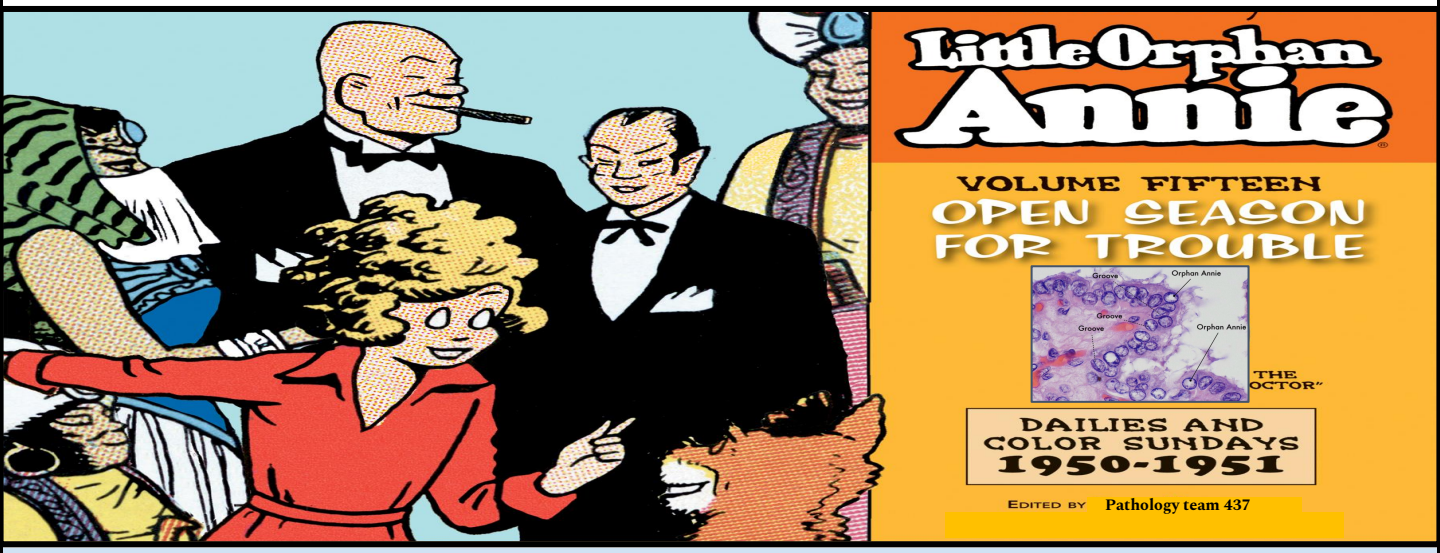
واعلموا أن مهمتكم ليست ورقة تنالونها.....
إنما مهمتكم أمة تحيونها.....

Thyroid Nodules and Neoplasms



Little orphan annie

هي سلسلة كوميك ابتكرها الرسام هارولد جراي عام 1924 مقتبسة من قصيدة بنفس الإسم تم تأليفها عام 1885
استمر نشر هذه السلسلة حوالي 86 سنة حتى نزول العدد الأخير منها عام 2010 تتميز هذه السلسلة بمعاصرتها لأحداث كثيرة مثل الحرب العالمية الثانية وغيرها من الأحداث المؤثرة التي تم تضمينها بين ثنايا هذه السلسلة

Annie white eyes have been used by pathologists to resemble the clear appearance nucleus of Papillary thyroid carcinomas

الشكر موصول لجميع من عمل على هذه المحاضرة:

القادة: فايز غياث الدرسوني — شيرين العكيلي

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Golden member عبدالجبار اليماني
عبدالرحمن آل الشيخ

رناد الفرم
غادة الحيدري
رزان الزهراني
غرام جليدان
ريناد الغريبي

Golden member دانه القاضي
Golden member منيرة المسعد
مشاعل القحطاني
نورة القاضي
بتول الرحيمي
مها بركه

Color index:
-Text
-important
-Notes
-Extra

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 behaviour of thyroid carcinoma

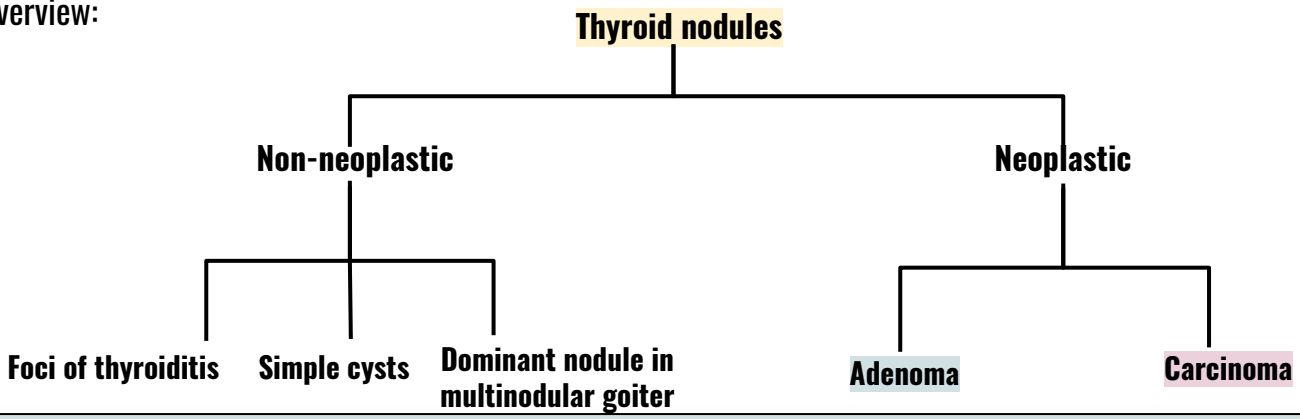
Thyroid nodules

Several clinical criteria provide a clue to the nature of a given thyroid nodule:

- Solitary nodules, in general, are more likely to be neoplastic than are multiple nodules. diffuse or multinodular are more toward a non neoplastic cause they're hyperplastic.
- Nodules in males are more likely to be neoplastic than are those in females.
- Nodules in younger patients are more likely to be neoplastic than are those in older patients.
- A history of radiation treatment to the head and neck region is associated with an increased incidence of thyroid malignancy.
- Nodules that take up radioactive iodine in imaging studies (hot nodules) are more likely to be benign than malignant.
- Ultimately, it is the morphologic evaluation of a given thyroid nodule by fine needle aspiration, combined with histologic study of surgically resected thyroid parenchyma, that provides the most definitive information about its nature.

note: 1. not always but usually benign= take up radioactive I = FUNCTIONAL (HOT NODULES)
malignant= don't take = NON FUNCTIONAL (COLD NODULES)
2. we usually see the nodules by ultrasound then the first line for DX is FNA (cells). We don't do biopsy unless to differ between follicular adenoma and carcinoma

Overview:



Adenoma (Follicular Adenoma)

Character

-Adenomas of the thyroid are benign neoplasms derived from follicular epithelium. Follicular adenomas usually are solitary.
-In general, follicular adenomas are not forerunners to carcinomas They can't 1 be differentiated by FNA so we do surgery.

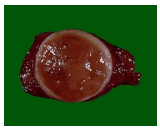
1:Pathoma:FNA only examines cells and not the capsule hence a distinction between follicular adenoma and follicular carcinoma cannot be made by FNA

Morphology

-On clinical and morphologic grounds, they may be difficult to distinguish from a dominant nodule in multinodular goiter, or from follicular carcinomas

-The typical thyroid adenoma is a solitary, spherical lesion that compresses the adjacent non-neoplastic thyroid.

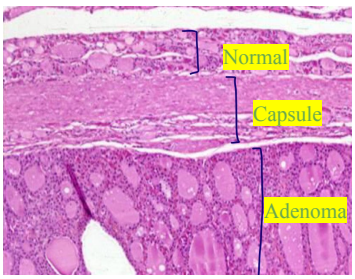
-The neoplastic cells are demarcated from the adjacent parenchyma by a well-defined, intact capsule .These features are important in making the distinction from multinodular goiters, which contain multiple nodules on their cut surface, do not demonstrate compression of the adjacent thyroid parenchyma, and lack a well-formed capsule.

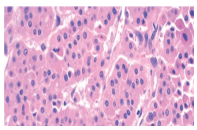


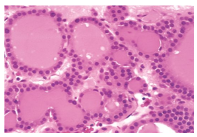
-On microscopic examination, the constituent cells are arranged in uniform follicles that contain colloid . capsules helps us exclude multinodular goiter but it is still present in adenoma or carcinoma.

Histology

-Occasionally, the neoplastic cells acquire brightly eosinophilic granular cytoplasm (oxyphil or Hürthle cell change)(the change is due to mitochondria)
-The clinical presentation and behavior of a Hürthle cell adenoma are no different from those of a conventional adenoma.
-Careful evaluation of the integrity of the capsule is critical in distinguishing follicular adenomas from follicular carcinomas, which demonstrate capsular and/or vascular invasion. invasion = carcinoma normally benign can be differentiated by the presence of mitosis however follicular carcinoma show the exact morphology of follicular adenoma .







Diagnose and treatment

-On radionuclide scanning, adenomas appear as cold nodules relative to the adjacent normal thyroid gland.
-Essential techniques used in the preoperative evaluation of suspected adenomas are ultrasonography and fine needle aspiration biopsy.
-Suspected adenomas of the thyroid are removed surgically to exclude malignancy. Thyroid adenomas carry an excellent prognosis and do not recur or metastasize.

Carcinomas

Carcinomas of the thyroid: 1.5% of all cancers	Pathogenesis (The genetic changes are very important)
1- Papillary thyroid carcinoma (> 85% of cases) Very common	rearrangements of the tyrosine kinase receptors RET or NTRK1 or activating point mutations in BRAF(protooncogene)
2- Follicular thyroid carcinoma (05% to 15% of cases)	mutations in the RAS family of oncogenes
3- Medullary thyroid carcinoma (5% of cases) Less common	Familial medullary thyroid carcinomas occur in multiple endocrine neoplasia type 2 (MEN-2) RET proto oncogene mutation Medullary carcinoma can be sporadic (occurs in anyone) or within a syndrome (MEN-2) with other endocrine neoplasm RET proto oncogene mutation.
4- Anaplastic thyroid carcinoma (<5% of cases) Least common	Inactivating point mutations in the p53 tumor suppressor gene are rare in well-differentiated (Follicular + Papillary + Medullary carcinomas) thyroid carcinomas but common in anaplastic tumors.

Pathogenesis

- Environmental Factors. The major risk factor predisposing to thyroid cancer (PTC) is exposure to *ionizing* radiation
- Most often between the ages of 25 and 50
- Majority of thyroid carcinomas associated with previous exposure to ionizing radiation.
- The incidence of papillary carcinoma has increased markedly in the last 30 years
- Solitary or multifocal lesions
- Iodine deficiency has association with Follicular carcinoma.

Anaplastic Carcinomas

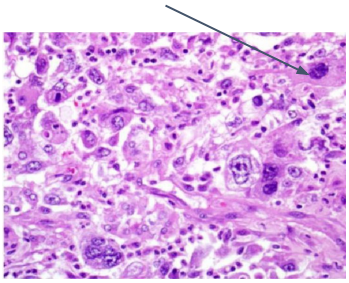
Character

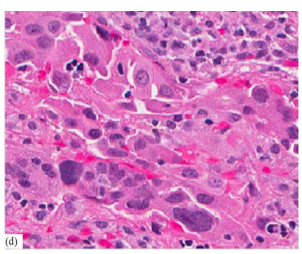
Anaplastic carcinomas of the thyroid are undifferentiated tumors of the thyroid follicular epithelium.
Can be arising from a more differentiated carcinoma (papillary)
Lethal (100%)
Older age group > 65 year

Histology

Highly anaplastic cells:
(1) large, pleomorphic giant cells, including occasional osteoclast-like multinucleated giant cells
(2) spindle cells with a sarcomatous appearance (epithelium like)
(3) mixed spindle and giant cells
(4) small cells

enlarged nucleus





Papillary carcinoma(PTC)

Mnemonic:Papi and Moma adopted Orphan Annie

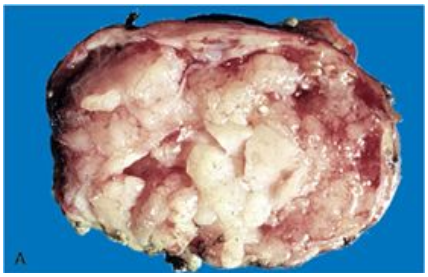
Character

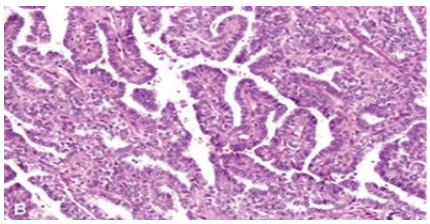
- papillary carcinomas represent the most common form of thyroid cancer. These tumors may occur at any age, and they account for the vast majority of thyroid carcinomas associated with **previous exposure to ionizing radiation**.
- Papillary carcinomas are nonfunctional tumors, so they manifest most often as a **painless** mass in the neck, either within the thyroid or as **metastasis in a cervical lymph node.**
- Papillary carcinomas are indolent lesions "prognosis is good" with 10-year survival rates in excess of 95%.
- There are over a dozen variants of papillary thyroid carcinoma, but the most common is one composed predominantly or exclusively of follicles (follicular variant of papillary thyroid carcinoma).

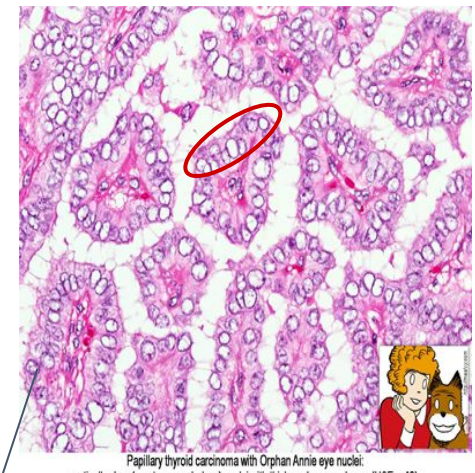
Histology

- **papillary architecture** "Could be absent. If present, it's a classical variant of PTC"
- Concentrically calcified structures termed **psammoma bodies** "Ca deposits" often are present.
- There are over a dozen variants of papillary thyroid carcinoma, but the most common is one composed predominantly or exclusively of follicles (**follicular variant** of papillary thyroid carcinoma).

- The nuclei of papillary carcinoma cells:
- very finely dispersed chromatin, with an **optically clear** appearance, giving rise to the designation **ground glass** or "**Orphan Annie eye**" nuclei.
- Grooves.
- invaginations of the cytoplasm may give the appearance of intranuclear inclusions (**pseudoinclusions**)







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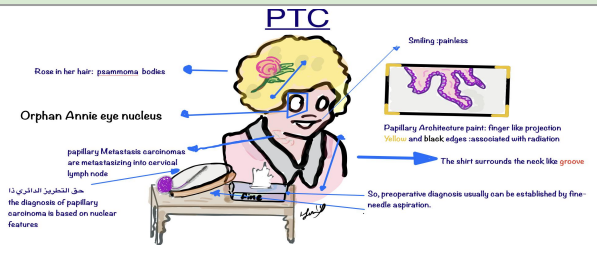
Prognosis

- 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 extrathyroidal extension, and presence of distant metastases (stage).
"In general it has good prognosis. But it could be worse depending on the stage, age"

Diagnosis

- A preoperative diagnosis usually can be established by fine-needle

- **The diagnosis of papillary carcinoma is based on nuclear features** even in the absence of a papillary architecture.



Medullary carcinoma

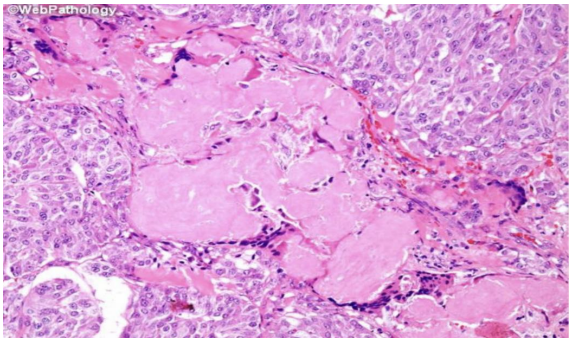
Mnemonic:
C: cells
Calcitonin
Congo-red stain=Amyloid

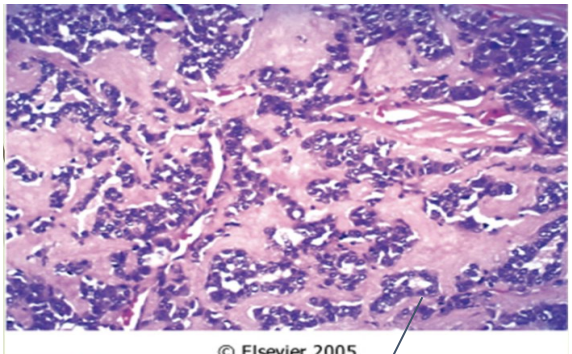
Character

- **Neuroendocrine neoplasms** derived from the **parafollicular cells, or C cells**, of the thyroid.
- Similar to normal **C cells, secrete calcitonin**, the measurement "in blood" of which plays an important role in the diagnosis and postoperative follow-up of patients.
- About 70% of tumors arise sporadically. "Not associated with syndromes or run in family"
- The remainder occurs in the setting of **MEN syndrome (2A or 2B** or as **Familial tumors** without an associated MEN syndrome
(familial medullary thyroid carcinoma, or FMTC)

Histology

- Polygonal to spindle cells
- Amyloid deposition "Characteristic as pink area. It's a protein we can see it by congo red stain"
- Bilaterality
- Multicentricity
- Necrosis
- Hemorrhage
- No Colloid or follicles





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Follicular carcinoma

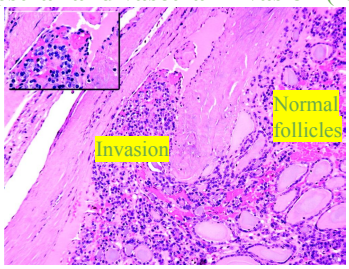
Character

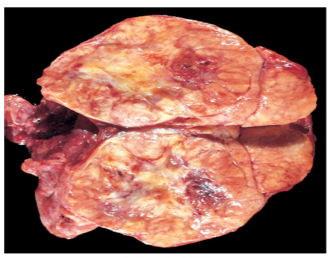
- 5% to 15% of primary thyroid cancers.
- More common in **women** (3 : 1).
- Peak incidence between 40 and 60 years.
- More frequent in areas with **dietary iodine deficiency.**
- Follicular carcinomas manifest most frequently as solitary *cold thyroid nodules*. "Non-functional"
- These neoplasms tend to **metastasize through the bloodstream (not through lymph nodes)** to the lungs, bone, and liver.
- Minimally invasive (well encapsulated), 10 year survival rate 90%.
- Widely invasive carcinoma, 10 year survival rate less than 50%.

Histology

- On microscopic examination, most follicular carcinomas are composed of fairly **uniform cells forming small follicles**, reminiscent of **normal thyroid.** "looks like normal thyroid"
- Follicular carcinomas may be:
  - **widely invasive,** infiltrating the thyroid parenchyma and **extrathyroidal soft tissues**
  - **minimally invasive.** are sharply demarcated lesions that may be impossible to distinguish from follicular adenomas on gross examination.
- **This distinction requires extensive histologic sampling of the tumor capsule–thyroid interface, to exclude capsular and/or vascular invasion.**

"Follicular adenoma and carcinoma morphology looks the same (No atypia, mitosis) the only features to distinguish are **capsular and vascular invasion** (follicular carcinoma)"





Summary: pathoma

Thyroid neoplasia

I. BASIC PRINCIPLES

A. Usually presents as a distinct, solitary nodule
1. Thyroid nodules are more likely to be benign than malignant.
B. 1311 radioactive uptake studies are useful to further characterize nodules.
1. Increased uptake ('hot' nodule) is seen in Graves disease or nodular goiter.
2. Decreased uptake ('cold' nodule) is seen in adenoma and carcinoma; often warrants biopsy
C. Biopsy is performed by fine needle aspiration (FNA).

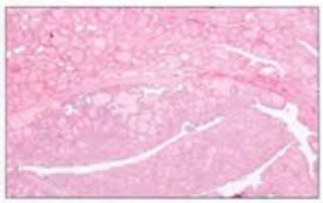


Fig. 15.4 Follicular adenoma.

II. FOLLICULAR ADENOMA

A.Benign proliferation of follicles surrounded by a fibrous capsule (Fig. 15.4)
B. Usually nonfunctional; less commonly, may secrete thyroid hormone

III. PAPILLARY CARCINOMA

A. Most common type of thyroid carcinoma (80% of cases)
B. Exposure to ionizing radiation in childhood is a major risk factor.
C. Comprised of papillae lined by cells with clear, 'Orphan Annie eye' nuclei and nuclear grooves (Fig. 15.5A); papillae are often associated with psammoma bodies (Fig. 15.5B).
D. Often spreads to cervical (neck) lymph nodes, but prognosis is excellent (10-year survival > 95%)

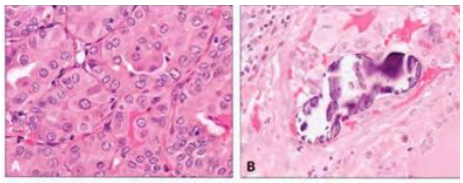


Fig. 15.5 Papillary carcinoma. **A**, Nuclear features. **B**, Psammoma bodies.

IV. FOLLICULAR CARCINOMA

A. Malignant proliferation of follicles surrounded by a fibrous capsule with invasion through the capsule (Fig. 15.6)
1. Invasion through the capsule helps distinguish follicular carcinoma from follicular adenoma.
2. Entire capsule must be examined microscopically.
3. FNA only examines cells and not the capsule; hence, a distinction between follicular adenoma and follicular carcinoma cannot be made by FNA.
B. Metastasis generally occurs hematogenously.

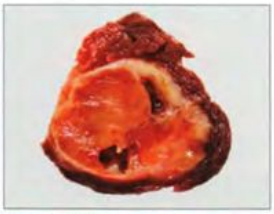


Fig. 15.6 Follicular carcinoma. (Courtesy of Bulent Celasun, MD)

V. MEDULLARY CARCINOMA

A. Malignant proliferation of parafollicular C cells; comprises 5% of thyroid carcinomas
I. C cells are neuroendocrine cells that secrete calcitonin.
2. Calcitonin lowers serum calcium by increasing renal calcium excretion but is inactive at normal physiologic levels.
3. High levels of calcitonin produced by tumor may lead to hypocalcemia.
4. Calcitonin often deposits within the tumor as amyloid.
B. Biopsy reveals sheets of malignant cells in an amyloid stroma (Fig. 15.7).
C. Familial cases are often due to multiple endocrine neoplasia (ME) 2A and 2B, which are associated with mutations in the RET oncogene.
I. MEN 2 results in medullary carcinoma, pheochromocytoma, and parathyroid adenomas (2A) or ganglioneuromas of the oral mucosa (28). 2. Detection of the RET mutation warrants prophylactic thyroidectomy.

V I. ANAPLASTIC CARCINOMA

A. Undifferentiated malignant tumor of the thyroid (Fig. 15.8); usually seen in elderly
B. Often invades local structures, leading to dysphagia or respiratory compromise
C. Poor prognosis

Questions

Q1: An electrical microscopic image was taken from a patient with a thyroid tumor and showed a neurosecretory granules what is the most likely diagnosis?

A. Follicular adenoma
B. Medullary carcinoma
C. Anaplastic carcinoma
D. Papillary carcinoma

Q2: 71 years old male who suffered from severe headache and clinical examination revealed a mass in the thyroid and CT scan showed a tumor in the frontal lobe, histological test showed spindle cell and giant cell. What is the diagnosis?

A. MEN type2
B. Anaplastic carcinoma
C. Medullary carcinoma
D. Follicular carcinoma

Q3: Which ONE of the following mutations is commonly seen in cases of papillary carcinoma?

A. RAS
B. Ret/NTRK1
C. P53
D. FAP

Q4: Which ONE of the following carcinomas is characterized by the presence of Congo red material in its stroma?

A. Medullary
B. Anaplastic
C. Papillary
D. Metastatic

Q5: The least common carcinoma in general practice?

A. Follicular carcinoma
B. Papillary carcinoma
C. Anaplastic carcinoma
D. Medullary carcinoma

Q6: A 24 years old male has solitary thyroid lesion which was reported as colloid nodule on the thyroid imaging scan. The lesion was later on excised & histopathological exam shows encapsulated neoplasm consist of intact of fibrous capsule & numerous thyroid follicular lined by uniform cells & minimal polymorphism. Which ONE of the following is likely the diagnosis:

A. Follicular Adenoma
B. Papillary carcinoma
C. Follicular carcinoma
D. Multinodular goiter

Q7: The histopathological features of enlarged thyroid gland biopsy showed solitary encapsulated nodule. What is the most-likely diagnosis?

A. Follicular carcinoma of thyroid
B. Hashimoto's thyroiditis
C. Grave's disease
D. Thyroid adenoma

Q8: 26-year-old female patient presented with enlarged lymph node around her neck, fine needle aspiration of the mass showed infiltrate of lymphocyte, plasma cells and grooved clear nuclei with some degree of calcification. What is the diagnosis?

A. Metastasis in the lymph nose due to Papillary carcinoma
B. Metastasis in the lymph nose due to follicular carcinoma
C. Metastasis in the lymph nose due to anaplastic carcinoma
D. Metastasis in the lymph nose due to medullary carcinoma

Q9:which one of the following is associated with MEN-2 syndrome?

A. Follicular carcinoma
B. Papillary carcinoma
C. Anaplastic carcinoma
D. Medullary carcinoma

Q10:Which one of the following neoplasm tend to metastasize by hematogenous spread?

A. Follicular carcinoma
B. Papillary carcinoma
C. Anaplastic carcinoma
D. Medullary carcinoma

Questions

Q11.by which one of the following you can differentiate between follicular adenoma and follicular carcinoma?

A. By measuring the T3/T4 levels
B. The presence of oxyphil cell changes
C. Capsular invasion
D. The present of amyloid deposition on Congo red

Q12**:** What thyroid cancer affects people in puberty, has proximal spread (local lymph nodes) and is poly-focal?

A. Follicular carcinoma
B. Papillary carcinoma
C. Anaplastic carcinoma
D. Medullary carcinoma

Q13:Which thyroid cancer affects the ageing population, metastasises all over the body, and has an awful prognosis?

A. Follicular carcinoma
B. Papillary carcinoma
C. Anaplastic carcinoma
D. Medullary carcinoma

Q14:A 50 year old man presents with a thyroid neoplasm. Detailed history elicits that his aunt had died from a "thyroid illness". His family and first order blood relatives are examined. His sister and a nephew also are found to have small thyroid tumors. His son is found to have a pheochromocytoma. Which of the following gene mutations are most likely to be associated with this condition?

A.NTRK1
B. RAS
C. MEN-1
D. RET

Q15: Anaplastic carcinoma is associated with which one of the following?

A. activating point mutations in BRAF
B. inactivating point mutations in BRAF
C. Inactivating point mutations in the p53
D. activating point mutations in the p53

Q16: Which one of the following is most likely to have papillary carcinoma?

A.32 years old female with previous history of ionizing radiation
B.21 years old male with painful mass in the neck
C.69 years old male who has dyspnea
D.47 years old female with dietary iodine deficiency

Q17: which one of the following could be found in patient with medullary carcinoma?

A. hypercalcemia
B. hypocalcemia
C.metastasis in a cervical lymph node.
D.pseudoinclusions

Q18: you can find psammoma bodies in which of the following?

A. Follicular carcinoma
B. Papillary carcinoma
C. Anaplastic carcinoma
D. Medullary carcinoma

1.B
2.B
3.B
4.A
5.C
6.A
7.D
8.A
9.D
10.A
11.C
12.B
13C
14.D
15.C
16.A
17.B
18.B