



# A Rare Case of Neck Metastasis from a Thyroid Papillary Carcinoma After Seventeen Years Diagnosed with US-Guided Fine Needle Aspiration Cytology

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**Abstract:** Thyroid papillary carcinoma represents a quite indolent and relatively frequent malignant tumor of the thyroid gland. Most lesions have a good prognosis, with excellent disease-free survival after thyroidectomy [1-3]. In this report it's described a case of papillary carcinoma metastases with onset after 17 years from the first intervention. Some speculations are made regarding the reasons of the particular course of papillary carcinoma in this female patient. Clinical and anamnestic conditions together with B-RAF V600E point mutation could be responsible of a more aggressive biological potential.

**Keywords:** Thyroid, Papillary Carcinoma, Aspiration Cytology

## 1. Introduction

Papillary histology is the most frequent among the thyroid carcinomas, representing 80% of thyroid malignancy.

Nevertheless, it is a rare cancer: in Europe there are 1 to 5 new year cases for 100,000 individuals, with a strike prevalence in women.

Among the differentiated tumors, papillary morphology is the most easily diagnosable from pathologists for its peculiar cytological characteristics, even if many variants have been described, sometimes with microscopic aspects overlap with follicular lesions.

Cervical node localization of this malignancy is very common, without meaning a worse prognosis. Regional lymph node metastases are present at the time of diagnosis in 20-90% of patients with papillary thyroid carcinoma and this evidence seems to represent a low risk factor for death [4], while the presence of lympho-vascular involvement should be considered as an indicator of aggressive clinicopathological features and those patients should be

followed up carefully for recurrences and metastasis [5].

In this report, a case of lymph node recurrence is described in a female patient after 17 years from the first diagnosis on a thyroidectomy specimen, in absence of lymph vessels involvement and without lymph nodes localization at the time of surgical thyroid removal.

## 2. Methods

### 2.1. Case Presentation

F. R. is a 77 years old woman, no smoker, no drinker, in apparently good health. She complains of a mild depressive syndrome and takes escitalopram 10 mg/day. In 1999 she has been subjected to a total thyroidectomy because of a papillary thyroid cancer 3 cm in size of the left lobe, focally infiltrating the capsule, without cervical lymph node involving. She carried out postoperative radioiodine treatment. She has performed a close follow up: she has assumed levothyroxine therapy to keep TSH low until eight months ago, then to keep it normal (from suppressive to

replacement therapy according to modern guidelines). Serum Thyroglobulin levels are increased slightly over time, from <0,1 ng/ml right after thyroidectomy to 0,27 ng/ml in August 2016.

## 2.2. Recent Case Evolution

In November 2014 a small painless mass in anterior cervical region appeared, without symptoms.

In July 2015 she is diagnosed with a monoclonal gammopathy. In January 2016 an US-exam revealed the presence of three solid hypoechoic nodules, the major 6,5 mm in size, without particular suspicion patterns, in the left side of cervical anterior region. In December 2016 this nodule appeared increased in size, about 1 cm. To the semeiotic inspection, the rhino-pharyngo-laryngeal region was normal; in the left side of the anterior cervical region a small mass was palpable, painless, close lying but floating on the deep layers, about 5 mm in size.

## 2.3. Fine Needle Aspiration Results

A US-guided Fine Needle Aspiration Cytology with cytoassistance was performed. The on-site hematoxylin-eosin coloured slides showed a very cellular smear, with papillary aggregates of thyrocytes with nuclear grooves and pseudo-inclusions (Figures 1, Figure 2). Due to a strong suspicion of recurrence of papillary carcinoma, pathologist decided to make a second sample with a particular kind of needle named cytofoam core (Exmoor Innovations, Bio-Optica Italian distributor). It represents a disposable which allows a single passage to obtain a kind of cell-block, thanks to the presence of an adsorbent support in a 23 gauge needle on which the cells remain trapped (Figures 3A, 3B). Cytofoam core obtained was processed as a tissue fragment, formalin fixed an paraffin embedded. The hematoxylin-eosin coloured slide confirmed the presence of a lesion (Figure 4) and initial suspect of thyroid papillary carcinoma was corroborated thanks to the immunohistochemical profile of neoplastic cells detected on foam. B-RAF-V600E point mutation with Ventana V600E monoclonal antibody was detected too (Figure 5).

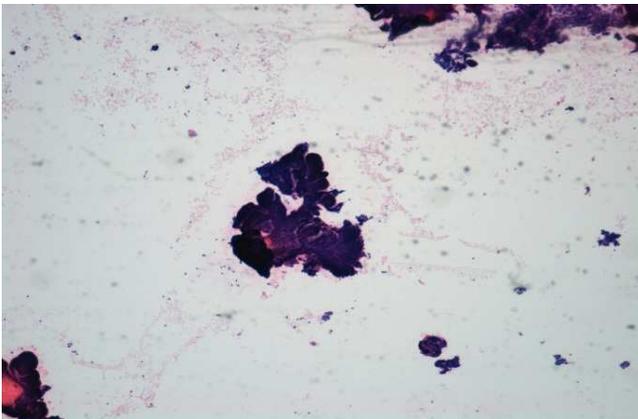


Figure 1. E-e coloured on site smear from fnac of node in anterior neck (4x).

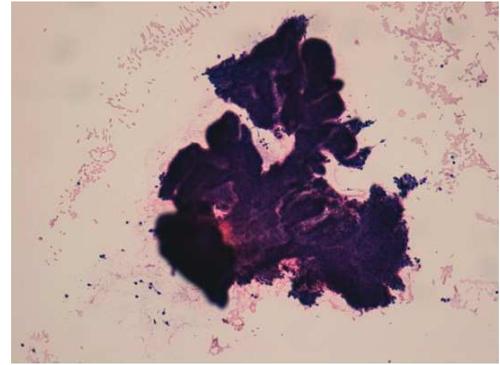


Figure 2. E-e papillary aggregates in fnac smear (10x).

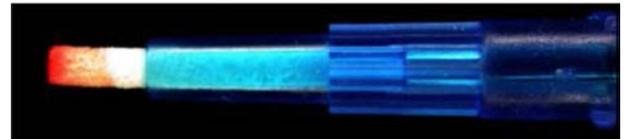


Figure 3A. CYTOFOAM- CORE STRUCTURE.

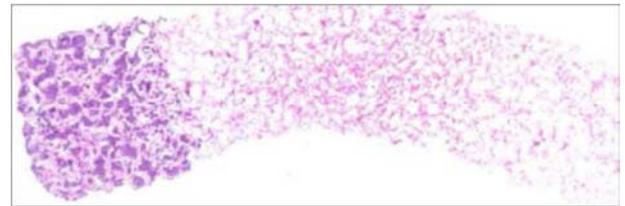


Figure 3B. Histological hematoxylin and eosin coloured slide of the foam.

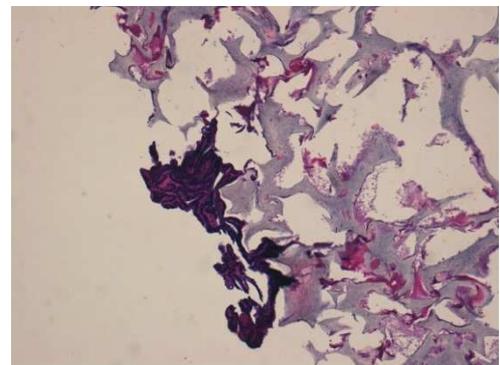


Figure 4. Cytofoam-core microscopic e.e coloured slide with neoplastic aggregates entrapped on foam.

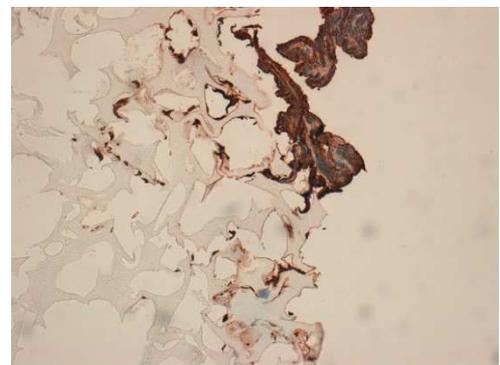


Figure 5. B-raf-v600e point mutation immunohistochemical positivity detected on material adsorbed on foam.

#### 2.4. Decision Making

In accord to multidisciplinary team (otorhinolaryngologist, pathologist, endocrinologist, radiologist) this patient underwent a left selective neck dissection and postoperative radiotherapy with good results. Histological exam was made on the material from definitive surgical excision. Surgical specimen corresponded to one metastatic lymph node and to one micro-aggregate of papillary carcinoma cells in adipose tissue with neoplastic embolism in lymphatic capillary vessels. After seven months from surgical excision of metastatic nodules, the patient enjoys good health and she is free from illness, with perfect hematochemical values.

### 3. Discussion

The described case can be considered interesting for two major reasons. The first and more evident one is represented from clinical history of the patient. Papillary thyroid carcinoma is indicated as an indolent tumor with little tendency to recur after surgical removal, above all in absence of metastatic localization at first diagnosis. Metastatic recurrence after seventeen years in thyroid region can be reviewed as a sporadic event in a patient with not any risk factor of progression at the time of previous surgery. In fact primitive tumor had big size only, without extracapsular involvement or vascular and nodal localizations.

The better biological behaviour of intra-thyroid tumors is reported in most recent article, as Feng-Hsuan Liu *et al* one, regarding the retrospective study of 909 patients with papillary thyroid carcinoma [6]. It represents a very important report for the great number of patients operated for papillary thyroid carcinoma, with a post-surgery follow up of about ten years. They compared 536 patients with tumor confined to thyroid with 373 cases with extra-thyroid extension of papillary carcinoma at the time of the surgery. In this investigation, recurrence and mortality are described above all in patients with extra-thyroid cancer involvement. Comparing the patients with papillary thyroid carcinoma and lymph-node metastasis with the patients with intra-thyroid carcinoma, the former group showed larger tumor size, higher postoperative thyroglobulin levels, advanced TNM stage, higher recurrence rates, and higher disease - specific mortality (12.6% vs. 1.3%).

The second reason of interest of the particular case reported in the present work can be the presence of B-RAF V600E point mutation. In fact, papillary thyroid carcinoma with this genetic alteration have a more aggressive clinical course, presenting loco-regional lymph node metastases at the first diagnosis [7, 8]. Even if it wasn't possible to detect B-RAF V600E point mutation on material from previous surgery, the presence of mutation on recurrent nodules makes think to an aggressive thyroid tumor. In fact, many reports have been published where there isn't concordance between B-RAF statement in surgical thyroid specimen and in subsequent lymph-node excision for metastasis [9].

On the other hand, the long latency of metastatic disease

and the absence of localization at distant sites cannot be considered typical characteristics of aggressive lesions. A possible speculation explaining this atypical clinical course can be that papillary thyroid tumor in ancient people have to be considered an aggressive one even in absence of risk factor [10]. Some retrospective analysis point the focus on the age of patients with thyroid papillary carcinoma, because it seems that older patients have a worse prognosis than young people, regardless to other risk factors (multicentricity, lymph node and vascular involvement). In this particular reported case, it cannot be excluded that B-RAF V600E point mutation could be produced in a second matter in metastatic cells. Studies have demonstrated a significant correlation between the B-Raf V600E mutation and reliable prognostic predictors, including extra-thyroid invasion, lymph nodal metastasis and an advanced tumor-node-metastasis (TNM) stage.

### 4. Conclusion

In consequence of the previous statement, B-RAF V600E point mutation could be considered as a mechanism of clonal selection of metastatic neoplastic cells. This genetic mutation may have given the ability to metastasize to cancer cells. The B-Raf V600E point mutation is frequently considered more potent in promoting aggressive pathogenesis and poorer clinicopathological outcomes in patients with papillary thyroid carcinoma.

It can be speculate that the acquisition of a new genetic advantage may have determined a more aggressive biological behaviour of the second tumor compared to the primitive one.

Molecular studies demonstrate tumorigenic role of BRAF V600E point mutation, suggesting that this genetic acquired alteration can be the initiator of thyroid tumorigenesis [7]. The strong kinase potency of BRAFV600E may able to induce genetic instability, silence iodide-metabolizing genes, and evade the feedback mechanisms, with a promotion of progression and aggressiveness of the tumor.

At the end, it can be pointed view on the method used for preoperative diagnosis. Fine Needle Aspiration Cytology (FNAC) represents the gold standard for diagnosis of nodular lesions in a preoperative phase. In fact, FNAC allows for obtaining diagnostic sample with low economic resources and poor discomfort for patients. One of the most important limitation of aspiration cytology is the lack of possibility to use some material for the determination of the neoplastic immunophenotype. Cytofoam-core needle makes possible immunohistochemical determination, because the cytological sample is treated as a tissue one. Formalin fixation ensures the maintenance of the cellular antigenicity necessary for the success of the immunohistochemistry. Furthermore, the presence of a paraffin embedded sample allows to get more sections to determine the immunoprofile of a lesion, as well as to detect prognostic factors of response to targeted molecular therapies. In fact, B-RAF V600E point mutation detection with immunohistochemical method can have both a

diagnostic value than a prognostic one. The presence of the mutation in cells from fine needle aspiration cytology could favour the diagnosis of papillary carcinoma, when associated to minor morphological characteristics. Then, the detection of BRAF V600E point mutation might have an important significance in the formulation of prognosis and possible target molecular therapies.

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