Abstract: We report a case of a 47-year-old woman who presented with a diffuse mass on her left thigh. FNAB was done and resulted in a bloody aspirate, approximately ± 5 cc. The preparation is stained with MGG and appeared in microscopic of micropapillary cluster with some rosetting structure. The cytologic featured nuclear enlargement and anisokaryosis that was relevant with metastases of papillary carcinoma of the thyroid. A papillary carcinoma of the thyroid with bone metastases is a rare case because distant metastases are less frequent in papillary carcinoma of the thyroid than with other thyroid carcinomas (only 5% to 7%), especially in femur. There are multiple criteria must be observed before making a confident cytological diagnosis of papillary carcinoma of the thyroid. Analysis of various criteria suggested that a combination of intranuclear cytoplasmic inclusions, papillary structures and dense cytoplasm were the three most important variables. With sensitivity and predictive value of cytological diagnosis ranged from 60% to 90%. But we should not forget, always confirm with the histopathology for the final diagnosis because cytology is not one definitive diagnosis.

Keywords: papillary carcinoma, thyroid, FNAB, bone metastases

BACKGROUND

In the United States, thyroid carcinoma comprises about 1% of all cancers and accounts for 0.4% of cancer related-deaths. It is therefore clear that only a very small proportion of clinically evident thyroid nodules are malignant. Nevertheless, thyroid carcinoma is the most common malignancy of the endocrine system. Papillary carcinoma is the most common type of thyroid malignancy and thus they present most often as a painless mass in the neck. These tumor tend to be biologically indolent and have an excellent prognosis. Females are more affected than males. It can present in any age group, the mean age at the time of initial diagnosis being approximately 40 years. Papillary carcinoma accounts for more than 90% of thyroid malignancies in children. In 5% to 10% of the cases, there is a history of irradiation exposure to the neck, and the non-neoplastic gland may show nuclear aberrations as a result. There is an increase in the incidence of papillary carcinoma in Hashimoto’s thyroiditis. Nearly all patients have clinically evident disease in the neck when they are first seen. (1,2,3,4,5)

Before the advent of fine-needle aspiration, the definitive diagnosis of a thyroid nodule required open biopsy, often with the resection of a significant portion of the gland and consequent morbidity. Today, fine-needle biopsy of thyroid nodules is a safe and rapid procedure that provides a diagnosis in the majority of cases. (6)

Primary mode of spread in papillary carcinoma is lymphatic. Blood-borne metastasis to distant sites is rare. However, when occurs it is usually to lung, bone, brain, and soft tissue. Involvement of other structures in neck is mainly due to direct infiltration of tumor into these structures. (6)

We report a case of papillary carcinoma of the thyroid with bone metastases in femur, that we diagnosed with performed FNAB. This is a rare case, because distant metastases are less frequent in papillary carcinoma of the thyroid than with other thyroid carcinomas (only 5% to 7%), especially in femur.
PATHOGENESIS

Although the etiology of papillary carcinoma of the thyroid remains to be establish, a number of associations have been identified.

- Iodine excess. In endemic goiter regions, the addition of iodine to the diet has increased the proportion of papillary carcinoma compared with follicular carcinoma.
- Radiation. External radiation to the neck of children and adults increase the incidence of later papillary carcinoma of the thyroid.
- Genetic factors. Somatic rearrangements of the RET protooncogene on chromosome 10q11.2 are common in papillary carcinoma of the thyroid, and 60% of such tumors in children exposed to radiation from the Chernobyl accident displayed this mutation. These rearrangement cause the fusion of the tyrosine kinase domain of RET to various other genes, creating the RET/PTC fusion oncogenes. The fusion product is constitutively activated by phosphorylation of a tyrosine residue. RET/PTC 1 and 3 are the most common forms that occur in sporadic papillary carcinoma.

MACROSCOPIC FEATURES

Papillary carcinomas may present as solitary or multifocal lesions within the thyroid. In some cases, they may be well circumscribed and even encapsulated; in other instances, they infiltrate the adjacent parenchyma with ill-defined margins. The lesions may contain areas of fibrosis and calcification and are often cystic. On the cut surface, they may appear granular and may sometimes contain grossly discernible papillary foci. The size of the primary tumor ranges from microscopic to huge. A very high proportion of thyroid cancers measuring less than 1 cm in diameter are of papillary type.

MICROSCOPIC FEATURES

Microscopically, the diagnosis of papillary carcinoma depends on the presence of certain architectural features (mainly in the form of true papillae) and/or characteristic nuclear changes. The papillae are usually complex, branching, and randomly oriented, with a central fibrovascular core and a single or stratified lining of cuboidal cells. The stroma of the papillae may be edematous or hyaline, and it may contain lymphocytes, foamy macrophages, hemosiderin, or exceptionally adipose tissue. These papillae are nearly always associated with the formation of follicles. The follicles tend to be irregularly shaped, often tubular and branching. Mitoses are very scanty or absent. Psammoma bodies are seen in approximately half of the cases. Their presence strongly suggests the diagnosis of papillary carcinoma.

Area with a solid/trabecular pattern of growth and foci of squamous metaplasia are present in 20% of the cases; these two patterns often merge. Lymphocytic infiltration of the stroma is seen in a fourth of cases; it is not clear whether this represents a reaction to the tumor or the expression of pre-existing thyroiditis.

The nuclei of papillary carcinoma cells contain very finely dispersed chromatin, which imparts an optically clear appearance, giving rise to the designation “ground-glass” or “Orphan Annie” nuclei. In addition, invaginations of the cytoplasm my cross-sections give the appearance of intranuclear inclusions (hence the term pseudo-inclusions). Another characteristic of the papillary carcinoma nucleus is the nuclear groove.

VARIANTS

- Papillary microcarcinoma. This is defined as a papillary carcinoma...
measuring 1 cm or less in diameter. It is a common incidental finding in thyroid glands removed for other reasons and in population-based autopsy studies. It is associated with cervical node metastases in about one third of cases, but distant metastases are exceptionally rare, and the prognosis is generally excellent.

- Follicular variant. This is a papillary carcinoma composed of follicles. The diagnosis is largely based on the presence of the set of nuclear features classically associated with papillary carcinoma. Supportive features for the diagnosis are an invasive pattern of growth, fibrous trabeculation, psammoma bodies, strongly eosinophilic colloid with scalloped edges, and the presence of abortive papillae. The prognosis of the follicular variant is apparently similar to usual papillary carcinoma, although there may be a greater risk for this variant metastasize outside the neck and for vascular invasion; regional nodal metastases are less common than in classic papillary carcinoma.

- Diffuse sclerosing variant. Representing only approximately 3% of all papillary carcinomas. The tumor, which most often affects children and young adults, may present as bilateral goiter. Tumor papillae have associated areas of squamous metaplasia. Numerous psammoma bodies are found. Lymphocytic infiltrate are found around the tumor foci. Clinically, it may be misdiagnosed as Hashimoto’s thyroiditis. Nodal metastases are nearly always present, lung metastases are common, and the disease-free survival rate is lower than for conventional papillary carcinoma.

- Tall cell and columnar variants. The tall cell variant is a type of papillary carcinoma characterized by papillae lined by a single layer of “tall” cells and abundant acidophilic, quasi-oncocytic cytoplasm. These features should be present in at least half of the tumor for it to be placed into this category. The pattern of growth is usually highly papillary. This variant tends to affect older patients and the clinical course is said to be more aggressive. In the columnar variant, there is prominent stratification, and the cytoplasm is clear (sometimes with subnuclear vaculization) rather than acidophilic. The prognosis in the few reported patients has been very poor. Occasionally cases have been seen in which tall and columnar features coexisted.

**SITOLOGI**

FNA specimens from papillary carcinomas shows a wide range of cytologic pattern. High cellularity is a common feature, and colloid usually scant. The epithelium may appear as true papillary fragments, but more commonly is arranged in multilayered syncytial fragments or branched sheets. Nuclear enlargement and pleomorphism are present, along with nuclear crowding, fine powdery chromatin, nuclear grooves, and sharply defined intranuclear cytoplasmic inclusions. The cytoplasm is usually dense and cyanophilic. Criteria for diagnosis:

- Cellular smears
  - Syncytial aggregates and sheets of cells with a distinct ‘anatomical’ border, focally nuclear crowding and overlapping.
  - Papillary tissue fragments with or without a fibrovascular core.
  - Enlarged, ovoid, strikingly pale nuclei, finely granular, powdery chromatin (Pap)
  - Multiple distinct nucleoli; intranuclear cytoplasmic inclusions; nuclear grooves.
  - Dense cytoplasm, distinct cell border (single cells)
  - Scanty, viscous, stringy colloid (‘chewing gum colloid’)
  - Squamoid or histioocyte-like, ‘metaplastic’ epithelial cells
  - Psammoma bodies
  - Macrophages and debris (evidence of cystic degeneration), multinucleate giant cells and lymphocytes variable.
A true papillary micro-architecture may be difficult to identify in smears. Most papillae are not removed intact by the needle but appear as flat sheets. The sheets partly have a well-defined ‘anatomical’ edge formed by a row of cuboidal or columnar cells. The ‘anatomical’ edge and focal crowding and overlapping of nuclei distinguish sheets of papillary carcinoma from those representing benign macrofollicles. The tip of a papillae may be seen as a finger-like aggregate of cells with a similar edge. True papillae with a fibrovascular core may be found in smears, but less frequently. Trabecular fragments are also represented in smears by cohesive finger-like structures and must not be mistaken for papillae. They occur in follicular neoplasms, benign or malignant. In some cases, smears show only dispersed single cells and syncytial aggregates similar to a follicular neoplasm. The diagnosis then relies mainly on the identification of nuclear features of papillary carcinoma.

In smears, a pale, very fine powdery nuclear chromatin is equally characteristic and is one of the most important diagnostic criteria. Intranuclear cytoplasmic inclusions are a characteristic but not specific feature of papillary carcinoma, seen in up to 90% of cases and in up to 5% of the cells. Intranuclear inclusions have a sharp, well-defined, membrane-like margin and are not optically clear but similar in colour and texture to cytoplasm. Irregularity of nuclear shape and convolution of nuclei is another feature seen in cells of papillary carcinoma. Cells with abundant vacuolated cytoplasm resembling histiocytes or with dense cytoplasm resembling squamous metaplastic cells are also a common finding. Macrophages and cell debris may be very prominent, especially when there is associated cystic change. Psammoma bodies are infrequently found in smears.

**IMMUNOHISTOCHEMICAL FEATURES**

Immunohistochemically, the cells of papillary carcinoma are reactive for low-as well as for high-molecular-weight keratin; the latter is of some diagnostic importance, because normal and hyperplastic follicles and follicular neoplasms usually show positivity only for the low-molecular-weight types. There is also positivity for S-100 protein, EMA, CEA (occasionally), vimentin, and ceruplasmin. Estrogen receptor proteins are usually present.

**STAGING**

The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification.

**TNM Definitions**

Primary tumor (T)

- **TX:** Primary tumor cannot be assessed
- **T0:** No evidence of primary tumor
- **T1:** Tumor 2 cm or less in greatest dimension, limited to the thyroid
- **T2:** Tumor larger than 2 cm but 4 cm or smaller in greatest dimension, limited to the thyroid
- **T3:** Tumor larger than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)
- **T4a:** Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
- **T4b:** Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
All anaplastic carcinomas are considered T4 tumors.
- T4a: Intrathyroidal anaplastic carcinoma—surgically resectable
- T4b: Extrathyroidal anaplastic carcinoma—surgically unresectable

Regional lymph nodes (N)
Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes.
- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis
  - N1a: Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
  - N1b: Metastasis to unilateral or bilateral cervical or superior mediastinal lymph nodes

Distant metastases (M)
- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

AJCC Stage Groupings.
Papillary or follicular thyroid cancer
- Younger than 45 years
  - Stage I
    - Any T, any N, M0
  - Stage II
    - Any T, any N, M1
- Age 45 years and older
  - Stage I
    - T1, N0, M0
  - Stage II
    - T2, N0, M0
  - Stage III
    - T3, N0, M0
    - T1, N1a, M0
    - T2, N1a, M0
    - T3, N1a, M0
  - Stage IVA
    - T4a, N0, M0
    - T4a, N1a, M0
    - T4a, N1b, M0
    - T1, N1b, M0
    - T2, N1b, M0

• T3, N1b, M0
• T4a, N1b, M0
  - Stage IVB
    - T4b, any N, M0
  - Stage IVC
    - Any T, any N, M1

SPREAD AND METASTASES
Papillary carcinoma thyroid typically invades lymphatics and spread to the regional cervical lymph nodes and they are seen in as many as 40% of all patients with papillary carcinoma, and it may be the first manifestation of the disease (particularly in younger patients). These metastases may not be clinically apparent because of their small size and also because their consistency may not differ from that of a normal node. Extrathyroid extension into the soft tissues of the neck is found in about one fourth of cases. Blood borne metastases are less frequent than with other thyroid carcinomas (5% to 7%), but when they occurs, the common sites including lungs, bone, the central nervous system, and other organs.

PROGNOSIS
The overall outcome of patients with papillary carcinoma is excellent, with 10-year survival rates of up to 85%. Factors relating to prognosis are:
- Age. Nearly all the deaths from papillary carcinomas occur when the tumor manifests itself after the age of 40 years.
- Sex. Females have a better prognosis than males.
- History of previous irradiation. The prognosis of tumors in which this antecedent is present does not seem to differ significantly from the others.
- Extrathyroid extension. This features affects adversely the prognosis in a very significant fashion.
- Microscopic variants.
- Tumor size. A rough inverse correlation is present between tumor size and prognosis.
- Capsule and margins.
- Distant metastases.
- Poorly differentiated, squamous, or anaplastic foci. These features have a markedly detrimental effect on prognosis. Fortunately, they are present in fewer than 5% of the cases.
TREATMENT
Standart treatment options in papillary carcinoma of the thyroid:
• Lobectomy/thyroidectomy
• $^{131}I$
• External-beam radiation therapy
• Resection of limited metastases
• Thyroid-stimulating hormone suppression.

DIFFERENTIAL DIAGNOSIS
Solitary benign encapsulated nodules with a striking papillary growth pattern but without nuclear features of papillary carcinoma, particularly in young patients. These are sometimes referred as 'adenomas' or as 'hyperplastic papillary nodules'. Hyalinising trabecular adenoma can mimic papillary carcinoma cytologically, showing similar nuclear features.

A CASE REPORT
We report a case of a 47-year-old woman who presented with a diffuse mass on her left thigh. Then we performed FNAB. The aspirate contained a bloody liquid, volume ± 5 cc. The preparation is staining with MGG.

Microscopic: The smear consists of sheet of cells with uniform large, pale nuclei and powdery chromatin, some nuclear crowding and overlapping; and dense cytoplasm. There is poorly cohesive cells and a micropapillary cluster. The background of smear consists of red blood cells. At another point of view, there is a cluster with some rosetting; bland nuclear chromatin, mild nuclear enlargement and anisokaryosis.

Conclusion: A metastases of papillary carcinoma of the thyroid.

DISCUSSION
Papillary carcinoma is the most common type of thyroid malignancy. Lymphogen is primary mode of spread in papillary carcinoma of the thyroid. Distant metastases (hematogen) is rare, when occurs usually to lung, bone, brain and soft tissue.

A papillary carcinoma of the thyroid with bone metastases is a rare case. A woman with an older age is suitable for the criteria of papillary carcinoma of the thyroid. There are
multiple criteria must be observed before making a confident cytological diagnosis of papillary carcinoma of the thyroid. Analysis of various criteria suggested that a combination of intranuclear cytoplasmic inclusions, papillary structures and dense cytoplasm were the three most important variables. With sensitivity and predictive value of cytological diagnosis ranged from 60% to 90%. And do not to forget, always confirm with the histopathology for the final diagnosis.

Immunostaining for Cytokeratin 19 and for CD44 is specific and has been show to be value in the diagnosis of papillary carcinoma of the thyroid.

REFERENCES
5. Download from F:\ Thyroid Cancer.