

CASE REPORT

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Management of the Patient with Aggressive and Resistant Papillary Thyroid Carcinoma

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ABSTRACT

Purpose: Papillary carcinoma is the most frequent type of thyroid cancer and was considered the most benign of all thyroid carcinomas, with a low risk of distant metastases. However, there are some variants of papillary thyroid carcinoma that have affinity to spread in many organs, such as: lymph nodes, lungs and bones. **Aim:** The aim of this study was presentation of a case with papillary carcinoma of the thyroid gland, very persistent and resistant in treatment with I 131. **Material and results:** A man 56 years old were diagnosed with papillary carcinoma of thyroid gland. He underwent a surgical removal of the tumor and right lobe of thyroid gland. With histopathology examination, were confirmed follicular variant of papillary carcinoma pT4. Two weeks later he underwent total thyroidectomy and was treated with 100 mCi of J 131. Six months later, the value of thyroglobulin was found elevated above upper measured limits (more than 500 ng/ml). Patient underwent surgical removal of 10 metastatic lymph nodes in the left side of the neck and has been treated with 145 mCi of radioiodine I 131. The examination after 5 months shows elevation of thyroglobulin, more than 20000 ng/ml and focally uptake of J 131 in the left lung. Patient was treated once again with 150 mCi radioiodine J 131. Whole body scintigraphy was registered focal uptake of radioiodine in the middle of the left collarbone. After a month, patient refers the enlargement of the lymph node in the right side of the neck. Currently patient is being treated with kinase inhibitor drug sorafenib and ibandronate. We have identified first positive response in treatment. Enlarged lymph node in the neck was reduced and the patient began feeling better. **Conclusion:** This study suggests that some subtypes of papillary thyroid carcinoma appear to have more aggressive biological course. Subtypes of papillary thyroid carcinoma such as diffuse sclerosing carcinoma, tall cell or columnar cell and insular variants, appears to have more aggressive biological course and need early detection and other kind of treatment.

Key words: papillary thyroid cancer (PTC), radioiodine (J131), sorafenib.

1. INTRODUCTION

Papillary thyroid carcinoma is the most frequent type of thyroid carcinoma (1-5). This type of carcinoma accounts approximately 70-85% of well differentiated thyroid cancer (6, 7). Generally, conventional papillary thyroid carcinoma is indolent with one associated 10 years survival of over 95% (2). However recently reported data suggest that some variants of papillary thyroid carcinoma such as diffuse sclerosing, tall cell or columnar cell and insular variants often display different degrees of

aggressive behavior in the spectrum between well differentiated classic PTC and the undifferentiated anaplastic carcinoma, including higher rates of metastases, recurrence, resistance to radioactive iodine (RAI) therapy, and possibly compromised survival. The other group variants of papillary thyroid carcinoma such as oncocytic, trabecular, solid, pseudo-Warthin, micro follicular and clear cell variants have variable prognoses, but many are closer to conventional papillary thyroid carcinoma (8-10). Establishing the diag-

nosis of one aggressive variant of thyroid papillary carcinoma it is based on the Turin criteria, which included architectural changes and presence of solid or trabecular or insular pattern of growth; absence of conventional PTC nuclear features; and the presence of at least one feature of convoluted nuclei, high mitotic activity, and tumor necrosis (10).

Follicular variant of papillary thyroid carcinoma is very difficult to distinguish from follicular adenoma. Follicular variant of papillary thyroid carcinoma may look like a follicular neoplasm except for the cytological features. Because these tumors can be easily confused with follicular adenomas and follicular carcinomas, the use of immunohistochemical and molecular markers can be very useful in confirming the diagnosis in difficult cases. The prognosis of these tumors is similar to the typical papillary thyroid carcinoma with an exception in cases with the diffuse or multi nodular follicular variant, which has a more aggressive clinical course. The prognosis of these tumors also depends on whether they are invasive or completely encapsulated (10-12).

The tall-cell variant of papillary thyroid cancer makes up only about 1% of papillary thyroid cancers and is reported to be more aggressive than classic type of papillary thyroid cancer. Tall cell variant is composed of cells whose height is at least 2–3 times as tall as they are wide. According the reported data from Bernstein J(1) spread of the cancer outside of the thyroid was seen in 33% of tall-cell cancers but in none of the classic micro carcinomas. Tall-cell type and spread of cancer to the lymph nodes were slightly higher in males than in females. The BRAF mutation was found in 93% of the tall-cell micro carcinomas and in 77% of the classic papillary micro carcinomas (1, 10).

Diffuse sclerosing variant of papillary thyroid carcinoma makes up 0.7-6.6 of all papillary thyroid carcinoma. The higher prevalence of this variant of papillary thyroid carcinoma was noted in pediatric patients and in patients affected by irradiation. Female group in third decade of life were more affected from this variant of papillary thyroid carcinoma (13). The T1799A missense mutation in exon 15 of the BRAF gene and RET/PTC rearrangement have been identified as the dominant genetic tumour initiation events in the pathogenesis of PTC leading to a constitutive activation of the RAS-RAF-MAPK pathway (11). This subtype exhibits a higher frequency of cervical and distant metastasis affiliating with a worse prognosis, female preponderance and younger age (9).

Insular thyroid cancer represented 0.3% of papillary thyroid cancer. The higher prevalence of this variant of papillary carcinoma was noted in older patients (48-61 years). Insular thyroid cancer was common in men, with a nearly 1:1 sex ratio (10). This variant of thyroid cancer were large, with a mean size of 5.9cm. Extra thyroidal extension (47.3%) and lymph node involvement (61.9%) were common. Over 30% of patients with this type of cancer presented with distant metastases. Patients with insular thyroid cancer often underwent total thyroidectomy (81.6%), postoperative RAI treatment (57%), and external-beam radiation therapy (15.8%) (6). The

majority of patients under 45 years of age who have differentiated thyroid cancer confined to the thyroid with lymph-node involvement have an excellent prognosis. The presence of distant metastases to the lungs at the time of initial diagnosis is not common and is reported to be between 3% and 15% (14). According the American Thyroid Association guidelines, patients younger than 45 years who have papillary thyroid cancer and distant metastasis are classified as stage II with a 100% 5-year disease-specific survival, while those patients over age 45 with distant metastases are stage IV, which confers a 51% 5-year disease specific survival (4). Good prognostic factors in patients with pulmonary metastases include young age (<45 years), micronodular pulmonary metastases, complete local control, and RAI-sensitive disease. Poor prognostic factors include age over 70 years, distant metastases not confined to the lungs, macronodular lung metastases (>2 cm), lymph-node metastases >3 cm, follicular histology, and a poorly differentiated component in the primary thyroid neoplasm (10).

2. CASE PRESENTATION

The patient 56 years old man who found a painless lump in his neck in December 2014. During clinical examination of the neck, we have noticed a tumor with size of fist, on the right side of the neck. Tumor was consistently strong with infiltration of the surrounding tissues with a grainy structure. On the left lobe of the thyroid gland was noticed 3- cm nodule, painless and fixed in the surrounding tissue. The patient was recommended for ehosonography and scintigraphy of thyroid gland.

In echo sonogram report of date 23.12.2014 was reported a nodular change with heterogeneous structure with dimensions 58x32 mm with easily pronounced vascularization on Doppler at the right lobe of thyroid gland.

In the left lobe of the thyroid gland were noticed some small nodular changes isoechoic structure, with the largest one with dimension 11x8mm.

Patient was referred for FNA cytology. In FNA report of date 24.12.2016 the citological material was described with high cellularity. In the examined material were noticed groups of thyrocytes which in some places had created the pseudopapillary formations. Some cells were noticed like cells with “ground glass” transparency. Also were noticed lymphocytes in rare cases and macrophages and erythrocytes. Histopathological verification was required for the differentiation of follicular hyperplasia from papillary neoplasia. The patient is instructed to the ORL clinic, with suggestion for total removal of thyroid gland and histopathological verification.

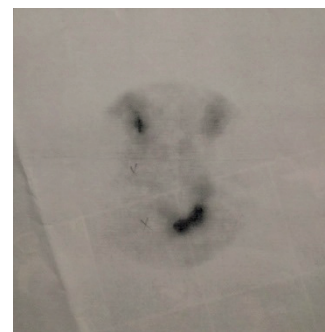


Photo 1. Scintigraphy 99mTc pertechnetate. Non functional nodule in the right lobe of thyroid gland

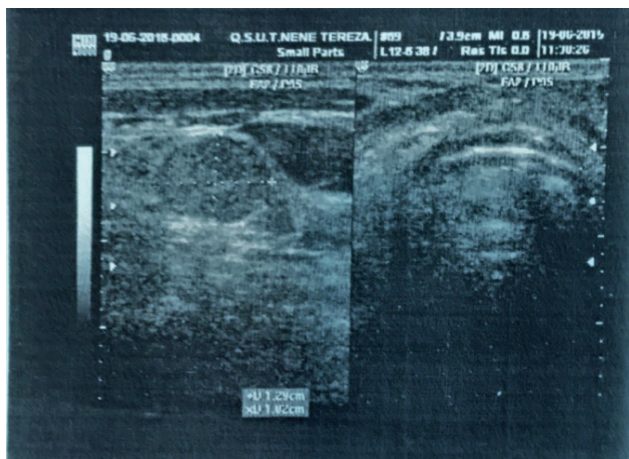


Photo 2. Ultrasound examination of the neck. Enlarged lymphatic glands in the right side of the neck

Before the surgery the concentration of Triiodothyronine (T3), thyroxin (T4) and thyroid stimulation hormone (TSH) in blood serum of patients were in normal range whereas the concentration of thyroglobulin was too high (Tg=450 ng/ml). In radiological examination, the lungs were with normal appearance and transparency. Echosonography examination of abdominal organs was without pathological findings.

The patient has undergone surgical intervention for the first time on 12.01.2015 at the Clinic of Otorhinolaryngology. The surgeons had removed the right lobe and isthmus of thyroid gland. Removed material was sent for histopathology verification at the Institute of Pathology. Histopathological report dated 22.01.2015 has confirmed that the material was received from the right lobe of the thyroid gland 7x3.5x3 cm, with gray color and nodular appearance. In histological description was reported that tumor tissue was build from complex papillary structure, coated with epithelial malignant cells. The tumor cells were cylindrical, with signs of nuclear stratification and intra nuclear furrow. In some microscopic areas, the tumor cells had features of opaque nuclear cells “ground glass”. Also in material were noticed foci of lymphatic invasion around the tumor borders. The histopathological diagnosis was: Carcinoma papillare glandulae thyroideae pT4.

Based on histopathological report, the team of physicians from ORL Clinic had required surgical removal of the left remaining lobe of the thyroid gland. Patient underwent the second surgery in the private clinic in Pristine on 06.02.2015. The surgery was conducted by the same surgeon who removed the left lobe of thyroid gland and five lymph nodes located at the left side of the neck. The samples of materials were sent for histopathology verification in Institute of Pathology. The histopathological report dated 10.02.2015 describes the material with malignant cells, similar as on previous case of the right lobe and malignant metastatic cells in 2 lymphatic glands

Nuclear medicine physician has recommended radiometabolic therapy with radioactive iodine 131. The radiometabolic treatment with Iodine 131 was conducted under supervision of the nuclear medicine physician at University clinical center in Tirana. Radiometabolic treatment is done with the award of the dose of activity 100 mCi of radioactive iodine 131 through the mouth. Patient was discharged after 3 days from the hospital with recommendation to take the substitution therapy L- thyroxin 150mcg every day.

In laboratory examinations after 6 months (18/06/2015) was found very high value of thyroglobulin in the blood serum Tg> 500.0 ng / ml. The repeated analysis after 9 days, has confirmed the high value of thyroglobulin in blood serum (Tg=10500ng/ml).

In examination with ultrasound, dated 19/06/2015, were noticed 10-15 enlarged lymph glands on both sides of the neck, with features suspicious for metastatic changes.

Patient underwent surgery for the third time on 06.07.2015. The surgical treatment was completed by the

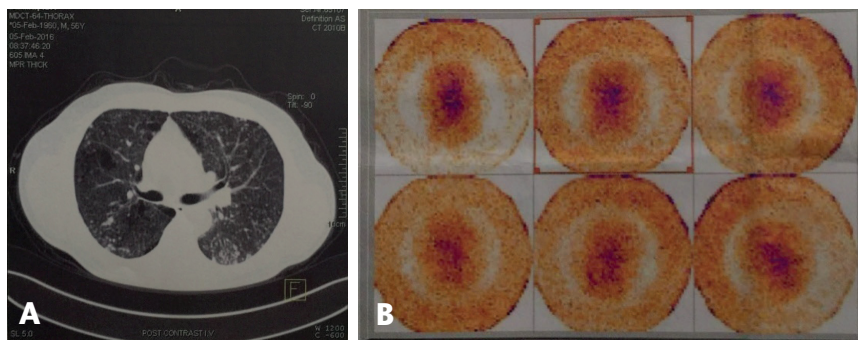


Photo 3. A. CT imaging of lungs. Nodular change in the left lung. B Focal uptake of J-131 in the left lung

same surgeon who completed the first two operations in Kavaja Hospital, in which case were removed the enlarged lymph glands on both sides of the neck (disectio colli functionalis bill.). The histopathological report dated 07.05.2015 has confirmed the presence of metastatic papillary carcinoma in 11 lymph nodes (2 nodes on the right side and 9 nodes on the left side of the neck)

In whole body scintigraphy (WBS) with 5 mCi radio iodine 131 made on the date 09.09.2015, were registered

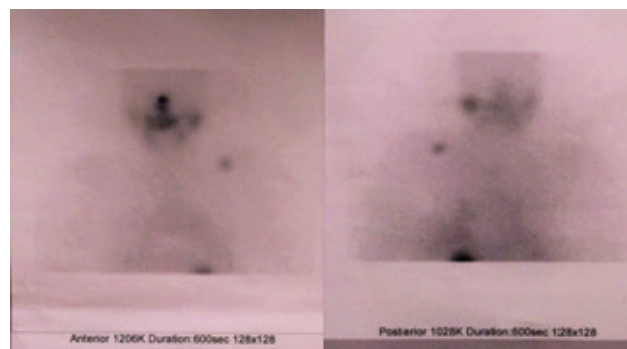


Photo.4. Focal activity in the middle of the left collarbone Two months later, on 14.06.2016, patient found painless enlarged lump with size of an egg on the right side of the neck. The concentration of thyroglobulin in the blood was too high Tg>20000.0ng/ml (1.7-56ng/ml)/

focal pathologic uptake of radioiodine 131 on the left lung, suspicious for metastases. The patient was recommended to cessation of the hormonal substitution therapy until the value of TSH concentration was raised above 50 UI/l. Then were administered 145 mCi of radioactive iodine 131 per os. The second treatment with radioactive iodine 131 was completed again at University Hospital in Tirana on 09.10.2015.

On 03.02.2016 patient complains of quick tiredness and difficulty in breathing. On laboratory examinations was noticed high concentration of thyroglobulin Tg=8900.0ng/ml. The Whole body scintigraphy has registered focal accumulation of radio iodine 131 in the left side of the lung. In images obtained with computed tomography, were presented suspicious changes for metastases in both lungs (05.02.2016).

The patient is advised to undergo treatment for the third time with 131 radioiodine at University Hospital in Tirana. On 03.04.2016 the patient was treated with 150 mCi radioiodine per os and was allowed to go home after three days treatment in the hospital. Patient was advised to take substitution therapy L-thyroxin 150 mg daily. In the Whole body scintigraphy of the date 06.04.2016, was registered abnormal uptake of the radio iodine 131 in the middle of the left collarbone.

In consultation with oncologist, was decided that patient should be treated with kinase inhibitor drug Sorafenib and ibandronate. Treatment with Sorafenib tab. 2x400mg and Ibandronate was started on 05.06.2016. After treatment with Sorafenib and Ibandronate, the enlarged lymph node on the right side of the neck was withdrawn and the patient began to feel easier and better.

3. DISCUSSION AND CONCLUSION

Papillary carcinoma of thyroid gland is the most common type of thyroid cancer. This type of cancer accounts 65-85% of cases of thyroid cancer. Papillary carcinoma of thyroid gland is recognized as a type of cancer with better cell differentiation and with better survival prognosis in all cancers of thyroid gland. The 5 years survival of patients with papillary carcinoma of thyroid gland is reported to be 95-98% (2). The surgical removal of tumor and ablation radioiodine radiotherapy with radio iodine 131 is the common forms of treatment of papillary carcinoma of the thyroid gland. Administration of the high doses of the radioiodine 131 consists on the affinity of the papillary carcinoma cells of the thyroid gland to uptake the iodine.

However, recent years many authors have presented cases of papillary carcinoma of the thyroid gland are quite aggressive and resistant to standard treatment with surgery and iodine131. Recently reported data suggest that some variants of papillary thyroid carcinoma such as diffuse sclerosing, tall cell or columnar cell and insular variants often display different degrees of aggressive behavior in the spectrum between well differentiated classic PTC and the undifferentiated anaplastic carcinoma, including higher rates of metastases, recurrence, resistance to radioactive iodine (RAI) therapy, and possibly compromised survival (13). Because of resistance

to therapy with radio iodine 131, was proven treatment with external radiation therapy and chemotherapy, but without any significant success. Last years for treatment of these resistant varieties of papillary thyroid carcinoma is used a kinase inhibitor drug called sorafenib. In our case our patient was resistant in surgery and radioiodine treatment. Last option for treatment of our patients was kinase inhibitor although until now without significant positive results.

4. CONCLUSION

Some variations of papillary carcinoma of the thyroid gland indicate aggressive growth, metastasis tendency to distant organs, especially to lymphatic nodes, lungs and bones, and are highly resistant to standard treatment with radioactive iodine 131. The early diagnosis enables better treatment and better prognosis of disease.

- Conflict of interest: none declared.

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