Fourth Lecture, Thyroid diseases

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IV .Graves Disease

- Is the most common cause of endogenous hyperthyroidism
- It is characterized by a triad of manifestations

1. Thy*rotoxicosis, caused by a diffusely enlarged, hyperfunctional* thyroid present in all cases
2. An infiltrative *ophthalmopathy with resultant exophthalmos, present in about* 40% of patients
3. A localized, infiltrative *dermopathy (sometimes designated pretibial myxedema), seen in a minority of cases*:

- Graves disease has a peak incidence between 20 and 40 years of age, with women being affected up to seven times more commonly than men.

Pathogenesis

- Many manifestations of Graves disease are caused by autoantibodies to TSH

1. Thyroid stimulating immunoglobulin

- *This IgG antibody* binds to the TSH receptor and mimics the action of TSH, causing increased release of thyroid hormones.
- Almost all individuals with Graves disease have detectable amounts of this autoantibody, which is relatively specific for Graves disease.

2. Thyroid growth stimulating immunoglobulin

- Directed against the TSH receptor, these antibodies have been implicated in the proliferation of thyroid follicular epithelium.

3. TSH binding inhibitor immunoglobulin

- *These anti-TSH* receptor antibodies prevent TSH from binding to its receptor on thyroid epithelial cells and in so doing may inhibit thyroid cell function.

Pathogenesis of infiltrative ophthalmopathy

- There is increase in the volume of retro-orbital connective tissue and extraocular muscles due to

(1) marked infiltration of the retro-orbital space by mononuclear cells, predominantly T cells;

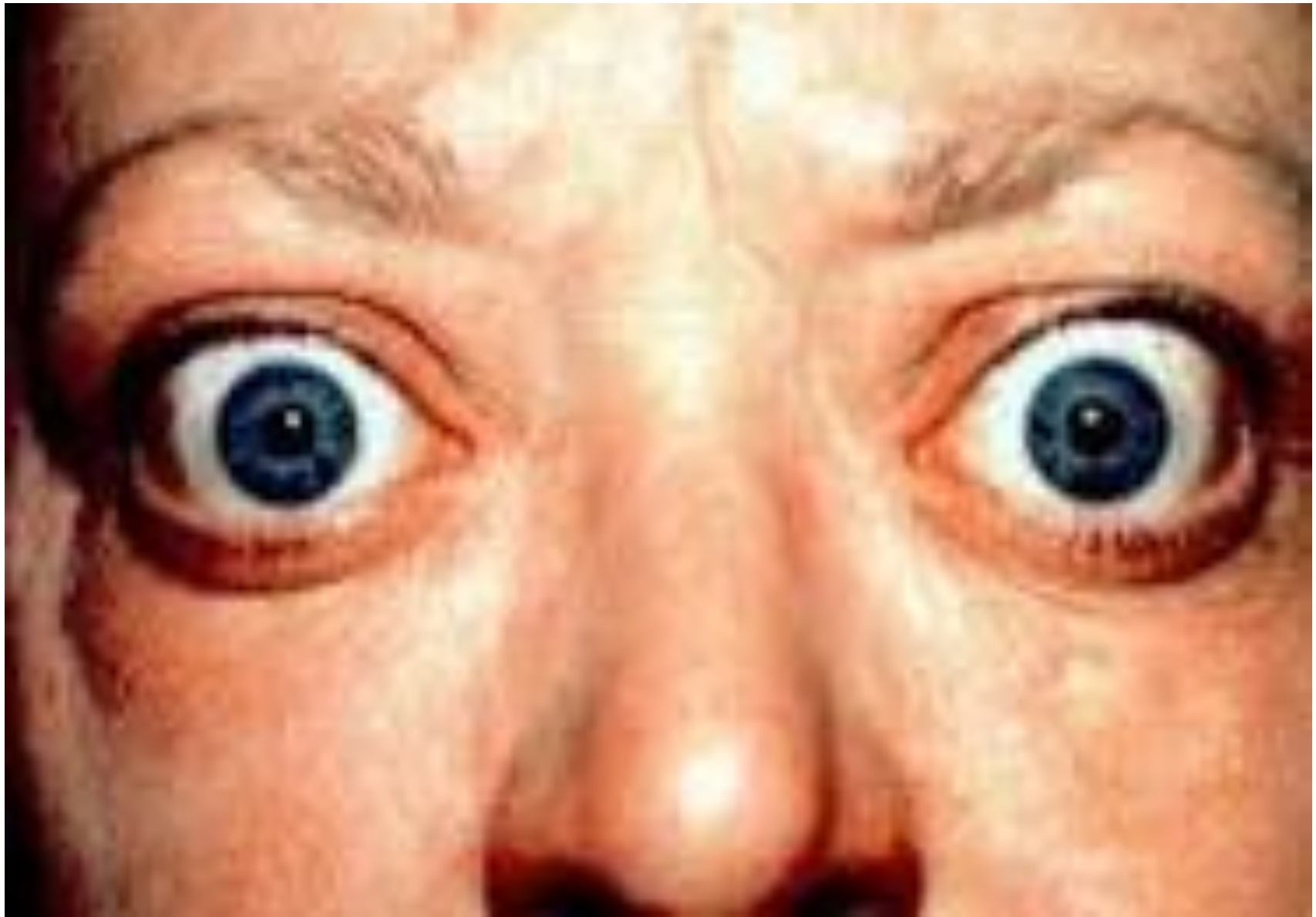
(2) Inflammatory edema and swelling of extraocular muscles;

(3) Accumulation of glycosaminoglycans such as hyaluronic acid and chondroitin sulfate;

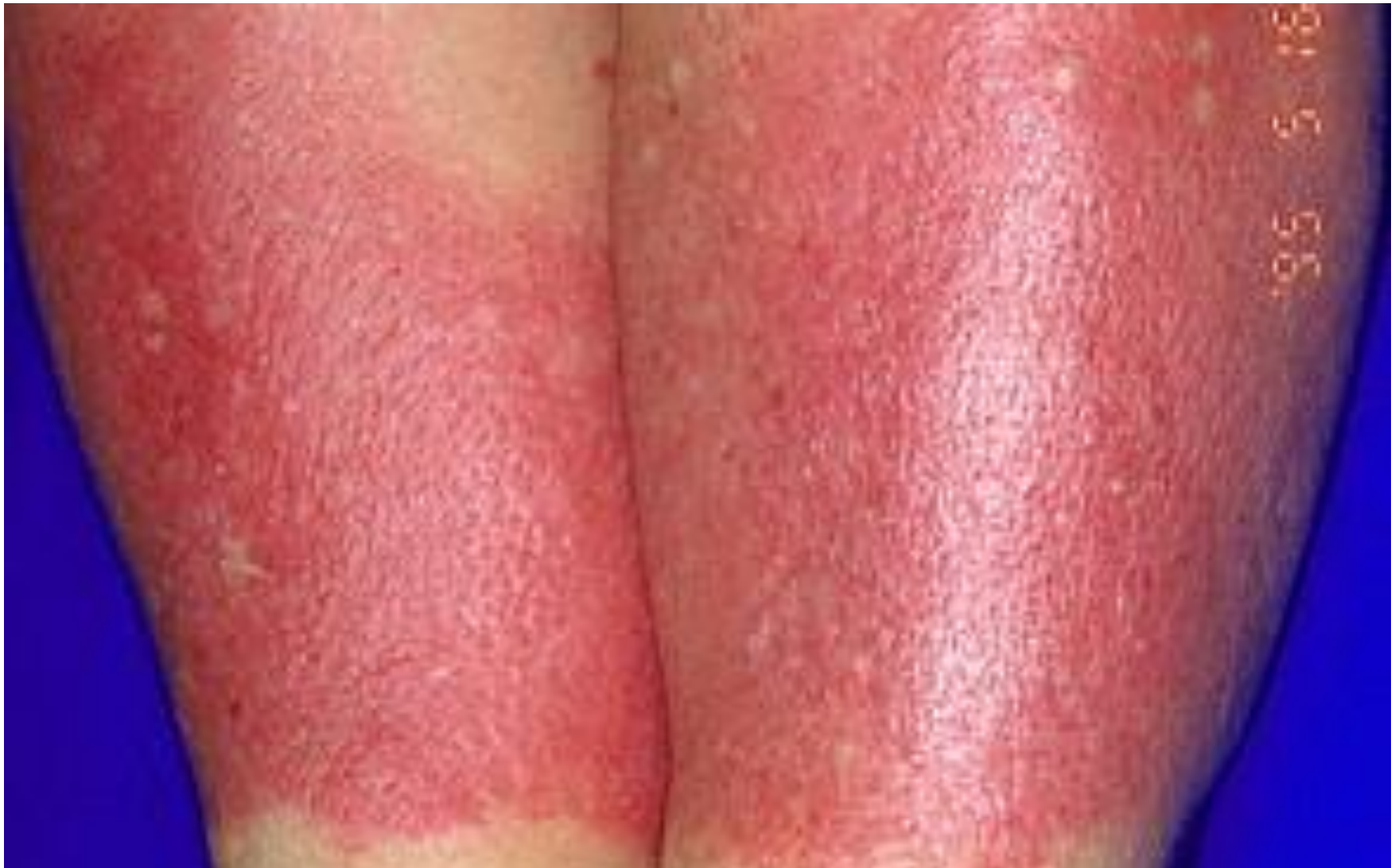
(4) Increased numbers of adipocytes (fatty infiltration).

- These changes displace the eyeball forward, potentially interfering with the function of the extraocular muscles

exophthalmos



Pretibial myxedema



MORPHOLOGY

- In the typical case of Graves disease, the thyroid gland is enlarged(usually symmetrically) due to diffuse hypertrophy and hyperplasia of thyroid follicular epithelial cells.
- On microscopic examination, the follicular epithelial cells in untreated cases are tall, columnar, and more crowded than usual.

-Lymphoid infiltrates is present throughout the interstitium

The clinical manifestations

- Include those common to all forms of thyrotoxicosis ,
- And those associated uniquely with Graves disease:

ophthalmopathy is specific to Graves disease and mot present in other causes of exophthalmos

-Sympathetic overactivity produces a characteristic wide, staring gaze and lid lag. Which are not specific to Graves disease

- The ophthalmopathy of Graves disease results in abnormal protrusion of the Eyeball(*exophthalmos)*

- *The exophthalmos may persist or* progress despite successful treatment of the thyrotoxicosis, sometimes resulting in corneal injury.
- The infiltrative dermopathy most commonly involves the skin overlying the shins, where it manifests as scaly thickening and induration of the skin

  (pretibial myxedema).

Laboratory findings in Graves disease include

a. Elevated serum free T4 and T3 and depressed serum TSH.

b. Because of ongoing stimulation of the thyroid follicles by TSIs, radioactive iodine uptake is increased diffusely.

V. DIFFUSE AND MULTINODULAR GOITER

- Enlargement of the thyroid, or *goiter, is the most common* manifestation of thyroid disease.
- Diffuse and multinodular goiters are the result of impaired synthesis of thyroid hormones most often caused by dietary iodine deficiency.
- Impairment of thyroid hormone synthesis leads to a compensatory rise in the serum TSH, which drives the hypertrophy and hyperplasia of thyroid follicular cells and, ultimately, enlargement of the thyroid gland.

- These compensatory changes overcome the hormone deficiency and maintain a *euthyroid metabolic state* *in the vast majority* of affected individuals.
- If the underlying disorder is severe (e.g., a congenital biosynthetic defect), the compensatory responses may be inadequate, resulting in goiterous hypothyroidism

Pathogenesis

- Goiters can be endemic or sporadic.

1. ***Endemic goiter*** *occurs in geographic areas where the* diet contains little iodine.

- The designation *endemic is* used when goiters are present in more than 10% of the population in a given region.
- Such conditions are common in mountainous areas of the world, including the Himalayas and the Andes.

- With increased availability of dietary iodine supplementation, the frequency and severity of endemic goiter have declined significantly

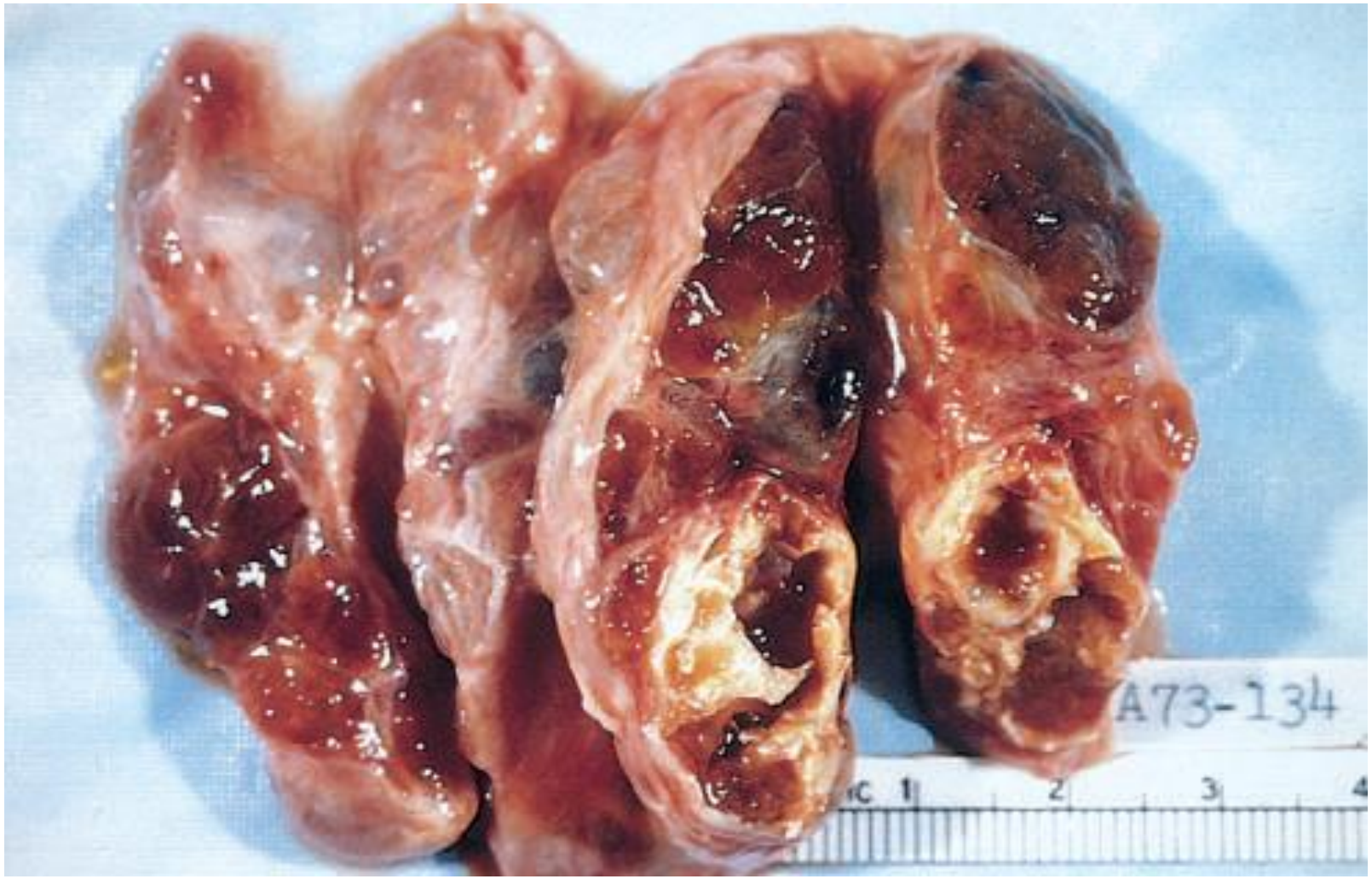
2. Sporadic goiter

- *Occurs less frequently than endemic* goiter.
- The condition is more common in females than in males, with a peak incidence in puberty or young adulthood, when there is an increased physiologic demand for T4.
- Sporadic goiter may be caused by several conditions, including

a. the excessive ingestion of substances that interfere with thyroid hormone synthesis, such as calcium and vegetables such as *cabbage, caulifower,*

2.Sporadic goiter :In other instances goiter may result from inherited enzymatic defects that interfere with thyroid hormone synthesis (*dyshormonogenetic goiter)*

Note *In most cases, however, the cause of sporadic* goiter is not apparent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Clinical Features

-The dominant clinical features of goiter are those caused by the mass effects of the enlarged gland causing

a. cosmetic problem of a large neck mass
b. Goiters also may cause airway obstruction, dysphagia, and compression of large vessels in the neck and upper thorax (so-called superior vena cava syndrome)

Note Multinodular goiters typically are hormonally silent,

- A a minority (approximately 10% over 10 years) manifest with thyrotoxicosis secondary to the development of

autonomous nodules that produce thyroid hormone independent of TSH stimulation

- This condition, known as *toxic multinodular goiter or Plummer syndrome, is not accompanied* by the infiltrative ophthalmopathy and dermopathy of Graves disease–associated thyrotoxicosis.

- The incidence of malignancy in long-standing multinodular goiters is low, (<5%) but not zero, and concern for malignancy arises with goiters that demonstrate sudden changes in size or associated symptoms (e.g., hoarseness

VI.THYROID NEOPLASMS

- From a clinical standpoint, the possibility of a tumor is of major concern in patients who present with thyroid nodules.
- Fortunately, the overwhelming majority of solitary nodules of the thyroid prove to be either

a. benign adenomas or
b. Localized, non-neoplastic conditions (e.g., a dominant nodule in multinodular goiter, simple cysts, or foci of thyroiditis).

- Carcinomas of the thyroid, are uncommon, accounting for less than 1% of solitary thyroid nodules.

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

1. *Solitary nodules, in general, are more likely to be neoplastic* than are multiple nodules.
2. *Nodules in very young <20 years or vey old more than 70 years individuals are more likely to be neoplastic.*

3. *Nodules in males are more likely to be neoplastic than are* those in females.

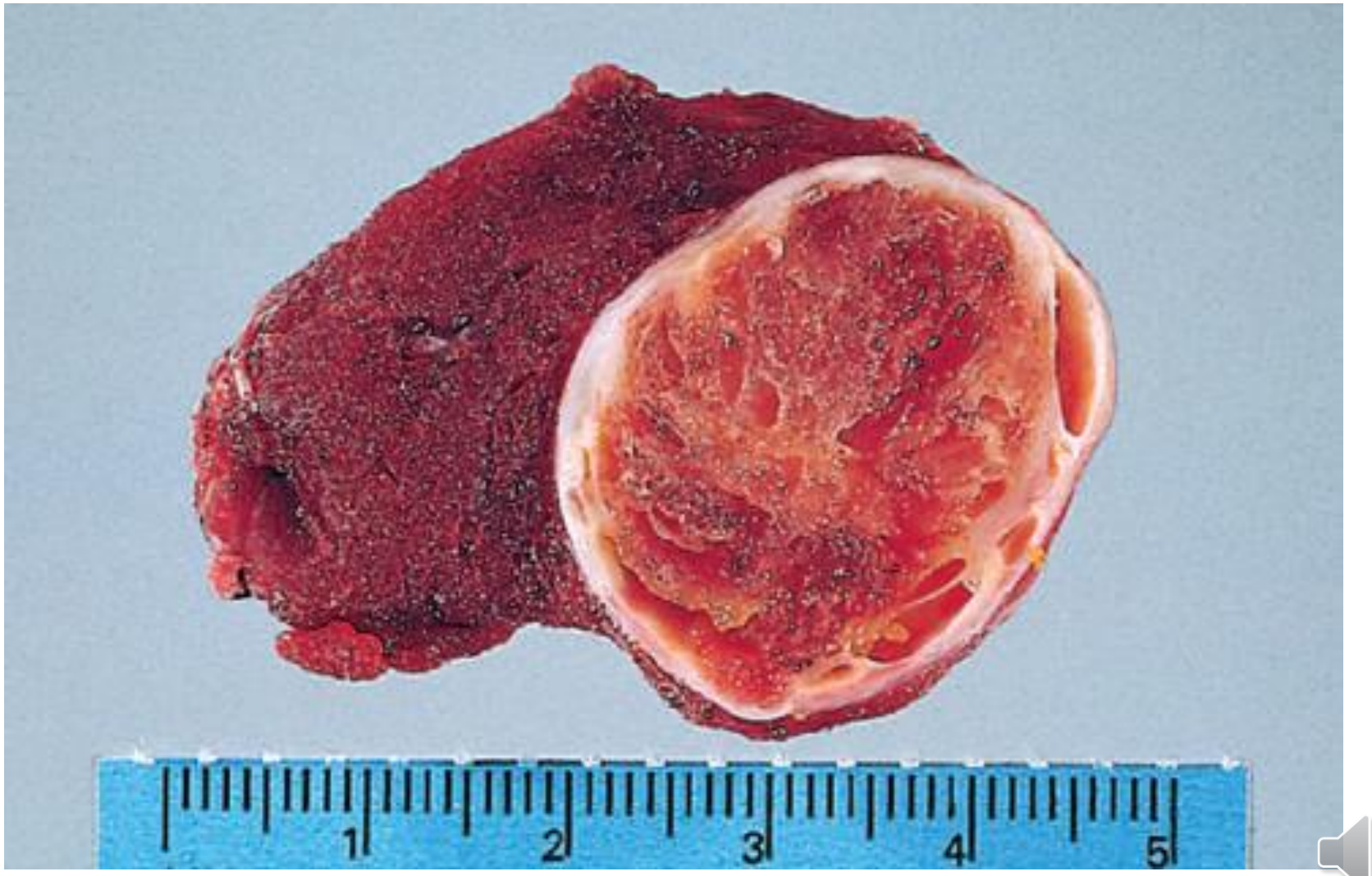
4. A history of *radiation exposure is associated with an* increased incidence of thyroid malignancy.

5. Nodules that take up radioactive iodine in imaging studies (*hot nodules) are more likely to be benign.*

Follicular Adenomas

- Are benign neoplasms derived from follicular epithelium
- Follicular adenomas usually are solitary.
- On clinical and morphologic grounds, they may be difficult to distinguish from a dominant nodule in multinodular goiter, or from less common follicular carcinomas.
- Although the vast majority of adenomas are nonfunctional, a small proportion produce thyroid hormones called toxic adenomas, causing clinically apparent thyrotoxico*sis*

Follicular Adenoma



Thyroid Carcinomas

- A female predominance has been noted among patients who develop thyroid carcinoma in the early and middle adult years.
- By contrast, cases seen in childhood and late adult life are distributed equally between males and females.
- Most thyroid carcinomas (except medullary carcinomas) are derived from the thyroid follicular epithelium

Subtypes of thyroid carcinomas

- The major subtypes of thyroid carcinoma and their relative frequencies are

a. Papillary carcinoma (accounting for more than 85% of cases)

b. Follicular carcinoma (5% to 15% of cases)

c. Anaplastic (undifferentiated carcinoma (<5% of cases)

d. Medullary carcinoma (5% of cases*)*

Environmental Factors

1. The major risk factors predisposing to thyroid cancer is exposure to ionizing radiation particularly during the first 2 decades of life.

- There was a marked increase in the incidence of papillary carcinomas among children exposed to radiation as treatment for malignant tumors such as lymphomas

2. Deficiency of dietary iodine (and by extension,

an association with goiter) is linked with a higher

Frequency of follicular carcinomas

I.Papillary Carcinoma

- Papillary carcinomas are the most common form of thyroid cancer.
- They may occur at any age
- They account for the vast majority of thyroid carcinomas associated with previous exposure to ionizing radiation.

MORPHOLOGY

- Papillary carcinomas are solitary or multifocal lesions.
- Some tumors may be well circumscribed and encapsulated
- others infiltrate the adjacent parenchyma
- The microscopic hallmarks of papillary neoplasms include the following:

a. Branching papillae having a fibrovascular stalks covered by a single to multiple layers of cuboidal epithelial cells

b. Nuclei are optically clear imparts empty appearance called ground-glass or Orphan Annie eye nuclei .

c. Intranuclear inclusions (“pseudo-inclusions”)

d. Intranuclear grooves

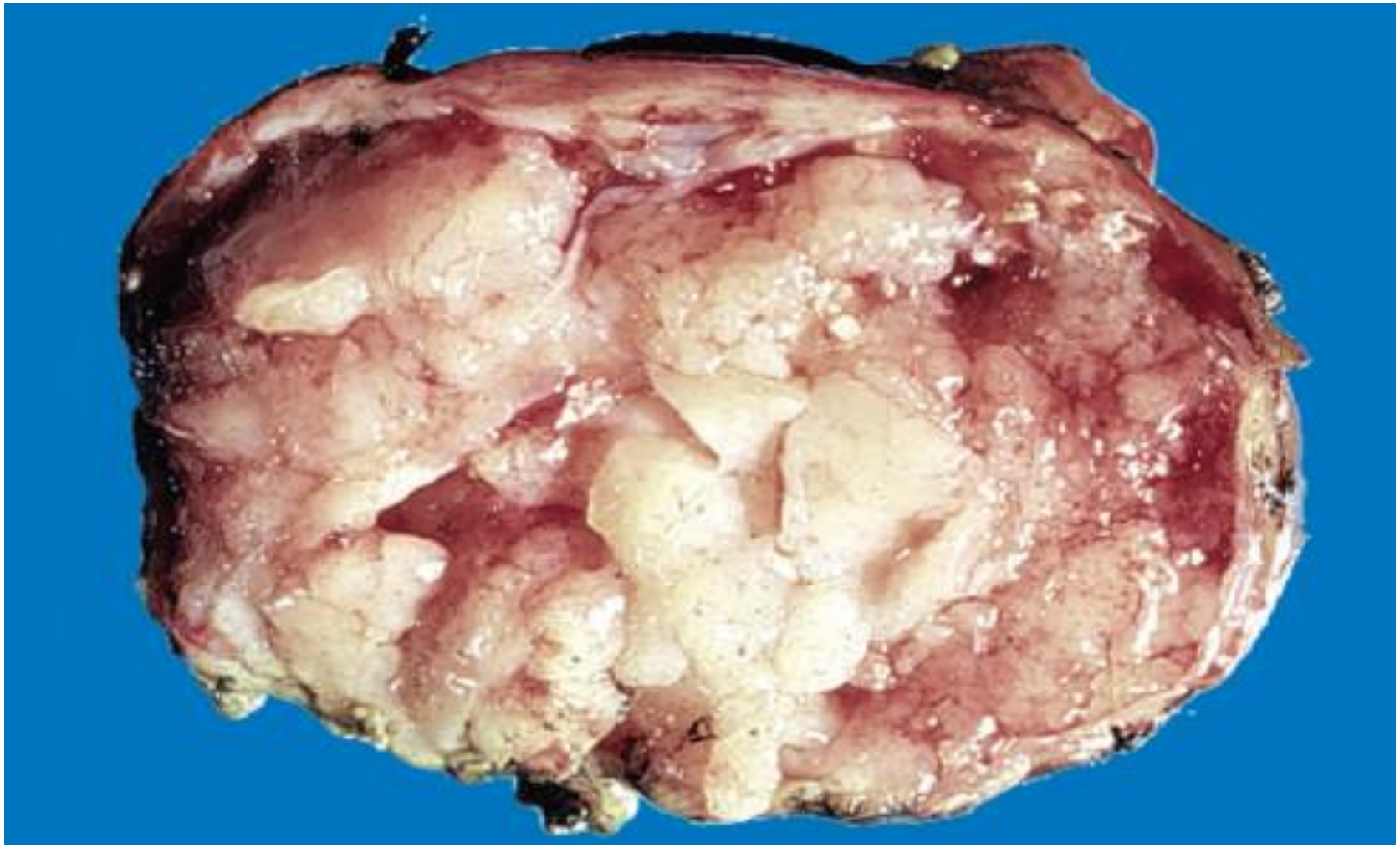
Note:

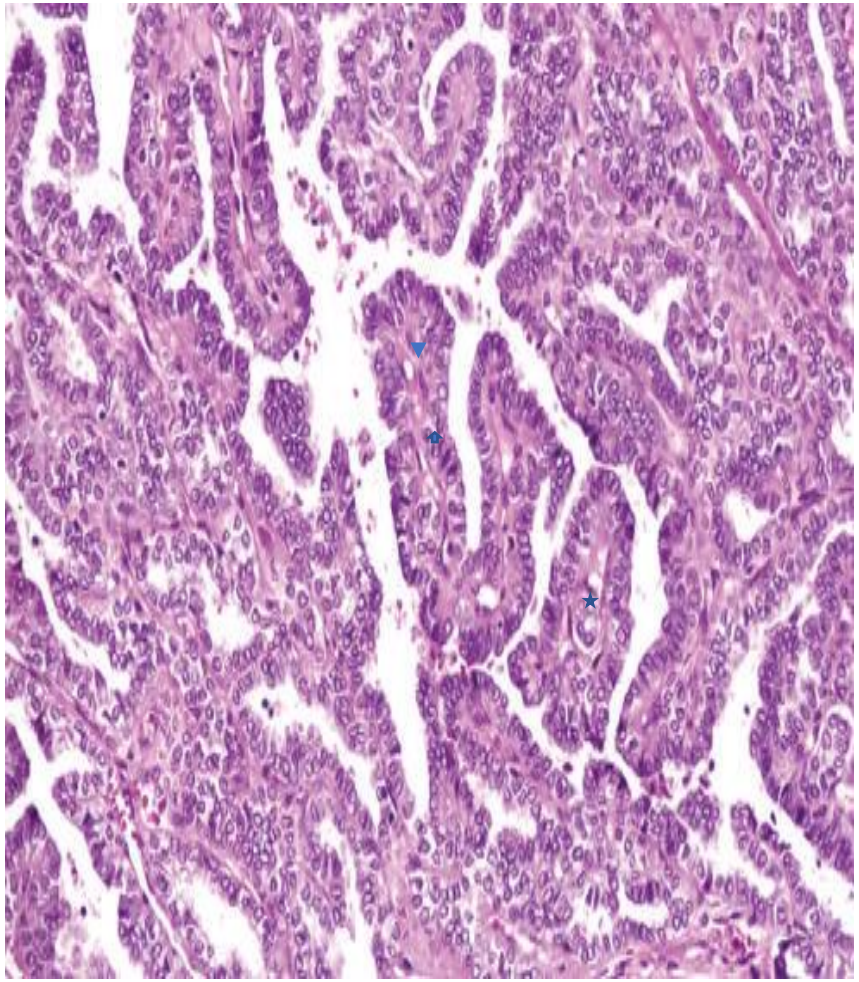
These nuclear features are sufficient for the diagnosis of papillary carcinoma, even in the absence of papillary architecture. .

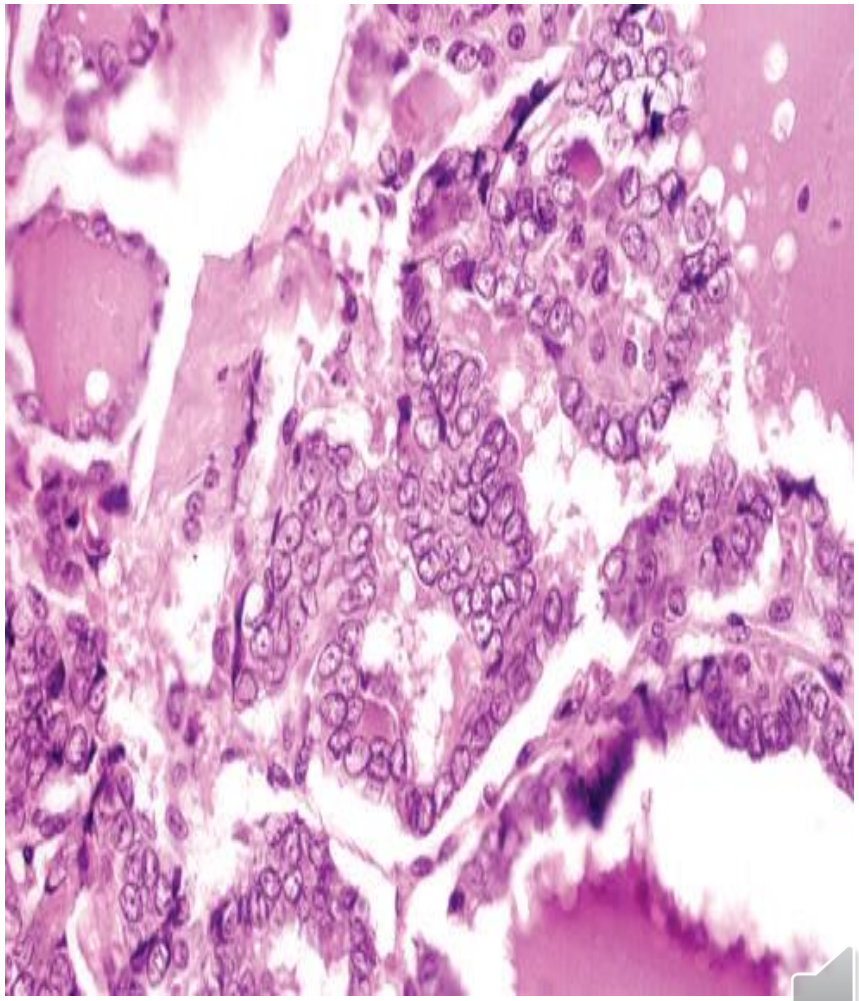
e. Concentrically calcified structures termed psammoma bodies

f. Foci of lymphatic invasion by tumor are often present, but involvement of blood vessels is relatively uncommon,

- Metastases to adjacent cervical lymph nodes occur in one-half of cases.







Clinical Features

- Papillary carcinomas are nonfunctional tumors
- Manifest most often as a painless mass in the neck, either within the thyroid or as a metastasis in a cervical lymph nodes
- Are indolent lesions, with 10-year survival rates in excess of 95%.
- The presence of isolated cervical node metastases does not have a significant influence on prognosis.
- In a minority of patients, hematogenous metastases are present at the time of diagnosis, most commonly to the lung

- The long-term survival of patients with papillary thyroid cancer is dependent on several factors, including

a. age (the prognosis is less favorable among patients older than 40 years of age),
b. presence of extrathyroidal extension,
c. and presence of distant metastases (stage).