Thyroid nodules & neoplasms

Objectives:

- Know the definition of a solitary nodule in the thyroid.
- Recognize the differential diagnosis of a solitary thyroid nodule.
- Understand the classification, pathology and behavior of thyroid carcinoma.

Important note: **Please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all of our work: Pathology Edit**

Red: Important
Grey: Extra notes

Introduction (Dr.Rekabi notes + Dr. Hala + Slides)

- ➢ Thyroid Tumors are not that common.
- ➢ Thyroid is not an important organ for metastasis. Metastasis to thyroid can happen mostly due the tumors close to thyroid.
- ➢ Thyroid Neoplasms usually presents **as solitary thyroid nodules**.

Solitary (one) thyroid nodule

- ❖ Palpably discrete swelling within an otherwise apparently normal thyroid gland.
- ❖ Incidence : 1% and 10%.
- ❖ Single nodules: Female/Male 4/1.
- ❖ Incidence increases throughout life.
- ❖ **Majority:** localized, non-neoplastic conditions or benign neoplasms such as follicular adenomas.
- ❖ Benign neoplasms outnumber thyroid carcinomas by a ratio of nearly 10 : 1

Radioactive uptake studies

Radioactive iodine uptake (RAIU) is a test of thyroid function. It measures how much radioactive iodine is taken up by the thyroid gland in a certain time period. Higher than normal uptake means that the thyroid gland is overactive, & vice versa.

- ● Increase uptake → in graves or nodular goiter.
- ● Decrease uptake → adenoma and carcinoma (needs a fine needle aspiration biopsy).

Thyroid Neoplasms

Ranges in severity from benign adenomas to highly aggressive carcinoma. If a patient presents with thyroid nodule it's most likely to be a tumor (very common).

Clinical criteria providing a clue to the nature of a given thyroid nodule		
Are all more likely to be neoplastic (might be adenoma or carcinoma)	**More likely to be benign**	**More likely to be malignant**
1. **Solitary nodules** (in general are more likely than multiple nodules) 2. **Nodules in younger patients** (more likely than those in older patients) 3. **Nodules in males** (more likely than females)	**Nodules uptaking radioactive iodine (hot nodules)**	A history of radiation treatment to the head and neck.

What is a toxic tumor/adenoma?

Hyper active tumors that cause thyrotoxicosis (it's rare but can occur).

- **HOT nodule:** Toxic "hormone secreting nodule" + takes up the radioactive iodine (or other radioactive substance) + very dark nodules.
- **COLD nodule:** Doesn't secrete hormones + NO uptake of the radioactive iodine (or other radioactive substance) + light nodules.

Note: **Most of the thyroid tumors are** nonfunctioning → cold nodules.

Case Study:

A lady presents with a thyroid swelling involving the right lobe and part of the isthmus:

1- First you should examine her, taking a very good clinical history (nervousness, increased appetite, increase metabolic rate..etc) → To make sure the patient is euthyroid not a toxic tumor.Second you should investigate by taking blood test and see the levels of TSH and T4 (not T3), If TSH is low and T4 is high then its thyrotoxicosis (you might then ask for T3, if you want to be more sure).

After we are sure that she is euthyroid..

2- Then, you do a radioactive iodine scan or imaging to know whether it's a cold or hot nodule.

After knowing its cold and TSH and T4 is normal..

3- Fine needle aspiration (FNA) cytology: (to decide if there's a follicular neoplasm) if the swelling is palpable and can be felt by hands you do it in your clinic. If the swelling is not palpable and was discovered by radioactive iodine and imaging study, we do the aspiration in the radiology department either under ultrasound or by CT scan.(To localise it accurately).

Dr hala : From FNA you can decide whether you don't need surgery as in → nodular goiter or Remove it now as in → papillary Carcinoma or just to follow up as in→ follicular lesion.

4- To decide if the neoplasm is benign or malignant, you must find that there is invasion to adjacent organ or tissue (but cytology cannot tell you invasion).

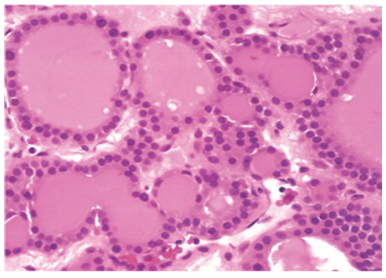
5- If you decided that it is a tumor you have to remove it and do histological examination on the removed part to decide if it is a malignant or benign tumor.

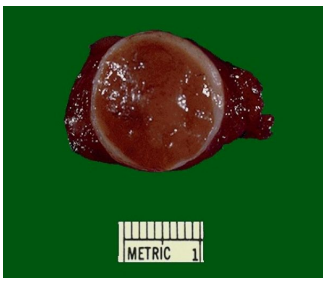
Thyroid Adenomas (Follicular adenoma)

- Benign thyroid tumor.
- Adenomas of the thyroid are typically discrete[1], solitary masses.
- Derived from follicular epithelium
- The hallmark of all follicular adenomas is the presence of intact well-formed fibrous capsule encircling the tumor.
- Painless (usually discovered during a routine physical examination.)
- large masses → produce local symptoms ex:difficulty swallowing
- **The definitive diagnosis of thyroid adenoma can be made only → histological examination or restricted specimen.**
- Usually nonfunctional rarely secrete thyroid hormone → on radionuclear scanning appear cold .

Morphology:

Degree of follicle formation and the colloid content of the follicles		
1- Simple colloid adenomas (macrofollicular adenomas)	2- A common form recapitulate stages in the embryogenesis of the normal thyroid (fetal or microfollicular, embryonal or trabecula	3- Hürthle cell adenoma: Large follicular cells, eosinophilic cytoplasm "reddish" and full of mitochondria.





Gross:

- Capsule encircling the tumor.
- solitary, well-circumscribed encapsulated mass lesion.
- No invasion of capsule or blood vessel.

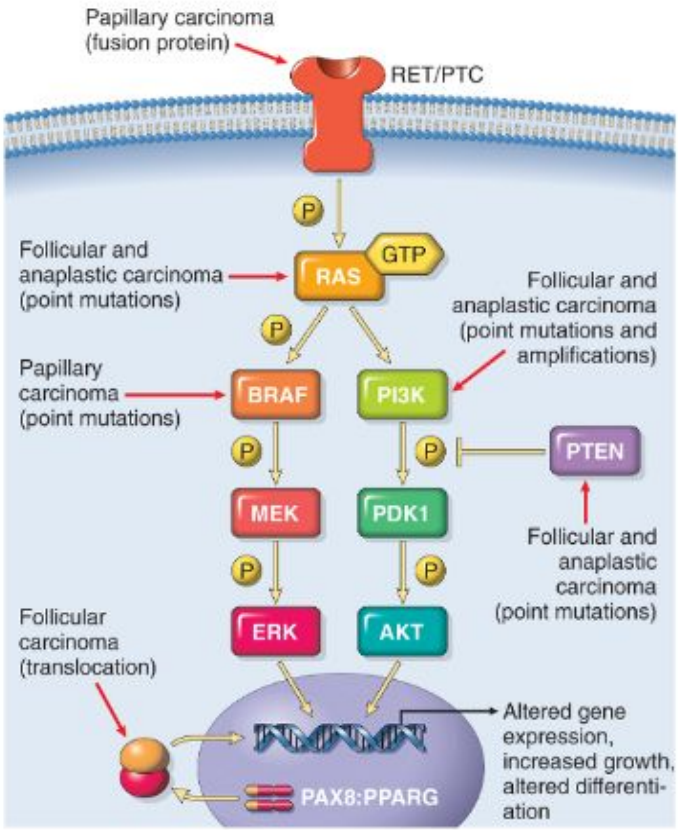
Treatment: Excision → Excellent prognosis do not recur or metastasize.

[1] individually separate and distinct.

Carcinomas

- Malignant thyroid tumors.
- Carcinomas of the thyroid : 1.5% of all cancers.
- Majority of thyroid carcinomas associated with previous exposure to ionizing radiation.

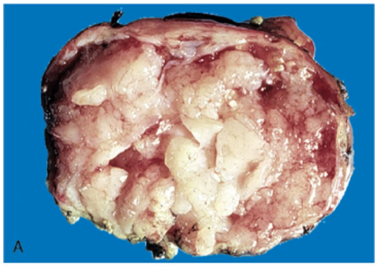
Carcinoma	Papillary Thyroid Carcinomas	Follicular Thyroid Carcinomas	Medullary Thyroid Carcinomas	Anaplastic Carcinomas (Undifferentiated)
Gene mutation	Rearrangements of the tyrosine kinase receptors RET or NTRK1 or activating point mutations in BRAF	RAS family of oncogenes and Pax8/PPAR γ gene.	Familial medullary thyroid carcinomas occur in multiple endocrine neoplasia type 2 (MEN-2) RET protooncogene mutation	Inactivating point mutations in the p53 tumor suppressor gene are rare in well-differentiated thyroid carcinomas but common in anaplastic tumors.
Percentage	> 85% Most common	5% to 15%	5%	< 5%



1- Papillary Thyroid Carcinoma

Characteristics:

- Most common type of carcinomas.
- Most often between the ages of 25 and 50 "younger age group".
- Usually affecting females more than males.
- The incidence of papillary carcinoma has increased markedly in the last 30 years.
- Solitary or multifocal lesions with **COLD nodules.** (cold⇒ less uptake of iodine⇒ inactive follicular cells)
- Hashimoto's thyroiditis can predispose to papillary thyroid carcinoma.
- Papillary carcinoma are recognized based on nuclear features even in the absence of papillae.



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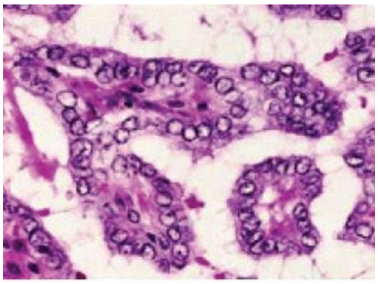
Environmental Factors: The major risk factor is exposure to *ionizing radiation* (in childhood mainly).

Morphology

Gross: Papillary structures (finger like projections).

Histology:

Nuclear features are the following: mnemonic=Boss

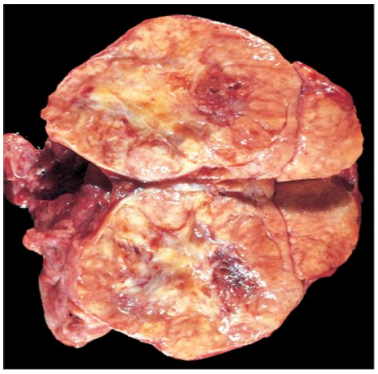


- Grooved nuclei "coffee Bean nuclei".
- Orphan Annie nuclei: The nuclei of papillary carcinoma cells contain very finely dispersed chromatin, which imparts an optically clear appearance.
- Psammoma bodies: Concentrically calcified structures
- Pseudoinclusions: invaginations of the cytoplasm may give the appearance of intranuclear inclusions.
- Chewing gum colloid.

Variants

- Tall cell variant
- Hyalinizing trabecular tumors (ret/PTC gene rearrangement)
- Follicular (Most frequent shape of papillary carcinoma)
- Encapsulated
- Diffuse sclerosing

Clinical Course



- Most present as asymptomatic thyroid nodules.
- The first manifestation may be a mass in a cervical lymph node "spreads mainly to lymph nodes".
- Slowly growing and causes morbidity and not mortality "rarely" .
- Papillary thyroid cancers have an excellent prognosis.
- Prognosis of PTC is dependent on several factors including age (in general, the prognosis is less favorable among patients older than 40 years), the presence of extra-thyroidal extension, and presence of distant metastases (stage).

2- Follicular Carcinomas

- Malignant proliferation of Follicular cells that are surrounded by fibrous capsule but with invasion through the capsule.
- Metastasis occurs **hematogenously.**

Epidemiology:

- More common in women (3 : 1).
- Peak incidence between **40 and 60 years "older age group"**.
- More frequent in areas with **dietary iodine deficiency.**

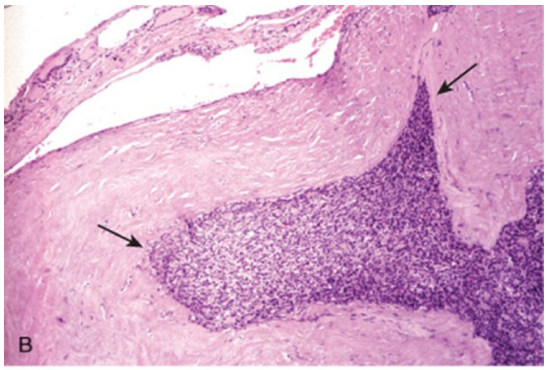
Diagnosis

- Examine the entire capsule by microscope or See the gross specimen.
- Fine needle aspiration (FNA) **cannot distinguish** between Follicular carcinoma and Follicular adenoma.

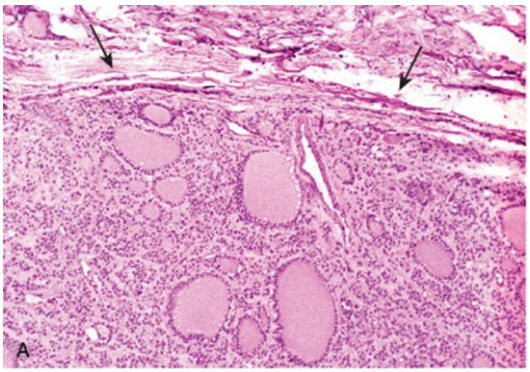
Note that: in follicular ADENOMA there was *no invasion of capsule* while in follicular CARCINOMA *there's capsular or vascular invasion.*

Types: (based on Morphology)

Minimally invasive	Widely invasive
Only invading the capsule or/and blood vessel (well encapsulated)	**Invading other organs like bones or lungs.**
10 year survival rate 90%.	**10 year survival rate *less* than 50%**



Follicular carcinomas demonstrate *minimal* capsular invasion



Follicular Adenoma
Thin fibrous capsule, surrounds the neoplastic follicles and *no* capsular invasion is seen.

3- Medullary Carcinomas

- ➢ Medullary carcinomas are **neuroendocrine neoplasms**[2] characterized by malignant proliferation **parafollicular C cells**, of the thyroid.
- ➢ Similar to normal C cells, **Secrete high levels of calcitonin**→ **hypocalcemia**(by causing renal excretion).
- ➢ Calcitonin deposits within the tumor as amyloid → **local amyloidosis**

Note: Calcitonin secretion is the measurement of which plays an important role in the diagnosis and postoperative follow-up of patients.

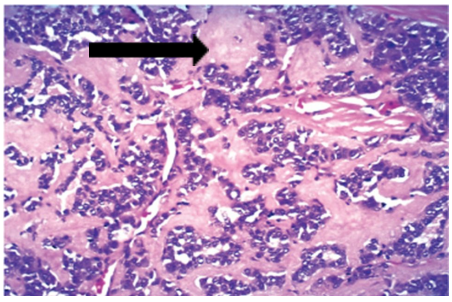
Epidemiology:

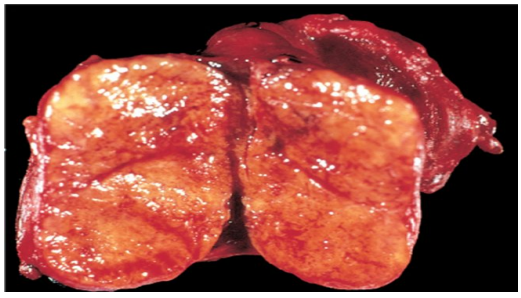
- About 70% of tumors arise **sporadically.**
- **The familial cases** occurs in the setting of **Multiple Endocrine Neoplasia (MEN) syndrome 2A or 2B** associated with mutation of RET oncogene.
- Familial tumors without an associated MEN syndrome is called **Familial medullary thyroid carcinoma (FMTC).**

Multiple Endocrine Neoplasia (MEN): Characterized by medullary carcinoma with other neuroendocrine neoplasms such as pheochromocytoma of adrenal gland. Not all people who suffer from medullary thyroid carcinoma have MEN.

Morphology

- These tumors typically show a solid pattern of growth and do not have connective tissue capsules.
- Polygonal to spindle cells "having **granular chromatin** and **neurosecretory granules** in the **cytoplasm secreting calcitonin".**
- **Multicentricity** [3]
- **Amyloid deposition** (arrow in pic).
- **Necrosis**
- **Bilaterality**
- **Hemorrhage**





REMEMBER: We use two stain for Medullary Carcinomas:

1. Immunohistochemistry stain for calcitonin.
2. Congo red stain for amyloid

[2] Also called **carcinoid** tumors
[3] having multiple centers of origin.

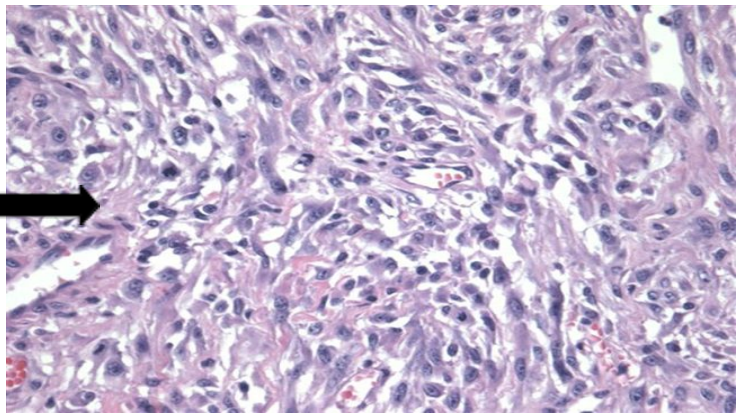
4- Anaplastic Carcinomas (worst type)

- **Undifferentiated** malignant tumors of the thyroid **follicular epithelium**.
- Can be arising from a more differentiated carcinoma **(papillary).**
- More common in **elderly (**> 65 year).
- **Highly Malignant (**Rapidly growing mass**) & metastasized widely especially** to local structure **such as trachea** which can lead to respiratory compromise & dysphagia.
- Lethal 100%.

Morphology.

1. Large, pleomorphic giant cells and atypical, including occasional osteoclast-like multinucleate **giant cells**.
2. **Spindle** cells with a sarcomatous appearance.
3. **Mixed** spindle and giant cells.
4. Small cells in size.

Spindle cells



Prognosis

- **Very bad**, patient usually die from 6 month to 1 year.
- Lethal 100%.

Lymphoma of the thyroid (Dr.Rekabi)

- Can occur in the thyroid either primary or secondary.
- **Hashimoto's thyroiditis can also predispose to lymphom**a.

Summary

Thyroid gland carcinoma	Papillary carcinoma	Follicular carcinoma	Medullary carcinoma	Anaplastic carcinoma
Percentage	> 85%	5% to 15%	5%	<5%
Age	Between 25 & 50	Between 40 & 60		**> 65 year**
Incidence	Increased markedly in the last 30 years	More common in women (3:1)		Rare in well differentiated thyroid carcinomas but common in anaplastic tumors.
Mutation	**RAS** family of oncogenes	1- rearrangements of the tyrosine kinase receptors RET 2- Neurotrophic Tyrosine Kinase, Receptor, Type 1 (NTRK1) 3- activating point mutations in BRAF	- 70% sporadic - Multiple endocrine neoplasia type 2A or 2B (MEN-2) RET protooncogene mutation - Familial medullary thyroid carcinoma (FMTC)	Inactivating point mutations in the **p53** tumor suppressor gene
Risk factor	Exposure to **ionizing radiation**	**dietary iodine deficiency**		
Morphology	- Solitary - multifocal lesions - Papillary structures - **Orphan Annie nuclei** - Psammoma bodies - Pseudoinclusions - Grooved nuclei		Polygonal to spindle cells **Amyloid deposition** Bilaterality Multicentricity Necrosis Hemorrhage	Highly anaplastic cells: 1-Large, pleomorphic **giant cells,** including occasional osteoclast-like multinucleate giant cells 2- Spindle cells with a sarcomatous appearance 3- Mixed spindle and giant cells 4- Small cells
Types or Variants	- Tall cell variant - Hyalinizing trabecular tumors (ret/PTC gene rearrangement) - Follicular - Encapsulated - Diffuse sclerosing		**Neuroendocrine** neoplasms derived from the parafollicular cells, or C cells	-Undifferentiated tumors of the thyroid follicular epithelium. - Can be arising from a more differentiated carcinoma (papillary)
Clinical	- Mostly **asymptomatic** - First manifestation: mass in a cervical lymph node.		C cells secrete **calcitonin** → may lead to hypocalcemia	
Prognosis	- Excellent prognosis Factors affecting prognosis: - Age (older than 40 years) - Extra-thyroidal extension - Distant metastases	10 years survival rate: - Minimally invasive (well encapsulated) 90% - Widely invasive 50%		**Lethal** (100%)

MCQ's

1. **A 45-year-old male feels a small lump on the left side of his neck. He feels fine and has no other complains his physician palpates a firm painless, 1.5-cm cervical node the thyroid glands is not enlarged. A chest radiograph is unremarkable. Laboratory test findings, is cluding thyroid function tests, are normal. A fine-needle aspirate of the thyroid gland is most likely to show findings consists with?**
   A. Papillary carcinoma
   B. Follicular carcinoma
   C. Medullary carcinoma
   D. Anaplastic carcinoma

2. **A 44-year-old male without previous illness presents with a 3-week history of progressive hoarseness, shortness of breath, and stridor. He is found to have a firm, large, tender thyroid mass that by CT scan extends posterior to the trachea and into the upper mediastinum. A fine-needle aspirate shows pleomorphic spindle cells. He is taken to surgery, and the mass is resected. The mass infiltrates into adjacent skeletal muscle. Four of seven cervical lymph nodes have metastasis. Pulmonary metastases are also identified by a chest radiograph. Which of the following neoplasms is most likely?**
   A. Papillary carcinoma
   B. Follicular carcinoma
   C. Medullary carcinoma
   D. Anaplastic carcinoma

3. **What it's the type of carcinoma it has RAS gene mutation?**
   A. Papillary thyroid carcinoma.
   B. follicular thyroid carcinoma.
   C. Anaplastic carcinoma.

4-Which of the following is the characteristics of the Papillary Thyroid Carcinoma?
   A. Most common type of carcinomas.
   B. Peak incidence between 40 and 60 years
   C. Secrete high levels of calcitonin

5-Which of the more frequent in areas with dietary iodine deficiency?
   A. Papillary carcinoma
   B. Follicular carcinoma
   C. Medullary carcinoma
   D. Anaplastic carcinoma

6- which of the following is seen in anaplastic carcinomas?
   A. Most common type of carcinomas.
   B. Large, pleomorphic giant cells and atypical,
   C. Secrete high levels of calcitonin

7- which of the following has the worst prognosis?

A. Anaplastic carcinoma
B. Follicular Carcinoma
C. Medullary carcinoma

8- Hashimoto's thyroiditis can also predispose to lymphoma.

A. True
B. false

Answers:
1-A
2-D
3-B
4-A
5-B
6-B
7-A
8-A

For any suggestions or questions please don't hesitate to contact us on: Pathology434@gmail.com
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