal values: 4,000-9,500/ μ L) with moderately elevated erythrocyte sedimentation rate (60 mm/h, normal values: 1-10 mm/h). The calcitonin levels were normal.

Taking into account the characteristics of the nodular goiter, i.e. increased dimensions, hard consistency, fixation to the surrounding tissues, presence of an ipsilateral left laterocervical adenopathy with similar features like thyroid nodule, with accelerated growth in a short period of time (4 weeks) and compressive symptoms (dysphonia, dyspnea,

cough), associated with a personal history of left nodular goiter (with recommendation for surgery more than 10 years before), we suspected the presence of anaplastic thyroid cancer, possibly an anaplastic transformation of a pre-existing differentiated thyroid cancer. The patient was referred immediately for surgery. A negative PCR-test for COVID-19 was required before surgery. Due to COVID-19 pandemic situation, to establish a definite diagnosis, a partial excision of the left latero-cervical adenopathy was performed on August 2020. The pathological examination revealed high grade tumor proliferation, with tumor cells showing diffuse and intense positivity for pan-cytokeratin (pan-CK), negativity for S-100, CD45, TTF-1, PAX8 and positivity for CK7, CK8/18 and EMA, concluding that it was a massive lymph node metastasis from an

anaplastic carcinoma, most probably located within the thyroid gland.

A total thyroidectomy was performed on September 2020, after another mandatory negative PCR-test for COVID-19. The postoperative pathological exam identified in the right thyroid lobe a papillary microcarcinoma with irregular, infiltrating margins and follicular architecture, having a diameter of 9 mm. In the left thyroid lobe, a high-grade tumor proliferation was identified, accompanied by large areas of tumor necrosis; the tumor infiltrated the thyroid capsule, with large extension into perithyroidal connective tissue and tumor cell emboli in the lymph and blood vessels from the thyroid and perithyroidal connective tissue (Figures 4 and 5).

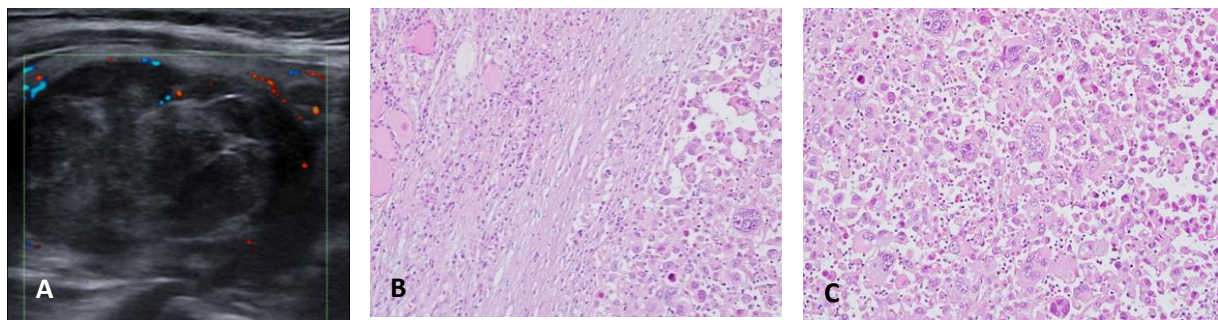


Fig. 4: Ultrasound (A) and pathological aspects (B, C) of anaplastic thyroid carcinoma in the left thyroid lobe, with hypercellularity, discohesive tumor cells, marked pleomorphism and multinucleated giant cells, (HE, x200)

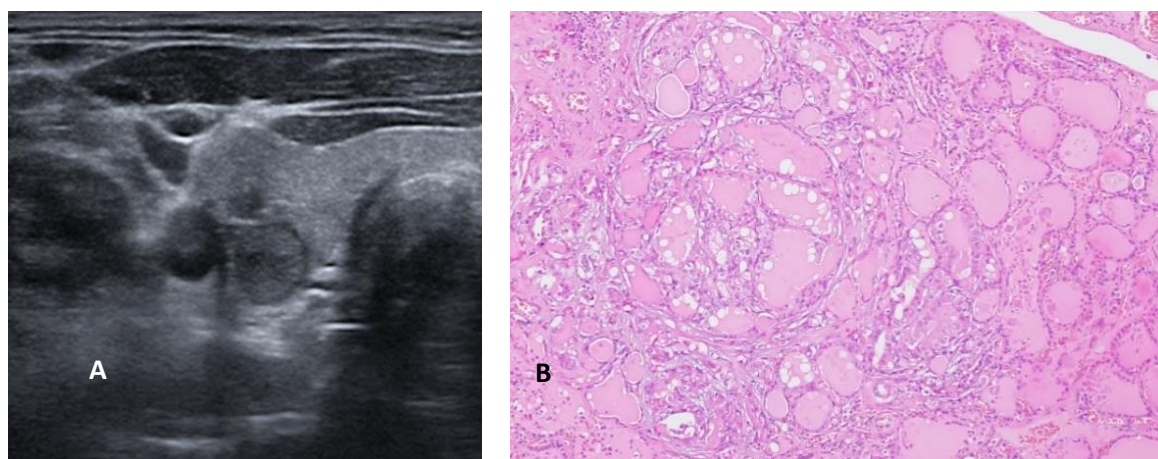


Fig. 5: Ultrasound (A) and pathological aspect (B) of papillary thyroid microcarcinoma in the right thyroid lobe, follicular variant, unencapsulated (HE, x200)

The conclusion of the postoperative pathological result was: 1. Undifferentiated thyroid cancer (anaplastic thyroid cancer), pleomorphic subtype, developed in the left

thyroid lobe with large extrathyroidal tumor extension (pT_{4a}N₁L₁V₁R₀); 2. Papillary microcarcinoma with follicular architecture and irregular, infiltrating margins, developed in the

right thyroid lobe; 3. Coexisting chronic autoimmune thyroiditis. From a pathological point of view, the concurrence of two different tumors, split by normal tissue architecture and appearing in the same organ, is the definition for collision tumor, in our case, of the thyroid. Postoperatively, levothyroxine replacement therapy was immediately started, in order to avoid transient hypothyroidism during this period of COVID-19 pandemic. The patient was on a stable euthyroid status with 75 micrograms Levothyroxine, daily. After the oncologic evaluation, the patient was referred to radiotherapy.

At follow-up, in November 2020, the CT scan of the brain, abdomen and pelvis did not show any pathological findings. The CT scan of the cervical area revealed multiple left lymphadenopathies, in group IV, with a diameter of up to 22 mm and a necrotic center, interposed between the internal jugular vein medially, the sternocleidomastoid muscle anteriorly, the external jugular vein laterally, without a clear cleavage plane. Also, the CT scan identified internal jugular venous thrombosis. The CT scan of the thorax confirmed the persistence of the solid pulmonary nodule, with lobulated margins, measuring 8/4 mm, localized in the apex of the right lung.

After 1 year (August 2021), the patient is in a better clinical condition, but she developed a left axillary lymph node that was surgically removed, the pathological examination revealed a metastasis of anaplastic thyroid carcinoma.

Discussion

We describe herein the case of a patient, who presented with a rapidly enlarging, firm, palpable cervical mass, pathologically proven to be an anaplastic thyroid carcinoma, associated with a papillary thyroid microcarcinoma in the contralateral lobe, a case of a collision tumor of the thyroid.

The diagnosis of anaplastic thyroid carcinoma was suspected, in our case, by clinical and US examination. Based on the ultrasound findings and on the fact, that surgery was recommended back in 2007 for a nodular goiter in this patient, suspicion was

raised for an anaplastic transformation of a previously differentiated thyroid cancer. In the scientific literature, failures are observed in obtaining an accurate diagnosis of anaplastic thyroid carcinoma on FNAB, because of sampling in tumor areas, consisting of necrosis, fibrosis or hemorrhage [12, 13]. It seems difficult to obtain enough cells for a correct cytological diagnosis from tumor masses, consisting of both solid and cystic portions, explaining why false negative diagnosis appears frequently in mixed compositions [13]. Taking this into account, the patient was referred immediately to surgery, despite the pandemic of COVID-19 period.

The pathological examination of tissue obtained by surgical excisional biopsy of the left latero-cervical lymphadenopathy indicated that it was a lymph node metastasis from an anaplastic cancer. Our suspicion was confirmed by the definitive postoperative pathological exam that revealed an anaplastic thyroid carcinoma in the left thyroid lobe, accompanied by a papillary microcarcinoma in the right thyroid lobe. Therefore, it is the case of a patient with a collision tumor of the thyroid.

In the scientific literature, several hypotheses are mentioned, explaining the pathogenesis of collision tumors:

- a. a coincidental finding,
- b. one of the tumors predisposing to the other one,
- c. the existence of a carcinogenic factor, predisposing to both tumors,
- d. both tumors originate from stem cell remnants [14].

Our case shows a collision tumor, containing papillary thyroid microcarcinoma and anaplastic thyroid cancer, also in association with Hashimoto's thyroiditis. This association has already been mentioned in the literature, but the relationship between chronic autoimmune thyroiditis and the pathogenesis of the thyroid cancer, is still controversial [15]. In our case, we assume that the second hypothesis is the most valid, meaning that a long-standing history of neglected papillary thyroid carcinoma predisposed to anaplastic transformation. The scientific data point to the fact that the development of anaplastic thyroid

carcinoma can be considered part of the natural course of untreated differentiated thyroid cancer. Studies show that approximately 2% of differentiated thyroid cancers are believed to develop into anaplastic thyroid carcinomas [16, 17].

Radioiodine therapy had no role in the primary treatment of this collision tumor of the thyroid, because it included a papillary microcarcinoma, correctly treated by total thyroidectomy. Radioactive iodine ablation therapy should be taken into account in survivors, one to two years after the initial therapy, if a large component of the collision tumor was well differentiated or if the serum levels of thyroglobulin are high during follow-up. Treatment guidelines for these collision tumors of the thyroid are poorly defined, because of the scarce literature data. Each tumor of the combination in the collision tumor should be treated in an independent manner. In our case, the larger size and the aggressiveness of the anaplastic thyroid carcinoma suggested a predominance of the undifferentiated thyroid cancer.

The anaplastic thyroid cancers express three major pathological patterns: spindle cell, giant cell and squamoid [9], but, in many tumors, two or all the above-mentioned patterns coexist. Many cancers having a mixed morphology of 2 or all 3 patterns; there are a lot of mitotic figures, atypical mitoses and extensive necrosis. As opposed to differentiated thyroid cancer, anaplastic thyroid cancer cells are less probable to stain positive for thyroid transcription factor 1 (TTF1) or PAX-8 and do not stain positive for thyroglobulin. In our case, the anaplastic tumor cells exhibited an intense and diffuse immunohistochemically positivity for pan-CK, a positive reaction also to CK7, CK8/18, EMA (epithelial membrane antigen), but a negative reaction to TTF-1, PAX-8, S100, CD45.

We used US of the neck and a CT of the cervical area and thorax, for defining the extent of disease and for planning appropriate surgical therapy. Patients with anaplastic thyroid cancer are being evaluated and monitored with increasing frequency, using PET/CT scan because these cancers are very hypermetabolic lesions, being very fluoro-deoxyglucose avid, as compared to

differentiated thyroid cancer. Because PET/CT was not immediately available, we used CT for initial staging and for follow-up, with accurate delineation of the extent of the anaplastic tumor.

The latest ATA guidelines identify a significant role for molecular testing in the evaluation of anaplastic thyroid cancer, because these cancers have an approximately six-fold higher tumor mutational burden, compared to well-differentiated papillary thyroid cancers [18]. The main driver mutations are classified as early and late events in the progression of the dedifferentiation process. Genetic alterations, encountered in differentiated thyroid tumors and also in anaplastic ones, are activating mutations, occurring in the oncogenes BRAF and RAS and are supposed to be early events in the dedifferentiation process. Late events, observed more frequently in the anaplastic thyroid tumor than in the precursor differentiated thyroid tumor, are: TP53 and TERT mutations, beta1-catenin mutations, ALK fusion genes, NTRK fusion genes and PI3KCA gene mutations. Molecular testing is being used more frequently to search for therapeutic targets, that could form the basis of individualized targeted therapy. The BRAF V600E mutation codes for a permanently activated kinase and is associated with more aggressive features, like a bigger tumor burden, extrathyroidal and lymph node metastases with a worse prognosis. Data from the literature point to a prevalence of BRAF V600E mutations of 25-30% in anaplastic thyroid cancers [19]. For patients with anaplastic thyroid neoplasms, harboring the BRAF V600E mutation, the combination treatment of dabrafenib (BRAF inhibitor) plus trametinib (MEK inhibitor) was given FDA (Food and Drug Administration) acceptance, after the publication of the outcomes of a clinical trial, showing a significant response rate in this type of thyroid tumor [20].

Consistent with the ATA and the NCCN (National Comprehensive Cancer Network) guidelines for the treatment of patients with anaplastic neoplasms of the thyroid gland, patients who present with resectable tumors should undergo complete resection, followed by combined chemotherapy and radiation. Our



patient, having been in stage IVB according to AJCC classification for anaplastic thyroid cancers or, even, in stage IVC (if we take into account the pulmonary nodule as a metastasis), but in a good clinical condition, underwent a total thyroidectomy with central and lateral neck lymph node dissection. Initially, no residual local disease was detected after the second surgery that was followed by external beam radiation therapy. Unfortunately, the follow-up CT scan of the cervical area, performed in November 2020, identified multiple left latero-cervical lymphadenopathies, proving locoregional recurrence.

Patients with anaplastic thyroid tumors, who have distant metastases and who seek active therapy, rather than palliative care, should be enrolled in clinical trials, but if these trials are not available, the most recent guidelines recommend the administration of dabrafenib plus trametinib [21, 22]. If the disease progresses on this association of drugs, systemic radio-chemotherapy should be offered.

The scientific literature reports that the thyroid cancer type associated with Hashimoto thyroiditis is almost always of the papillary type. Papillary thyroid carcinoma, associated with autoimmune thyroiditis, seems to be less aggressive; it tends to be a disease of younger patients. Multifocality of papillary thyroid cancer is characteristic in the thyroid affected

by autoimmune thyroiditis, but lymph node metastases and extrathyroidal extension are rarely observed [23, 24]. Studies also suggested that Hashimoto thyroiditis might be an independent risk factor for thyroid cancer. This is a good example, expressing a continuous process of development into papillary thyroid cancer, starting with the existence of Hashimoto thyroiditis, then transformation/dedifferentiation of this papillary thyroid cancer into a malignant anaplastic thyroid carcinoma and later on, the development of lymph node metastases.

Conclusion

A collision tumor of the thyroid, consisting of papillary thyroid microcarcinoma and anaplastic thyroid cancer implies a bad prognosis, due to the presence of the anaplastic tumor portion and should be evaluated and treated by surgery without delay, even in pandemic condition.

Conflicts of interest

There are no personal, financial, or other conflicts of interest to disclose.

Consent for publication

Written informed consent from the patient has been taken and is available for review by Editor in chief of the journal.

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