Essentials of

Head and Neck Cytology

Gia-Khanh Nguyen
Thomas A. Thomson
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Preface

Tumors arising from the head and neck are numerous and have complicated and diversified histopathologic features. Cytodiagnosis of those neoplasms by fine needle aspiration is challenging and compounded with diagnostic pitfalls. However, with a representative cell sample and a careful evaluation of different cellular and non-cellular components, a correct diagnosis may be safely made in the majority of cases.

This monograph is written for practicing pathologists in community hospitals, pathology residents and cytotechnologists who are interested in acquiring a basic knowledge in diagnostic cytology of head and neck tumors. It consists of four chapters describing the cytologic manifestations of important tumors of the thyroid, parathyroid, salivary glands, lymph nodes, soft tissues and brain... The text is concise and illustrations are abundant. For most tumors cytologic and histologic images are presented side by side for cytohistologic correlation. Immunohistochemical features of commonly encountered neoplasms that are important for tumor typing and differential diagnosis are stressed.

For improvement of the future editions of the monograph, constructive comments and suggestions from the reader will be highly appreciated.

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Remarks and abbreviations

- Histologic sections were stained with hematoxylin and eosin and most figures/images were taken at medium magnification
- Cytologic figures: most figures were taken at high magnifications
- Commonly used abbreviations in this monograph:
    - ABC: avidin-biotin complex technique
    - CP: conventional preparation (smear, cytospin preparation…)
    - DQ: Diff-Quik stain
    - FNA: fine-needle aspiration/fine-needle aspirate
    - GMS: Gomori methenamine silver stain
    - HE: hematoxylin and eosin stain
    - IHC: immunohistochemistry/immunohistochemical
    - LBP: Liquid-based preparation (ThinPrep)
    - MGG: May-Grünwald-Giemsa stain
    - Pap: Papanicolaou stain

Chapter 1

Thyroid

Gia-Khanh Nguyen and Thomas Thomson

Fine-needle aspiration (FNA) for cytologic evaluation of thyroid cancer was originally used by Martin and Ellis at the New York Memorial Hospital for Cancer and Allied Diseases in 1930. However, this diagnostic procedure was subsequently found to have a limited value, and it was then discontinued at the above-mentioned institution. Thyroid FNA was not further developed and did not gain acceptance in the United States for nearly 50 years until the early 1980s when its diagnostic value was firmly demonstrated by Scandinavian investigators. The 1974 report by Crockford and Bain and the 1979 paper of Miller and Hamburger were apparently the first North American publications attesting to the value of thyroid FNA. This method of clinical investigation now is practiced worldwide and has become the cornerstone in the management of thyroid nodules (TN).

Indication and Goal of Thyroid FNA

Thyroid nodular lesions are a common clinical problem. In the United States, 4-7% of adult population has a palpable TN. The incidence of thyroid cancer in a clinically solitary TN or in a multinodular goiter is equal and about 5% in non-endemic areas. TNs constitute the main indication for FNA, and the goal of this diagnostic procedure is to detect thyroid neoplasms for surgical resection and to identify non-neoplastic lesions that may be managed conservatively. This method of clinical investigation has reduced the number of diagnostic thyroid surgeries for TNs by 60-85%, and the difference in rates of thyroid surgery reflects the cytodiagnostic accuracy rates among different medical centers.

Contraindications and Complications of Thyroid FNA

The main contraindication to thyroid FNA is bleeding diathesis, as the formation of a large hematoma at the biopsy site may cause compression of the trachea and respiratory distress. Therefore, a bleeding time, PT and PTT should be ordered to screen this condition in all patients prior to thyroid FNA. This diagnostic procedure, if properly performed, is almost free of complications. Subcutaneous hematoma at the biopsy site, accidental puncture of the trachea and local infection are rare complications. Hematoma may be prevented by local pressure of the overlying skin at the biopsy site. Tracheal injury is manifested by minimal and transient hemoptysis. Seeding of thyroid cancer cells along the needle tract is also an exceedingly rare complication with FNA.

Procurement and Preparation of cell samples

Procurement of cell samples

Interpreting thyroid cytology is challenging and requires expertise. The greatest impediment to proper diagnosis is an inadequate or poorly prepared sample. Obtaining a satisfactory sample is simple but not trivial. Appropriate training and practice are essential to develop and maintain competence in thyroid FNA. Aspiration can be done directly on palpable nodules or with ultrasound (US) guidance. In general it is preferable to have a prebiopsy US examination to provide detailed information on gland anatomy, complexity of cysts and number, size, location and vasularity of TNs. If the TN is difficult to identify by palpation (small nodule, posterior location…) the FNA is best done under US guidance.

FNA begins with a clinical examination, review of imaging findings and a focused history including specific questions regarding anticoagulant use and bleeding risk. Consent for the procedure should be obtained after discussion of the procedure and possible complications. Patient positioning, usually supine with slightly extended head is important for patient safety and to optimize the biopsy approach. Local skin anesthesia is usually sufficient for adult patients. The target cyst or nodule and the location of major vessels and the trachea are identified. Needle insertions are generally best performed in a direct anterior-posterior direction with attention to depth of insertion to avoid the trachea and major vessels. Large cysts can be drained using a 22-gauge needle with a syringe with or without an aspiration. Any residual nodules should be then sampled. Solid nodules are best sampled with a 25- or 27-gauge needle using a non-aspiration technique, which is more tactile and precise and causes less bleeding. As under sampling is a frequent problem, 3 or 4 separate punctures from different regions of the nodule are recommended. Additional FNAs around the TN are helpful in detecting other thyroid lesions that may be associated with the nodule under investigation. (An excellent instructional guide is available on the Papanicolaou Society website: http://www.papsociety.org)

Preparation of cell samples

Cytologic evaluation can be done on appropriately prepared and stained smears or on monolayer slides prepared from material saved in a preservative fluid such as CytoLyt®.

For smears one of the following preparation techniques is used:

a. Place a small drop of aspirate near the frosted end of a glass slide and quickly and gently smear with a cover slip.

b. Place a small drop of aspirate near the frosted end of a glass slide. Use a second slide to spread the aspirated material as if preparing a peripheral blood smear.

c. Place a small drop of aspirate in the center of a glass slide and gently crush with a second slide that is then separated vertically from the first one. (Pull apart technique)

d. Cytospin smears or a cellblock should be prepared from the liquid contents of all cystic thyroid lesions. To obtain adequate material for cellblock preparation, rinse all needles used for slide preparation and add material from one or two aspirates dedicated for cellblock. Obvious tissue fragments should also be added to the cellblock rinse tube.

Note: For smear preparation it is important that only a small drop of material is used. A large drop will give an unevenly thick smear with a thick bloody cell film at the end of the slide, which will obscure cell details making evaluation difficult if not impossible.

Routine staining methods

Depending on personal preference, either air-dried and Romanowsky-stained smears or ethanol-fixed and Papanicolaou-stained smears are prepared. For Papanicolaou staining, the smears must be fixed quickly before drying with 95% ethanol or with a commercial spray fixative. A delay in fixation will result in air-dried artefactual changes with loss of nuclear details. Air-dried smears for staining with one of the Romanowsky modified methods (Wright stain, May-Grünwald-Giemsa or Diff-Quik method) now are widely used, as air-drying artifactual changes can be avoided. However, nuclear details in Romanowsky-stained smears are not as well-visualized as in wet-fixed and Papanicolaou-stained smears. A parallel use of air-dried and wet-fixed smears is usually recommended, as these two staining methods are complementary. Fixation of aspiration smears in Carnoy solution for 3 to 5 minutes may be used to lyse red blood cells prior to staining with the Papanicolaou method.

Specimen adequacy

Obtaining an adequate cell sample is a prerequisite to the success of thyroid cytology. Therefore, immediate microscopic assessment of the needle aspirate by a pathologist or a cytotechnologist is desirable. If the first sample is judged inadequate for cytologic evaluation, the TN can be re-aspirated immediately. If a rapid evaluation is not available, multiple FNAs of different areas of the TN should be performed.

The rate of inadequate or unsatisfactory specimens reported in the literature range from 2 to 21% (mean, 17%). Currently, criteria for specimen adequacy vary from institution to institution:

(a). **The Bethesda System** requires that an adequate sample should contain at least six groups of well-preserved and well-visualized follicular cells with each group containing at least 10 cells. In experienced hands, adequate cell samples should be obtained in 70-90% of cases.

(b). One institution requires multiple punctures of the TN to be evaluated, with at least six properly prepared smears and a minimum of 8 to 10 tissue fragments of well-preserved follicular epithelium on each of two slides.

(c). Another institution requires 10 clusters of follicular cells with at least 20 cells in each cluster.

(d). The Papanicolaou Society of Cytopathology Task Forces on Standard of Practice do not specify any numbers and groups of thyroid follicular epithelial cells for specimen adequacy.

(e). Thyroid FNA under US guidance achieved higher rates of adequate cell samples, in the range of 79-99.3% (mean, 91%). US-guided thyroid FNA proved to be useful in sampling TNs smaller than 2 cm in greatest dimension, complex or solid-cystic TNs and abnormal thyroid beds.

Two practical exceptions to these adequacy criteria are applied:

(a). A benign colloid nodule may be suggested if a large amount of thick colloid material is present, regardless of the number of follicular epithelial cell clusters.

(b). If a cell sample contains one or two small clusters of malignant or highly atypical cells, it should be reported as malignant or suspicious for malignancy and not as unsatisfactory or inadequate for cytodiagnosis.

Cytodiagnosis and Reporting

The cytodiagnosis of TNs by FNA is complex for the following reasons:
a. Overlap of cytologic patterns between neoplastic and non-neoplastic lesions.
b. Overlap of cytologic features between various neoplasms.
c. Coexistence of non-neoplastic and neoplastic processes and multiple malignancies.

Prior to the introduction of The Bethesda System for Reporting Thyroid Cytopathology there were no universal and standard reporting systems to report thyroid FNA, and Thyroid FNA has been reported descriptively without categorization or by using surgical pathology terminology.

The Bethesda System for Reporting Thyroid Cytopathology

In 2007, following several months of preparation and discussion, the National Cancer Institute hosted "The NCI Thyroid Fine Needle Aspiration State of the Science Conference" which included pathologists and endocrinologists and produced a consensus, category-based terminology linked to management guidelines. TBS has been widely adopted and the benefits of a uniform reporting system include improved communication, facilitated cytologic-histologic correlation and standardized data for collaborative studies.
The system has 6 general categories; each assigned a cancer risk ranging from 0 to 3% for the Benign category to virtually 100% for the Malignant category. The recommended terminology of thyroid FNA interpretation was as follows: Non-diagnostic, Benign, Atypia of undetermined significance/Follicular lesion of undetermined significance, Follicular neoplasm/Suspicious for a follicular neoplasm, Suspicious for malignancy and Malignant. (Table 1).

Table 1. The Bethesda System for reporting Thyroid Cytopathology

1. Non-diagnostic or Unsatisfactory
    - Cyst fluid only
    - Virtually acellular specimens
    - Other (obscuring blood, clotting artifact, etc)
2. Benign
    - Consistent with a benign follicular nodule (includes adenomatous nodule, colloid nodule, etc...)
    - Consistent with lymphocytic (Hashimoto) thyroiditis in proper clinical context
    - Consistent with granulomatous (subacute) thyroiditis
3. Atypia of undetermined significance (AUS) or Follicular lesion of undetermined significance (FLUS)
4. Follicular neoplasm or Suspicious for a follicular neoplasm
    - Specify if Hürthle cell (oncocytic) type
5. Suspicious for malignancy
    - Suspicious for papillary carcinoma
    - Suspicious for medullary carcinoma
    - Suspicious for metastatic carcinoma
    - Suspicious for lymphoma
    - Other
6. Malignant
    - Papillary thyroid carcinoma
    - Poorly differentiated carcinoma
    - Medullary thyroid carcinoma
    - Undifferentiated (anaplastic) carcinoma
    - Squamous cell carcinoma
    - Carcinoma with mixed features (specify)

- Metastatic carcinoma
- Non-Hodgkin lymphoma
- Other

Explanations and comments:

1. Non-diagnostic or **Unsatisfactory:** 10-30% of all thyroid FNAs reveal no follicular epithelial cells and may contain only macrophages and cell debris. The associated risk of malignancy is 1-4%, according to recently reported studies.

In the Mayo Clinic experience, repeating the FNA in cases with initial non-diagnostic FNAs revealed diagnostic material in 30-80% of the cases, although other investigators have found repeat FNAs of limited value. Generally, repeat FNAs should be US-guided, which yield adequate cytologic materials in about 90% of cases. If a patient with no specific risk factors for thyroid malignancy and a non-diagnostic FNA refuses a re-biopsy he or she should be followed clinically. An increase in nodule volume alone is not a reliable predictor of malignancy, as benign TNs may grow in size.

There are **3 exceptions** in which a cytodiagnosis of a thyroid lesion may be made in the absence of an adequate number of follicular epithelial cells:
- A diagnosis of thyroiditis may be made if abundant inflammatory cells are present.
- A benign colloid nodule may be diagnosed if abundant thick colloid is present.
- A diagnosis of atypia or malignancy may be made if atypical or malignant cells are clearly identified.

2. Benign category: This category accounts for 70% of all thyroid FNAs. The false-negative rate is less than 1-3%. Patients with benign TNs are followed by periodic clinical examination with or without US-guided FNA. This category includes benign follicular nodule (colloid nodule, adenomatoid nodules), macro-follicular adenoma, Hashimoto thyroiditis and other lesions (subacute thyroiditis, amyloid goiter…). The associated risk of malignancy in this benign category is 0-3%.

3. AUS or FLUS: This is a heterogeneous category that is often associated with a compromised specimen (scanty, obscuring blood…). The findings in this category include:

a. Scanty cellular samples but predominantly microfollicular
b. Atypical cyst lining cells
c. Atypical lymphoid infiltrate
d. Features mixed between nodular hyperplasia and follicular neoplasm
e. Focal features suggestive of papillary carcinoma (nuclear grooves, enlarged nuclei with pale chromatin, alterations in nuclear contour and shape) in an otherwise predominantly benign-appearing sample, especially in patients with Hashimoto thyroiditis or with abundant colloid and other benign follicular cells.

The associated risk of malignancy in this category varies from 5 to 15%. An AUS or FLUS interpretation should not be overused and a rate of not more than 7% of all thyroid FNAs has been suggested. Generally, a close follow-up with repeat FNA in 3 to 6 months is recommended. Often a repeat FNA will allow a more specific diagnosis in most cases. If the repeat FNA remains atypical a thyroid lobectomy is recommended.

4. Follicular neoplasm or Suspicious for follicular neoplasm: Aspirate material shows significant architectural or cytologic atypia that raises the possibility of a follicular neoplasm. The associated risk of malignancy varies from 15 to 30%, and after resection up to 35% of TNs in this category prove not to be neoplasms. The Hürthle cell variant is reserved for cases showing exclusively Hürthle cells, and from 16 to 25% of the cases prove not to be neoplastic by histology. In most cases it is not possible to separate a follicular adenoma from follicular carcinoma by FNA, and a lobectomy is necessary for a definitive diagnosis.

5. Suspicious for malignancy: This category excludes cases suspicious for a follicular or Hürthle cell neoplasm. Suspicious and malignant needle aspirates account for 3-7% of all thyroid FNAs, and the associated risk of malignancy in this suspicious category is 60-75%. An FNA is suspicious for a papillary carcinoma (PC) if it shows some cellular features of PC but it is not sufficient for a firm diagnosis. An aspirated material is suspicious for a medullary carcinoma if the atypical cells contain cytoplasmic azurophil granules and a needle aspirate is suspicious for lymphoma if it shows atypical lymphoid cells that raise the possibility of a non-Hodgkin lymphoma. Therefore, when a FNA is suspicious for a primary thyroid carcinoma a near total thyroidectomy or a lobectomy is recommended for futher histologic confirmation.

6. Malignant: Included in this category are papillary, medullary, poorly differentiated, anaplastic and metastatic carcinomas and lymphoma. The reported false-positive rates in this category vary from 1 to 3%.

Cytologic Findings

A. Non-diagnostic category is characterized by non-diagnostic or inadequate cellular material.

B. Benign lesions

1. Benign Colloid Nodule

Solitary prominent colloid nodules in multinodular colloid goiters are the most common lesions in the general population. Histologically, the lesion consists of large thyroid follicles distended with thick colloid material. (Fig.1.1). FNA of a colloid nodule yields sheets of benign follicular epithelial cells in honeycomb arrangement and abundant thick colloid material (Figs.1.2 and 1.3). Clusters of slightly hyperplastic Hürthle cells may

be present. By cytology it may not be possible to separate a benign colloid nodule from a **macrofollicular adenoma**, as both lesions show abundant, thick colloid and similar follicular cells in FNAs.

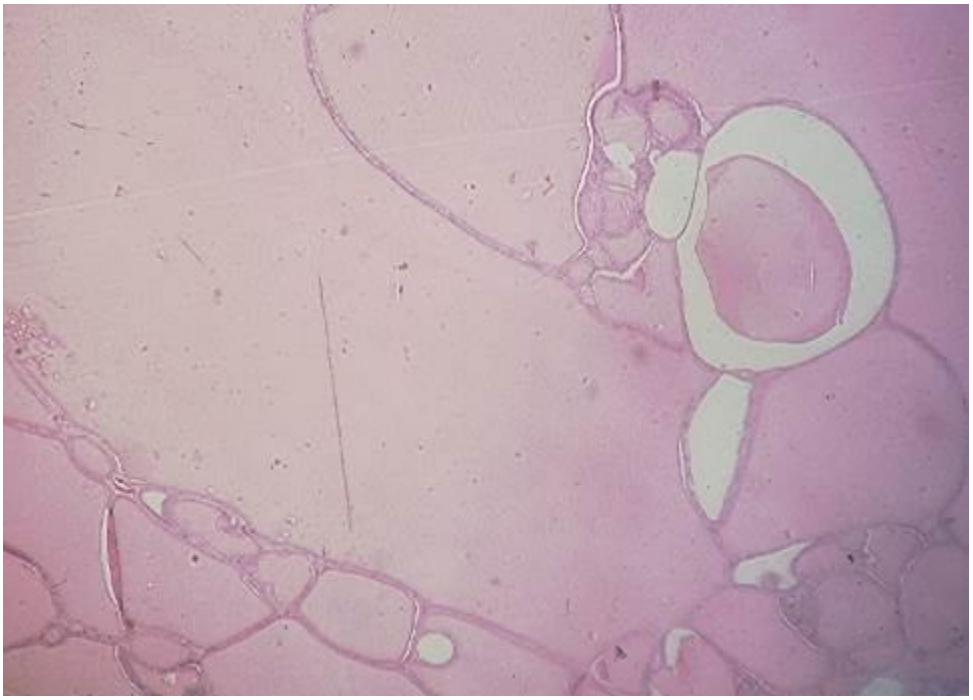
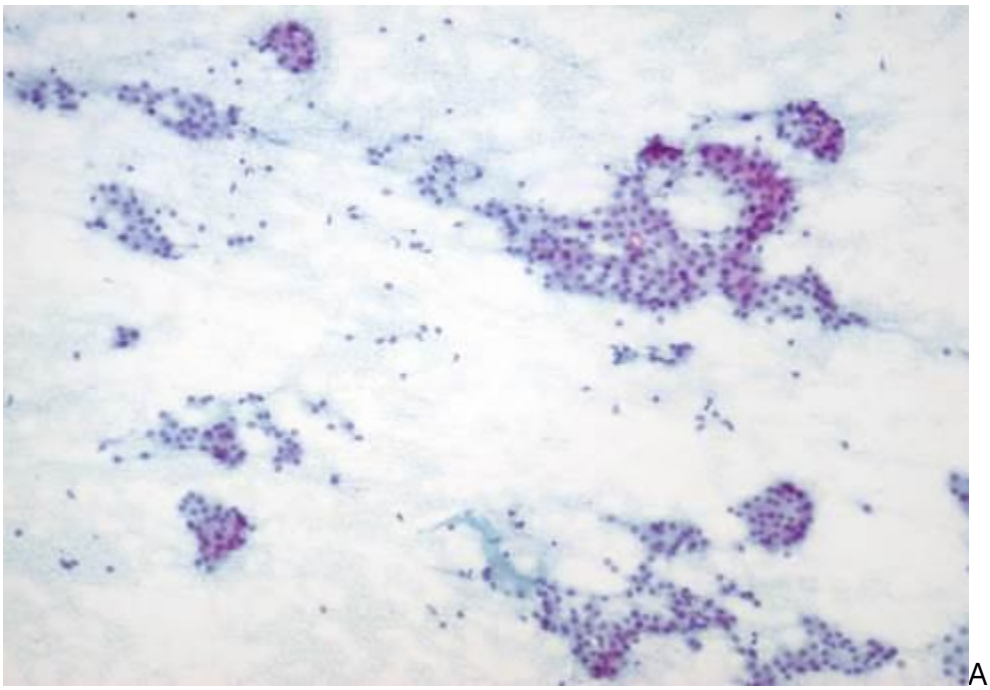


Fig.1.1. Histology of a multinodular colloid goiter showing large thyroid follicles distended with thick colloid. (HE)



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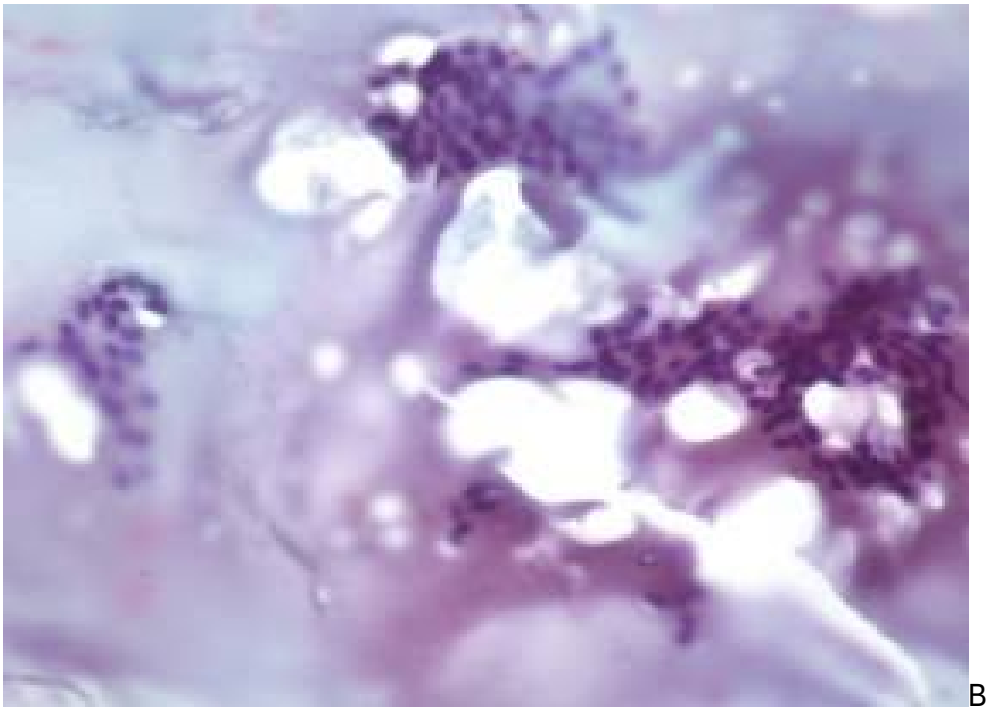

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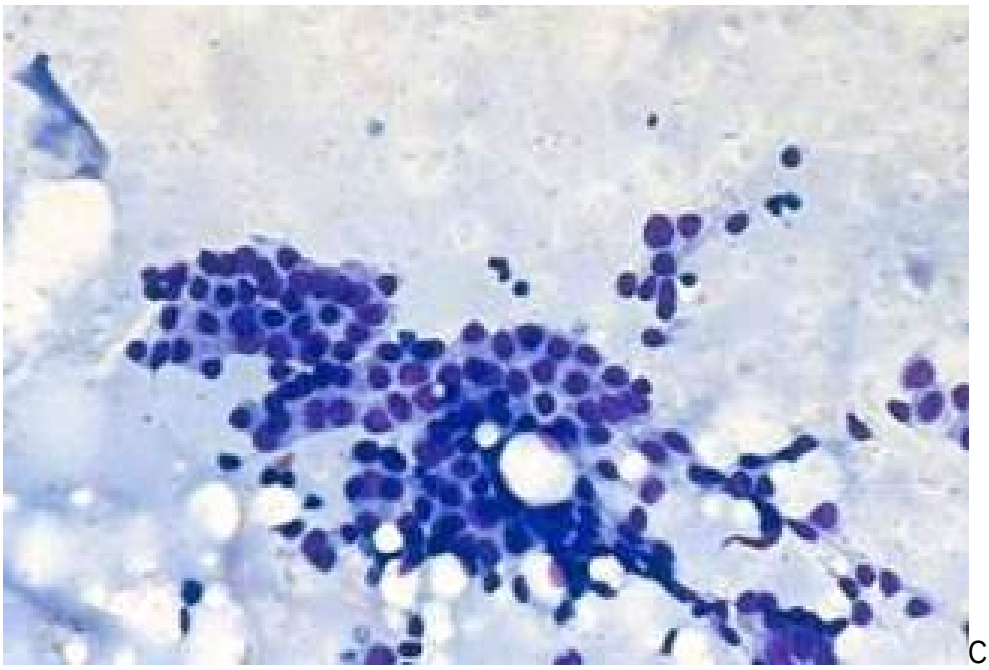

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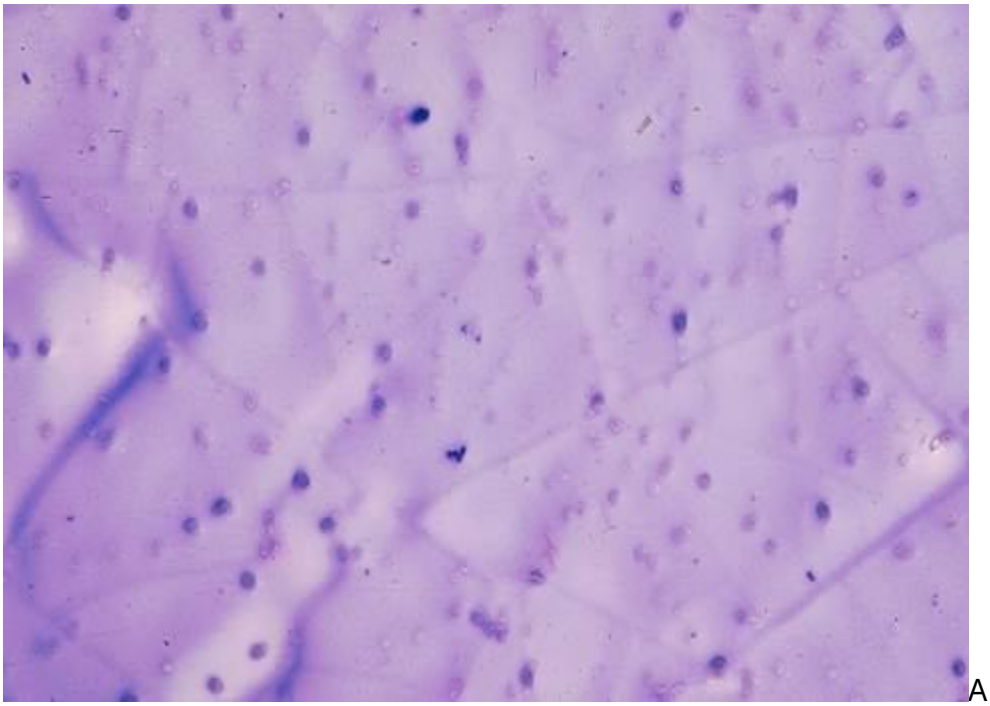
Fig.1.2. FNA cytology of benign colloid nodule. Irregular sheets and fragments of follicular epithelium in honeycomb arrangement admixed with variable amounts of colloid. (A, B, CP, Pap; C, CP, DQ).



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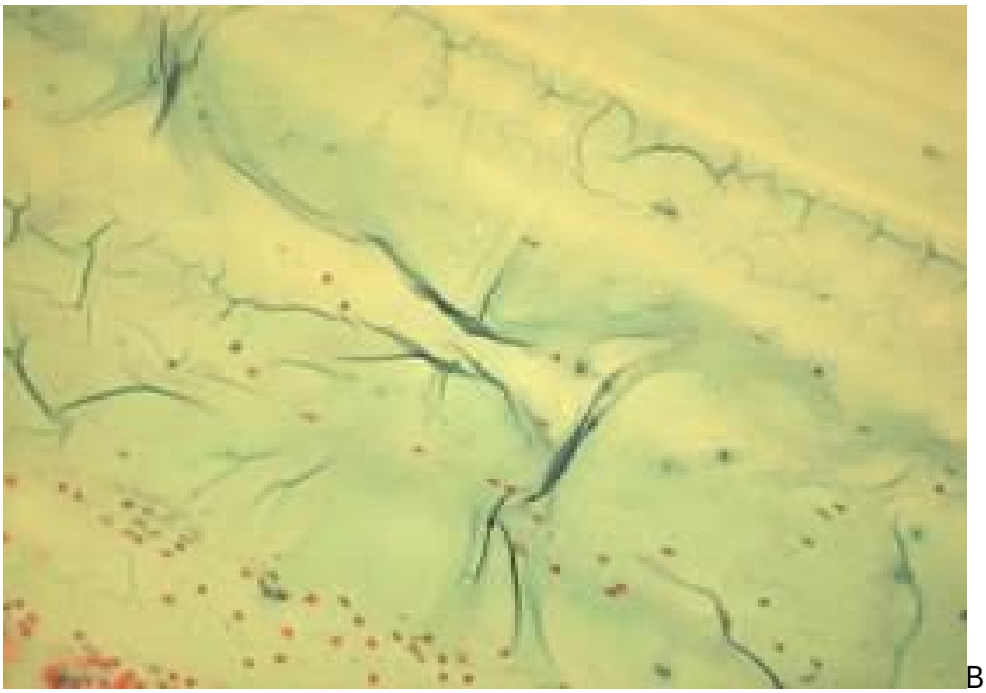

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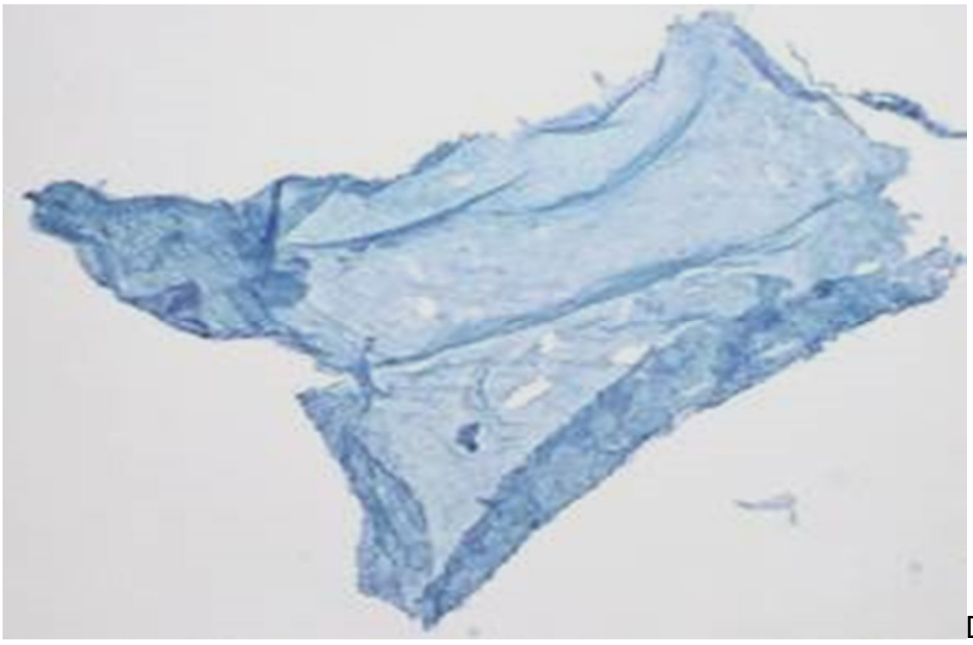
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Fig. 1.3. The ‘many faces’ of colloid: A, B. Cracking pattern. (A, CP, DQ; B, CP, Pap). C. Bubble pattern. (CP, DQ). D. “Wet tissue paper” pattern. (LBP, Pap).

2. Thyroiditis

Acute thyroiditis is clinically evident and it is not a usual target for FNA. It shows in FNA necrotic debris and abundant polymorphonuclear leukocytes.

Hashimoto thyroiditis and subacute thyroiditis commonly have fairly distinctive clinical findings. Rarely, these lesions may present as a nodular lesion mimicking a thyroid neoplasm.

Hashimoto thyroiditis is characterized by the presence of numerous benign lymphoid cells admixed with benign follicular cells and Hürthle cells that may have a bizarre morphology. (Fig.1.4).

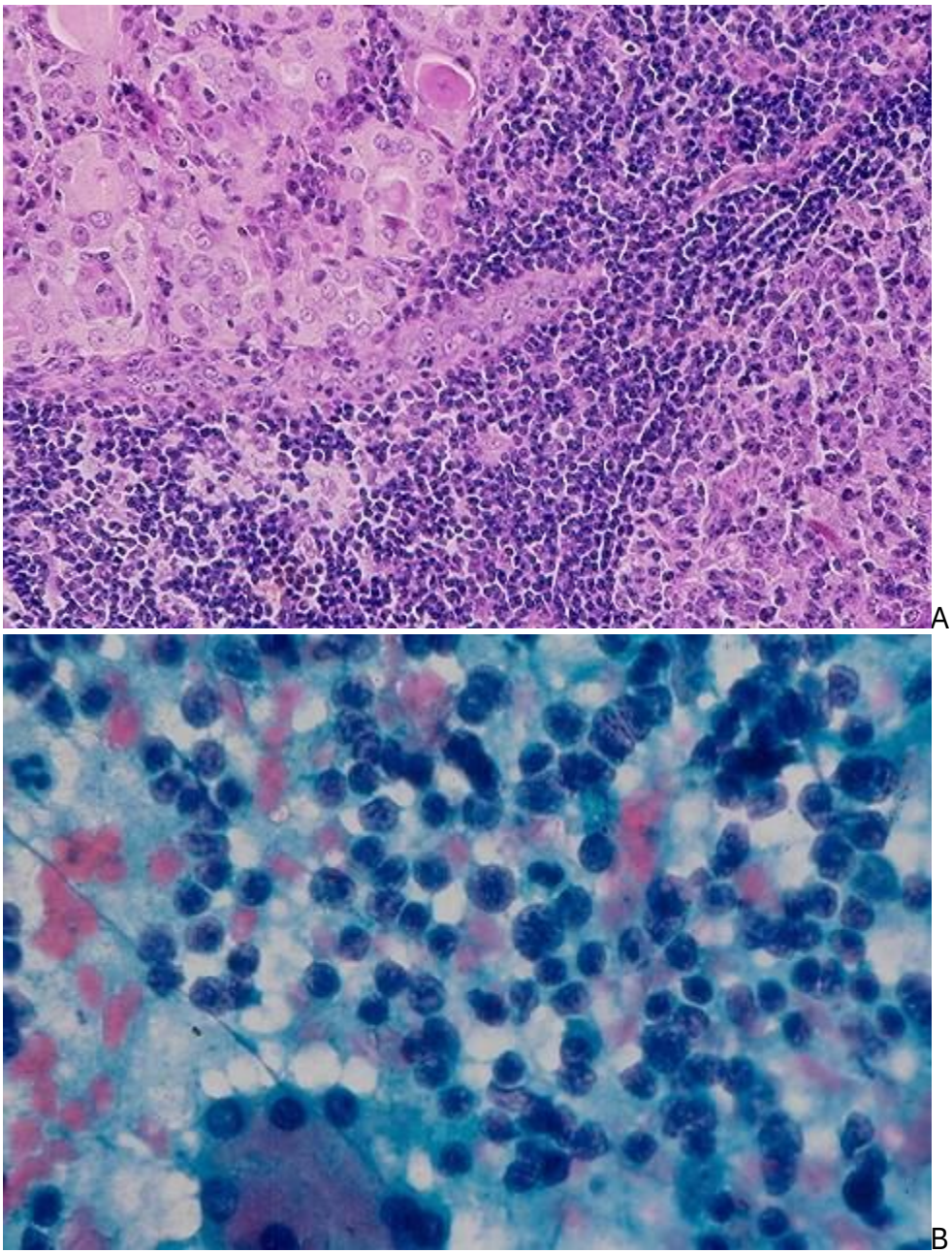
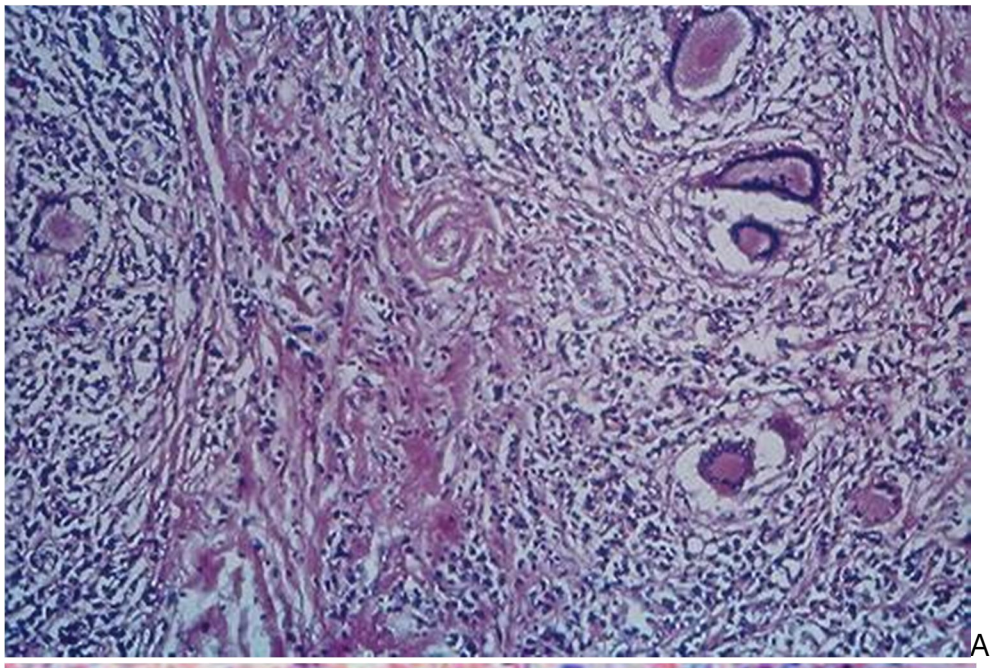


Fig.1.4. Hashimoto thyroiditis: A. Histology of Hashimoto thyroiditis. (HE). B. Hashimoto thyroiditis showing in FNA abundant lymphoid cells and a Hürthle cell cluster. (CP, Pap).

Subacute thyroiditis may yield clustered epithelioid cells, scattered lymphocytes and a few multinucleated giant cells containing up to one hundred nuclei. (Fig.1.5).

It should be born in mind that Hashimoto thyroiditis may harbor hyperplastic follicular and Hürthle cell nodules, and these two nodules are cytologically indistinguishable from a cellular follicular neoplasm and a Hürthle cell neoplasm, respectively. Therefore, additional FNAs around the TN are important to detect associated thyroid lesions. In difficult cases, surgical excision of the TN is required for histologic study.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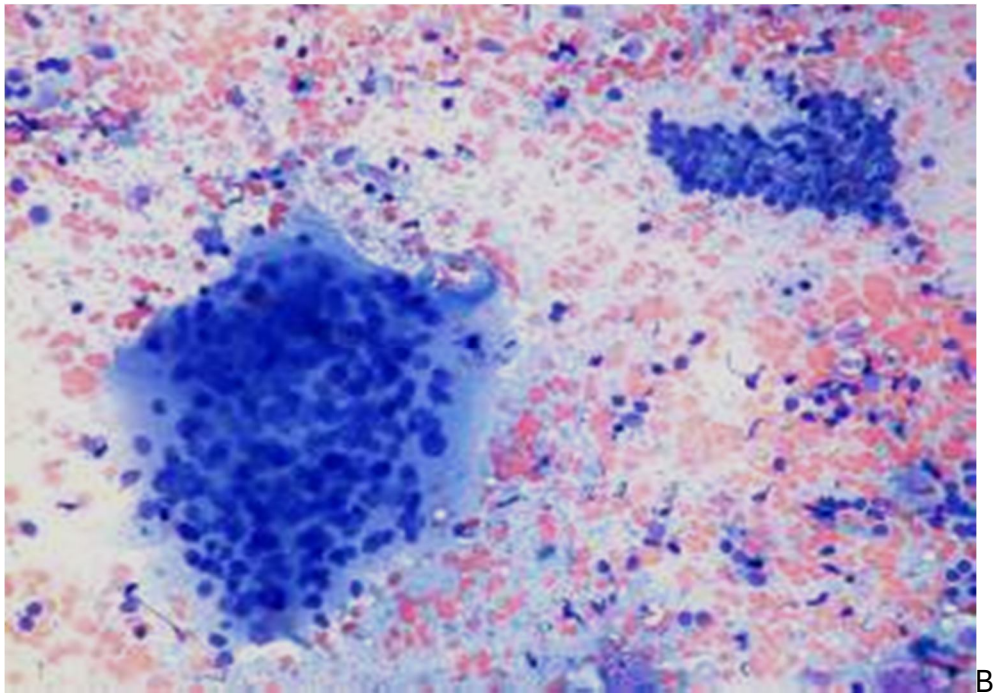
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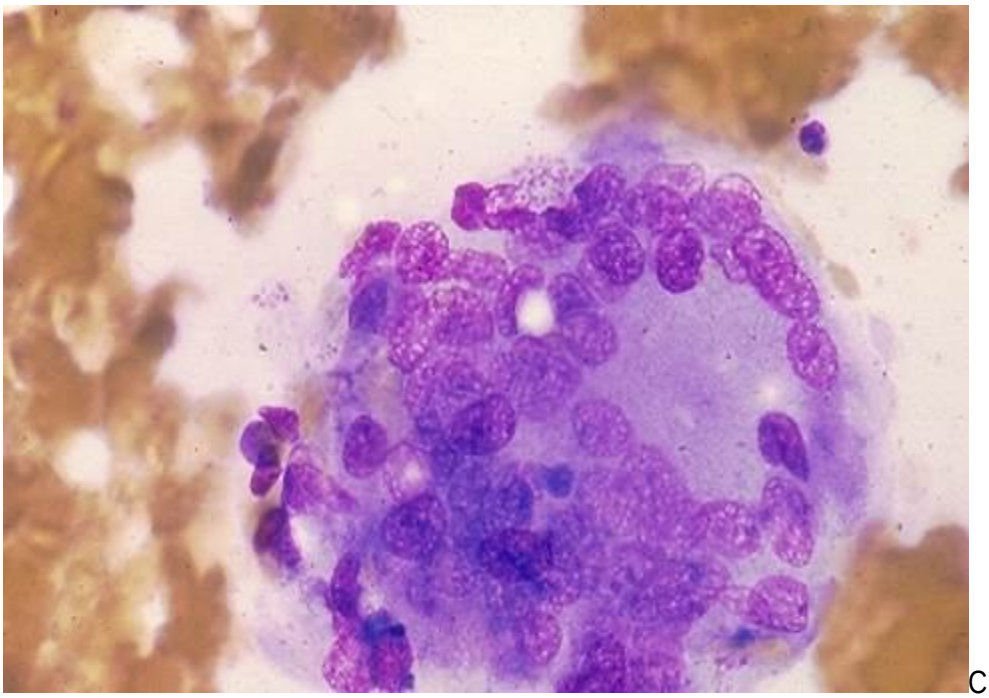
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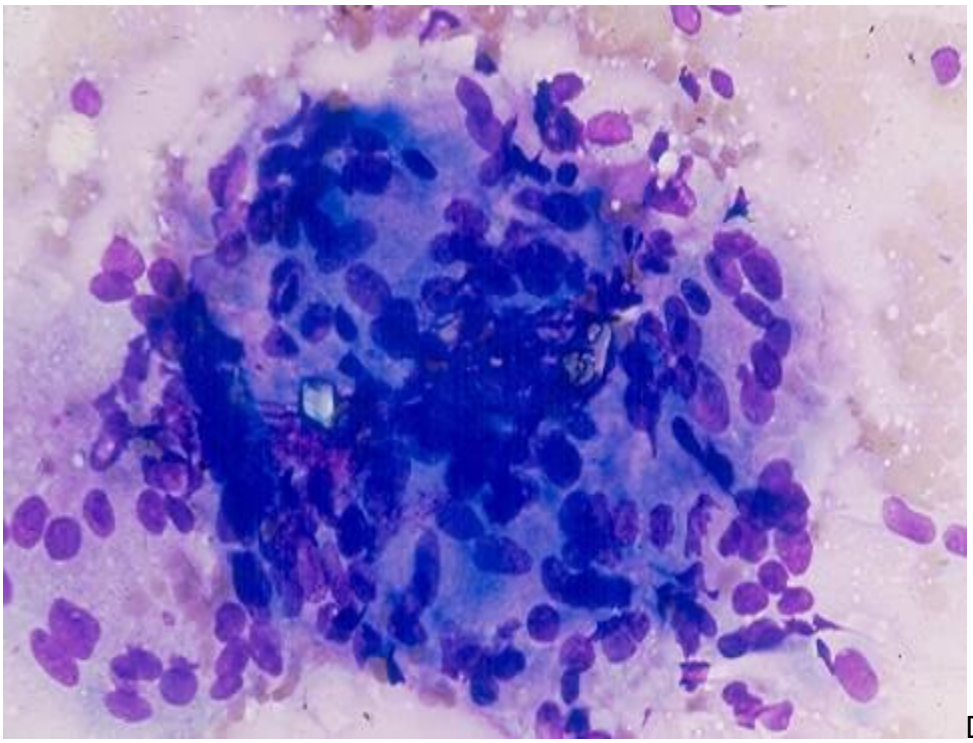
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Fig.1.5. Subacute thyroiditis: A. Histology of subacute thyroiditis. (HE). B. A multinucleated giant cells and a sheet of follicular epithelial cells. C. A large multinucleated giant cell. D. A syncytial cluster of epithelioid cells with carrot-shaped nuclei, seen in FNA of a subacute thyroiditis. (CP, DQ).

C. Indeterminate lesions including Follicular lesion of undetermined significance (FLUS) or Atypia of undetermined significance (AUS), Follicular neoplasm/Suspicious for Follicular neoplasm and Oncocytic (Hürthle cell) neoplasms

1.FLUS or **AUS**: the aspirated material is polymorphous rather than monomorphous both in cytology (i.e. small, large and oncocytic) and architecture (flat honeycomb sheets, microfollicular and crowded syncytial groups). Additional cytologic findings in AUS and FLUS lesions were previously mentioned (page 15).

2. Follicular neoplasm and **Suspicious for follicular neoplasm.** A micro-follicular adenoma and a low-grade follicular carcinoma are usually cytologically similar to a hyperplastic microfollicular nodule in a multinodular colloid goiter. Therefore, additional FNAs around the TN are needed to detect other associated thyroid lesions. In difficult cases, surgical resection of these lesions is recommended for histologic confirmation. FNA of a microfollicular adenoma commonly reveals abundant follicular cells in syncytial clusters, microfollicles and small monolayered sheets. Individual cells are monomorphous with scanty, ill-defined cytoplasm and round or slightly oval nuclei with regular nuclear contours, compact chromatin and inconspicuous or occasionally prominent nucleoli. (Figs.1.6 and 1.7).

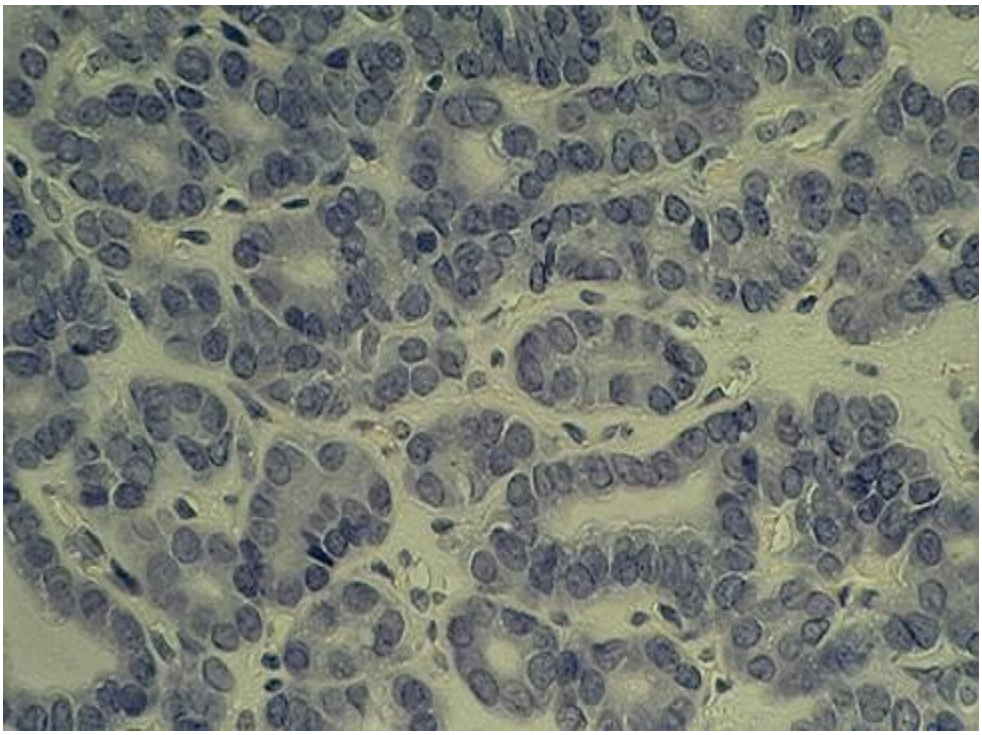
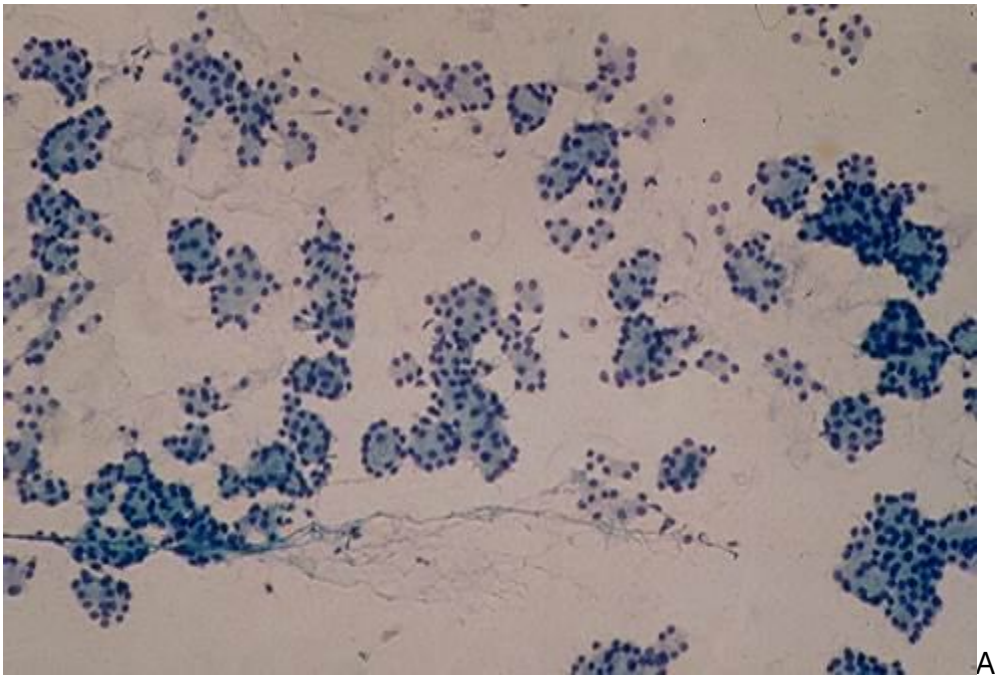


Fig.1.6. Histology of a thyroid microfollicular adenoma. (HE)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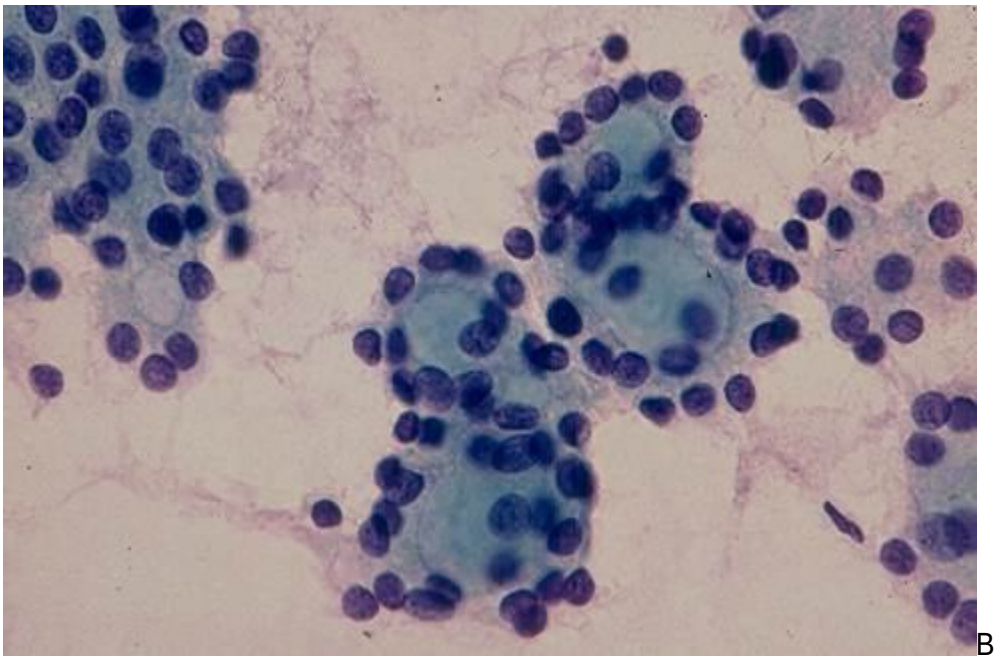
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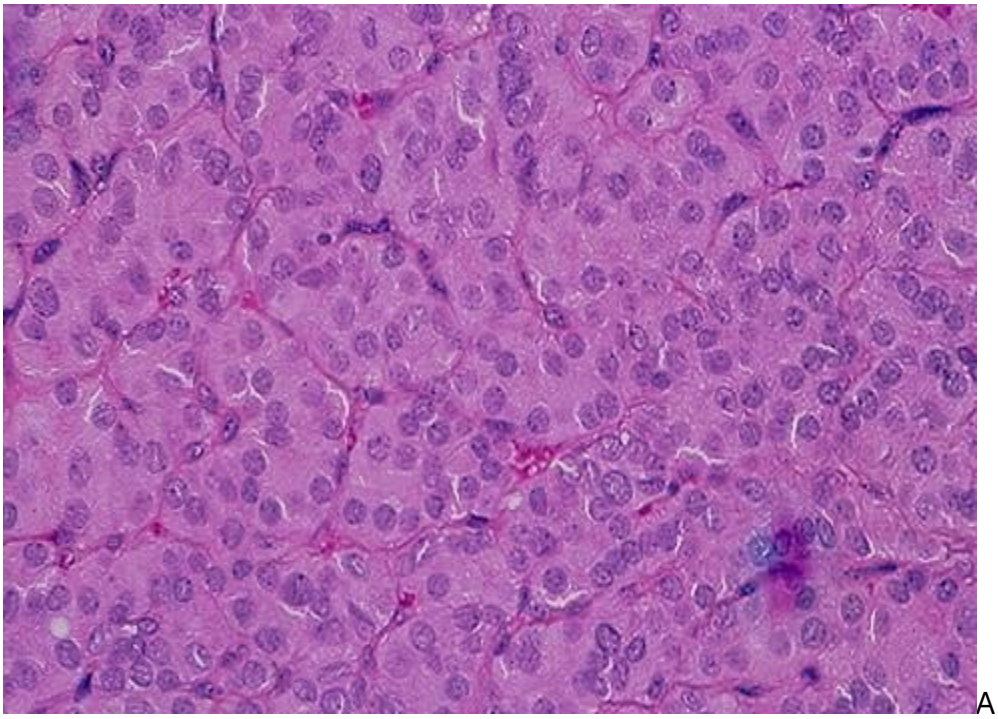
Fig.1.7. A, B. Microfollicular adenoma showing in FNA abundant follicular cells with round nuclei arranged in acini and small monolayered sheets. (CP, Pap).

3. Oncocytic (Hürthle Cell) Lesions

Diagnosis of oncocytic lesions is a challenge in thyroid cytology. A hyperplastic oncocytic nodule in a Hashimoto thyroiditis or in a multinodular goiter is cytologically similar to an oncocytic (Hürthle cell) neoplasm. The presence of numerous lymphocytes may indicate a hyperplastic nodule in Hashimoto disease and a large amount of thick colloid material is

suggestive of a multinodular goiter. These two associated thyroid lesions may be detected by additional FNAs around the TN under investigation. Oncocytic adenoma and carcinoma usually show similar cytologic findings characterized by sheets, clusters and single polygonal epithelial cells, which have abundant, granular, eosinophilic or basophilic cytoplasm, oval nuclei with regular nuclear contours and conspicuous or inconspicuous nucleoli. (Figs. 1.8 and 1.9). If an oncocytic tumor is suspected by FNA, surgical excision is indicated for histologic evaluation. In one large series 13% of Hürthle cell lesions were malignant.

The presence of syncytial clusters of oncocytic cells with or without prominent nucleoli and many naked tumor cell nuclei has been reported to be cytologic features of oncocytic carcinomas.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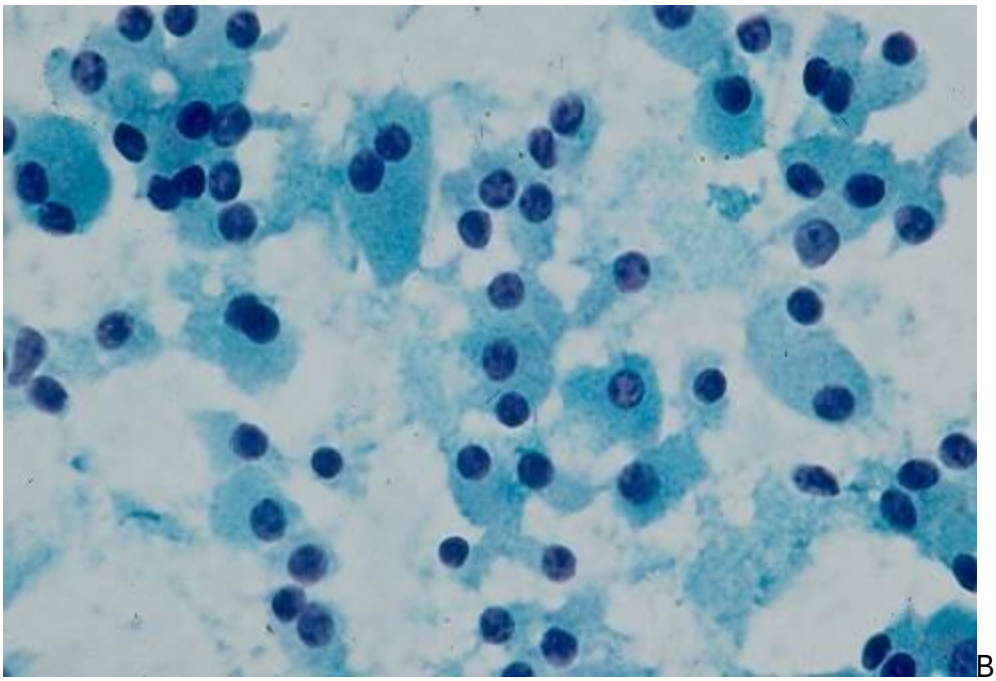

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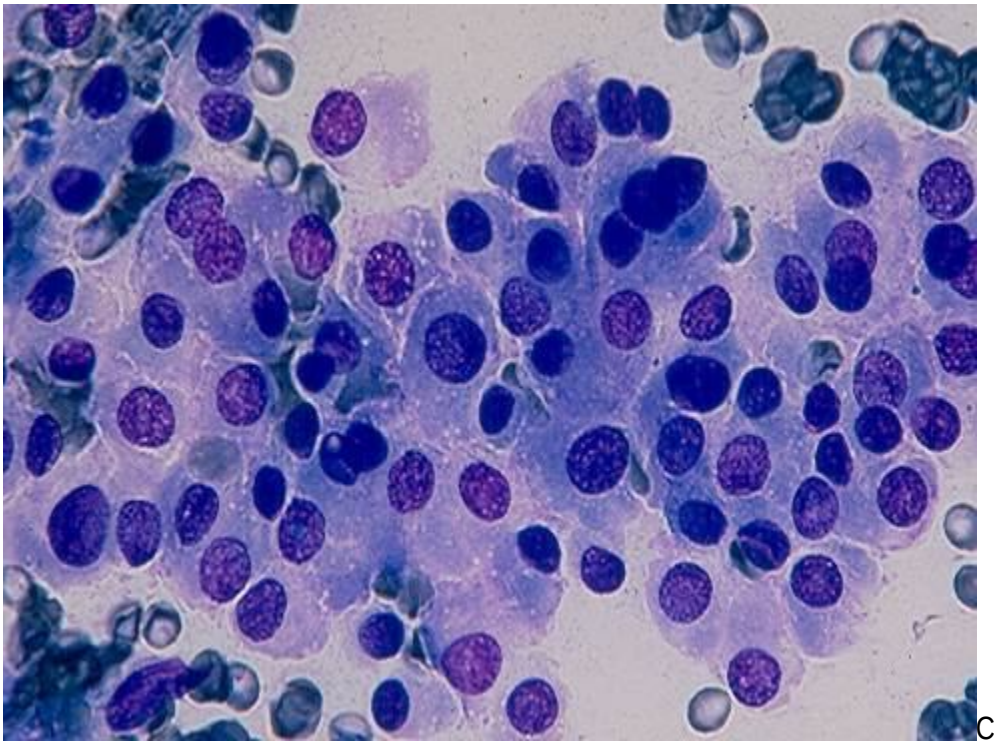
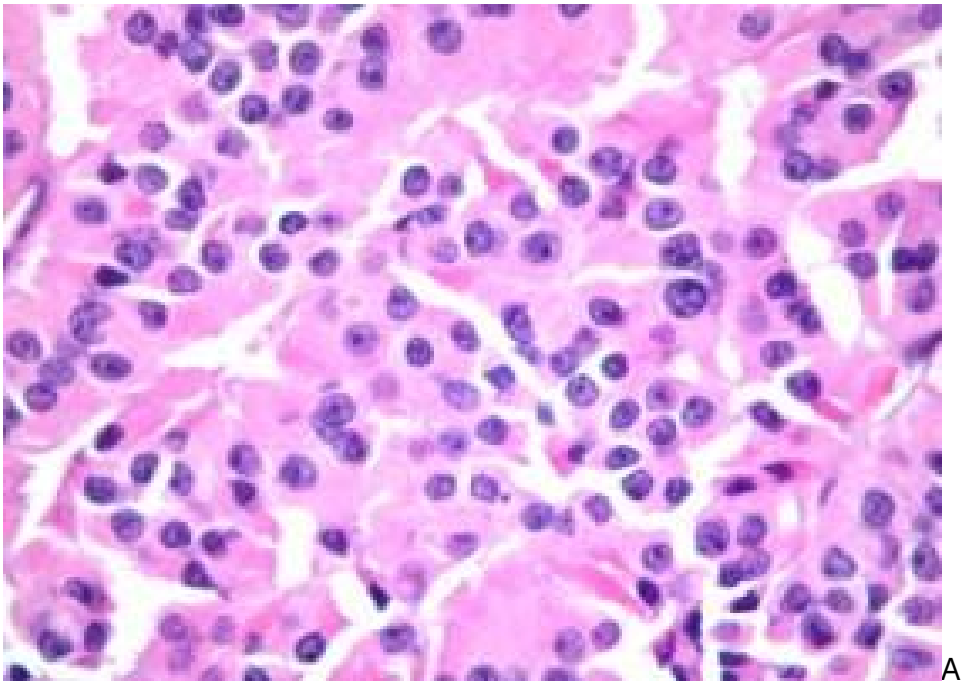


C

Fig.1.8. Hürthle cell adenoma. A. Histology of the lesion. (HE). B, C. FNA showing Hürthle cells singly and in loose clusters or monolayered sheets. (B, CP, Pap; C, DQ).



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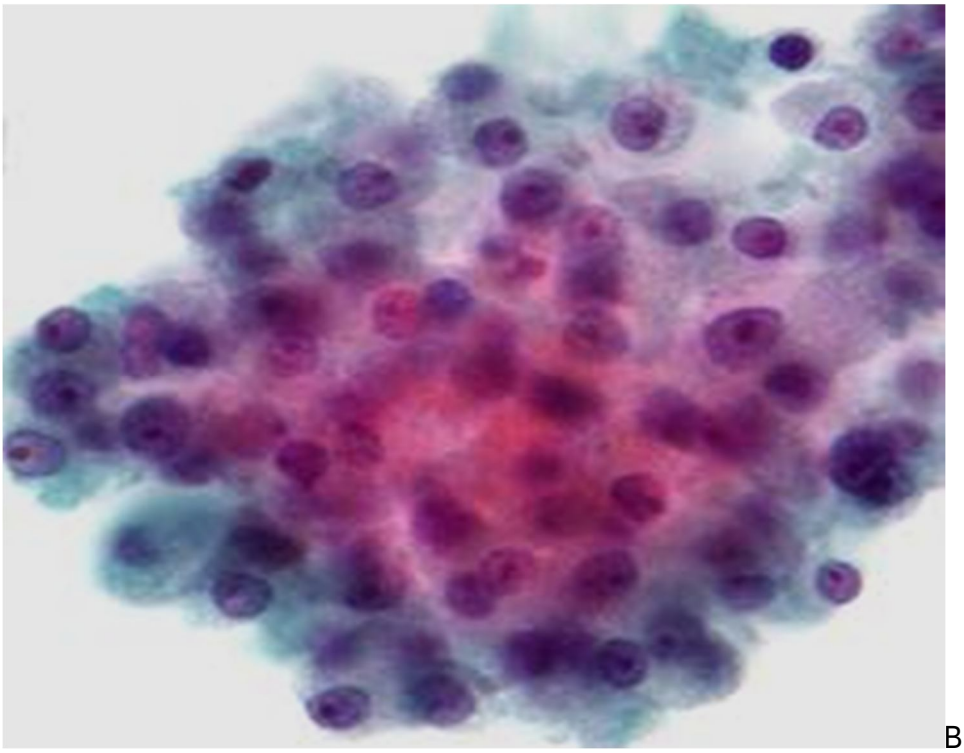

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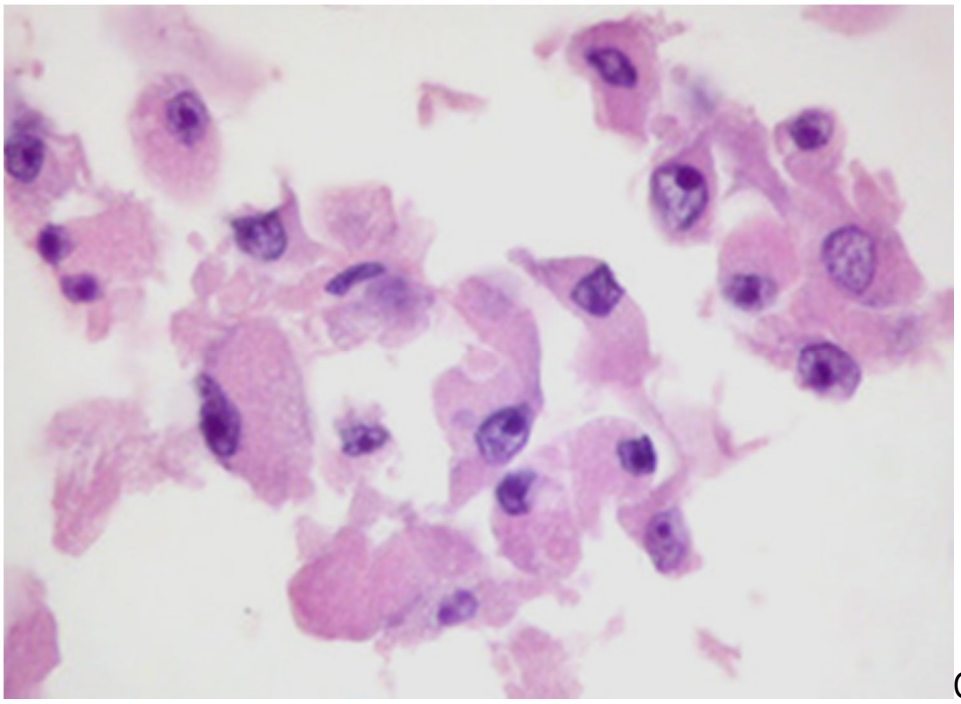
 C

Fig.1.9. Hürthle cell carcinoma. A. Histology of the tumor. (HE). B, C. FNA of the lesion showing a cohesive sheet of atypical oncocytes (B, CP, Pap) and dispersed atypical oncocytes (C, LBP, Pap).

D. Malignant lesions and Suspicious for malignant lesions

This group includes **papillary, high-grade follicular, insular, medullary and anaplastic carcinomas** and **lymphoma.** These lesions commonly show distinctive cytologic features that permit a correct identification in the majority of cases. An insular carcinoma or poorly differentiated carcinoma yields small cells similar to those of a high-grade microfollicular carcinoma. If the cellular findings are not characteristic for a given type of thyroid carcinoma the case under evaluation should be reported as suspicious for malignancy with a comment regarding its histologic type.

1. Papillary carcinoma

Papillary carcinoma (PC) is the most common thyroid malignant tumor and accounts for about 70% of all thyroid solid cancers. PCs may be divided histologically into conventional PC with well-formed papillae with fibrovascular cores and PC variants that are composed of micro- and macrofollicular, oncocytic, trabecular, tall-cell, columnar-cell and diffuse sclerosing variants. The tumor cells nuclei display nuclear crowding and overlapping, nuclear grooves and intranuclear cytoplasmic inclusions. (Fig.1.10).

1.1. Conventional PC is characterized in FNA by the presence of thick or thin papillary tissue fragments with fibrovascular cores, sheets of tumor cells showing focal nuclear

crowding and overlapping, irregular nuclear contours, nuclear grooves (NG). (Fig.1.11) and intranuclear cytoplasmic inclusions (INCI). Psammoma bodies and metaplastic squamous cells may also be present. (Fig.1.12). These nuclear changes are recognized with less difficulty in Papanicolaou-stained cell samples, but they may be difficult to identify in cell samples stained with the Romanowsky staining method. However, a presence of minute true papillary tissue fragments with fibrous vascular cores even without the identifiable above-mentioned nuclear changes is indicative of a PC. These papillary tissue fragments should be differentiated from thick and large follicular epithelial cell clusters with vascular transgression that may be found in FNA from different types of non-papillary epithelial neoplasm of the gland.

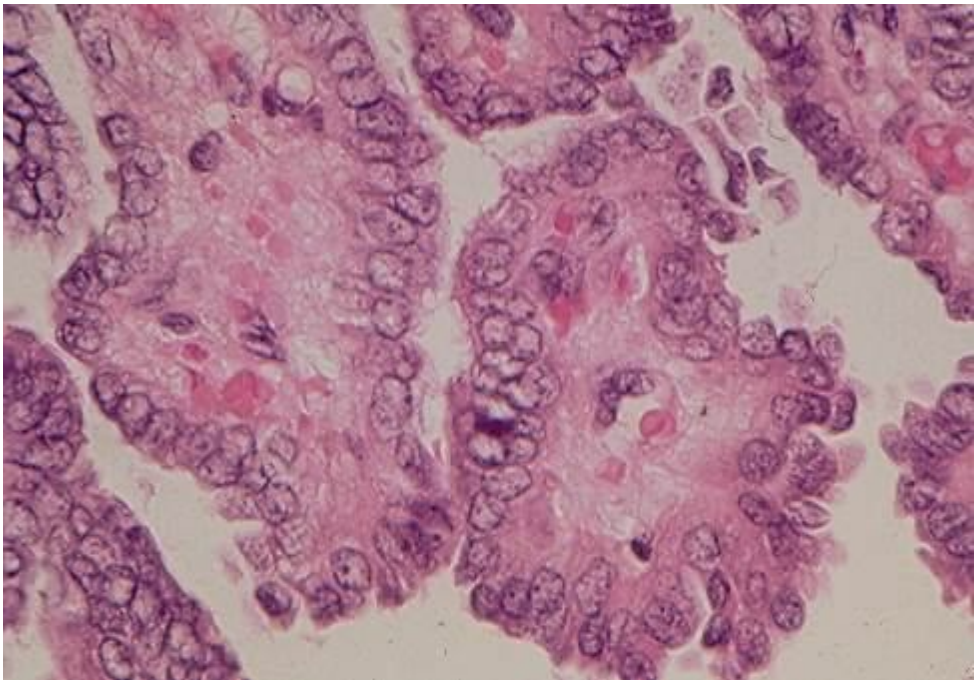
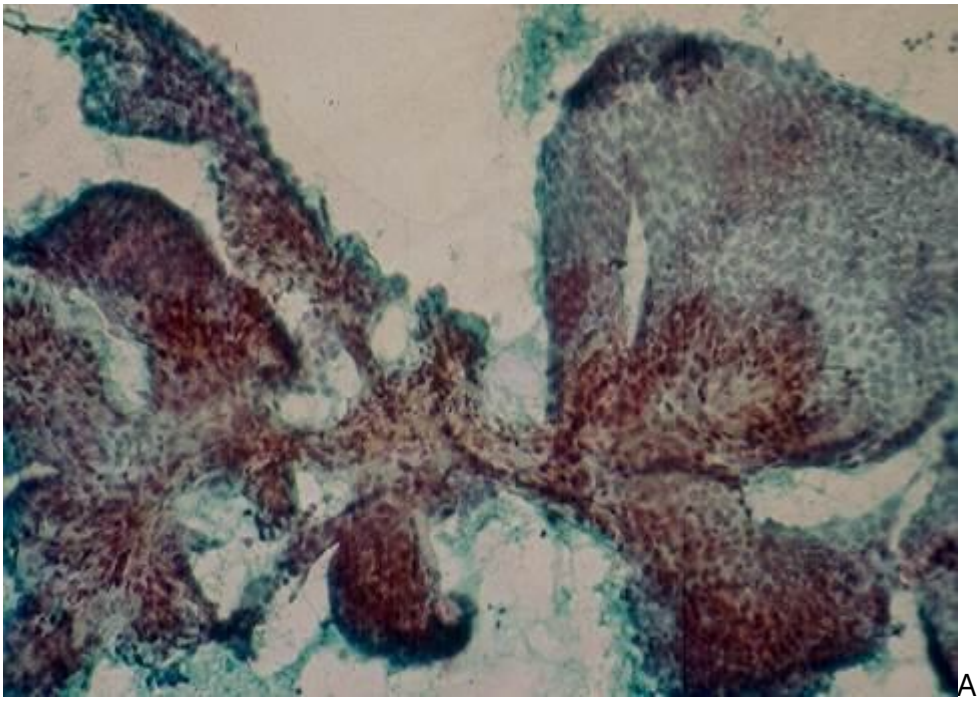


Fig.1.10. Histology of a conventional papillary carcinoma of the thyroid showing fibrovascular cores covered with a single layer of epithelial cells displaying nuclear crowding and overlapping. Nuclear grooves are present in some tumor cells. (HE)



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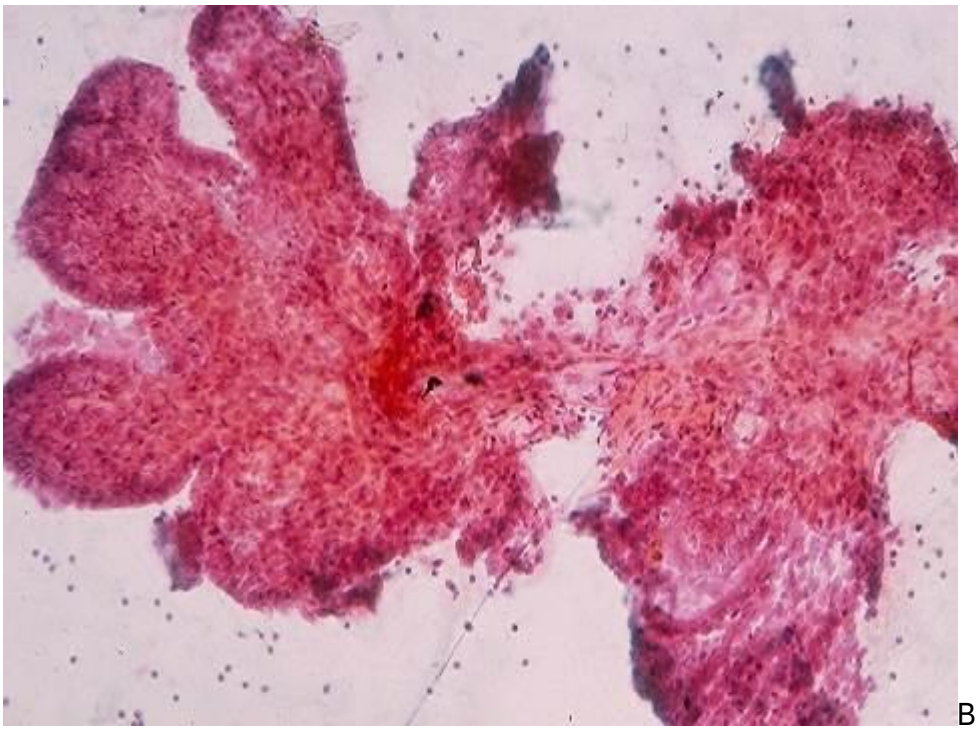

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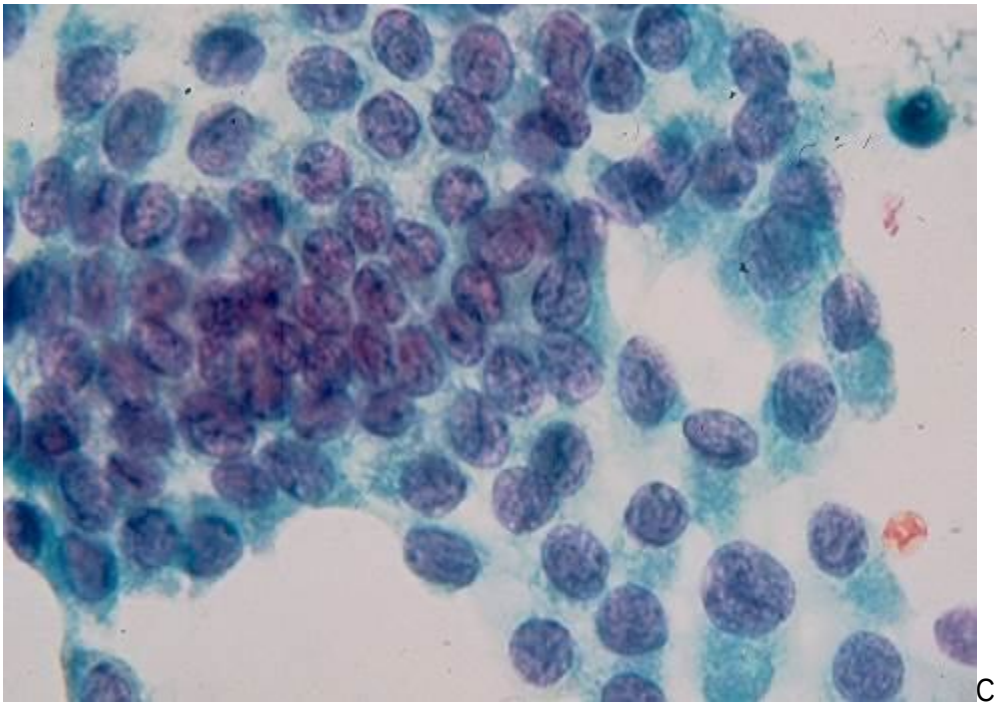
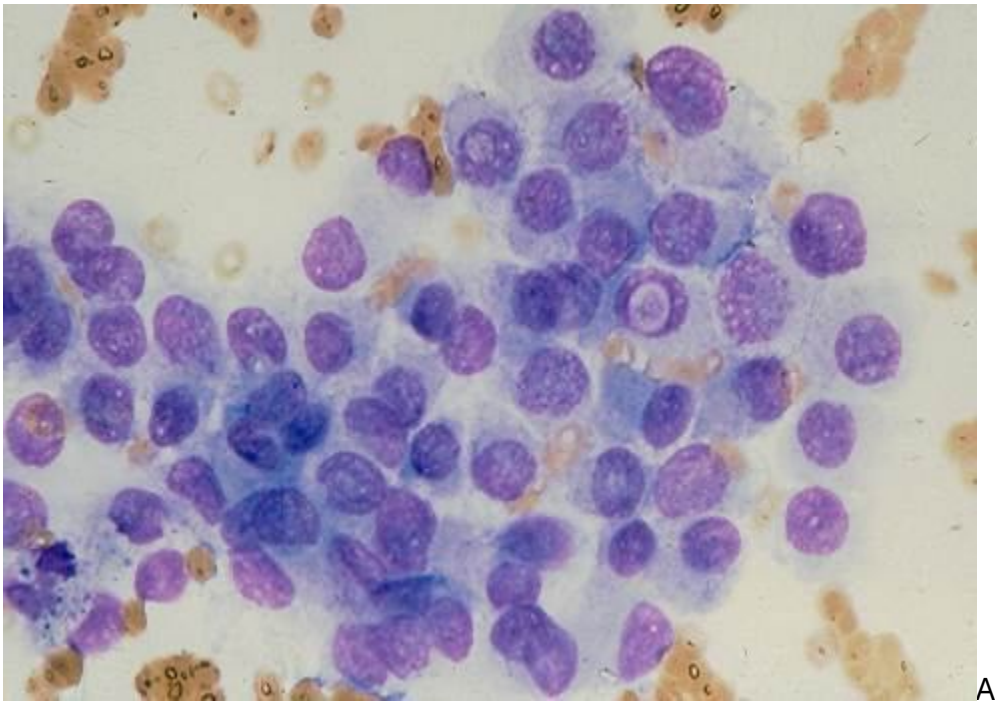


C

Fig.1.11. FNA cytology of conventional thyroid PC: A. Thin branching papillary tissue fragment with fibrovascular core. B. Thick branching papillary tissue fragment with fibrovascular core. C. A sheet of tumor cells showing focal nuclear crowding with several cells displaying nuclear grooves. (CP, Pap)



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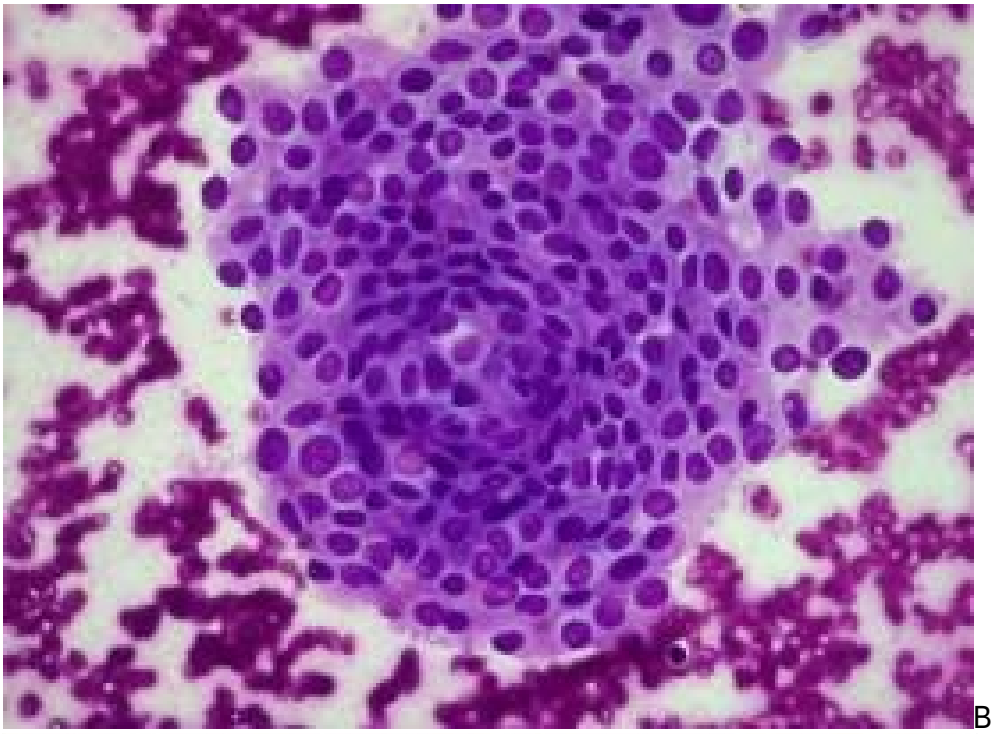

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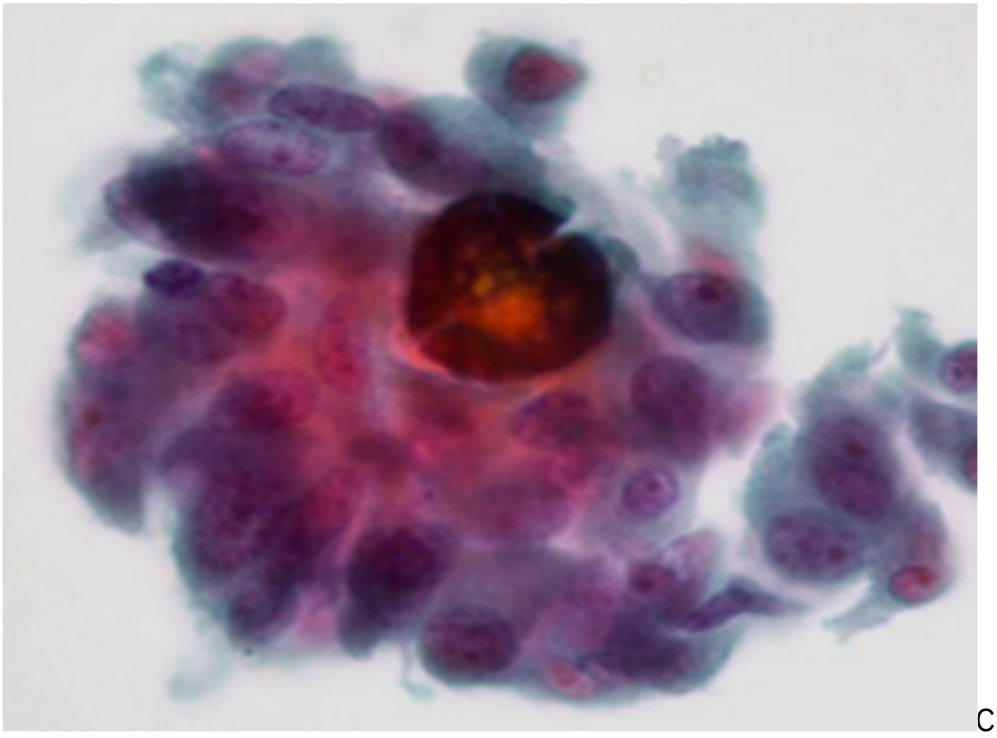

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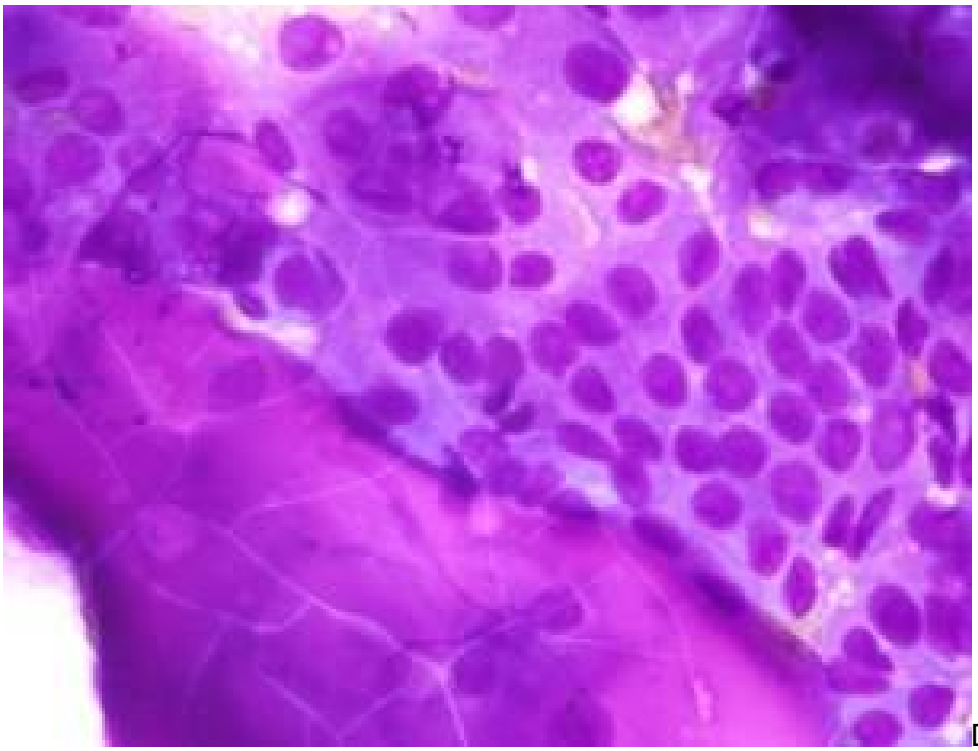
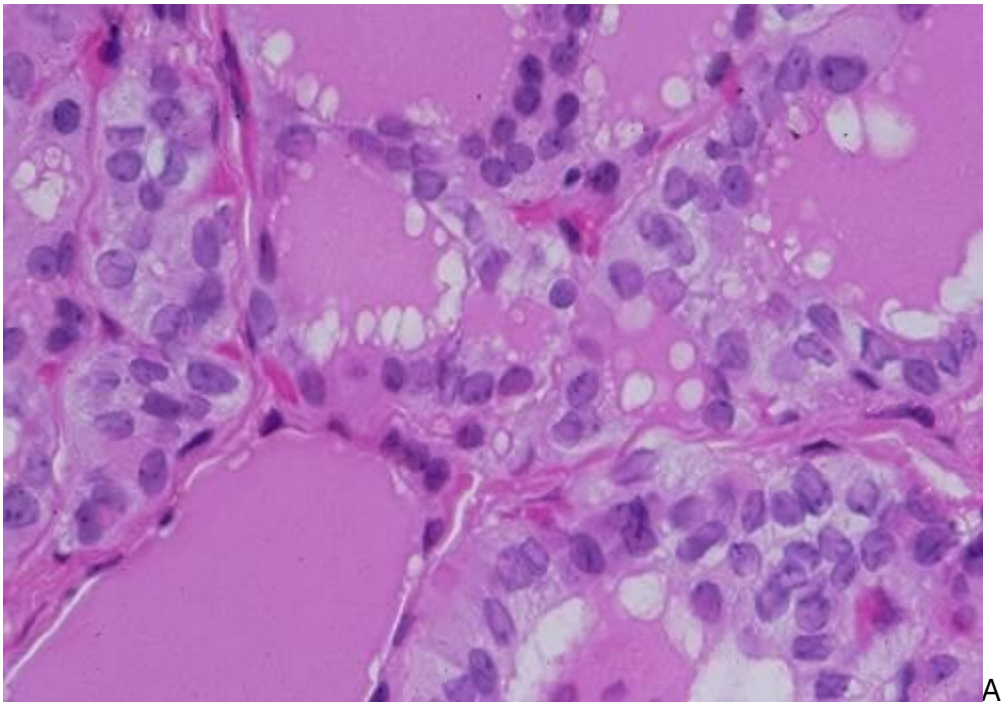
 D

Fig.1.12. FNA cytology of conventional thyroid PC: A. Loose sheets of tumor cells showing focal nuclear crowding. A few cells with INCIs are noted. (CP, DQ). B. Striking squamoid 'whirling'. (CP, DQ). C. A psammoma body in a cell cluster. (CP, Pap). D. A sheet of metaplastic squamous cells with adjacent thick colloid. (CP, MGG)

1.2. Micro- and macrofollicular PCs constitute a diagnostic challenge. A microfollicular PC may show in FNA follicular cells forming acini similar to those seen in a cellular microfollicular lesions, and a macrofollicular PC may be easily mistaken for a macrofollicular adenoma or a benign colloid nodule cytologically, as nuclear changes characteristic for a thyroid PC may not be seen. (Fig.1.13).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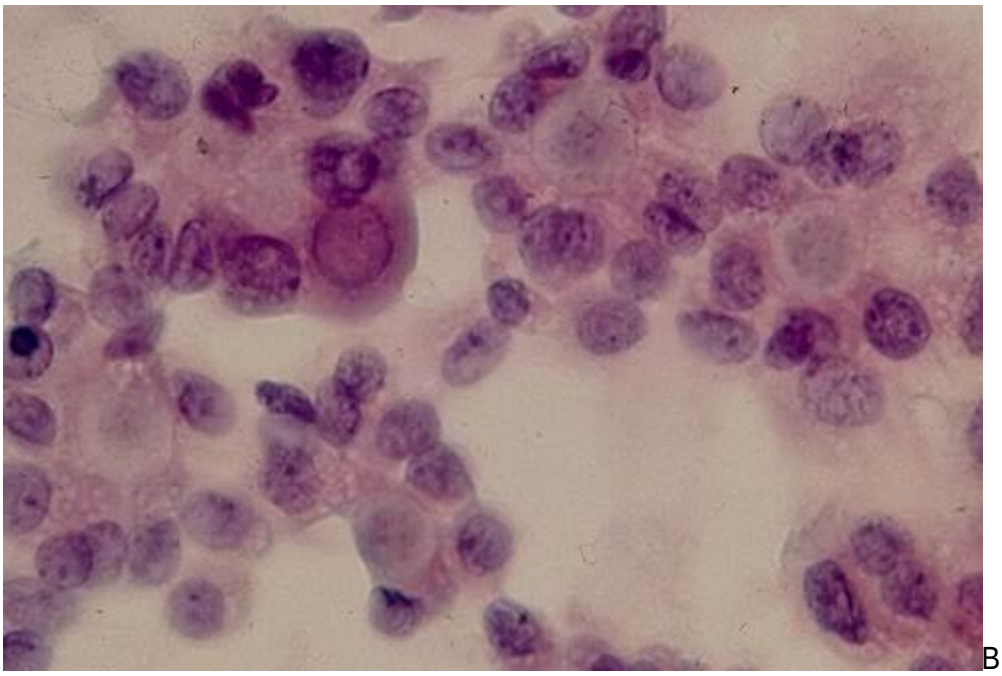

B

Fig.1.13. A. Histology of a thyroid PC, microfollicular variant. B. Tumor cells in acinar arrangement with occasional cells showing INCIs in FNA. (CP, Pap).

1.3. Other PC variants

Tall-cell PC is characterized by the presence of tall tumor cells with well-defined, granular cytoplasm and nuclei with NGs and single or multiple INCIs, making at least 30% of the aspirated cells. (Fig.1.14).

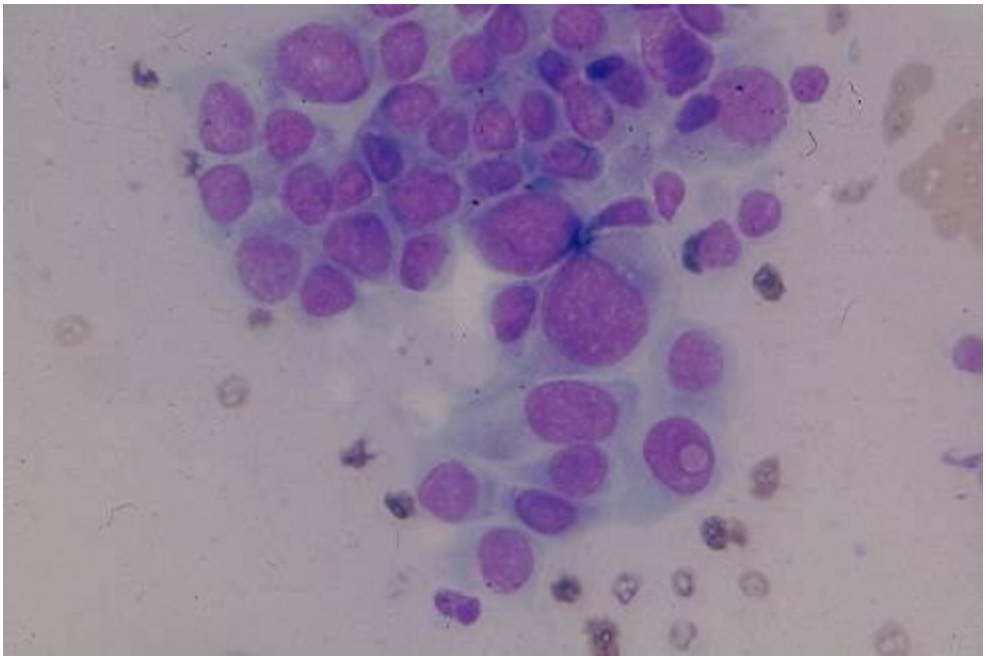


Fig.1.14. FNA cytology of thyroid PC, tall cell variant showing pleomorphic tumor cells with some cells having an elongated configuration and cytoplasmic tails. A tumor cell with an INCI is present. (CP, DQ).

Columnar-cell PC shows no classic nuclear features of thyroid PC, but a presence of clusters of columnar cells with palisading nuclei and absence of classic nuclear changes of thyroid PC are cytologic features of this neoplasm. (Fig.1.15).

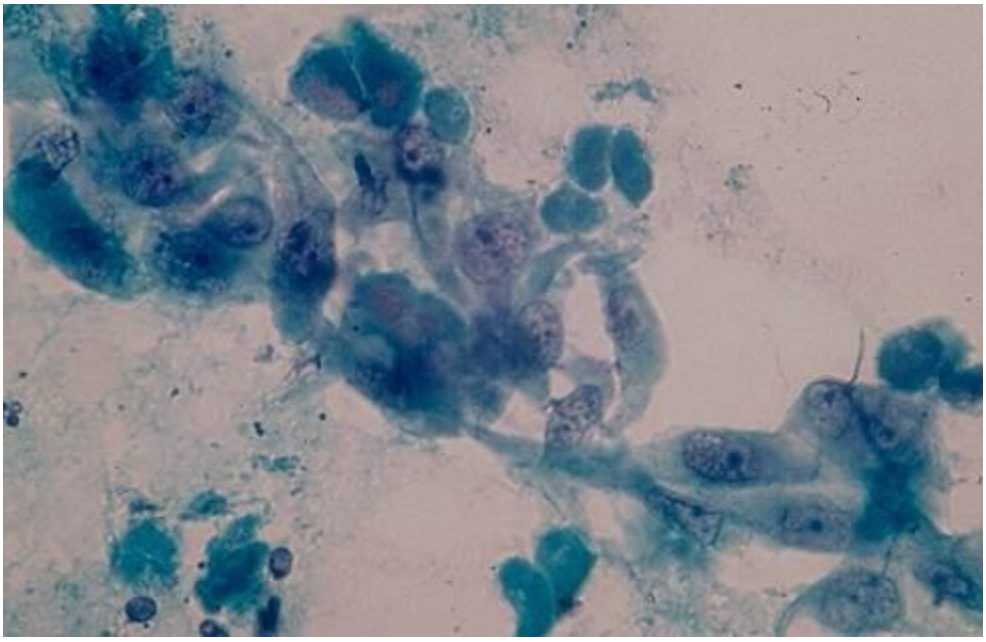
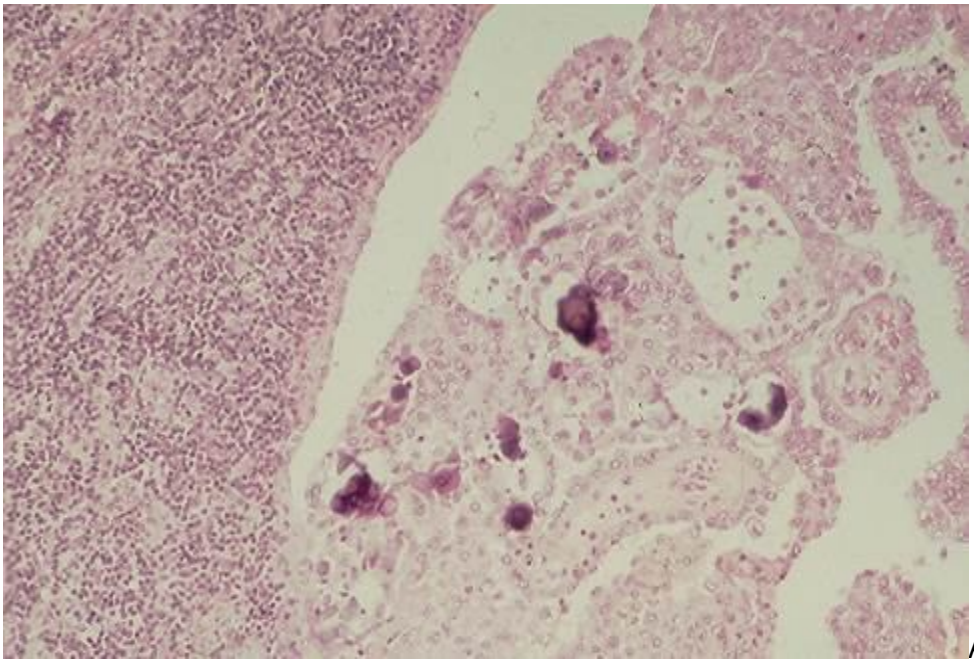


Fig.1.15. Thyroid PC, columnar cell variant, showing tall, columnar tumor cells without characteristic nuclear features of a conventional PC. (CP, Pap).

Diffuse sclerosing PC can be confidently suggested when abundant benign-appearing squamous cells admixed with lymphocytes, follicular epithelial cells with nuclear features of thyroid PC and a few psammoma bodies are noted. (Fig.1.16).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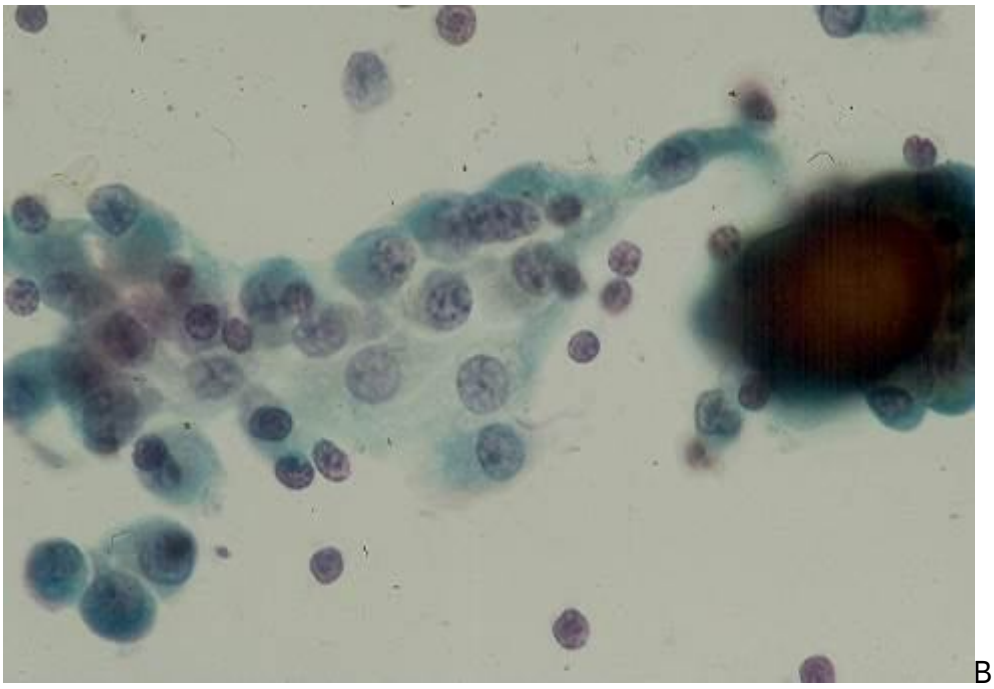
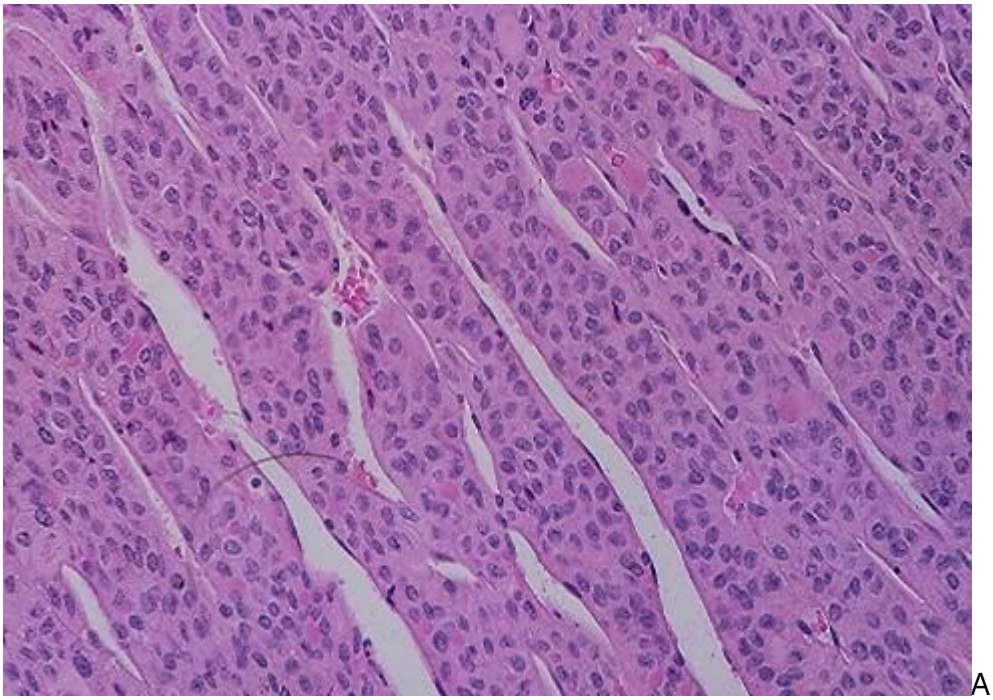
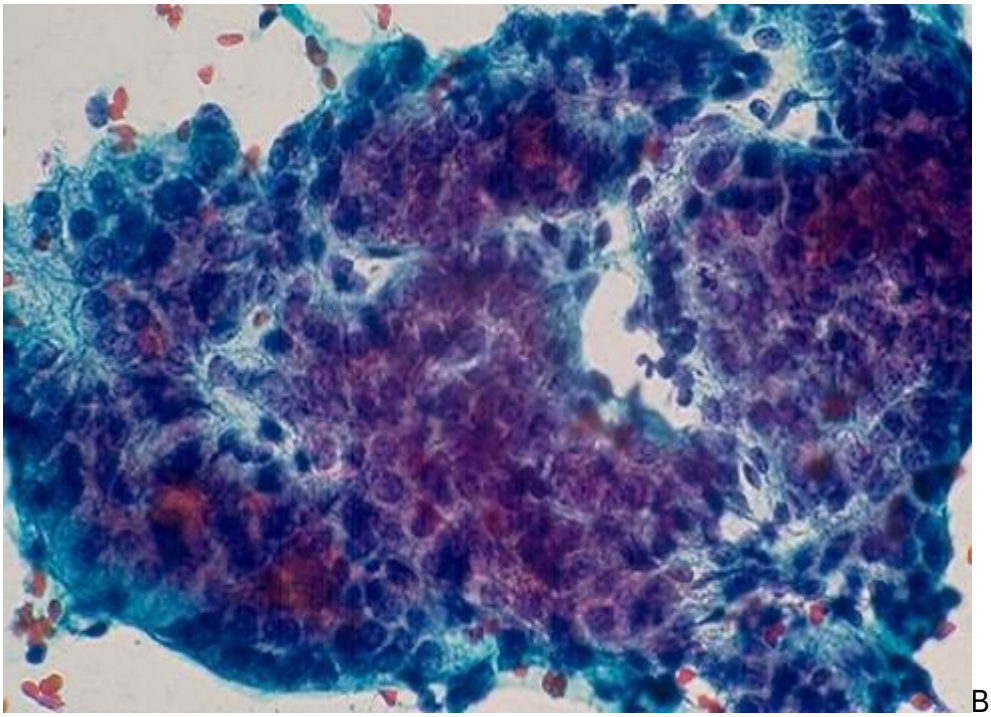

B

Fig.1.16. Thyroid PC, diffuse sclerosing variant: A. Tumor histology showing abundant lymphoid cells and psammoma bodies. (HE). B. A sheet of metaplastic squamous cells admixed with lymphoid cells and a psammoma body in FNA material. (CP, Pap).

Oncocytic variant PC is a rare neoplasm. Histologically, it is characterized by fibrovascular cores covered with follicular cells with extensive oncocytic change with nuclear crowding and overlapping. INCIs may be present. In FNA thick papillary tumor tissue fragments with fibrovascular cores are present as well as single and clustered oncocytes.

Solid/trabecular variant PC is an uncommon tumor. It yields in FNA thick sheets or anastomotic cords of tumor cells showing nuclear crowding. INCIs and nuclear grooves are present. (Fig.1.17).

 A



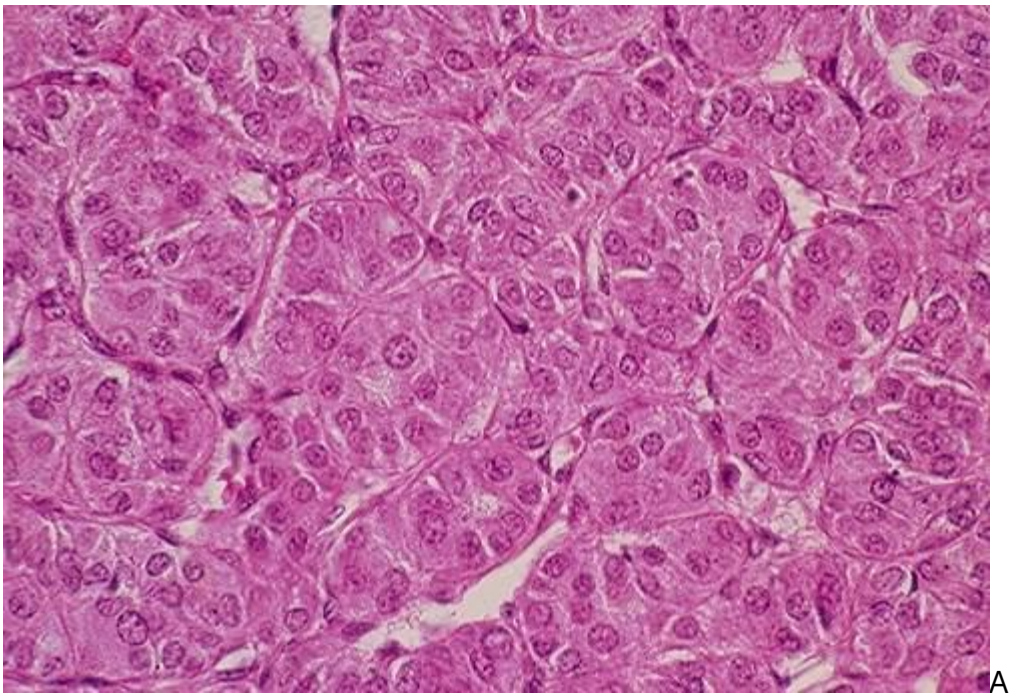
B

Fig.1.17. Thyroid PC, solid/trabecular variant: A. Histology of the lesion. (HE). B. Thick anastomotic cords of tumor cells seen in FNA. (CP, Pap).

Hyalinizing trabecular tumor. Although cytologically indistinguishable from a PC, the lesion yields in FNA cells with PC nuclear features. This tumor behaves as a benign adenoma with only rare reports of metastases. Some earlier studies suggested molecular features in favour of a PC but this has not been confirmed with recent reports.

2. High-grade follicular carcinoma and insular carcinoma

These two carcinomas are characterized by sheets and acinar clusters of pleomorphic epithelial cells with prominent nucleoli. (Figs.1.18 and 1.19). On rare occasion a follicular carcinoma may yield thick, globular colloid masses and small cancer cells, mimicking the needle aspirate of an adenoid cystic carcinoma of salivary gland.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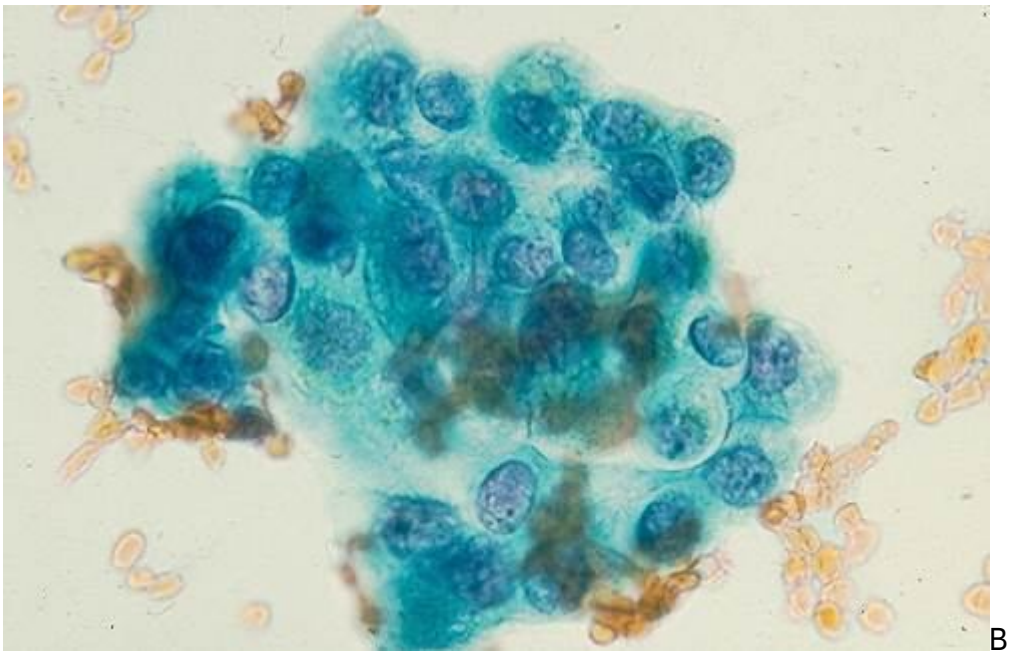
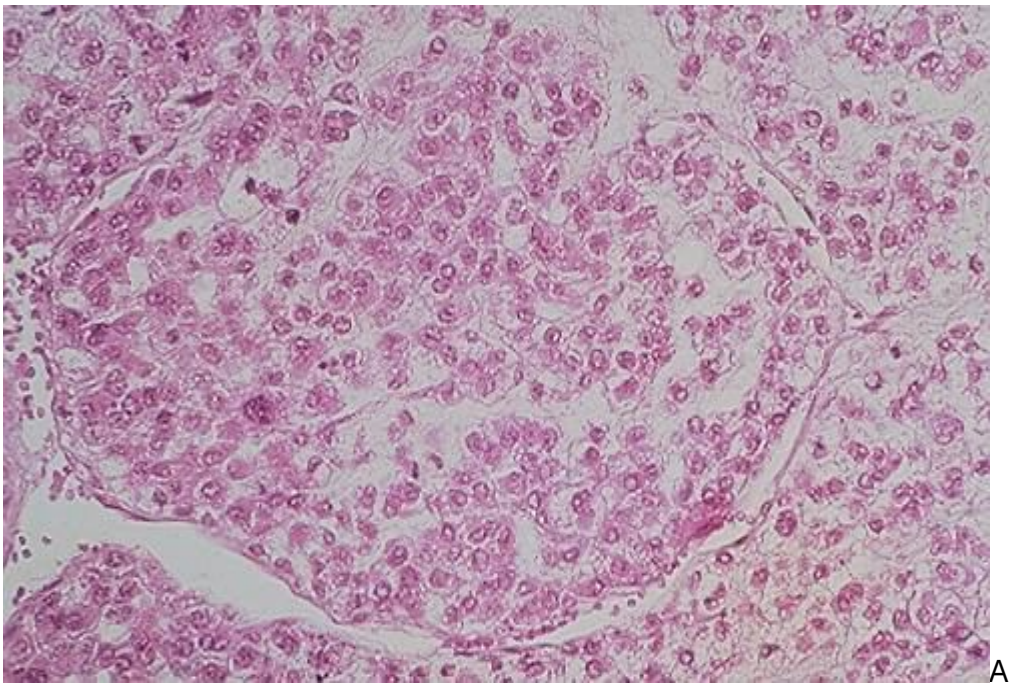

B

Fig.1.18. High-grade follicular carcinoma of the thyroid: A. Histology of the tumor. (HE). B. FNA cytology showing malignant glandular-type cells present in a cohesive cluster. (CP, Pap).



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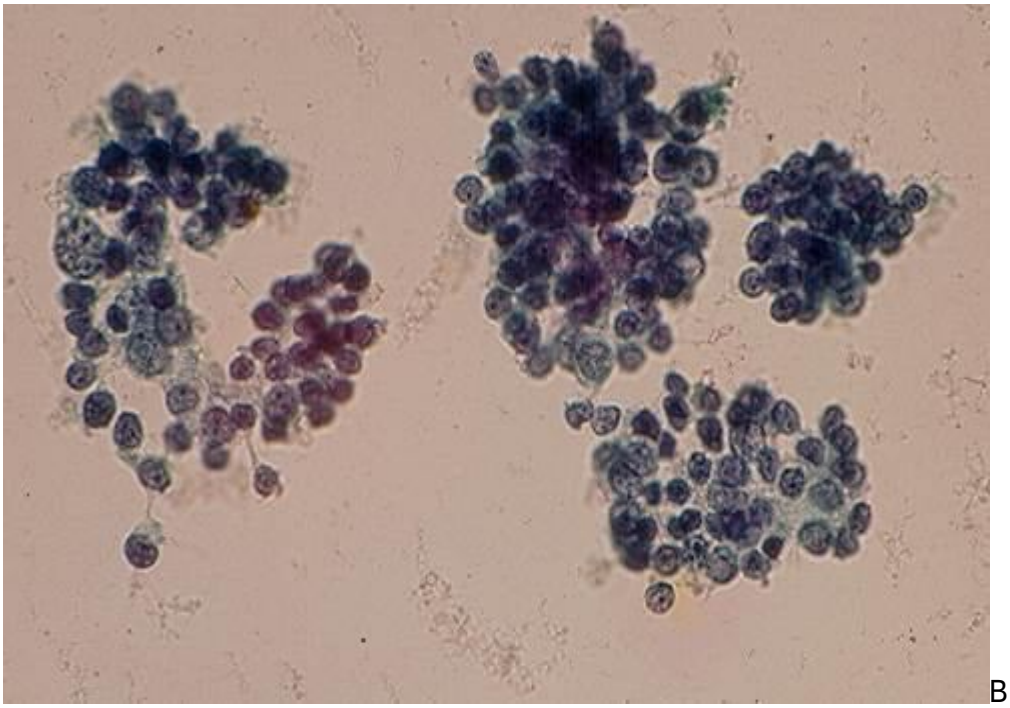

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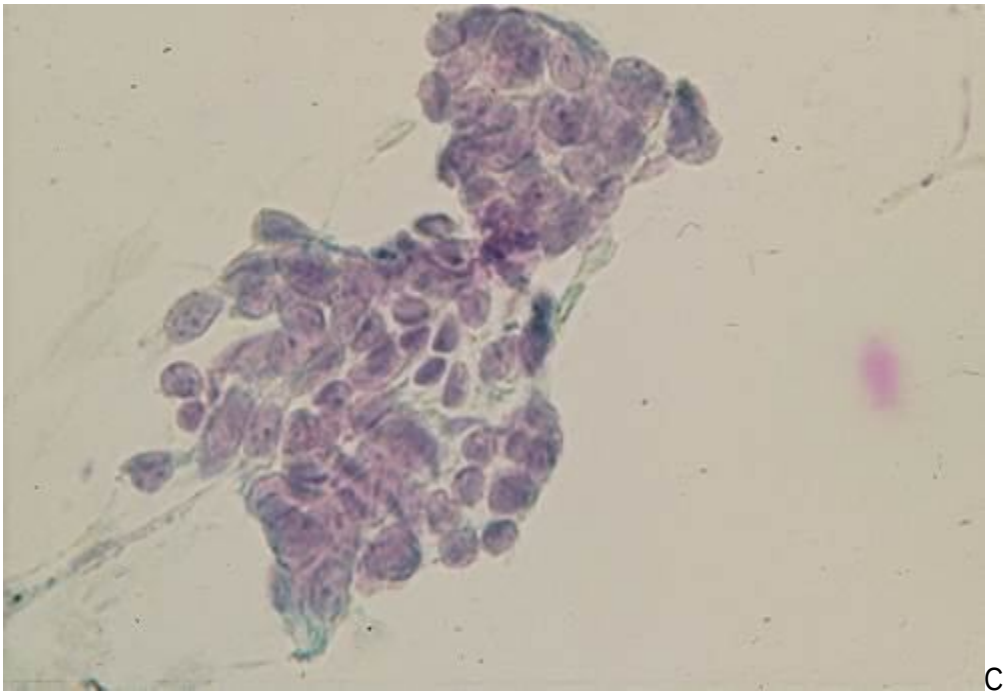
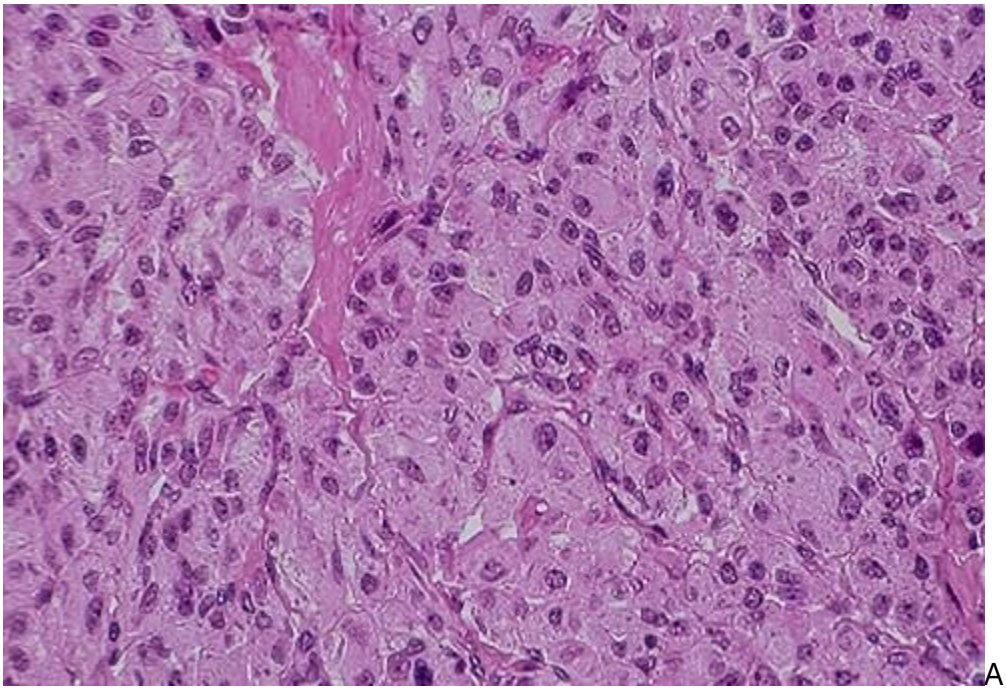
 C

Fig.1.19. Thyroid insular carcinoma: A. Histology of the tumor. (HE). B, C. Tumor FNA showing neoplastic cells in a large, cohesive three-dimensional cluster or nest. (CP, Pap).

3. Medullary carcinoma

This neuroendocrine carcinoma of C-cell origin shows in FNA a mixture of single and clustered polygonal cells and spindle cells that may display INCIs. The tumor cell cytoplasm may show intracytoplasmic pink azurophil granules that are well-visualized by MGG or DQ stain, and stains positively with calcitonin antibody. Amyloid material that stains positively with Congo red may be seen. (Figs.1.20 and 1.21).



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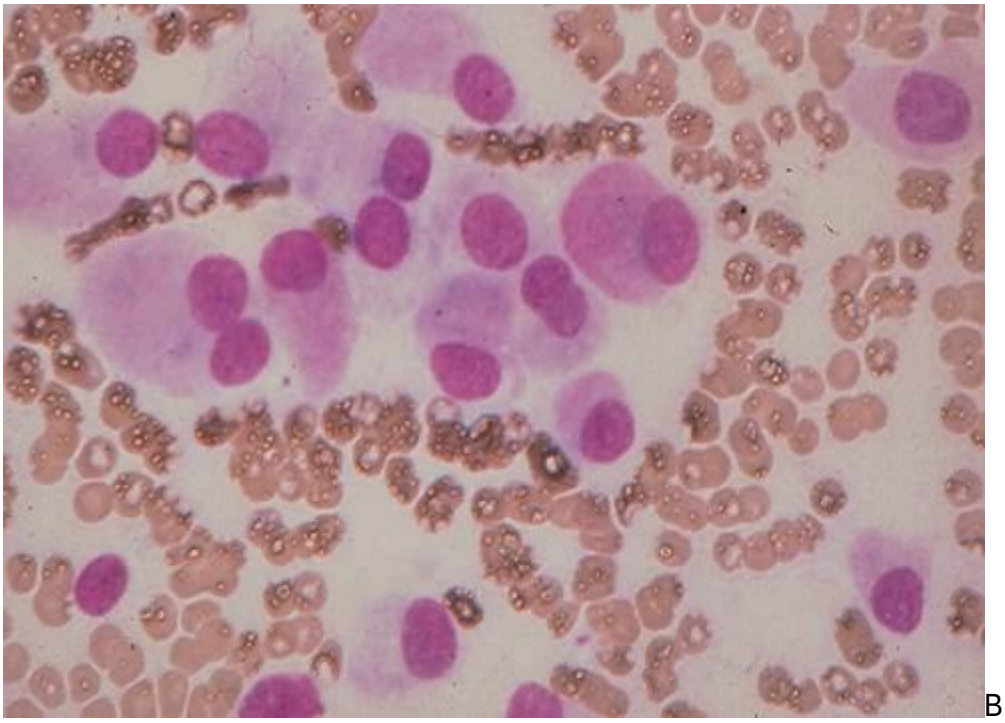

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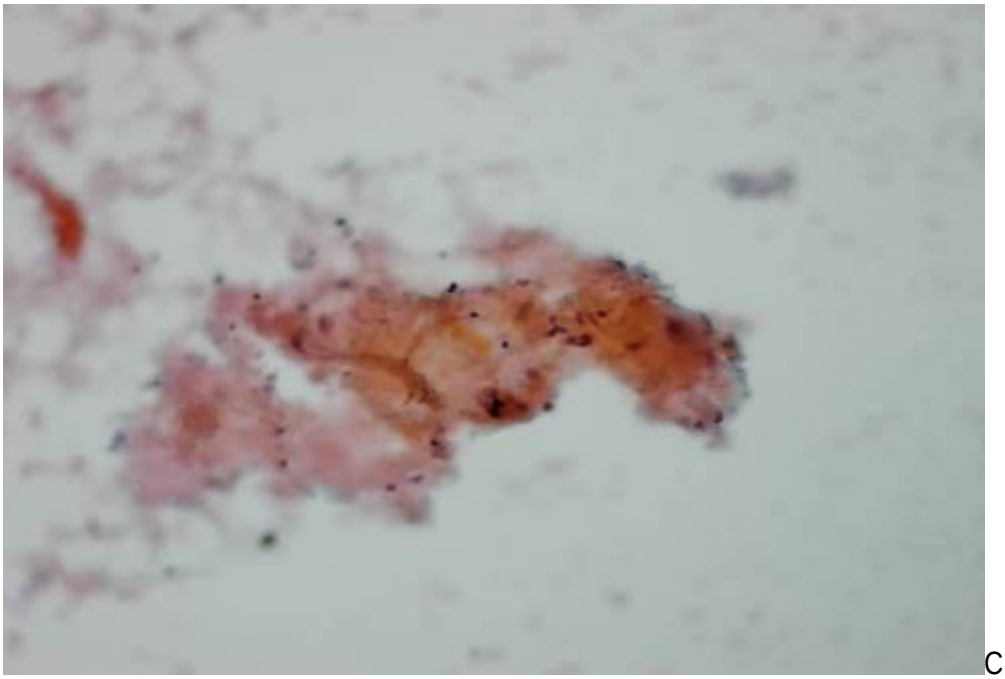
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Fig.1.20. Thyroid medullary carcinoma: A. Histology of the tumor showing focal amyloid deposit. (HE). B. Tumor FNA showing dyshesive plasmacytoid tumor cells with intracytoplasmic azurophil granules. (CP, DQ). C. A fragment of amyloid in smear background. (CP, Pap).

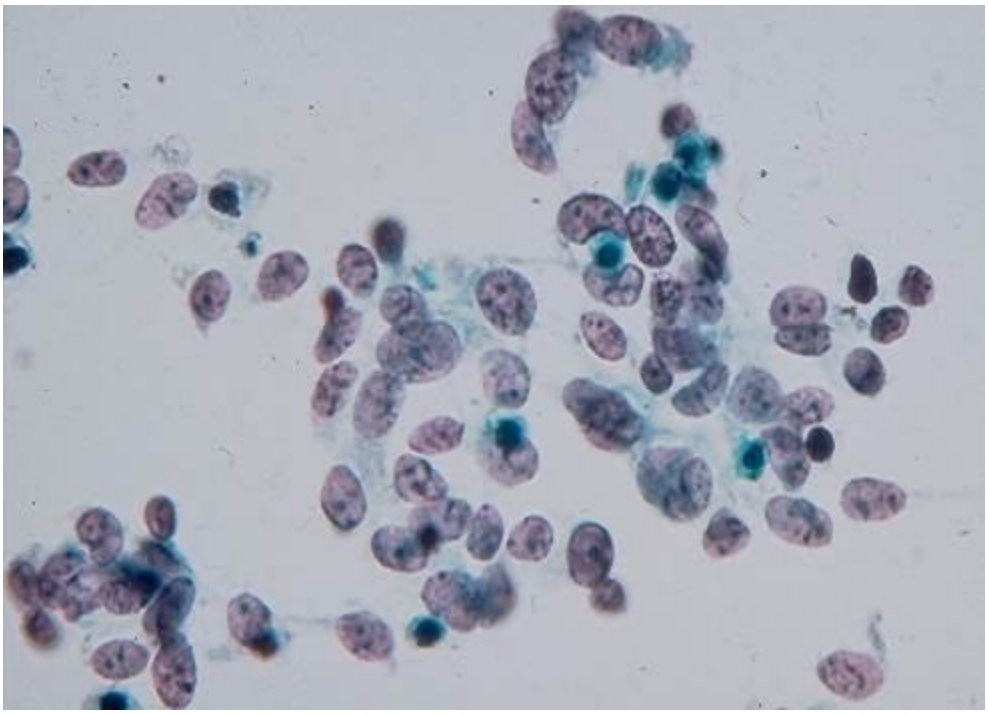
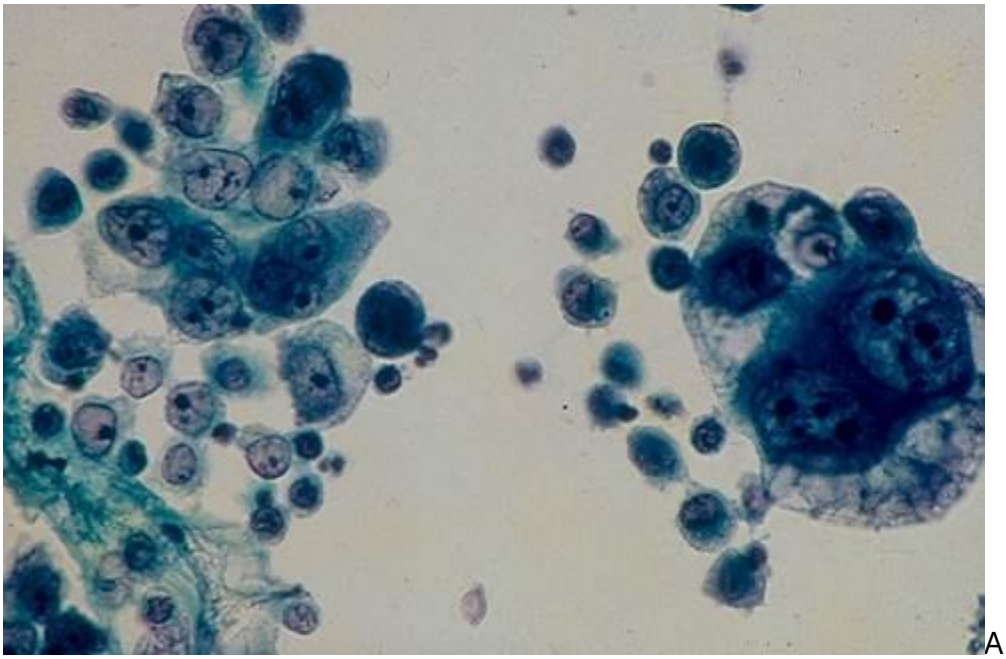


Fig.1.21. Medullary carcinoma showing in FNA loosely clustered spindle tumor cells with scant, ill-defined cytoplasm. (CP, Pap).

4. Anaplastic carcinoma

This tumor has 2 main histologic subtypes: Giant-cell and spindle-cell subtypes, and tumors consisting of epitheloid cells are rarely encountered. Thyroid anaplastic carcinomas yield in FNA bizarre single and clustered malignant cells in no specific patterns. (Fig.1.22).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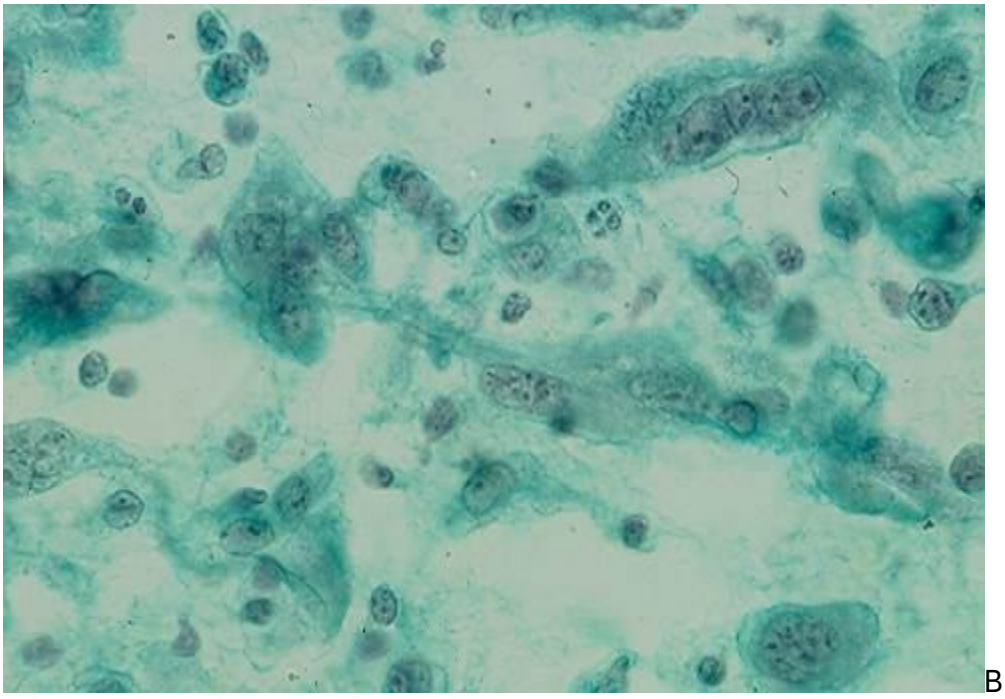
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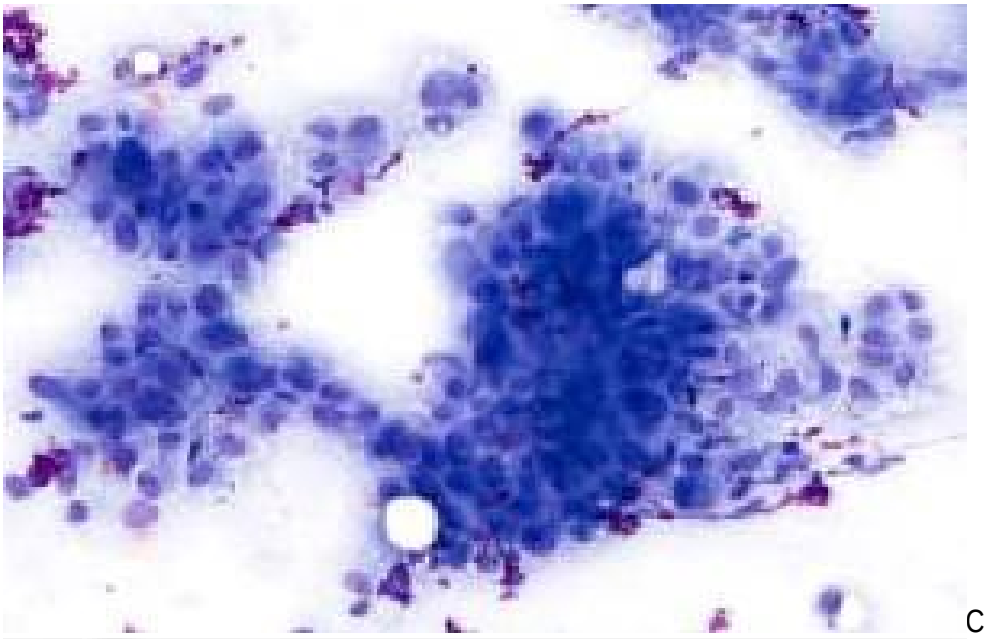
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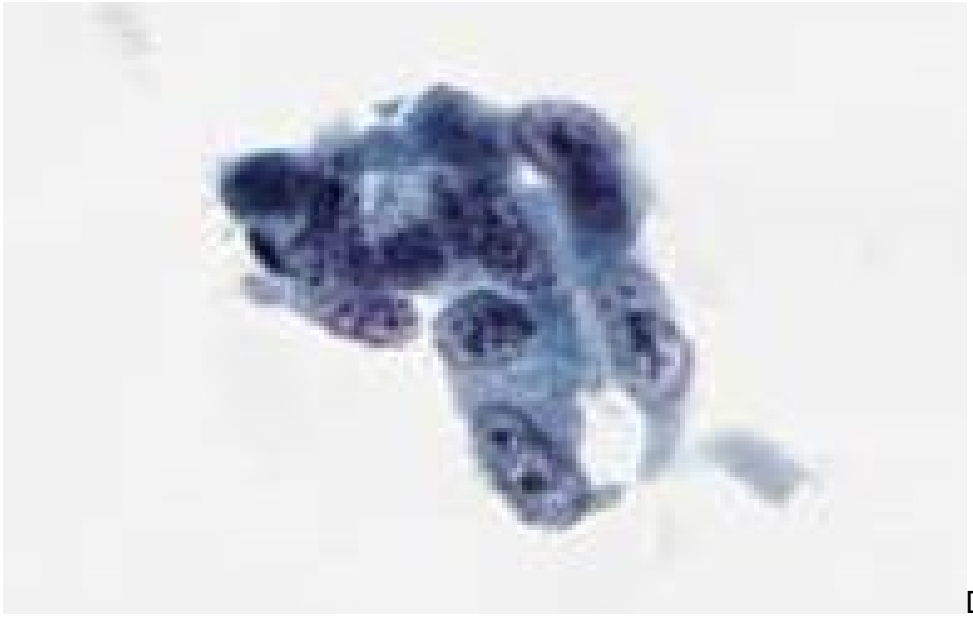
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Fig.1.22. Cytology of thyroid anaplastic carcinomas: A. Giant-cell type tumor showing single, large and bizarre malignant cells. (CP, Pap). B. Spindle-cell type tumor showing spindle malignant cells with scant, ill-defined cytoplasm. (CP, Pap). C, D. Epithelioid-type tumor showing polygonal malignant cells in cohesive clusters. (C, CP, DQ; D, LBP, Pap).

5. Metastatic cancer

Metastases to the thyroid are common in patients with advanced cancers arising from other body sites. However, solitary metastatic cancer to the thyroid gland presenting as a palpable TN is uncommon. For unknown reasons, renal cell carcinoma is the most common metastatic neoplasm to the thyroid, and cases of clinically occult renal cell

carcinoma presenting initially as a large thyroid mass have been documented. Cytodiagnosis of metastatic cancer to the thyroid is relatively straightforward as metastatic cancers usually display cytologic patterns distinctive from those of a primary thyroid carcinoma. However, a cytologic differential diagnosis between a metastatic renal cell carcinoma of clear cell type and a primary thyroid carcinoma with clear cell change may be difficult, and IHC staining of aspirated tumor cells with thyroglobulin antibody will be helpful to identify the aforementioned primary thyroid cancer. (Fig.1.23). Metastatic cancer to the thyroid is associated with a very poor prognosis with death occurring within 6 months.

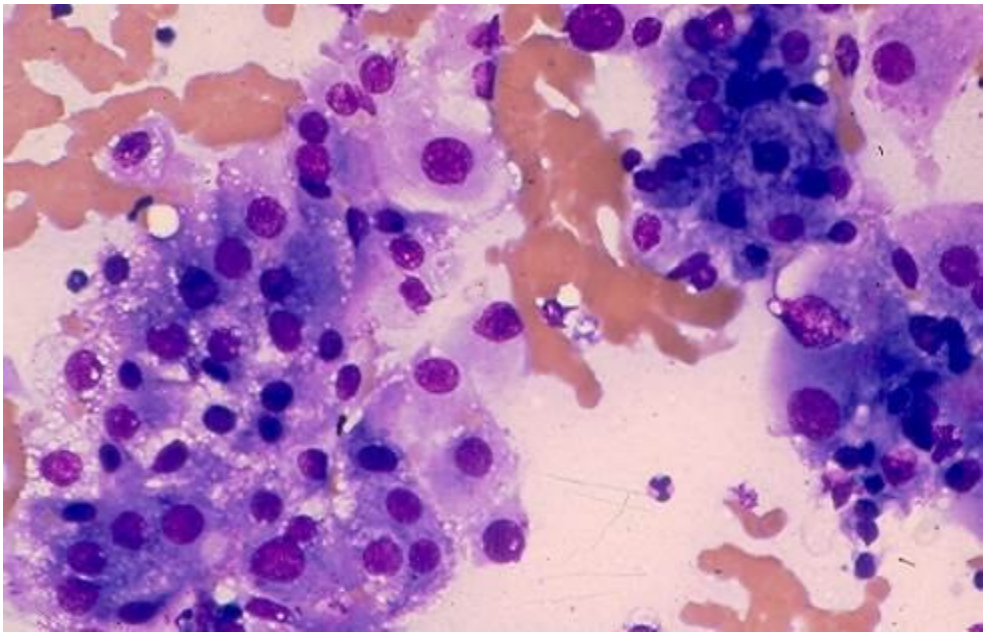


Fig.1.23. Cohesive sheets of epithelial tumor cells with granular or clear cytoplasm in FNA of a metastatic renal cell carcinoma to the thyroid. (CP, DQ).

6. Lymphoma

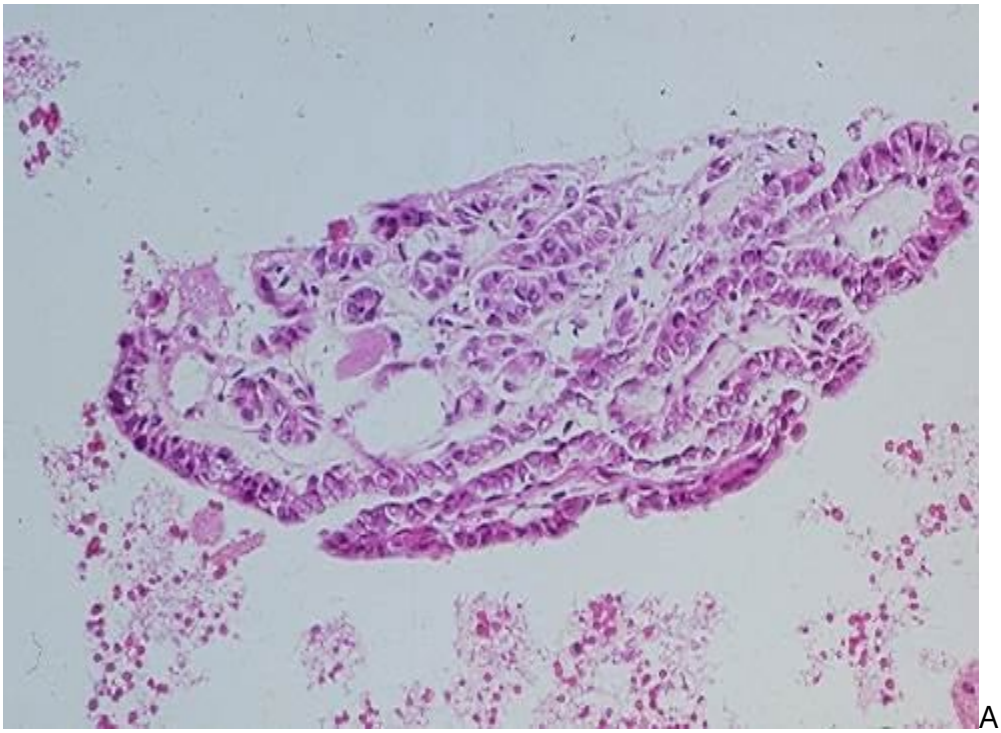
Non-Hodgkin lymphoma is the most common type of primary thyroid lymphomas, usually diffuse large B cell lymphoma but other types of lymphoma may occur. Hodgkin lymphoma arising from the thyroid is rare and is characterized by Reed-Steinberg cells admixed with benign lymphoid cells and eosinophils.

E. Other Lesions

1. Cystic Lesions

Benign cysts account for the majority of thyroid cystic lesions and they are formed as the result of hemorrhagic degeneration of benign colloid nodules. FNA from a benign colloid

cyst may show colloid material admixed with benign follicular epithelial cells and hemosiderin laden macrophages. However, any thyroid neoplasm may undergo hemorrhagic necrosis and become a cystic lesion. Of the thyroid neoplasms, PC tends to undergo marked hemorrhagic degenerative change. FNA from the tumor commonly shows a large amount of blood and the cystic lesion tends to recur rapidly. Cytologic examination of the aspiration smears usually reveals a large amount of blood and rarely tumor cells. However, sections from the cellblock prepared from the FNA may show diagnostic papillary tissue fragments with fibrovascular cores and nuclear features of a PC while that of a benign colloid nodule will show no true papillary tissue fragments with fibrovascular cores and nuclear features of a thyroid PC. (Figs 1.24 and 1.25).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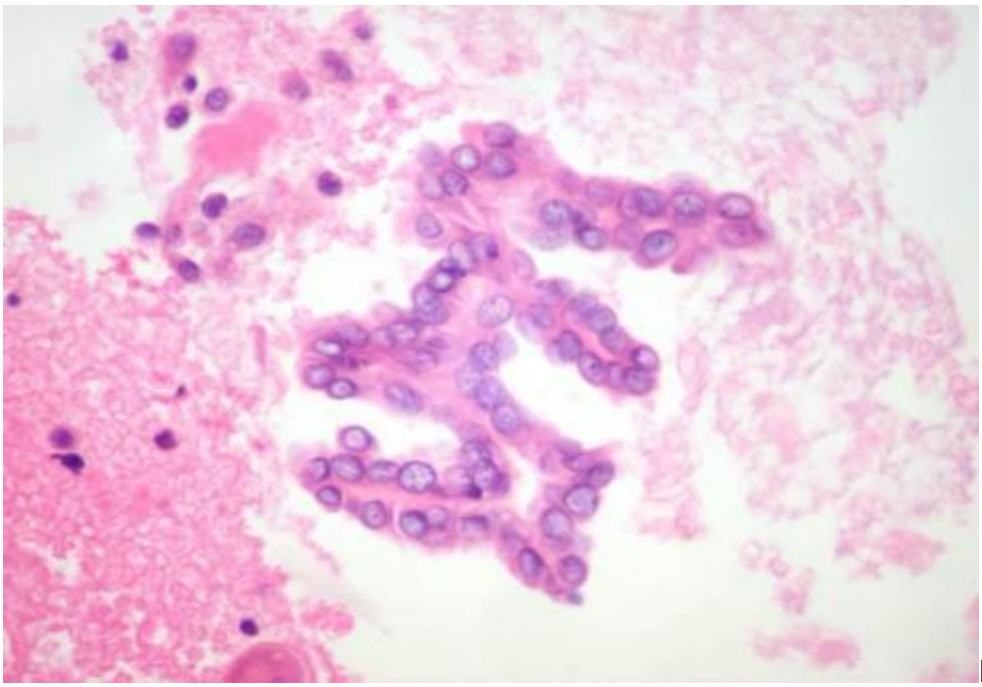
B

Fig.1.24. A. Papillary tumor tissue fragment with fibrovascular core covered with epithelial cells displaying nuclear crowding and occasional INCIs in a cellblock section prepared from the FNA of a thyroid PC with hemorrhagic cystic degenerative change. (HE). B. A minute papillary fragment of follicular epithelium showing nuclear changes of a conventional thyroid PC, in a cellblock prepared from FNA of a thyroid PC with marked hemorrhagic cystic degenerative change. (HE).

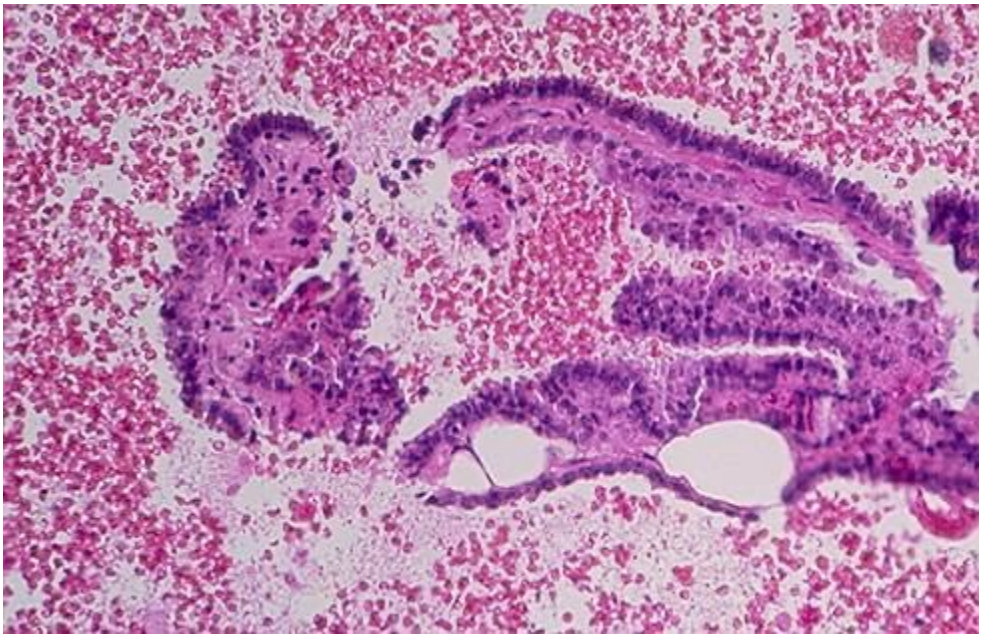

Fig.1.25. Tissue fragments in a cellblock section prepared from the FNA of a benign colloid nodule with hemorrhagic cystic degenerative change. The epithelial lining shows no nuclear changes characteristic for a conventional thyroid PC. (HE).

2. Graves Disease

Graves disease may rarely present as a nodular thyroid lesion. It yields in FNA clusters of follicular cells with cytoplasmic vacuoles that may contain pink material or “flare cells”. (Fig.1.26). However, this finding is non-specific for Graves disease.

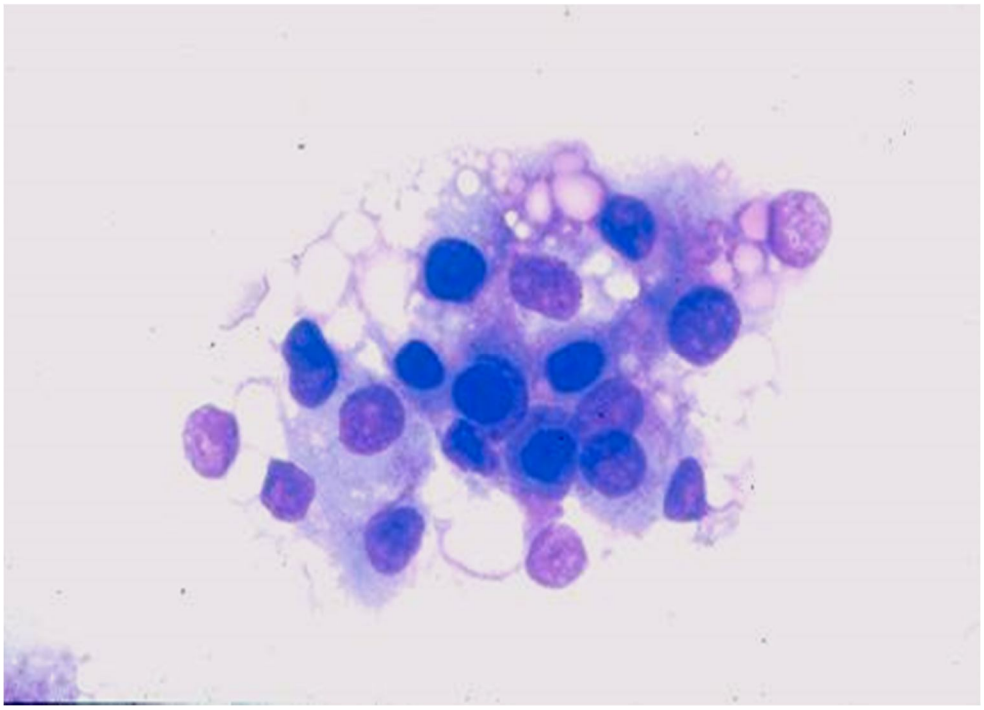

Fig.1.26. A group of “flare cells” showing intracytoplasmic pink material in FNA of a thyroid with Graves disease (CP, DQ).

Diagnostic accuracy and reporting

In a review of seven large series totalling 18,183 thyroid FNAs, Gharib and Goellner found that thyroid FNA had a sensitivity varying from 65 to 98% (mean 83%), and specificity from 72 to 100% (mean 92%). The false-negative rate varied from 1 to 11.5% (mean 5.2%) and the false-positive rate varied from 0 to 7.7% (mean 2.9%). According to several reported series about 20% of TNs yield indeterminate cytologic findings. The keys to successful thyroid FNA are an adequate or representative sample and expertise in thyroid cytology interpretation. Even if not diagnostic for malignancy FNA is often useful for triaging TNs into those that require surgical excision versus those that can be managed with observation.

Recommended Report Format

A thyroid FNA report should contain the following information:

1. Biopsy site.

2. Specimen adequacy (adequate/satisfactory or inadequate/unsatisfactory).
3. Results using The Bethesda System.
4. Ancillary tests, if applicable.
5. Result comment or recommendation, if indicated.

Adjunctive diagnostic value of ancillary techniques

Ultrafast Papanicolaou stain selectively swells the nuclei of PCs, making their nuclear grooves disappear and making the swollen nuclei look like "watery grapes", while this staining method has no effect on nuclei of a follicular adenoma. This artifactual change is due to the disorganization of nuclear lamins and permits a confident distinction in experienced hands between a follicular adenoma and a follicular variant PC.

Immunostains. All malignant tumors, regardless of histologic types, arising from the thyroid express Thyroid Transcription Factor-1 (TTF-1) although TTF-1 may be lost in anaplastic carcinoma. PAX-8, another transcription factor is positive in follicular and papillary thyroid cancers but negative in medullary carcinoma. It may be retained in anaplastic carcinoma when TTF-1 is lost. Tumor cells from follicular epithelial neoplasms react positively with thyroglobulin antibody, except anaplastic carcinoma and medullary carcinoma. Cells from follicular carcinomas are negative for CEA and neuroendocrine markers including calcitonin while those of a medullary carcinoma react positively. Thyroid carcinomas express vimentin and cytokeratins. HBME-1 and galactin-3 are useful although not completely specific markers for differentiated thyroid carcinomas. Immunostaining for p53, Ki-67 and Bcl-2 has no value in separating benign from malignant Hürthle cell tumors.

Ploidy determination has no value in distinguishing a follicular adenoma from a follicular carcinoma.

Molecular markers. The list of potential molecular markers for thyroid cancers is long. The most useful ones are listed below. Some may help to clarify the neoplastic status of indeterminate aspirates and some have prognostic value for certain types of thyroid cancer. Of the molecular and cytogenetic alterations in thyroid tumors, the most common are: BRAF mutation, RET/PTC rearrangement, RAS mutations and PAX8/PPARγ rearrangement. Cell samples obtained by FNA are suitable for molecular/genetics analyses.

- **RET/PTC rearrangements** are more specific for thyroid PCs. However, these may be rarely found in cells from adenomas and other benign thyroid lesions.

- **Of the RAS genes, H-RAS, K-RAS and N-RAS gene mutations** are found in both benign and malignant thyroid neoplasms. They are more commonly found in follicular and anaplastic carcinomas than in PCs. The role of oncogenic RAS in thyroid tumor progression is not known.

- **BRAF mutation** is associated with tumor aggressiveness, metastasis and recurrence of thyroid PCs. It is a molecular prognostic marker for poorer prognosis of thyroid cancer. BRAF point mutation and RET/PTC rearrangements are found in about 40% of thyroid PCs and may be used to refine the diagnosis of PCs that are considered either indeterminate or insufficient by FNA cytology. This mutation is not found in follicular adenomas and non-toxic nodular goiters.

- **PAX8-PPARγ rearrangement** is found in about one third of follicular carcinomas and follicular variant PCs but it is also present in follicular adenomas. The role of this arrangement in the progression and de-differentiation of follicular to poorly differentiated and anaplastic carcinomas is not known.

- **p53 mutations** are usually restricted to poorly differentiated and anaplastic carcinomas. In tumors with both well-differentiated and anaplastic components, p53 mutations are found only in the anaplastic component.

Microarray analysis and molecular profiling may have a significant role in the future evaluation of TNs, while providing an impetus for further insight into the molecular pathogenesis of both benign and malignant nodules. By analysis of cancer gene profiles a separation of benign from malignant thyroid tumors is possible with sensitivity and specificity over 90%. Molecular profiling may also permit the distinction between primary and metastatic malignancies when dealing with multiple suspicious nodules at various sites. Microarray analysis is limited by the amount of RNA retrieved from a sample, thereby often limiting analysis to surgically resected samples. However, refinement of the technique may make them applicable to FNA, with extraction of RNA from a cellblock from which molecular analysis of FNA material may have significant diagnostic benefit.

Remark: Some information and illustrations in this chapter are taken from the original paper authored by Nguyen GK, et al. Fine needle aspiration of the thyroid: an overview. Cytojournal. 2005;2:12. This paper received the Cytojournal Best Article Award-2005.

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Chapter 2

Salivary glands & other neck masses

Gia-Khanh Nguyen and Thomas Thomson

I. Salivary glands

The history of salivary gland FNA cytology can be traced back to 1950s. Zajdela of France and Zajicek of Sweden have initially developed this diagnostic procedure in the early years of 1950s, and its value in patient care was widely recognized in Europe some 20 years latter. In North America, this method of investigation was adopted for patient care in the 1980s, after a long period of reluctance. FNA of salivary gland mass lesions now is practiced worldwide. However, it is still underutilized despite of numerous published papers on this topic. The main reasons are the complexity of the histopathology of salivary gland tumors and their relative rarity, resulting in poor cytohistologic correlations and lack of pathologist's experience in interpreting salivary gland tumor cytology.

Indication and goal of FNA

Enlarged salivary glands and salivary gland mass lesions are targets of FNA for cytologic evaluation. The only relative contraindication for this diagnostic procedure is the presence of a bleeding disorder. The goal of FNA of salivary gland lesions is to triage the lesions for appropriate treatments and it can, in most cases, divide those lesions into the following categories:

1. Normal versus abnormal tissue.
2. Neoplastic versus inflammatory.
3. If neoplastic, epithelial versus non-epithelial with the most specific diagnosis possible.
4. If inflammatory, assessment of subtype with the most specific diagnosis possible.

Technical considerations

The techniques of FNA of salivary gland mass lesions are similar to those of a thyroid nodule. Usually, a 25-gauge needle is used. Depending on personal preference, FNA can be performed with or without a syringe. Usually anesthesia is not required but topical benzocaine or injected lidocaine is recommended for intraoral lesions. For submandibular lesions the patient should be cautioned that some blood may appear in the mounth and reassured that this will be transient and relieved by rinsing.

For a cystic lesion, the cyst contents must be evacuated first, and the viscosity and appearance of the fluid is noted. Any residual palpable nodule, if present, should be sampled as it may contain diagnostic cells. Large volumes of fluid may allow cellblock preparation. Small volumes can be smeared or processed as a monolayered preparation (cytospin, ThinPrep, etc.). Both the ethanol-fixed Papanicolaou and air-dried Romanovsky (Diff-Quik, MGG) staining methods are commonly used to stain the obtained cell sample. The use of both stains is complementary and provides more information for cytologic evaluation of salivary gland lesions. Occasionally IHC staining with selected antibodies may be useful for tumor typing. Mucin stains (mucicarmine, periodic-acid Schiff with prior diastase digestion [PASD]) may at time be useful. Stains for acid-fast bacilli or fungal elements and cultures should be done if a tuberculous or fungal infection is suspected.

Anatomy, histology and cytology of normal salivary glands

There are six major salivary glands: two parotid glands, two submandibular glands and two sublingual glands. The parotid gland is a serous gland with Stenson's excretory duct that is lined by a single layer of columnar epithelium. The parotid gland has a superficial and a deep lobe with facial nerve between the two lobes and a few intraglandular lymph nodes. The submandibular gland is seromucinous with mucous cells predominant and has Wharton excretory duct that is also lined by a single layer of columnar epithelial cells. Unlike the parotid gland, the submandibular gland does not contain any lymph nodes. The sublingual gland is also seromucinous and opens directly into the oral cavity. There are 500 to 1000 minor salivary glands that are located beneath the oral epithelium and that open directly into the oral cavity.

FNA of normal salivary gland usually reveals a mixture of acinar and ductal cells with acinar cells predominant. Acinar cells are cuboidal or pyramidal in shape with vesicular, bland, basally located nuclei and granular or vacuolated cytoplasm. They appear in uniform cell clusters in continuity with intercalated ducts, forming a ductal-acinar complex. Intercalated duct cells are cuboidal in shape and show scant cytoplasm and round, bland nuclei. (Figs.2.1 and 2.2). In older people fat is often present and focal oncocytic change may be apparent.

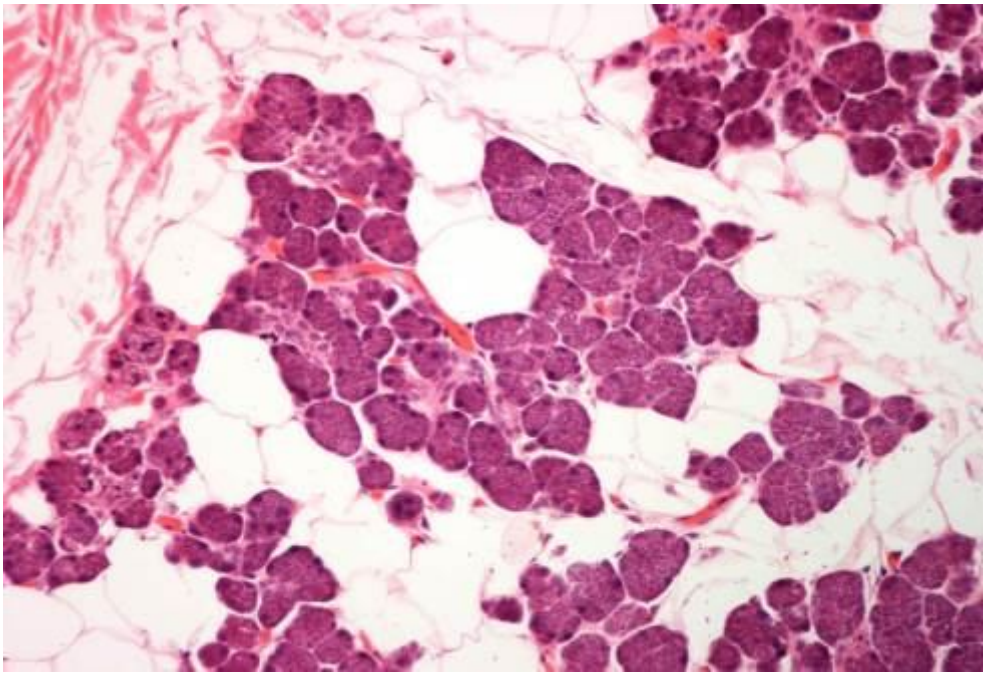
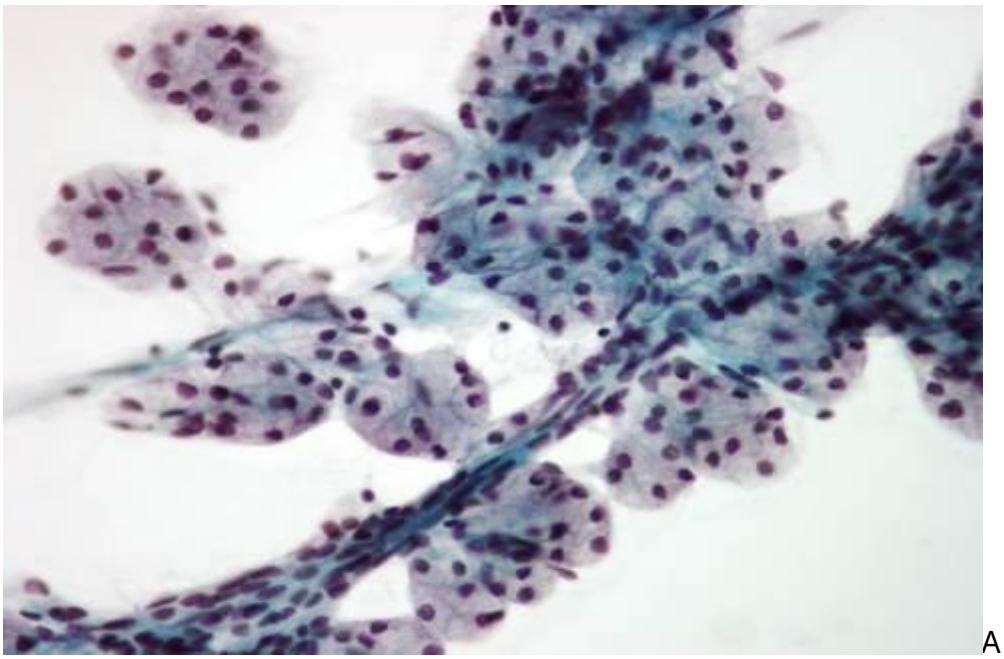


Fig.2.1. Histology of a normal serous salivary gland showing acinar cells in acini sepated by a variable amount of benign fat. A few small excretory ducts are also present. (HE)



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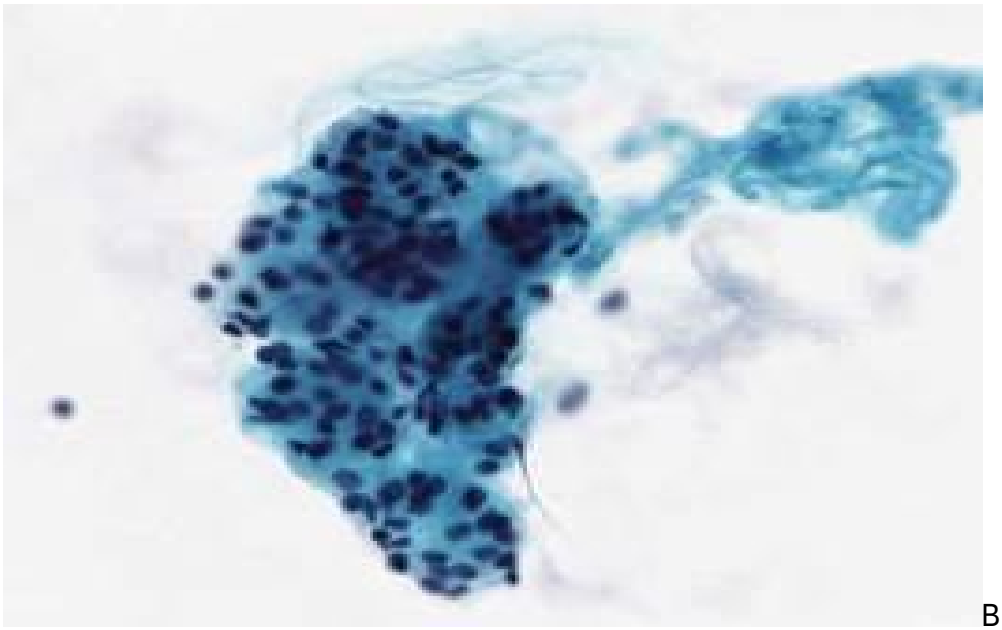

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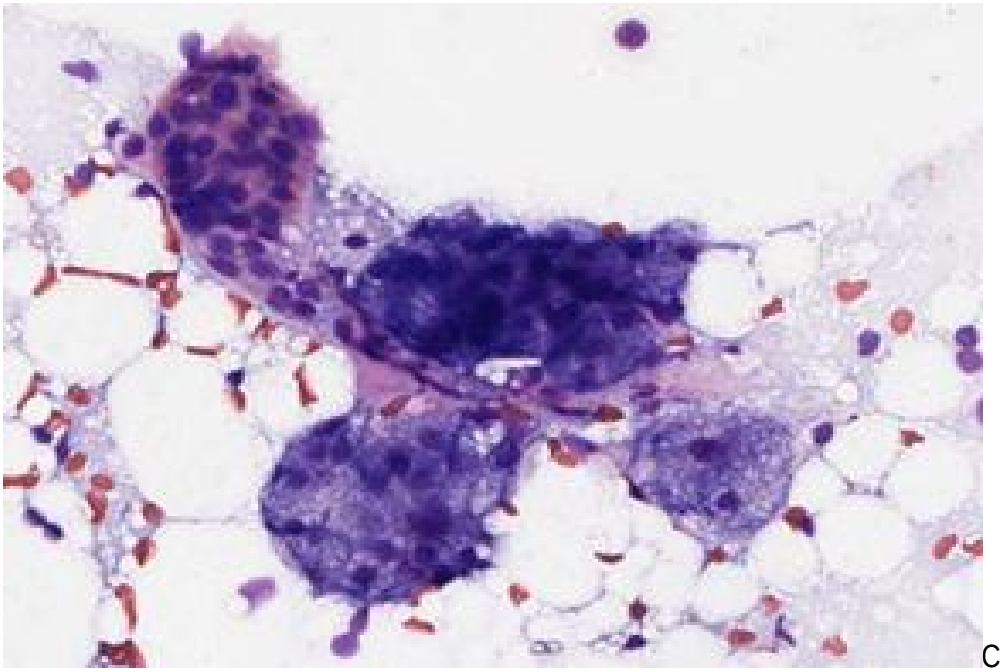

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Fig.2.2. FNA of normal serous salivary gland showing acinar cells in acinar arrangement and a small excretory duct and fat. (A. CP, Pap, B. LBP, Pap, C. CP, MGG)

Benign mass lesions

Chronic sialadenitis is most commonly present as a mass lesion of the submandibular gland and may clinically mimic a salivary gland neoplasm. FNA in the early phase is variably cellular with mainly small cohesive fragments of ductal cells and a variable amount of acinar epithelium admixed with lymphocytes and plasma cells. (Fig.2.3). FNA of longstanding lesions may be hypocellular, consistent with a gland fibrosis and yields

only scant fragments of ductal epithelium, some of them may show squamous metaplasia. Inflammatory cells, other than a small amount of crushed lymphoid tissue may not be apparent. Chronic sialadenitis in patients with previous radiation for oral cancer may yield in FNA fragments of ductal epithelium with post-radiation changes that can mimic cancer cells.

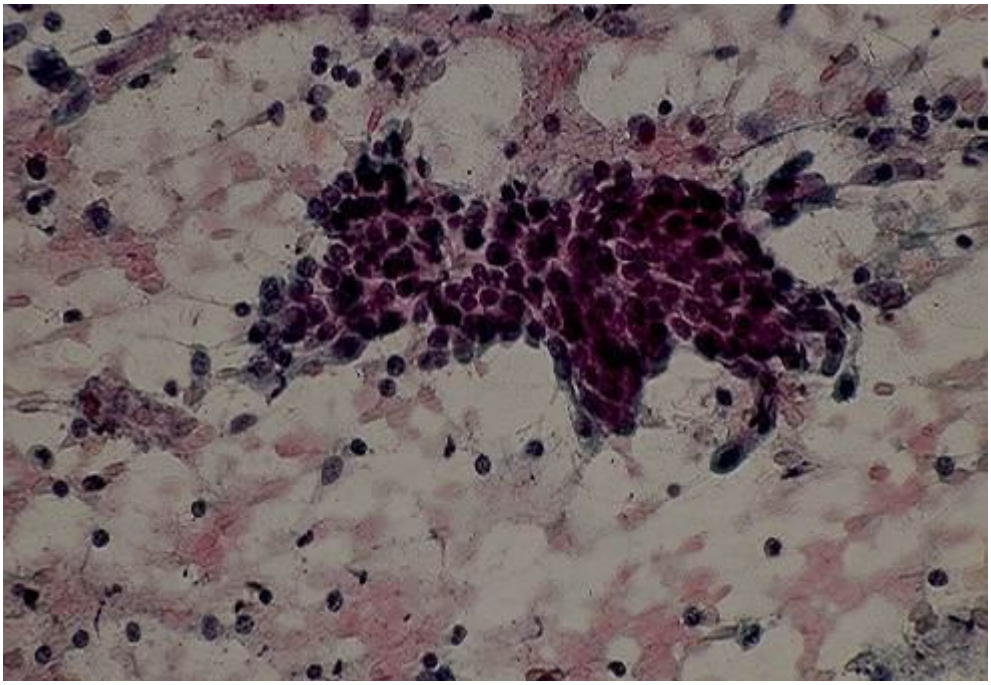
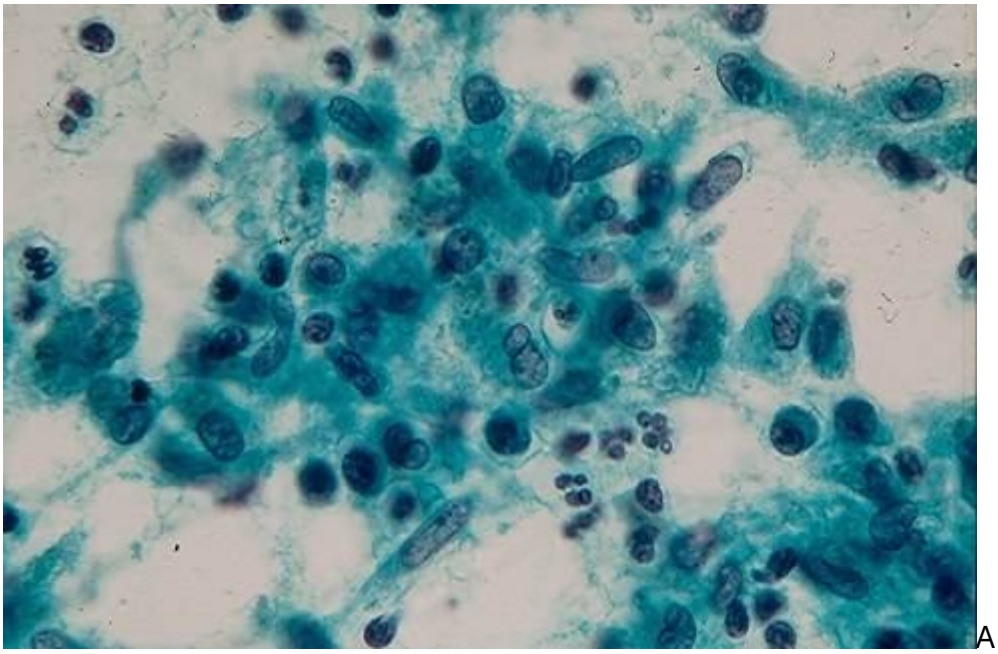


Fig.2.3. Chronic sialadenitis showing in FNA a large sheet of benign ductal epithelial cells and abundant lymphoid cells. (CP, Pap).

Granulomatous inflammations such as sarcoidosis, tuberculosis and cat scratch disease may cause a salivary gland enlargement, simulating a neoplasm. **Sarcoidosis** is characterised by clustered epithelioid cells with elongated or carrot-shaped nuclei and ill-defined cytoplasm admixed with lymphocytes. (Fig.2.4).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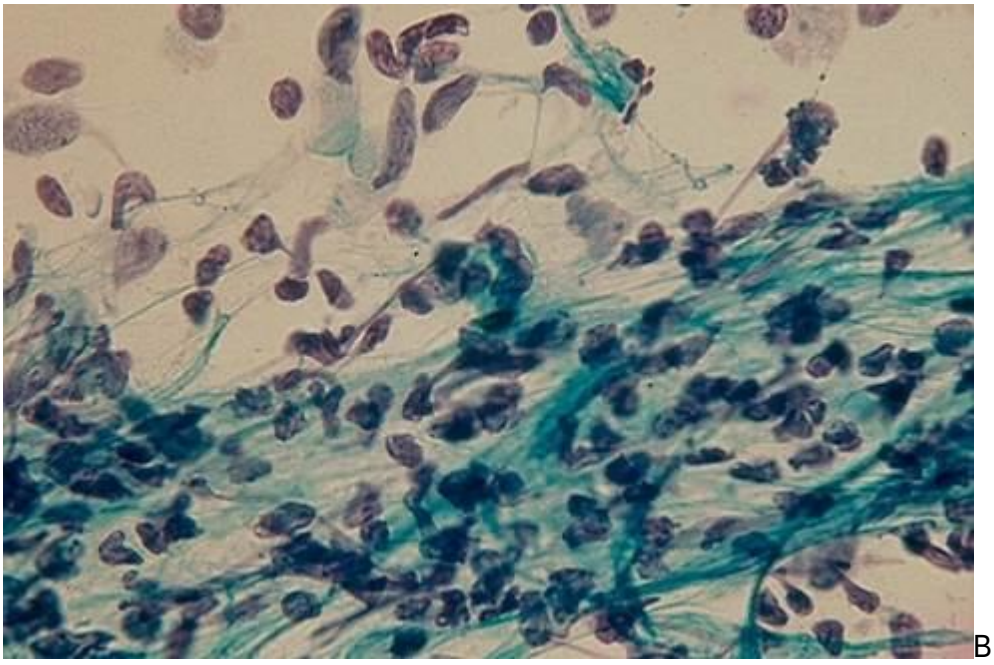
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Fig.2.4. A and B. Parotid gland with sarcoidosis showing in FNA an admixture of lymphoid cells and epithelioid cells with curved and elongated nuclei. (CP, Pap).

In **tuberculous sialadenitis** necrotic debris containing acid-fast bacilli and inflammatory cells is commonly found. Langhans giant cells and epithelioid cells may also be observed. In **cat scratch disease** epithelioid cells, lymphocytes and polymorphonuclear leukocytes can be seen.

Pleomorphic adenoma or mixed tumor accounts for over 75% of all salivary gland tumors (SGT) with 75% arising from the parotid gland, 5-10% from the submandibular gland and 10% from minor salivary glands. The tumor occurs more commonly in adult female patients over 30 years of age, and 75% of them arise from the superficial lobe of the parotid gland. Histologically, pleomorphic adenomas (PA) are circumscribed masses composed of achaotic mix of cuboidal ductal cells in sheets or small tubules surrounded by spindle or plasmacytoid myoepithelial cells drifting off into a chondromyxoid stroma. Mature cartilage may occasionally be found. (Fig.2.5). Sebaceous or metaplastic squamous or mucinous epithelium may be focally and rarely present.

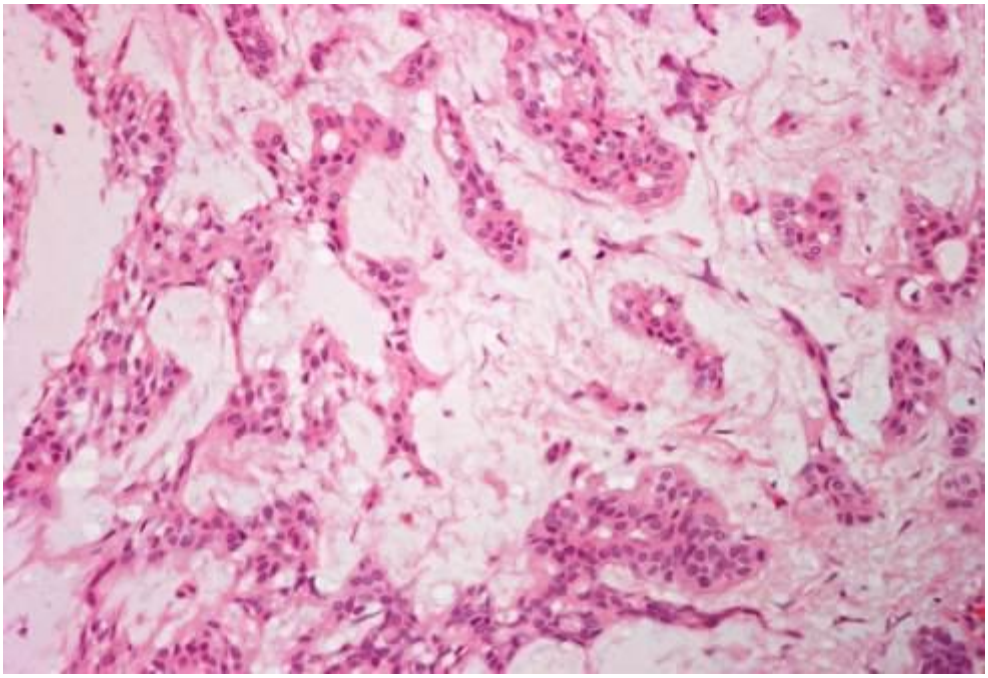
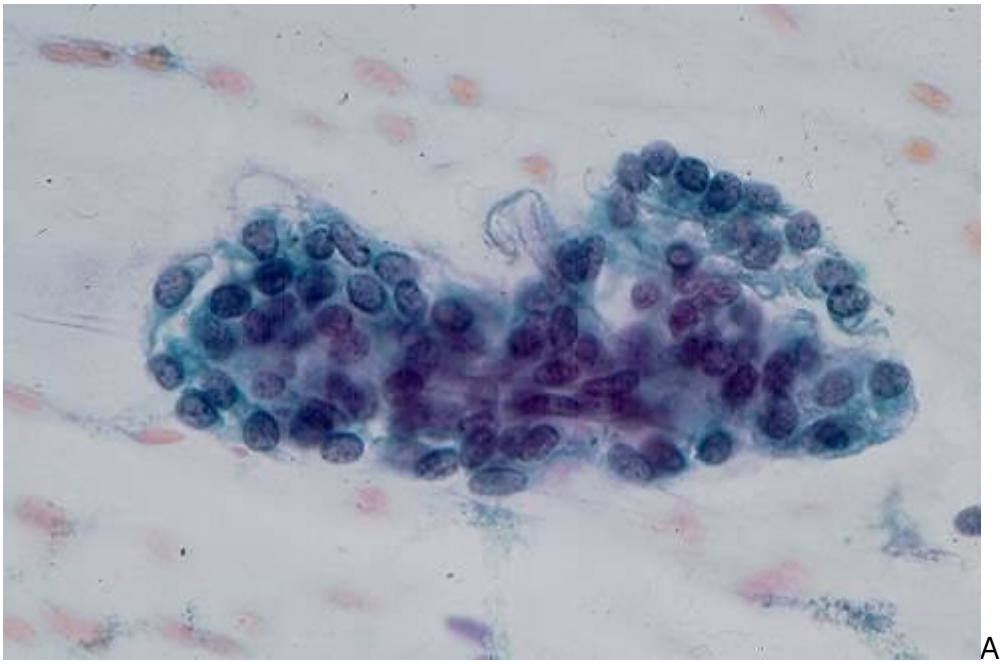


Fig.2.5. Histology of a pleomorphic adenoma of the parotid. (HE)

In most cases the FNA cytodiagnosis of PA is straightforward. Aspirates are usually cellular with a mixture of thick cohesive clusters of benign glandular epithelial cells, dyshesive ragged groups of plasmacytoid or spindle-shaped cells and oval, plasmacytoid myoepithelial cells with bland nuclei dispersed in mucoid or fibrillary chondromyxoid material. These findings are usually readily identifiable by Papanicolaou stain but Romanovsky stain (DQ or MGG) makes it easier to see the metachromatically stained stroma and faciliates the diagnosis. (Figs.2.6 and 2.7).



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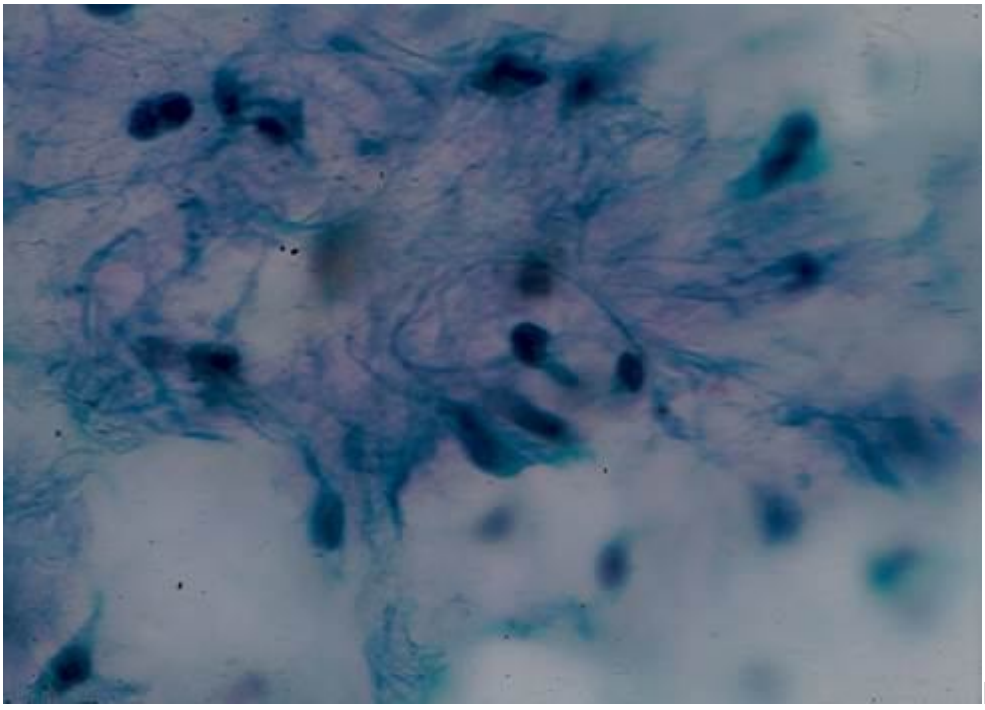

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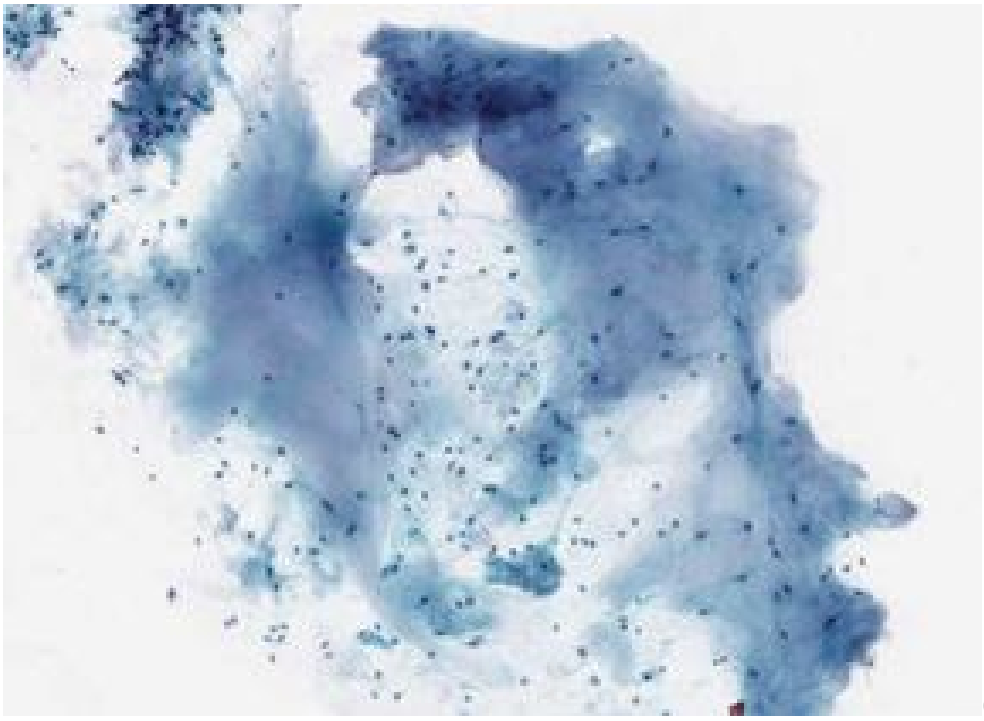

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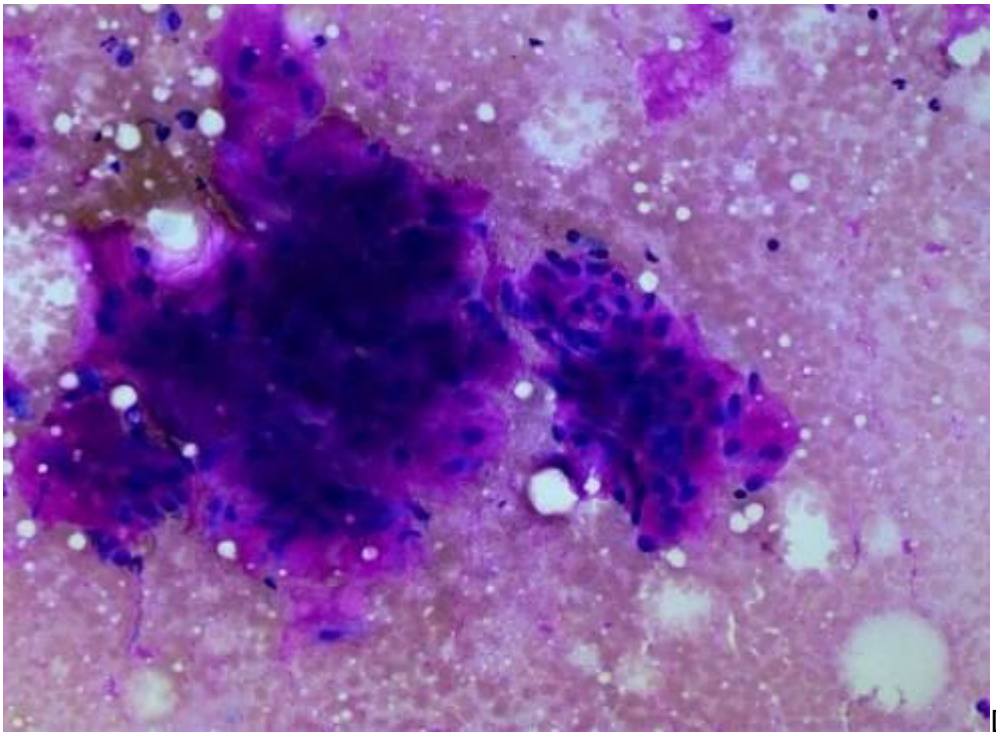

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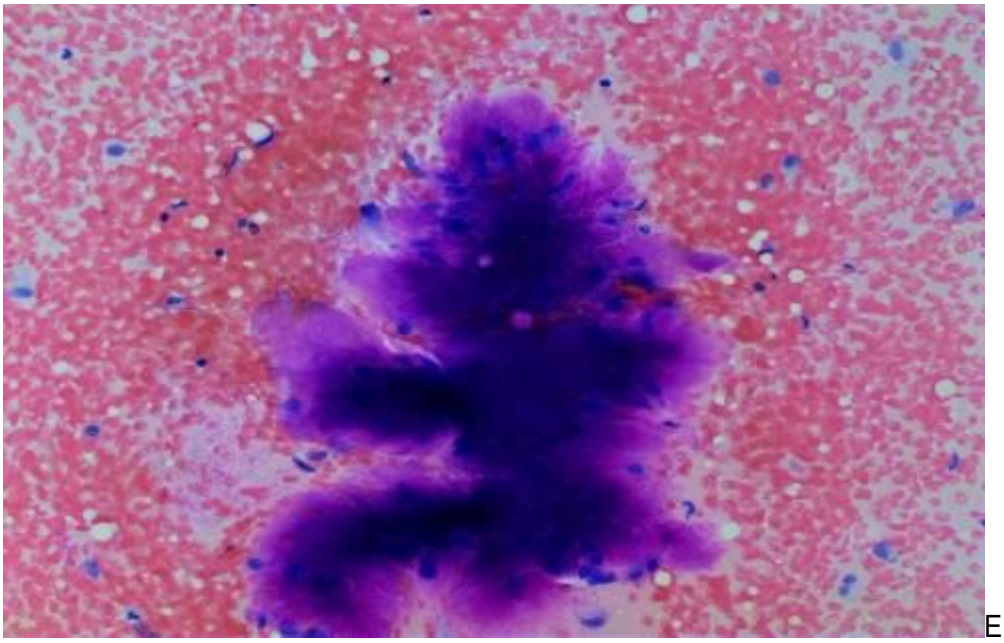
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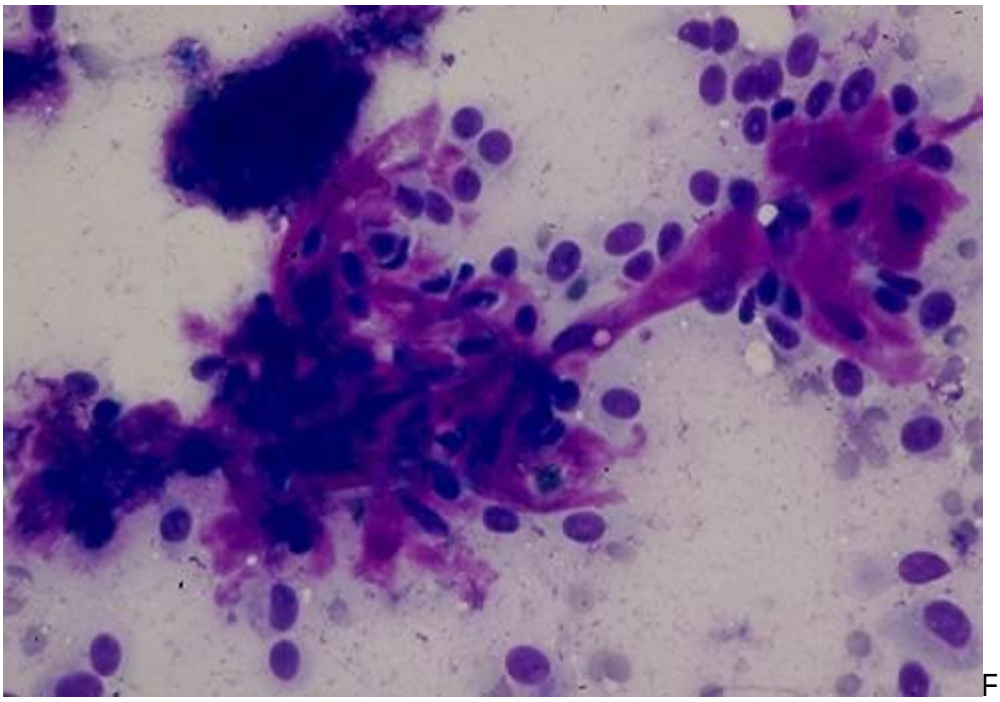
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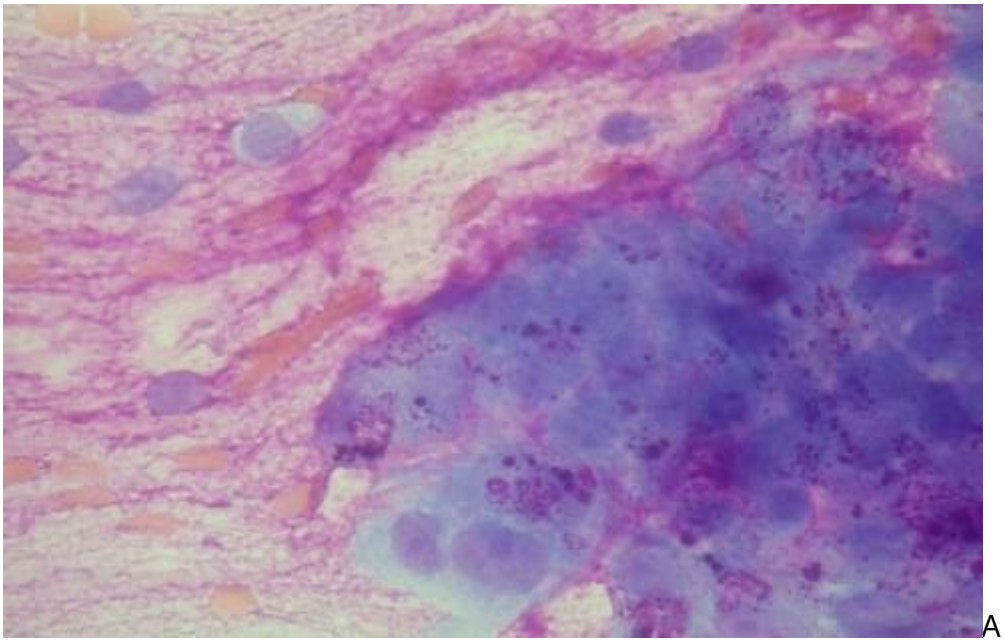
Fig.2.6. Cytology of pleomorphic adenoma: A. A cluster of benign epithelial cells. (CP, Pap). B. Chondromyxoid stroma containing stellate and elongated cells with fibrillary cytoplasmic extensions. (CP, Pap). C. Chondromyxoid stroma with dispersed myoepithelial cells. (LBP, Pap). D-F. Metachromatic stromal material admixed with epithelial and myoepithelial cells. (CP, DQ)

Pitfalls may be encountered in cases of PA. In some cases the epithelial or fibromyxomatous component predominates the smear pattern. As a rule, a minute amount of mucoid or chondroid material should raise the index of suspicion for PA, and a

repeat FNA should be performed for further evaluation. However, some cases of low-grade mucoepidermoid carcinoma (MEC) or acinic cell carcinoma may have a myxoid matrix that mimics a PA on FNA. An FNA with numerous epithelial cell clusters with glandular spaces containing round amorphous and metachromatic material may mimic an adenoid cystic carcinoma. (Fig.2.7). An FNA with abundant mucoid material may be mistaken for a low-grade MEC. The opposite is also true that malignant tumors may be mistaken for PA. Minor degrees of epithelial atypia, usually rare, may be encountered in a PA and can usually be ignored. However, groups of cells with marked epithelial atypia should be noted as malignant transformation may develop in longstanding tumors (carcinoma ex-pleomorphic adenoma).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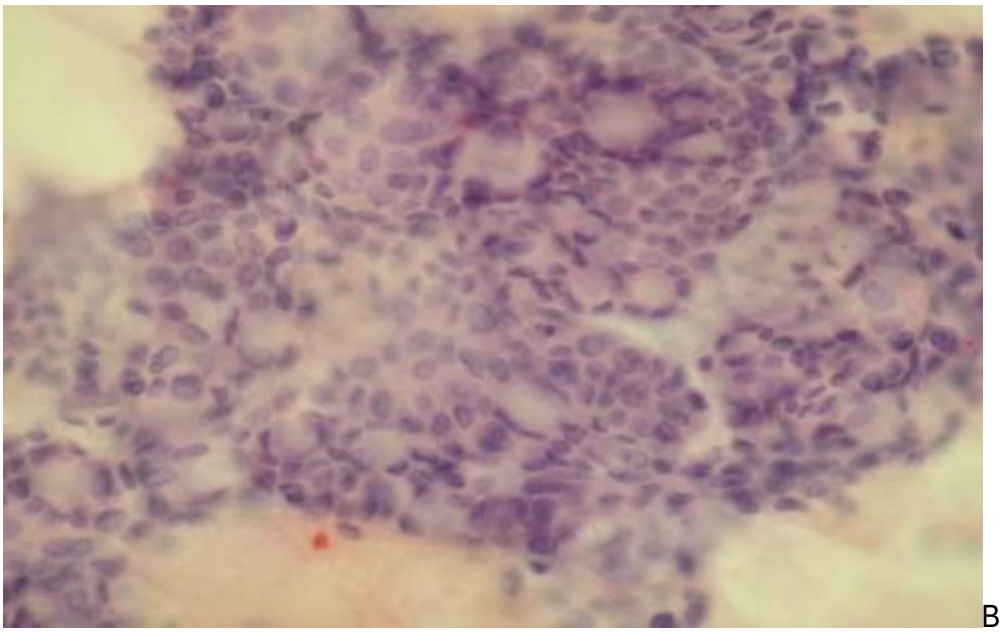
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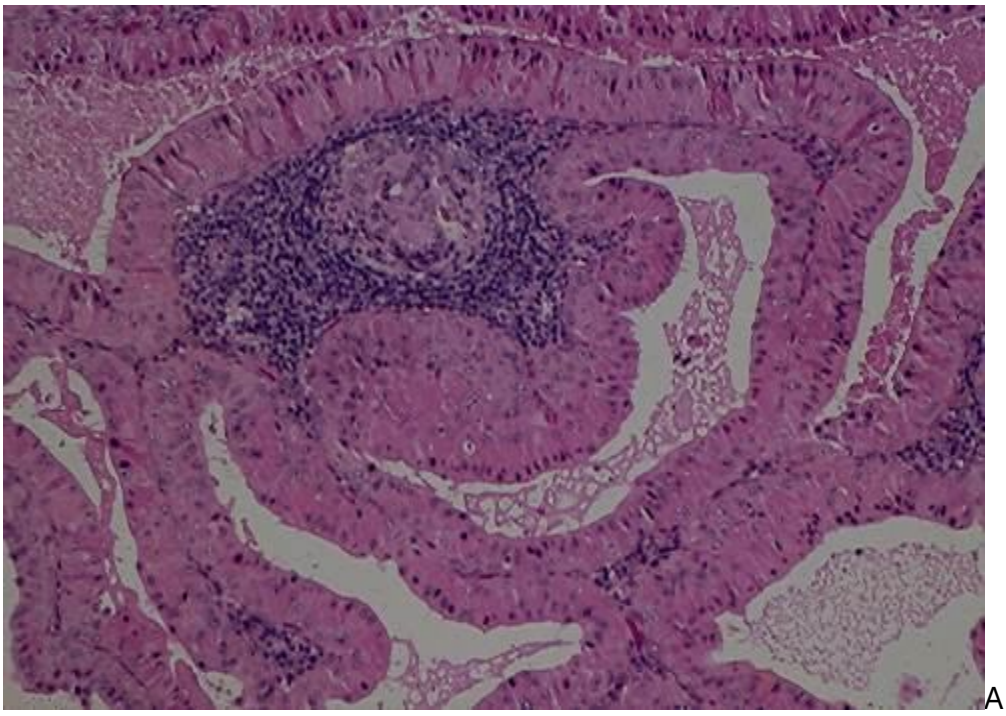
Fig.2.7. Pitfalls in PA cytology: A. Myxoid stroma suggests PA but the bland-appearing epithelial cells with metachromatic cytoplasmic granules favour acinic cell carcinoma. (CP, MGG) B. Adenoid globules in a PA showing a similar growth pattern as adenoid cystic carcinoma. (CP, Pap)

Monomorphic adenoma has several histologic variants such as adenolymphoma or Warthin tumor, oxyphilic adenoma or oncocytoma, basal cell adenoma, myoepithelioma and sebaceous adenoma.

Warthin tumor is the most common monomorphic adenoma of the salivary gland and accounts for 5-10% of all benign SGTs. The tumor predominantly arises from the lower pole of the parotid gland in patients over 60 years of age with a smoking history. It often has a characteristic soft, boggy texture to palpation. It usually undergoes cystic degenerative changes with turbid, rust-colored fluid contents and it is bilateral in 10-15% of cases. Histologically, it consists of oncocytic epithelial cells in solid and glandular patterns with stroma containing abundant lymphocytes often with germinal center formation. FNA reveals numerous benign lymphocytes, a variable number of sheet-like fragments of oncocytes that have abundant, granular cytoplasm and granular necrotic debris. Degenerated oncocytes or ghost cells may be present in variable number. Rare atypical oncocytes or atypical metaplastic squamous cells may be present and these cells may be mistaken for malignant squamous cells. (Fig.2.8).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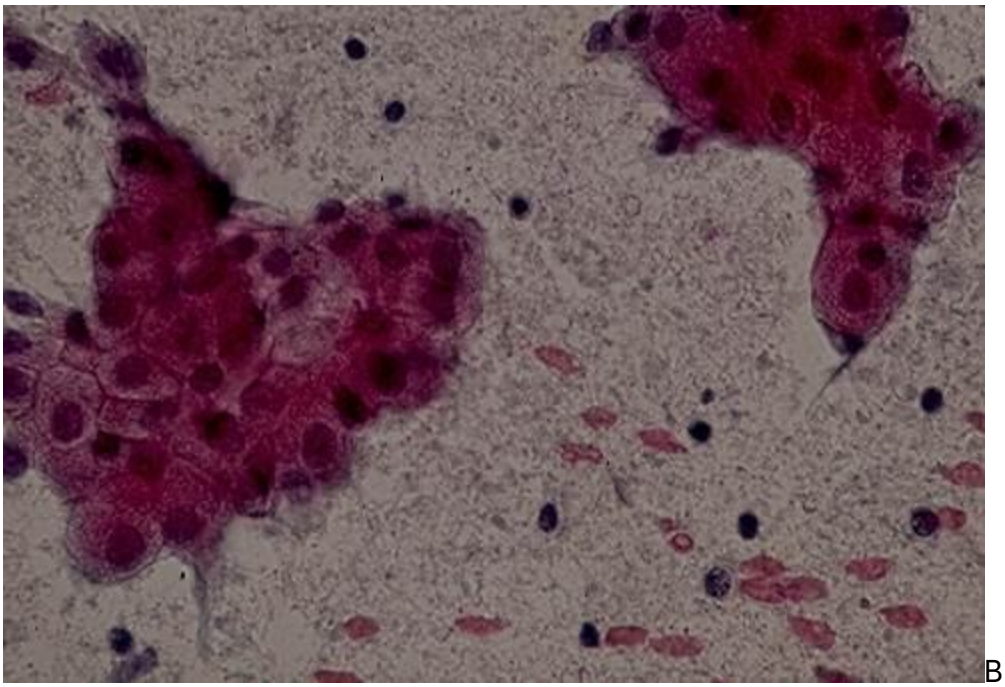

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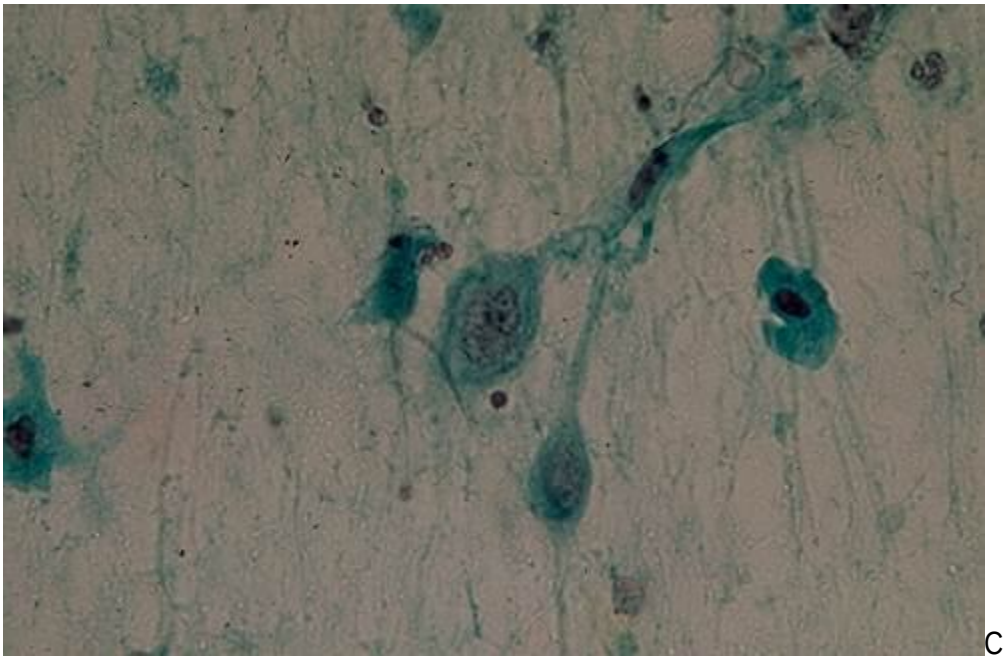
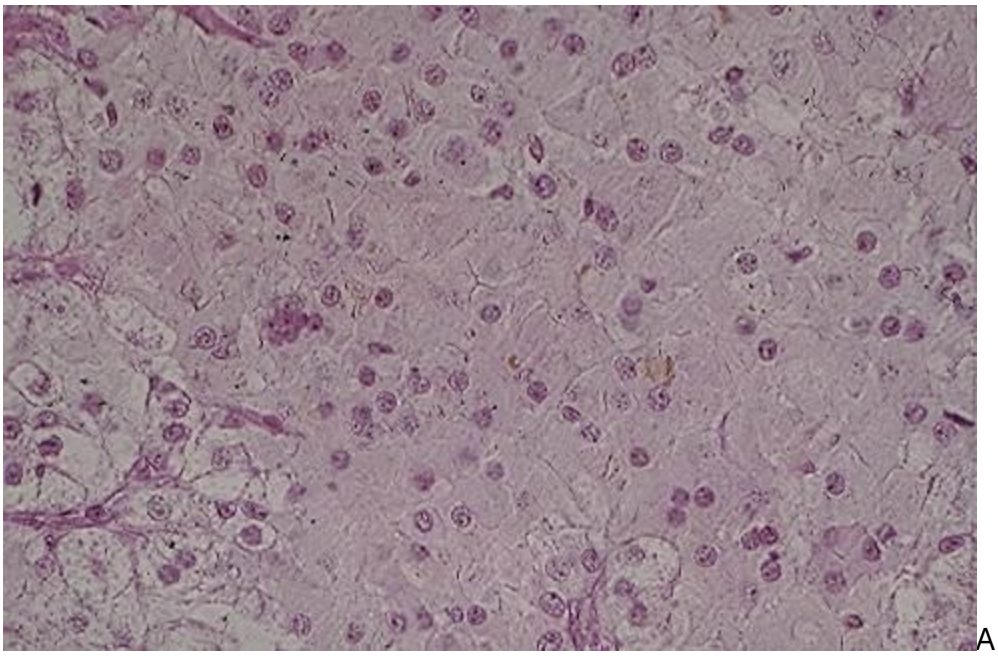


C

Fig.2.8. Parotid Warthin tumor: A. Histology of the tumor. (HE). B. FNA cytology of Warthin tumor: A. Monolayered sheets of oncocytes. (CP, Pap). C. Atypical squamous cells in a tumor with cystic degenerative change. (CP, Pap).

Oncocytoma is a rare salivary gland tumor that presents as a slow-growing, painless, firm and well-circumcribed nodule. It is characterised in FNA by abundant oncocytic cells that are predominantly arranged in cohesive monolayered sheets. (Fig.2.9). Cystic or inflammatory changes are usually not apparent or minimal.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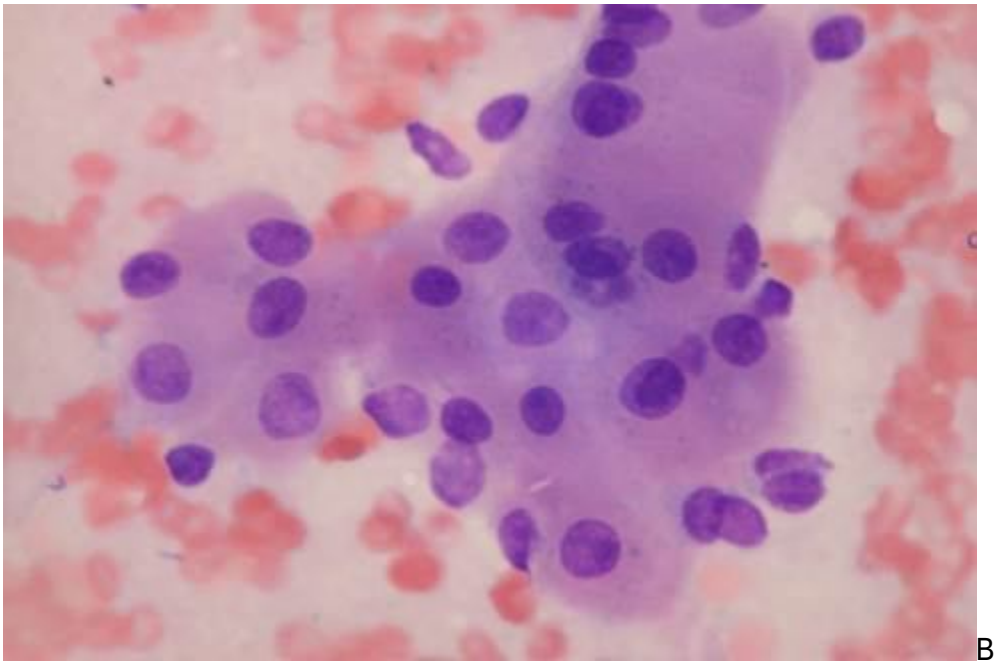
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Fig.2.9. Histology and cytology of a salivary gland oncocytoma: A. Histology of the tumor. (HE). B. Cohesive monolayered sheet of oncocytes with round, monomorphic nuclei. (CP, DQ).

Myoepithelioma is a rare tumor consisting exclusively of myoepithelial cells. It is characterised histologically by solid sheets of spindle tumor cells and amorphous granular stroma. In FNA the tumor is characterized by single and clustered spindle cells with scant cytoplasm and elongated nuclei arranged in a nonspecific pattern. There may be an amorphous background material that stains metachromatically with the DQ stain.

(Figs.2.10 and 2.11). The tumor cells show positive nuclear staining for p63 and express S-100 protein.

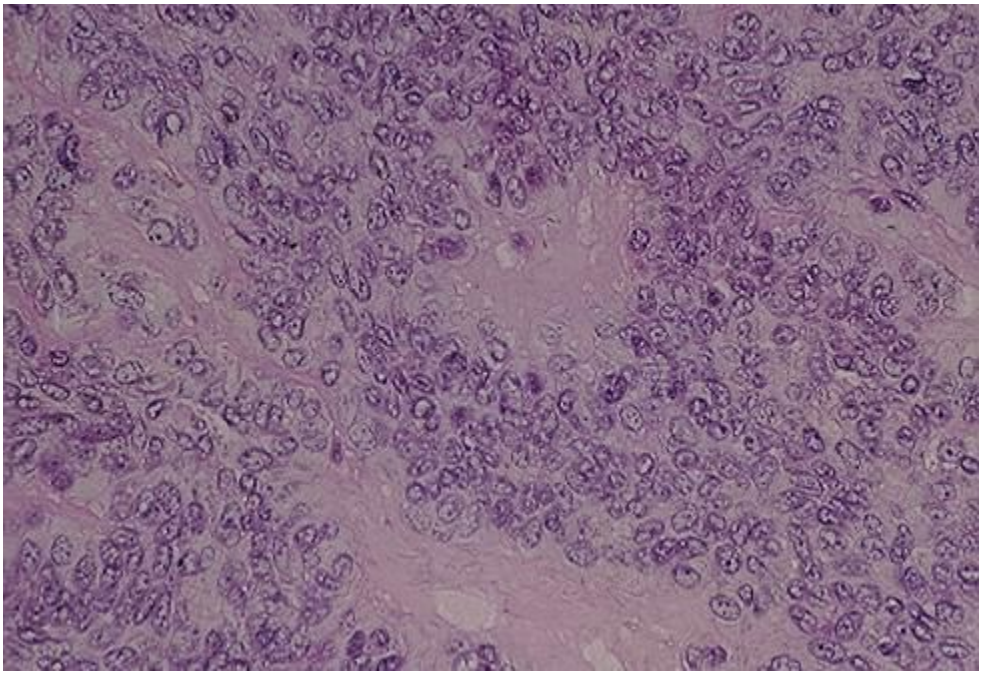
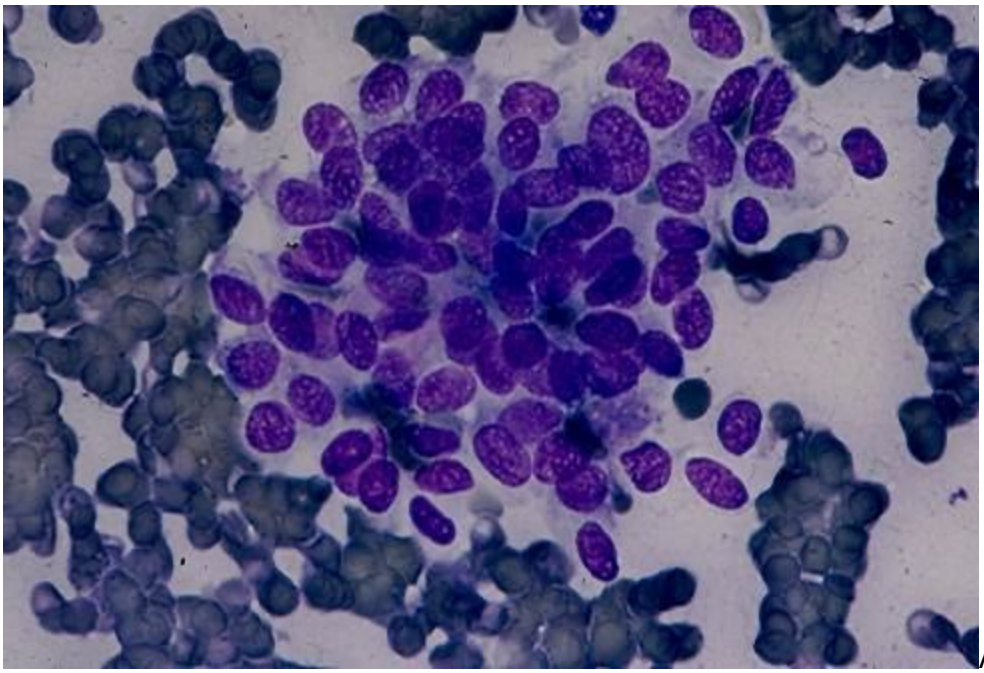


Fig.2.10. Histology of a salivary gland myoepithelioma. (HE)



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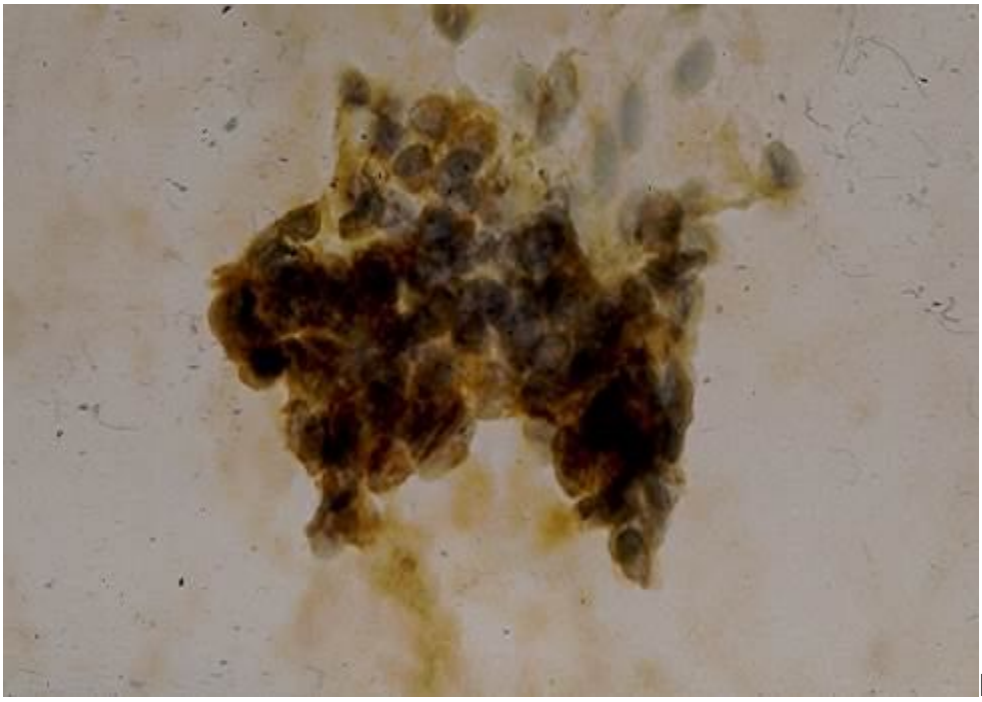
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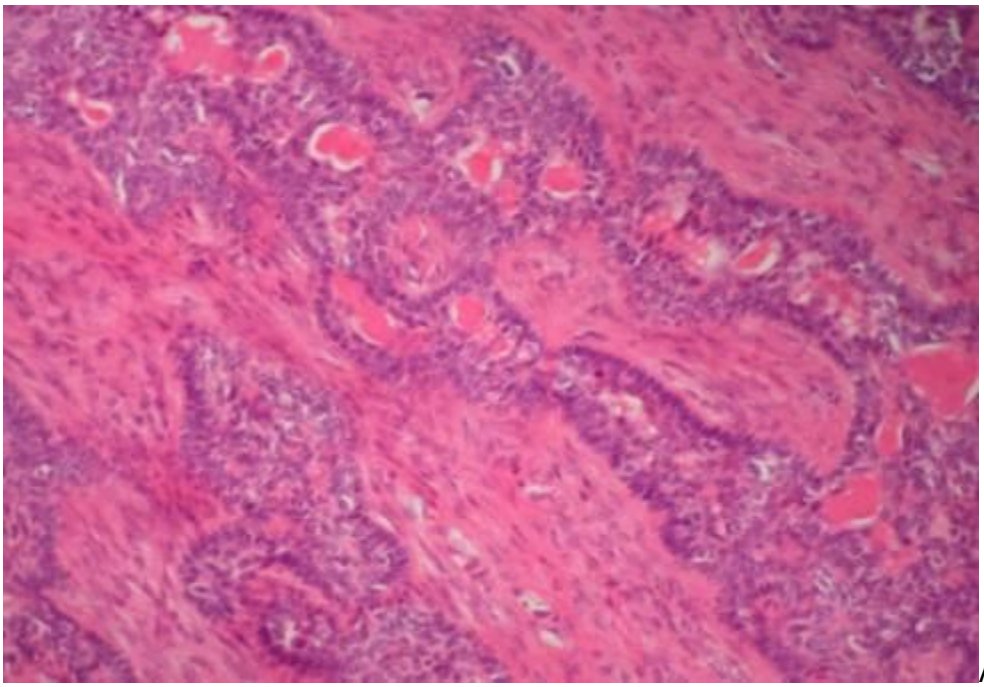
Fig.2.11. FNA cytology of a myoepithelioma showing: A. A cluster of tumor cells with oval nuclei and scant, ill-defined cytoplasm. (CP, DQ). B. The tumor cells stain positively with S-100 protein antibody. (ABC).

Basal cell adenoma is a rare neoplasm accounting for about 2% of all SGTs. The tumor occurs more commonly in adult patients in 6th decade of life and 75% of them arise from the parotid gland. There are two histologic variants: classic and membranous basal cell adenomas. Both variants have distinctive cytologic manifestations. The tumor cells are cuboidal in shape with round, bland nuclei and scant cytoplasm. They occur in large cohesive masses or sheets. In **classic basal cell adenoma** a small amount of basement membrane material is present. (Fig.2.12).



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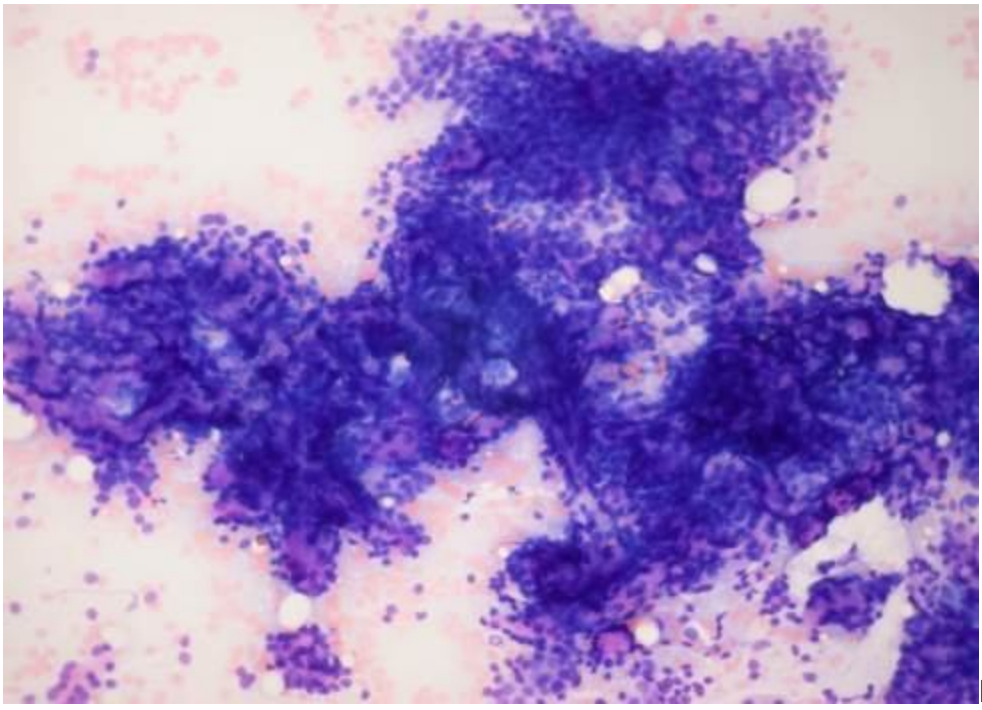

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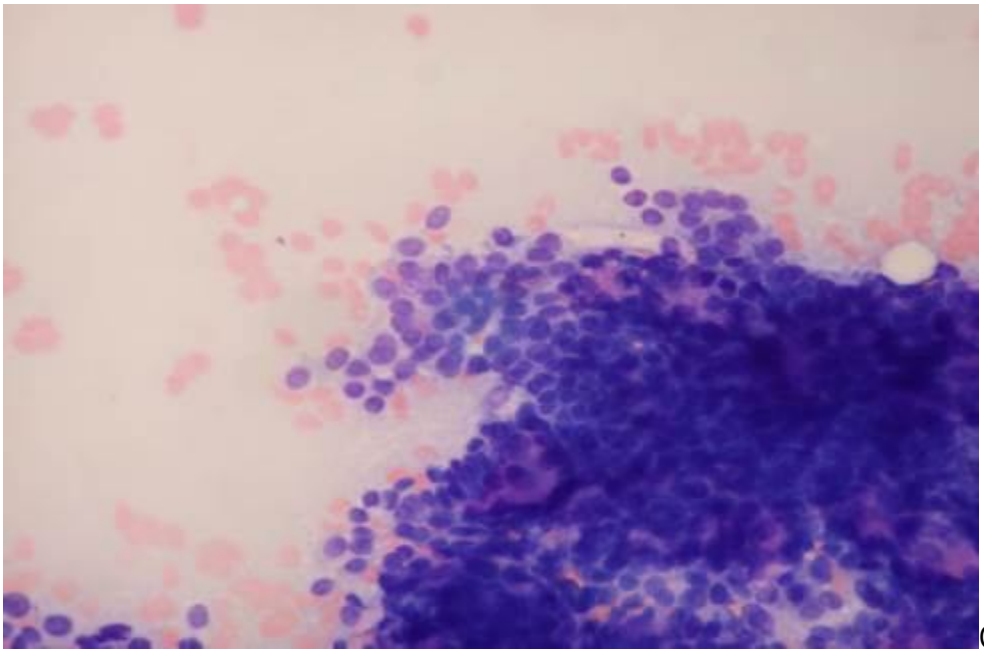
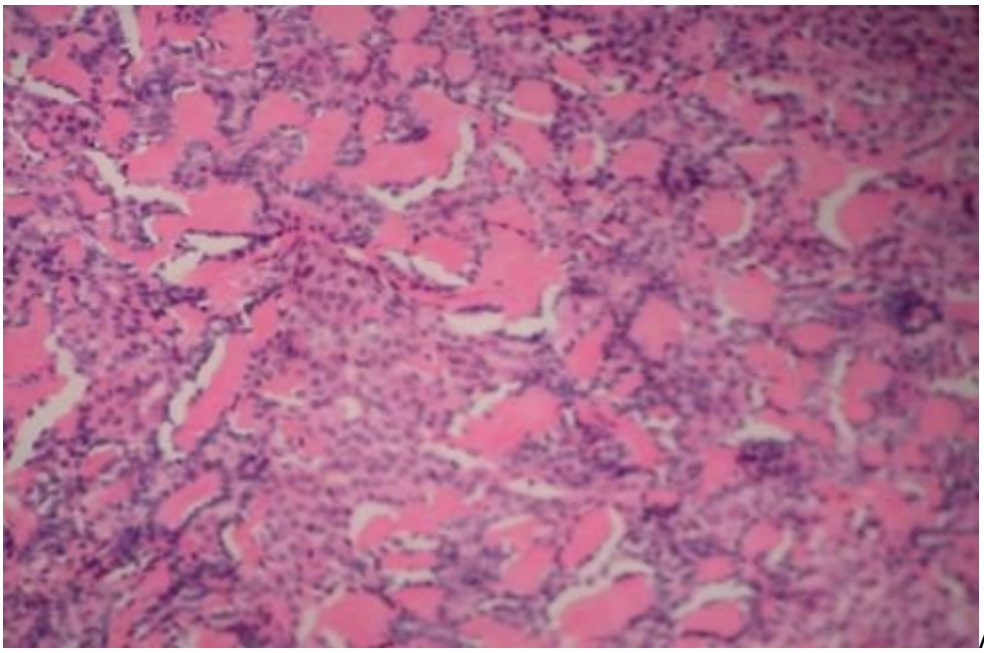
 C

Fig.2.12. Classic basal cell adenoma a salivary gland. A. Histology of a classic basal cell adenoma. (HE). B and C. The adenoma yields in FNA large and small cohesive groups of small benign tumor cells with round, bland nuclei. (CP, DQ).

Basal cell adenoma, membranous variant is characterized by abundant basement membrane material. It shows in FNA small round tumor cells surrounding round, granular, eosinophilic bodies, mimicking an adenoid cystic carcinoma. (Fig.2.13).

 A

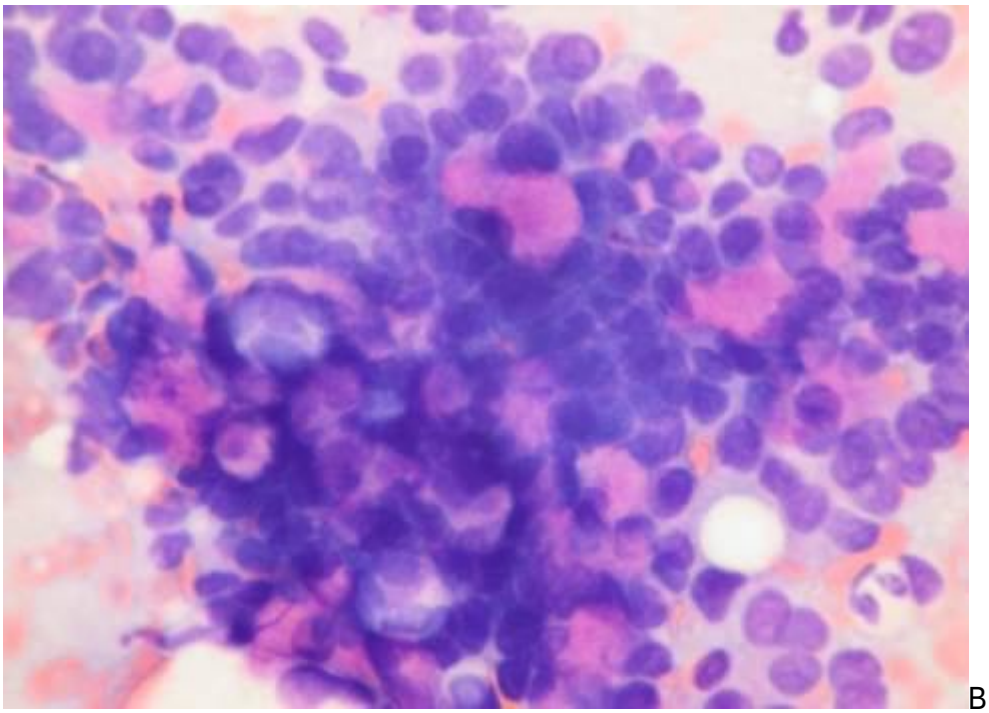

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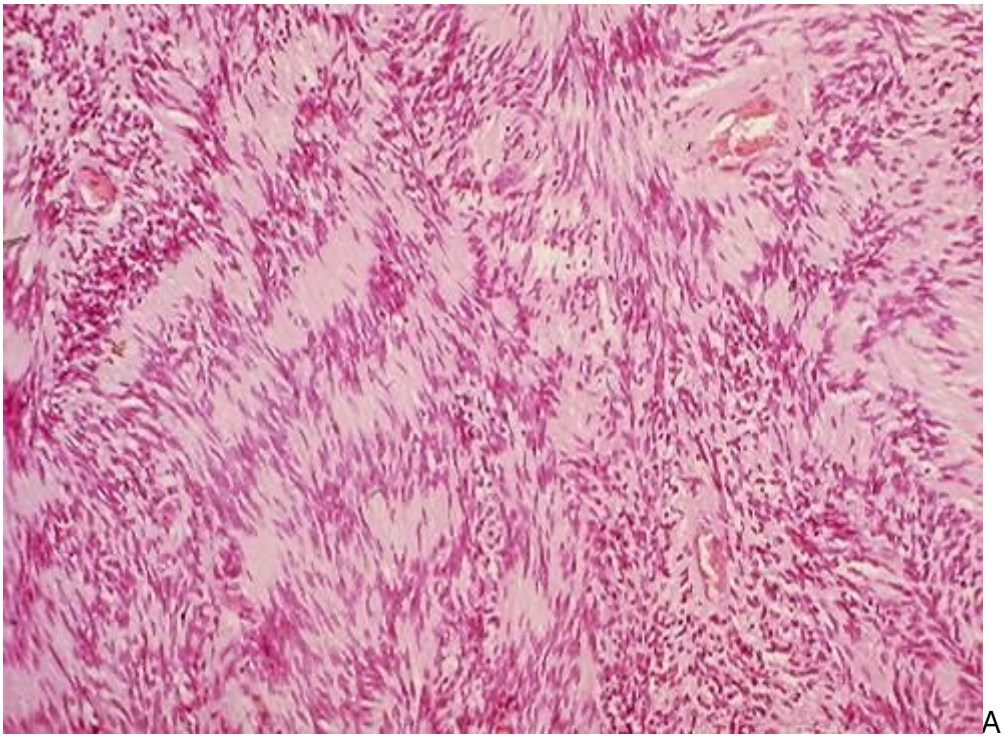
Fig.2.13. Membranous basal cell adenoma: A. Histology of membranous basal cell adenoma showing sheets of tumor cells admixed with a large amount of pink basement membrane material. (HE). B. FNA of the tumor showing cells arranged in acini containing a large amount of basement membrane material, mimicking an adenoid cystic carcinoma. (CP, DQ).

A sebaceous adenoma yields in FNA cells similar to those of a basal cell adenoma, but many cells with sebaceous differentiation are present.

Schwannoma, a benign neural tumor, rarely arises from facial nerve. FNA of the tumor will cause radiating pain. Histologically, schwannomas have a biphasic pattern with cellular Antoni A areas, consisting of interwoven fascicles of spindle cells with elongated nuclei in palisade forming Verocay bodies and relatively hypocellular Antoni B areas containing spindle cells in a loosely cellular background. (Fig.2.14) The two above mentioned components can be identified in tumor needle aspirates. (Fig.2.15)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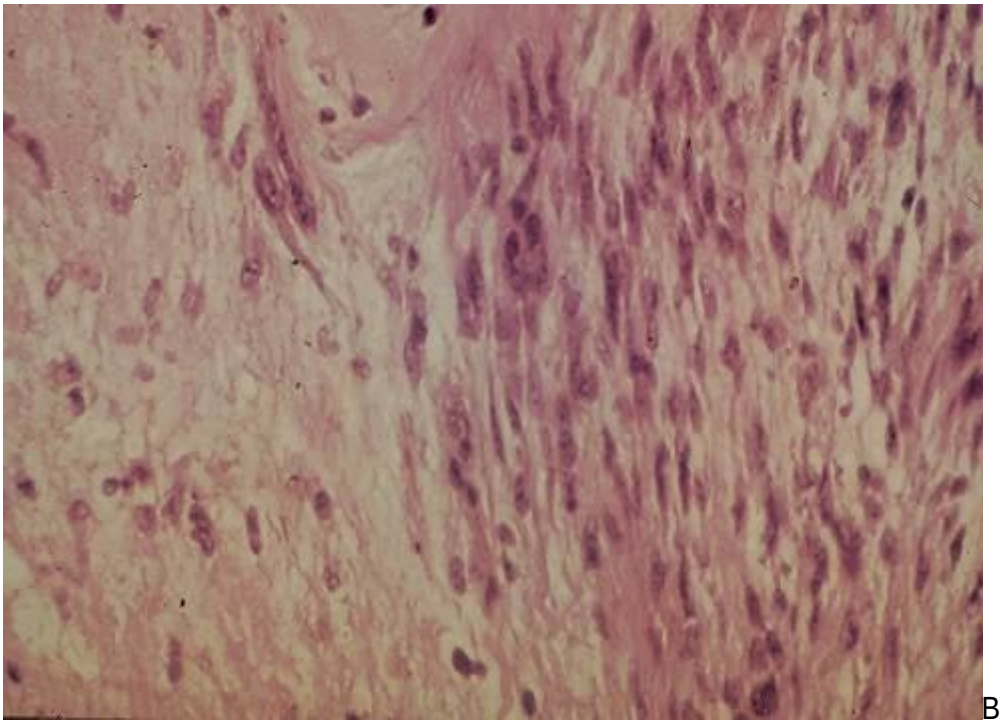
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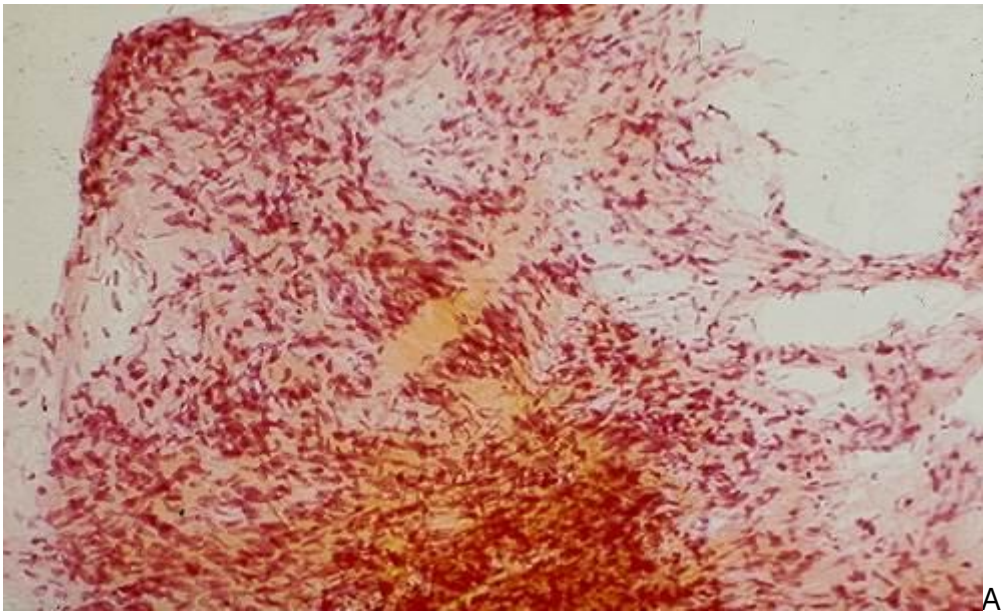
Fig.2.14. Histology of a schwannoma. A. Area of Antoni A in figure A and areas of Antoni A and Antoni B in figure B. (HE)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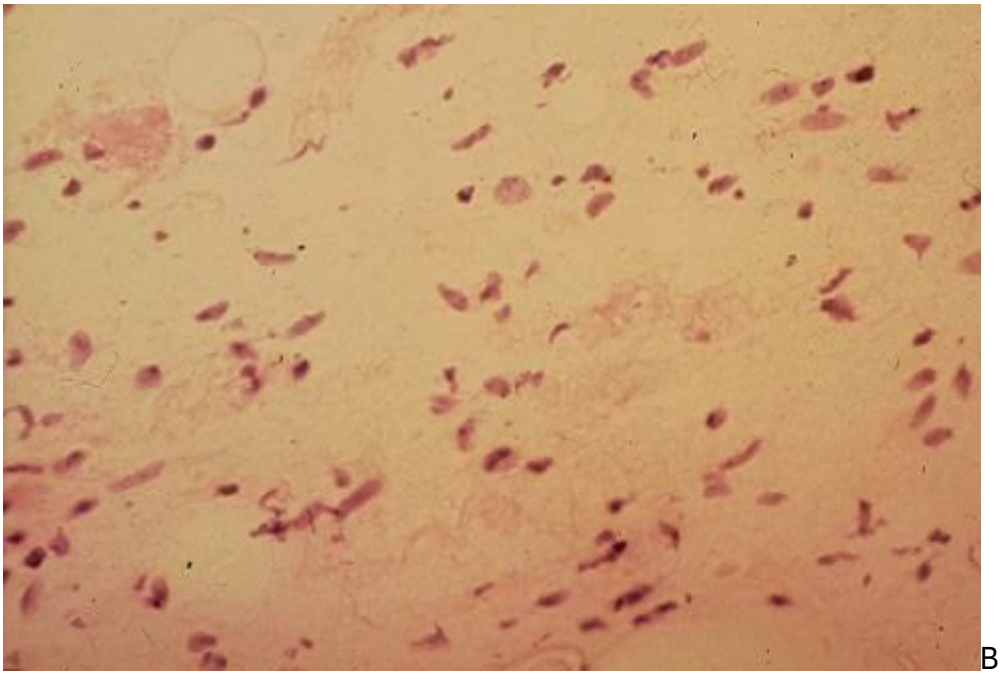
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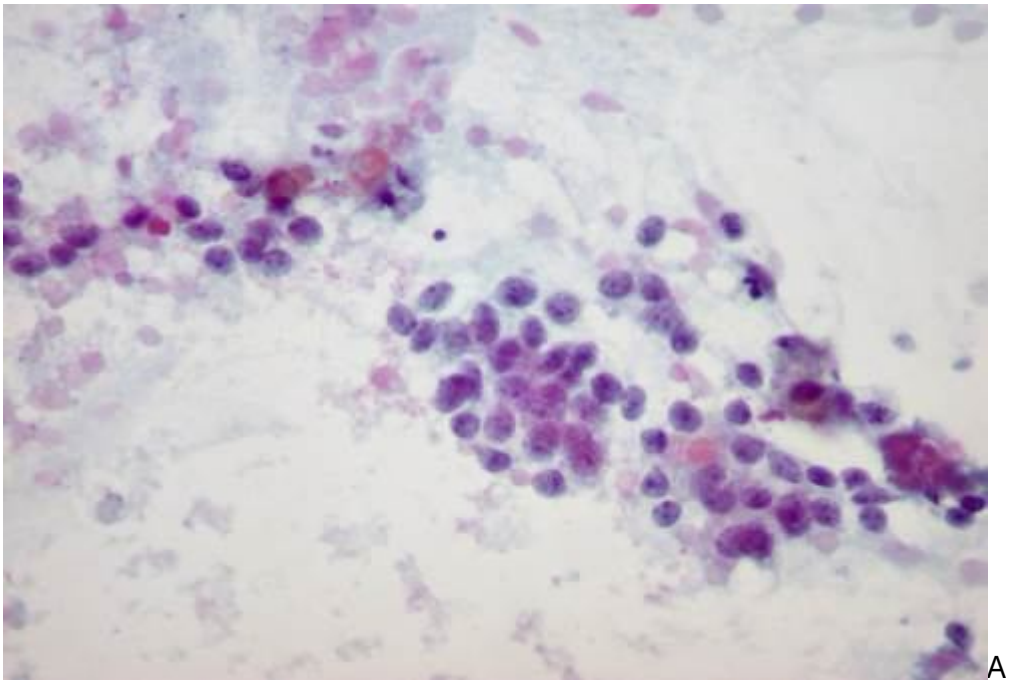
Fig.2.15. A and B: FNA of a schwannoma showing in A bundles of spindle cells with elongated nuclei in palisade or Verocay body and in B a loose myxomatous material containing spindle cells. (CP, Pap). Courtesy of Dr. K. C. Suen, Vancouver, BC, Canada.

Pilomatrixoma is a benign skin adnexal tumor that occurs in the head and neck (occasionally mimicking a parotid tumor) or in the upper extremity, usually before the age of 20 years. The growth especially in young children can be rapid raising concern for malignancy. FNA material is usually cellular with a mix of cohesive clusters of undifferentiated or epidermoid basaloid cells, anucleated cells in clusters (ghost cells),

multinucleated giant cells and necrotic debris. Mitoses may be present in undifferentiated basal cells. (Fig.2.16).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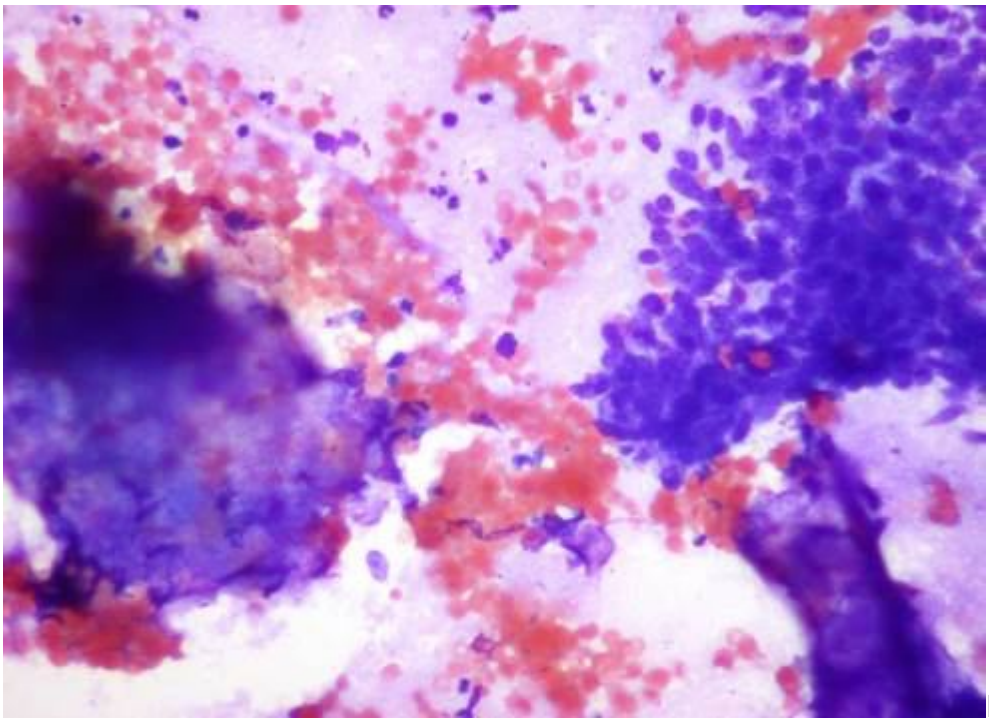
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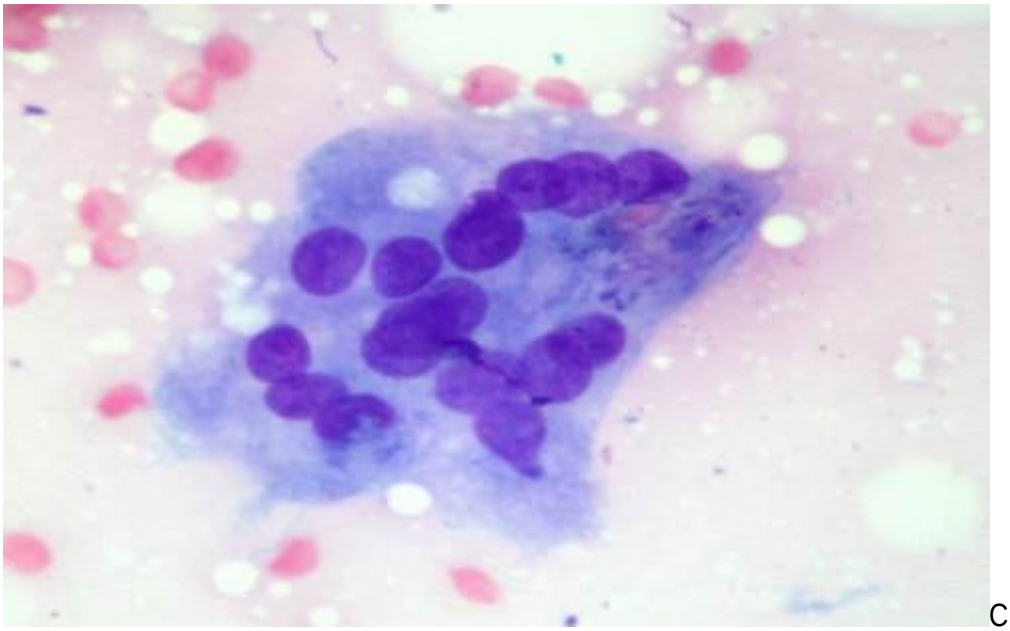

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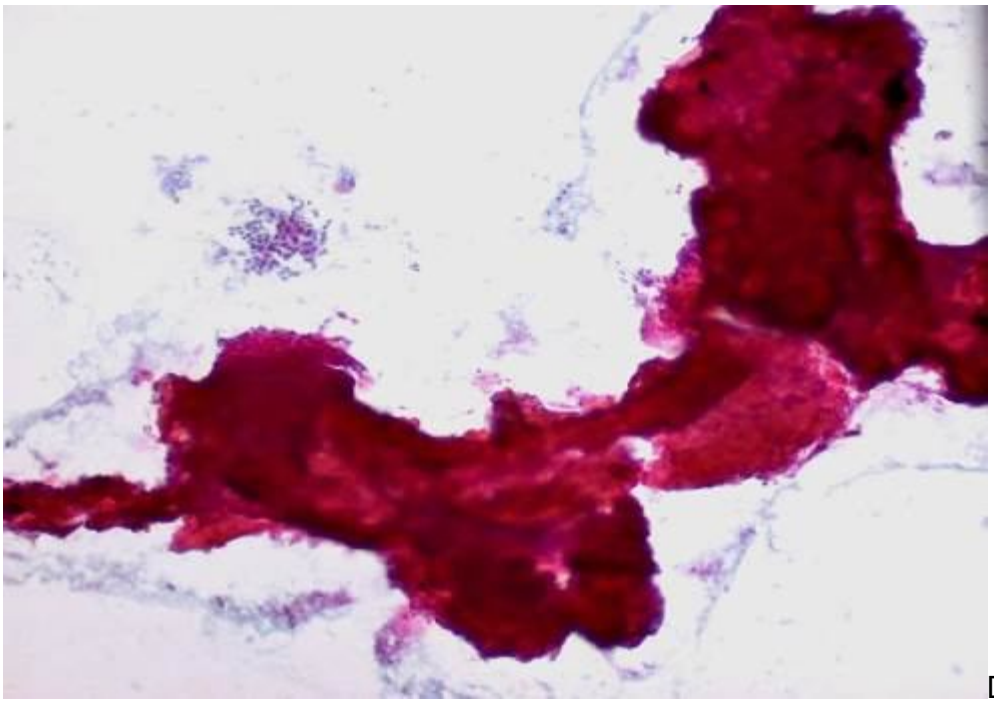


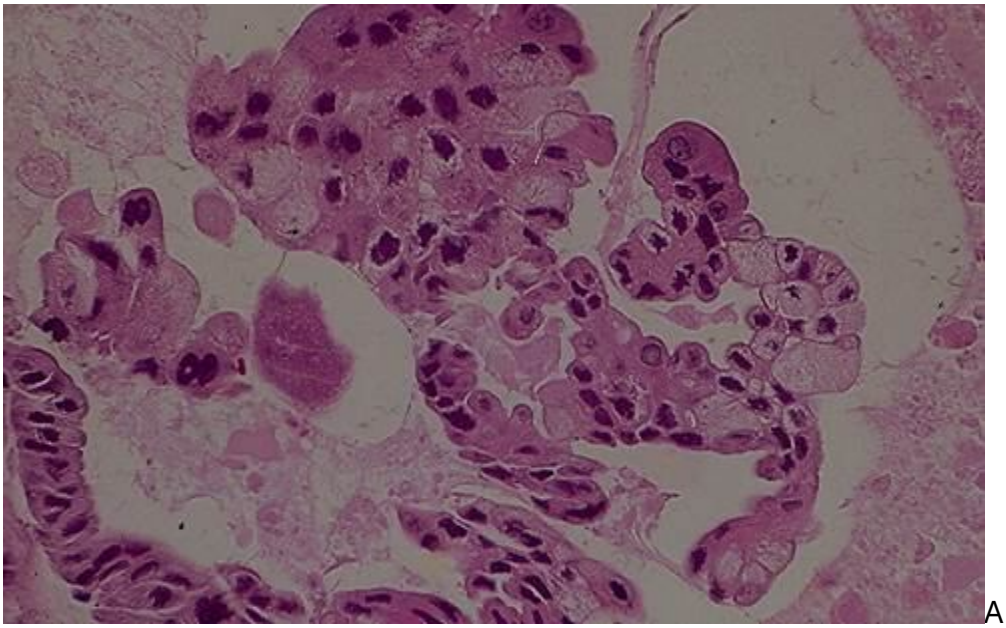
D

Fig.2.16. FNA of a pilomatrixoma showing: A. Clusters of undifferentiated small basaloid cells. (CP, Pap). B. Cohesive clusters of small basaloid cells and anucleated squames (ghost cells). (CP, MGG). C. A multinucleated giant cell of foreign body type. (CP, MGG). D. Fragments of anucleated squames. (CP, Pap).

Malignant epithelial tumors

Mucoepidermoid carcinoma (MEC) is the most common cancer of the salivary glands. Large tumor may undergo cystic degenerative changes with mucous contents admixed

with inflammatory cells. MEC may be classified as low- or high-grade depending on the degree of nuclear atypia of the epithelial cells, the extent of mucinous differentiation, the presence of necrosis and the growth pattern. (Figs.2.17 and 2.18) Mucus-secreting cells that have large cytoplasmic vacuoles and bland nuclei are abundant in low-grade tumors but rare in high-grade tumors. High-grade tumors may resemble non-keratinizing squamous cell carcinomas. Mucus cells are rare and difficult to visualize without staining with mucicarmine or PAS with prior diastase digestion. Low-grade tumors have a 5-year survival rate greater than 90% while high-grade tumors have a 5-year survival rate ranging from 20 to 40%.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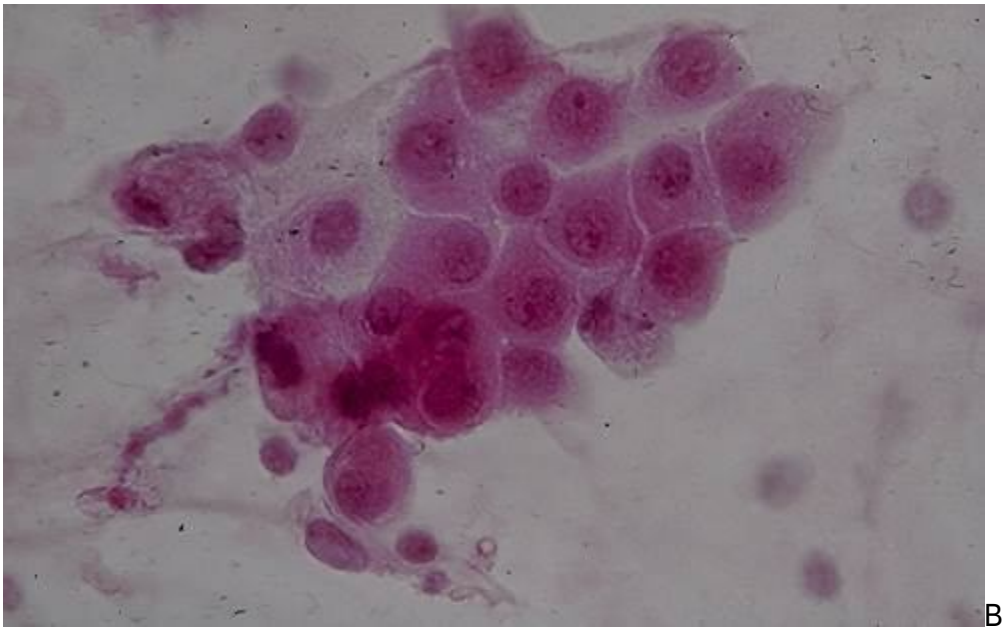
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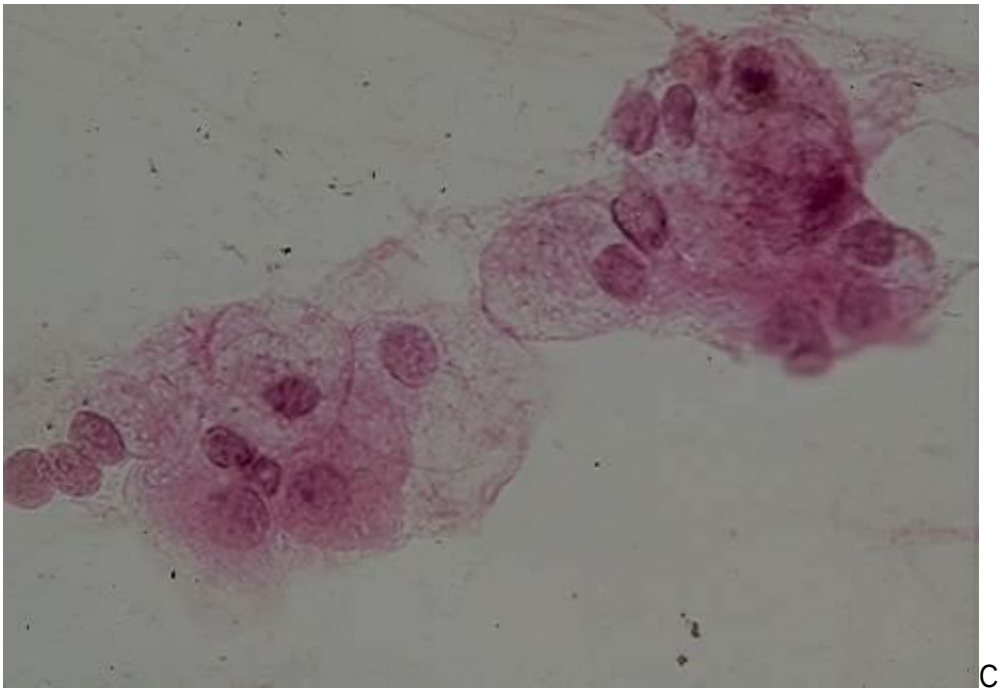
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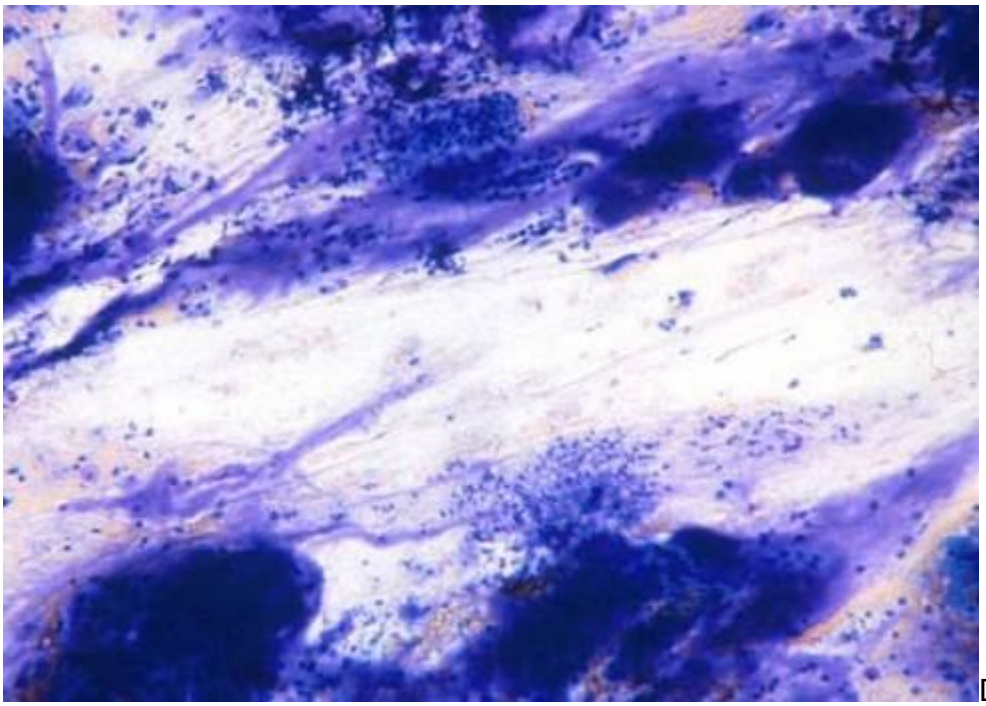
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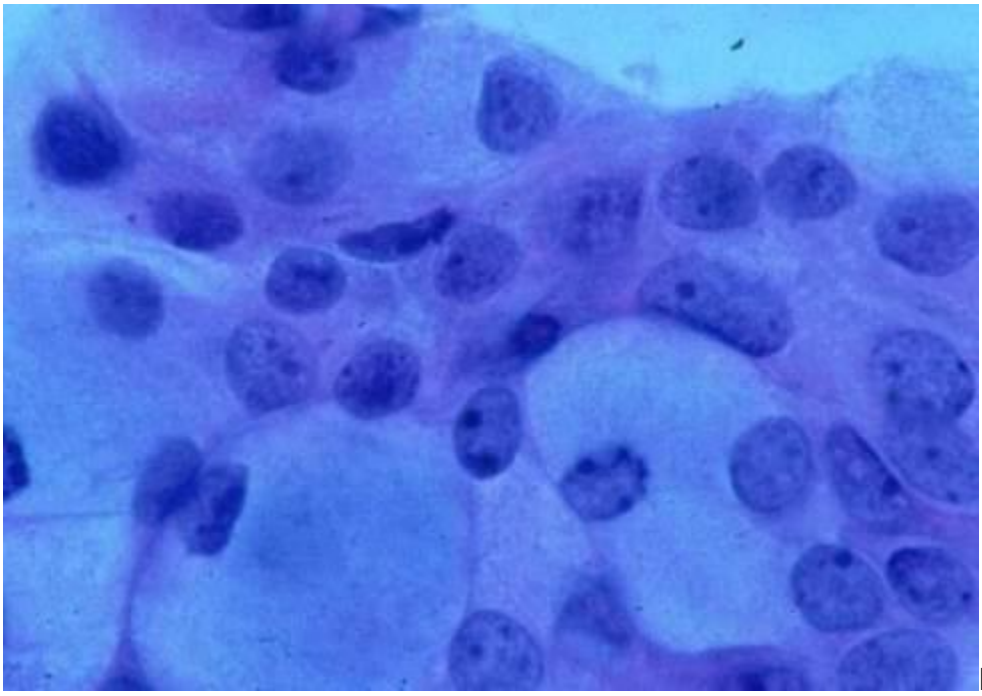
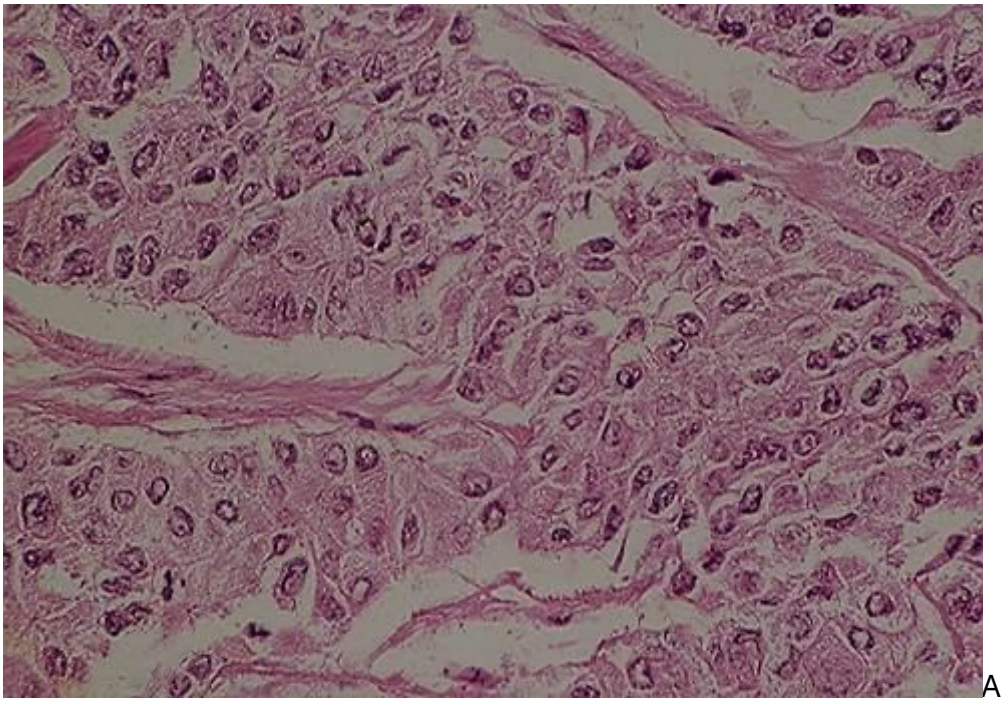


E

Fig. 2.17. Low-grade mucoepidermoid carcinoma: A. Histology of a low-grade MEC with cystic change. (HE). B, C. FNA of the tumor showing a sheet of benign appearing squamoid cells in B and two clusters of mucus secreting epithelial cells in C. (CP, Pap). D. Thick mucus from a low-grade MEC. (CP, MGG). E. A cohesive sheet of epidermoid cells and mucous cells. (CP, Pap, oil immersion).



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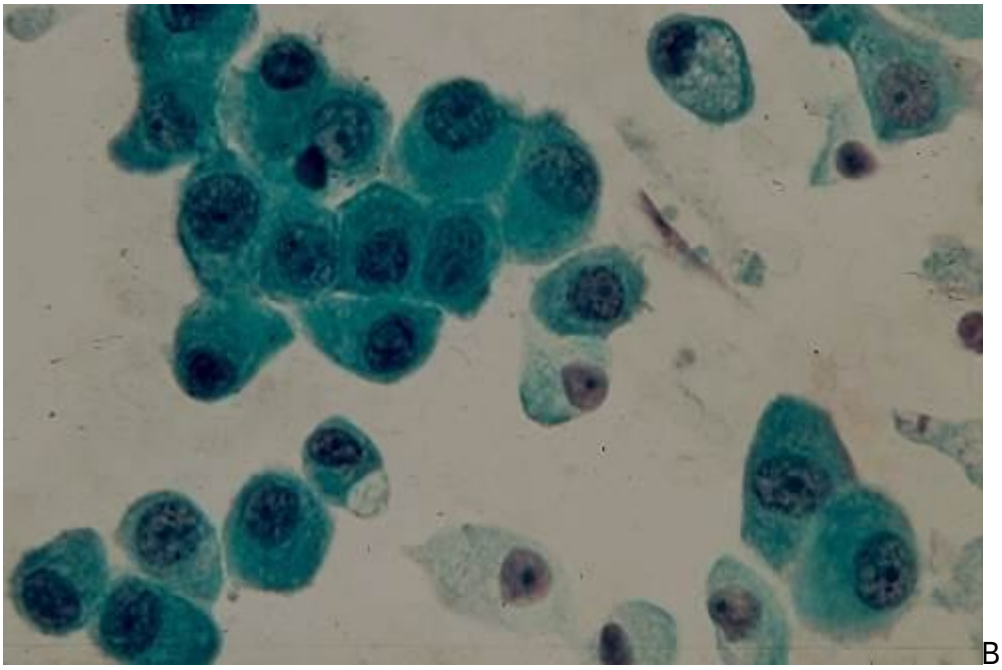
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Fig.2.18. High-grade mucoepidermoid carcinoma: A. Histology of a high-grade MEC showing solid sheets of more pleomorphic squamoid cells with conspicuous nucleoli.
B. Tumor FNA displaying single and clustered malignant squamoid cells with some showing a plasmacytoid configuration and intracytoplasmic mucus. (CP, Pap).

Adenoid cystic carcinoma accounts for about 10% of all SGTs and represents a greater percentage of malignant tumors arising in minor salivary glands. The tumor is commonly seen in patients between 40 and 60 years of age. Histologically, it is composed of a monomorphous population of small tumor cells with scant cytoplasm, so called basalloid cells, and small nucleoli may be present. The tumor cells are arranged in solid sheets, trabeculae or lobules with cystic spaces or cribriform arrangements that contain either eosinophilic basement membrane-like material or mucus. (Fig. 2.19). FNA from the tumor reveals three-dimensional spherical clusters of tumor cells wrapping around globules of basement membrane-like material and surrounding dispersed naked tumor cell nuclei. Cylindrical cell groups with central matrix cores, solid ball-like cell groups without matrix and irregular sheets of tumor cells with round, empty spaces may be present. Careful examination of sharply marginated cell groups may reveal a thin rim of surrounding basement membrane material. (Figs.2.20 and 2.21). Matrix material and globular bodies stain pink with HE, blue with Papanicolaou stain and purplish (metachromatic) with DQ or MGG method. Importantly, unlike PA, the background does not contain dispersed myoepithelial cells.

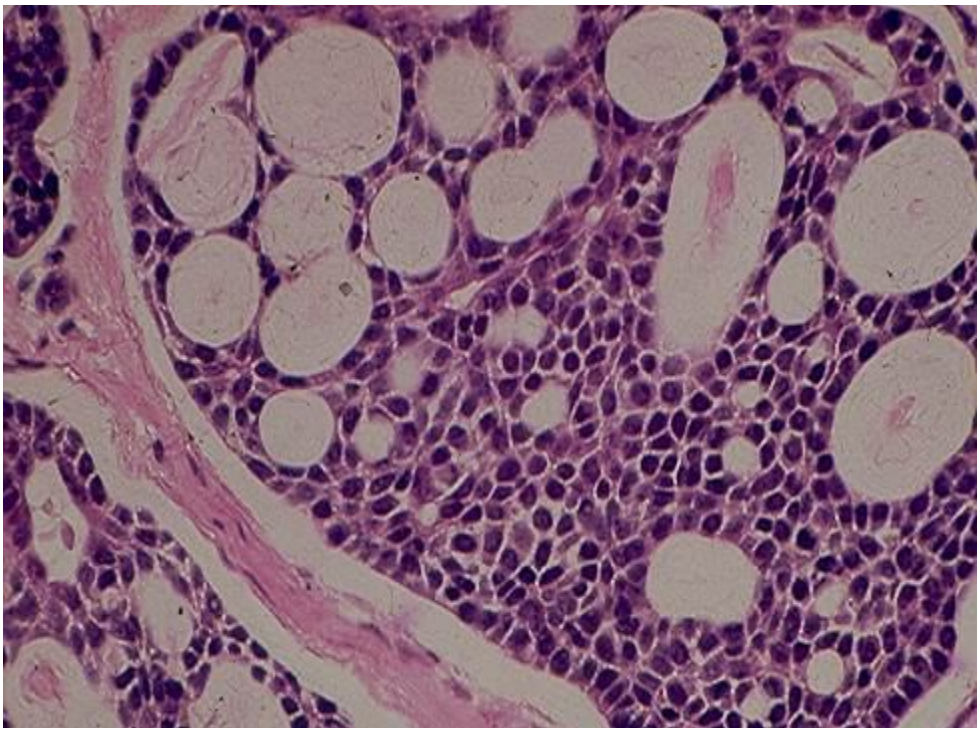
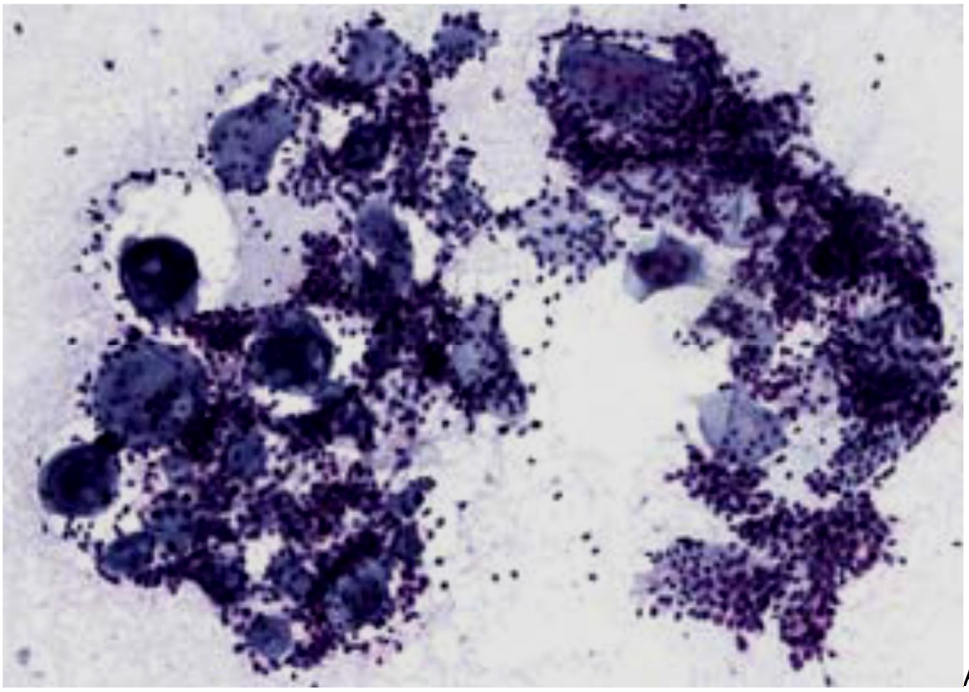


Fig.2.19. Histology of an adenoid cystic carcinoma of the parotid. (HE)



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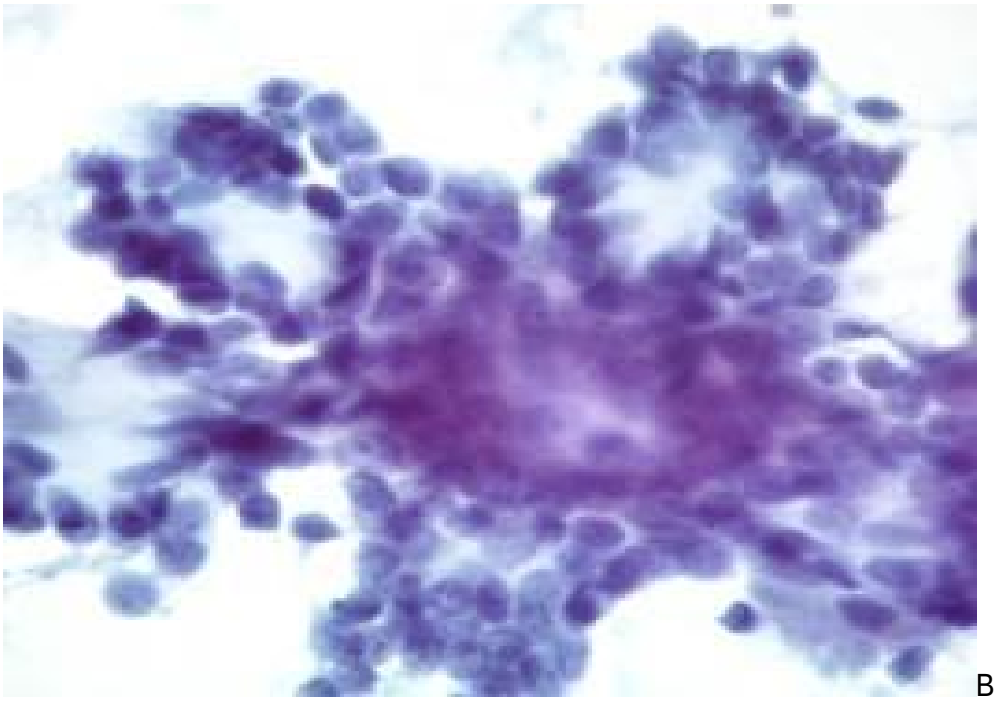

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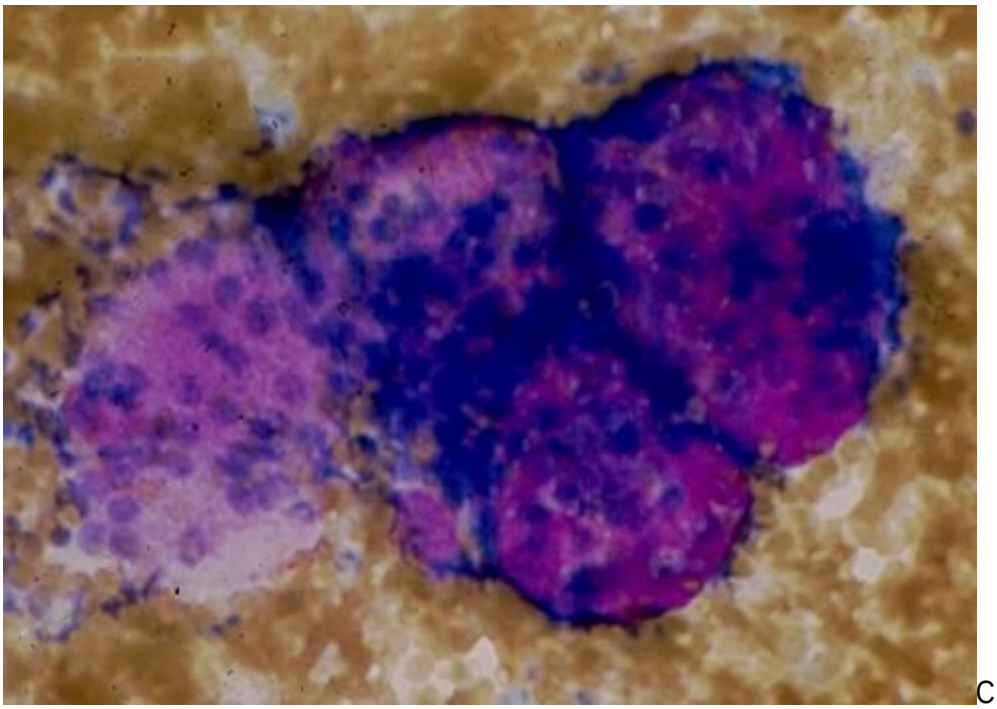

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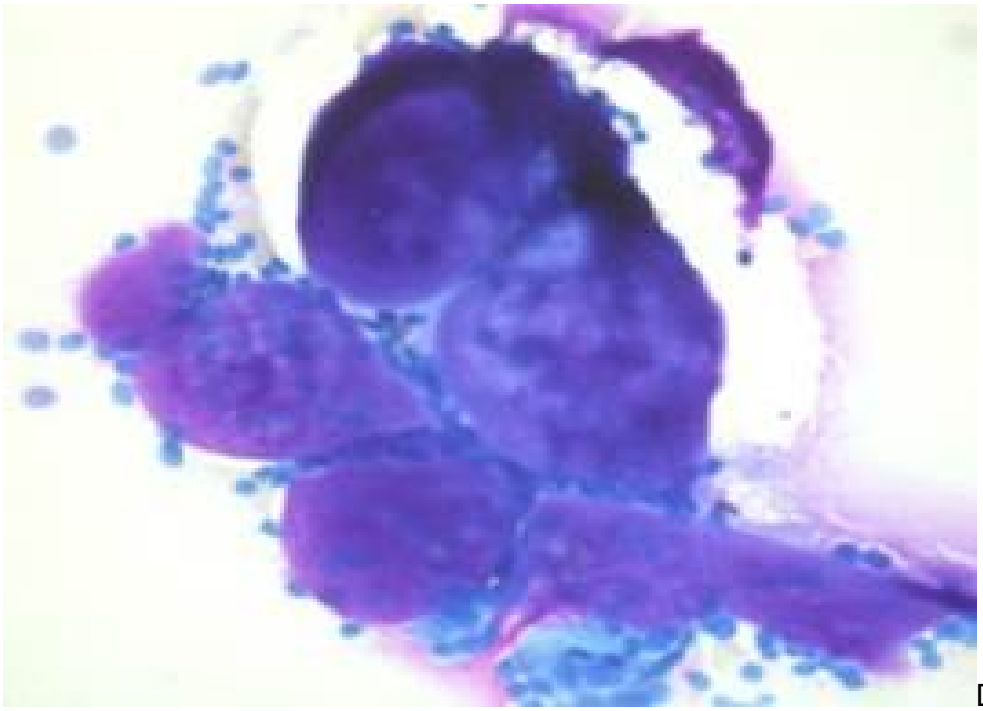

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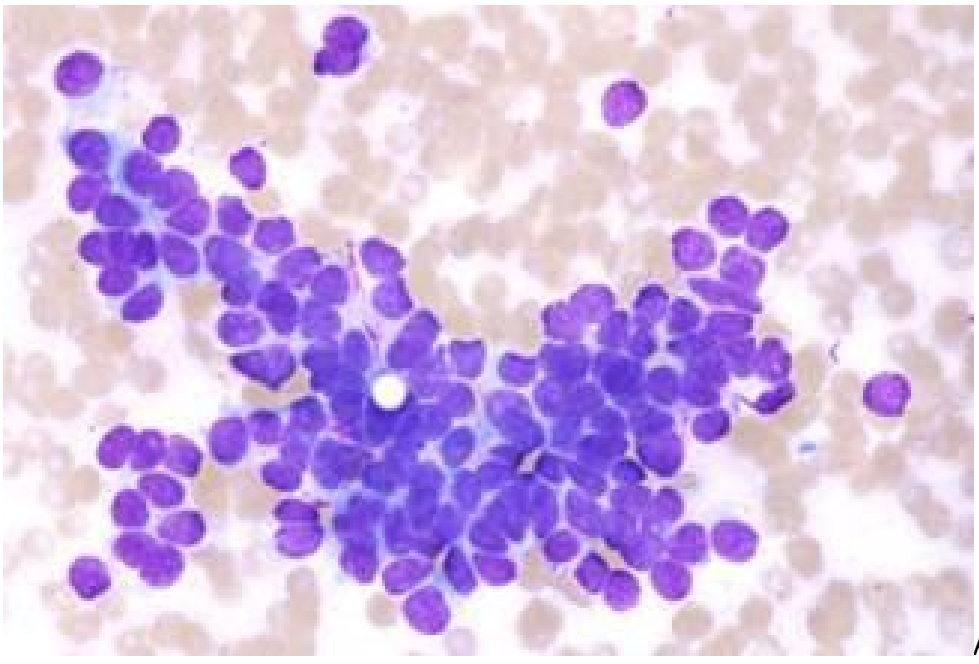
Fig.2.20. FNA of adenoid cystic carcinoma: A-D. Small tumor cells wrapping around globular bodies. (A, B, CP, Pap; C, D, CP, MGG)



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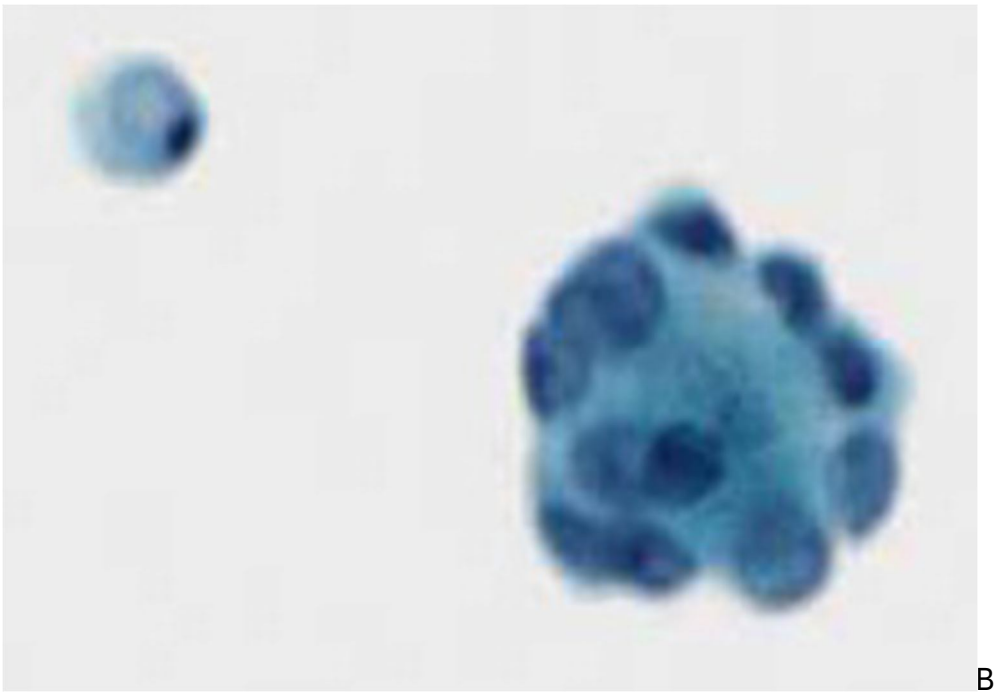

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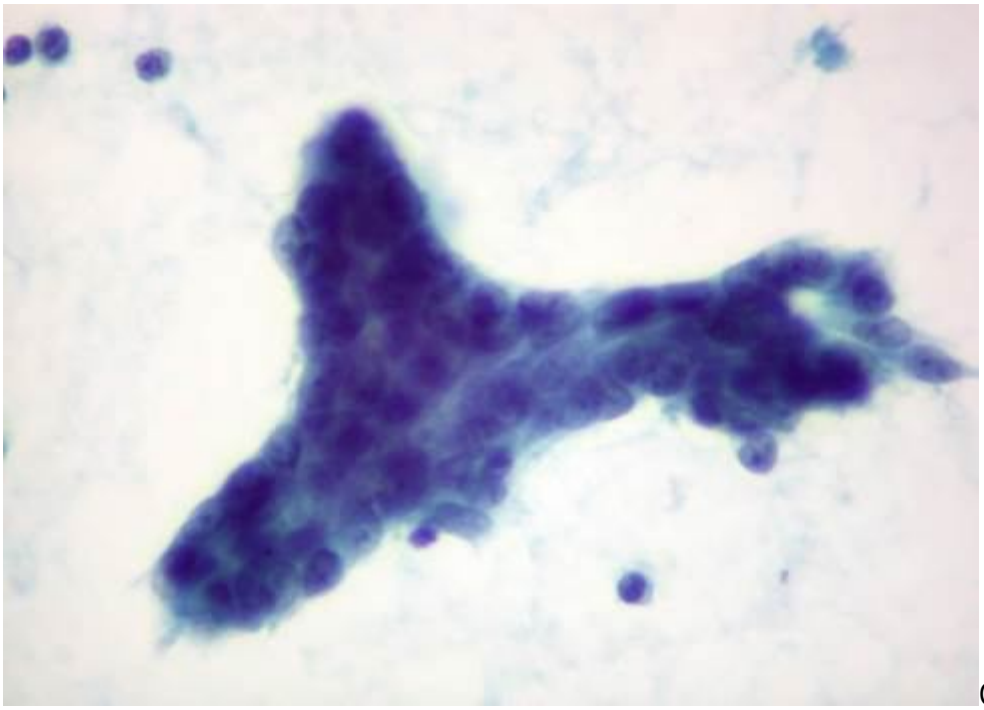

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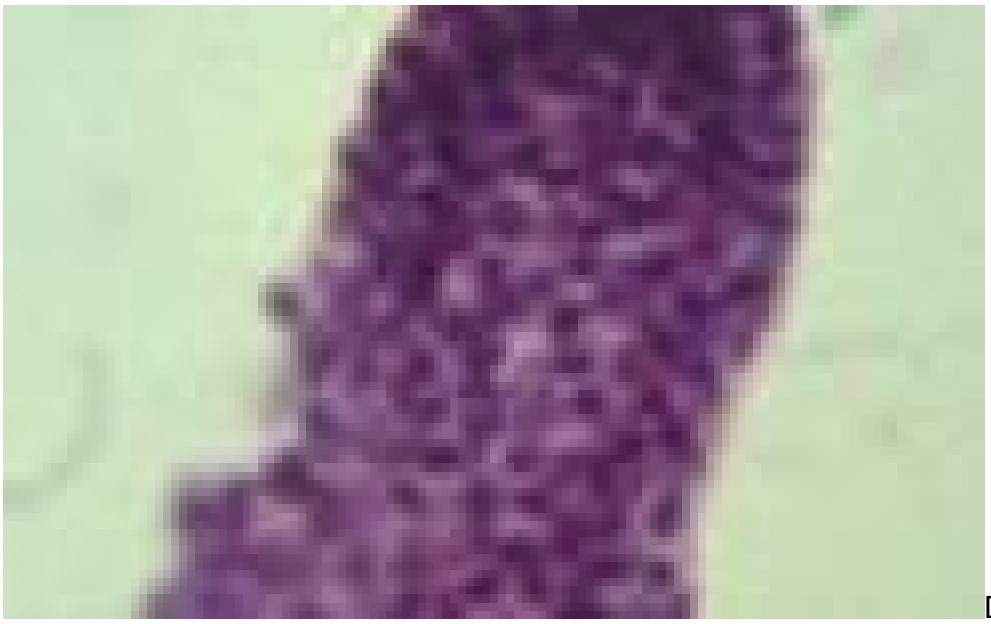
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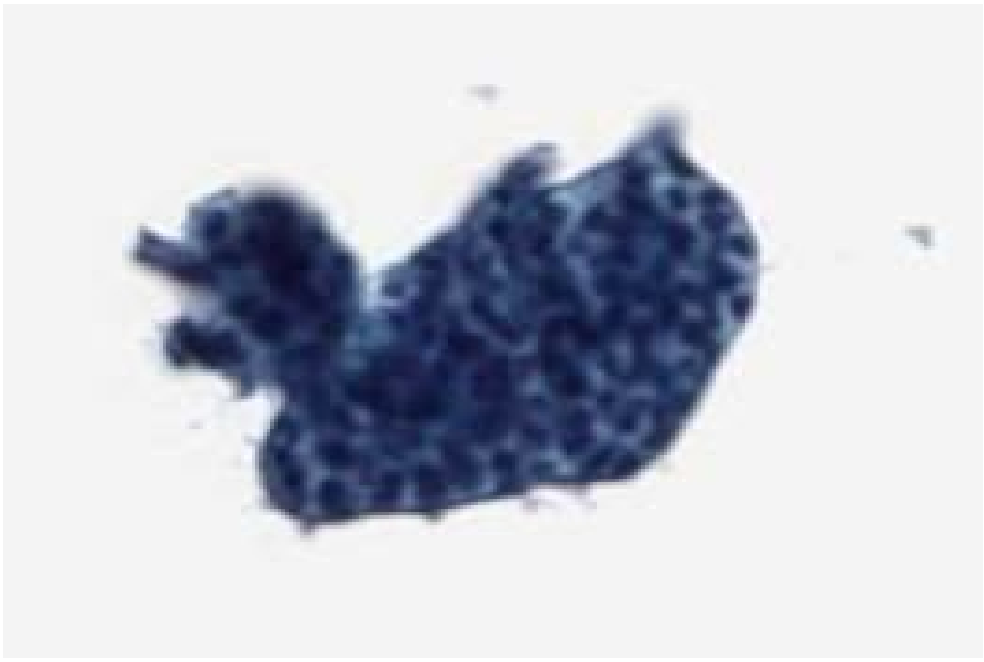
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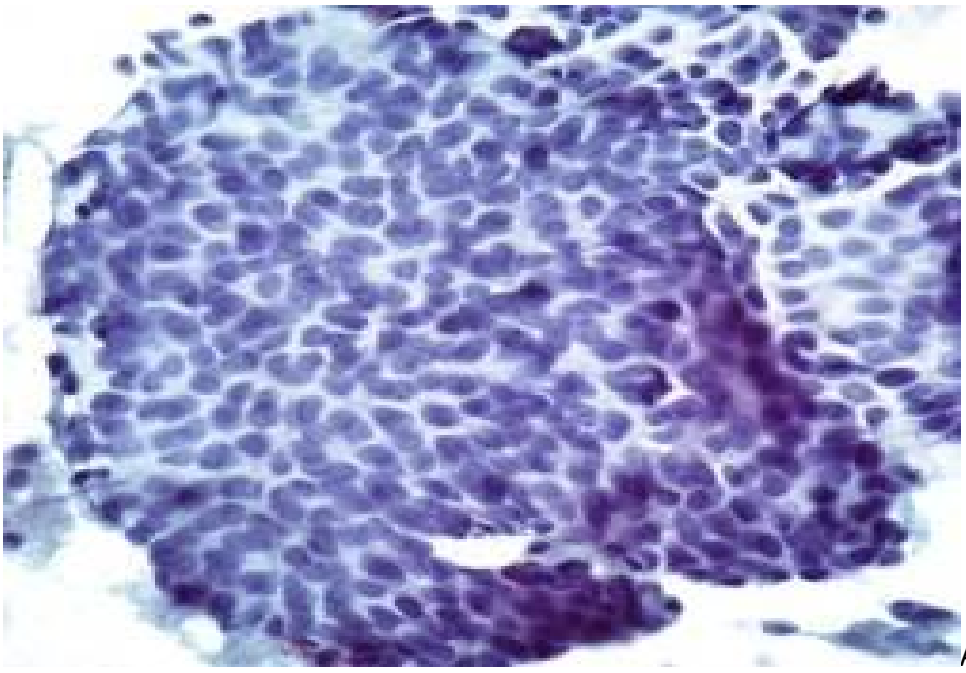
Fig.2.21. FNA of adenoid cystic carcinoma: A. Loose group of round basaloid cells with scant cytoplasm. (CP, MGG). B. Globular cluster of basaloid cells surrounding a tiny hyaline ball. (LBP, Pap). C-E. Papillary tumor tissue fragments with 2 (D and E) being partially surrounded by a thin rim of basement membrane material. (C, D. CP, Pap; E. LBP, Pap)

High-grade adenoid cystic carcinoma often grows as solid tumor lobules without adenoid hyaline cores of basement membrane material. It shows in FNA tight clusters and sheets of small malignant cells. (Fig. 2.22)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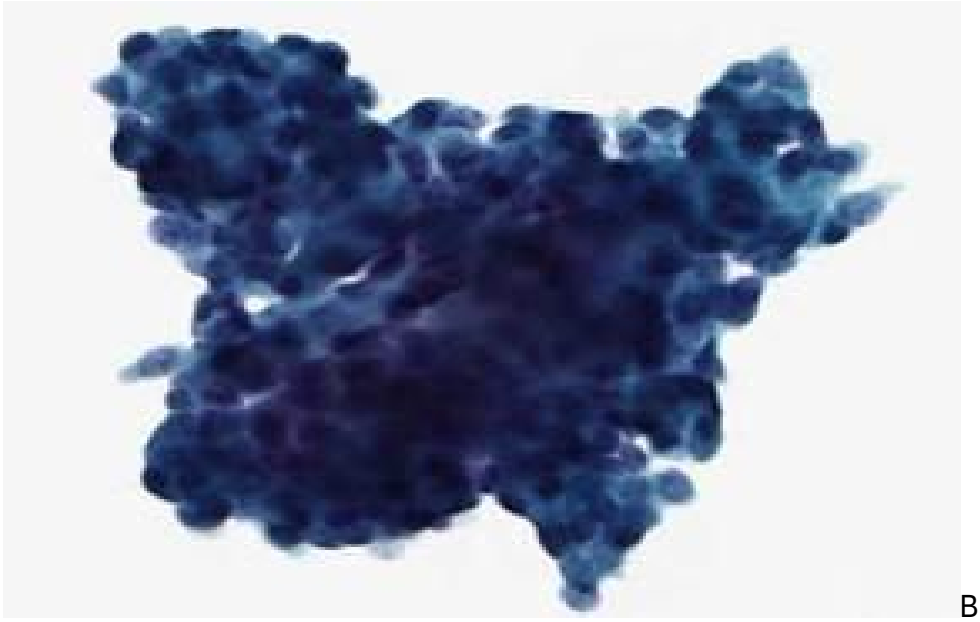
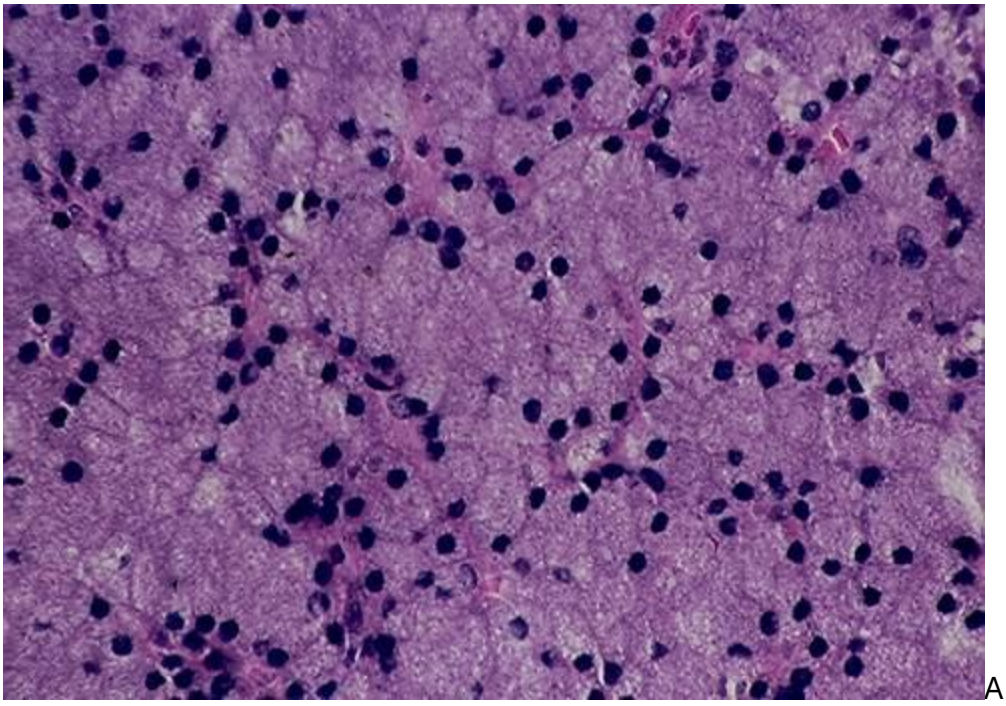

B

Fig. 2.22. A, B. High-grade adenoid cystic carcinoma, solid growth pattern, showing in FNA cohesive sheets or clusters of small malignant epithelial cells. (LBP, Pap)

Acinic cell carcinoma is a rare tumor and accounts for about 2% of all SGTs. It occurs predominantly in the parotid gland in women in their middle-age years. It can be occasionally seen in children. The tumor often has a solid growth pattern although papillary, tubular and cystic patterns are not unusual. The tumor cells resemble serous acinar cells, pyramidal in shape with finely vacuolated cytoplasm or show coarse cytoplasmic granules. FNA from the tumor reveals abundant polygonal cells with variably abundant granular or foamy delicate cytoplasm and round nuclei with fine chromatin,

distinct micronucleoli or occasionally macronucleoli. The tumor cells are seen arranged singly or in monolayered sheets. (Figs.2.23 and 2.24). A background of stripped nuclei resembling lymphocytes is commonly noted. These nuclei should be distinguished from true lymphocytes that can also be present. Giemsa stain may reveal coarse intracytoplasmic metachromatic granules that are helpful in making a correct cytodiagnosis. (Fig.2.25). These granules are PASD positive but mucicarmine negative, a helpful finding for separating an acinic cell carcinoma from a low-grade MEC which is sometimes a problem.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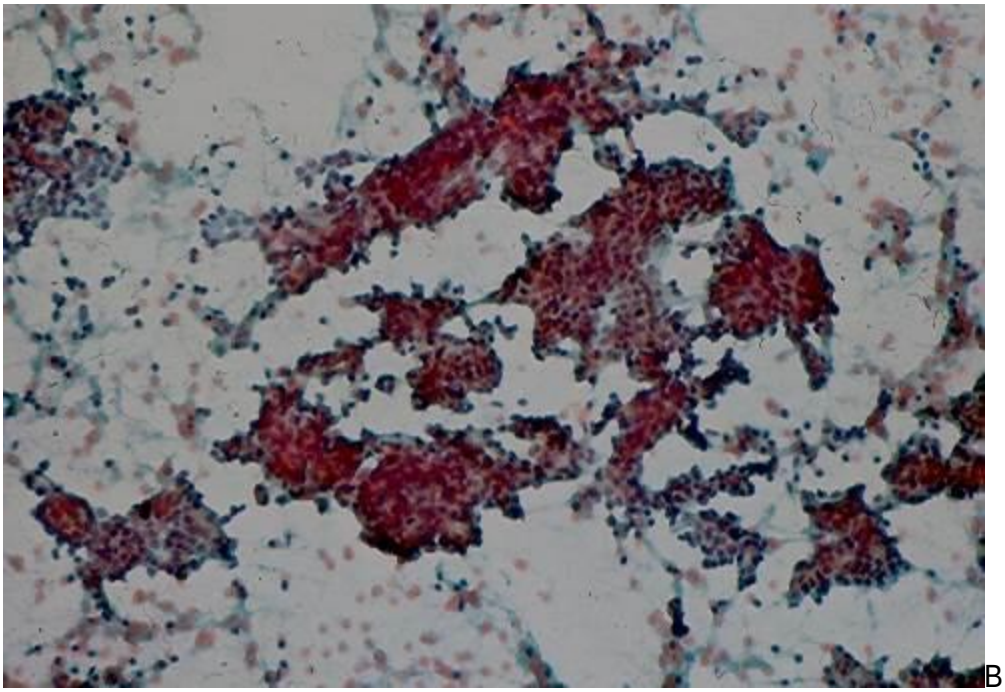
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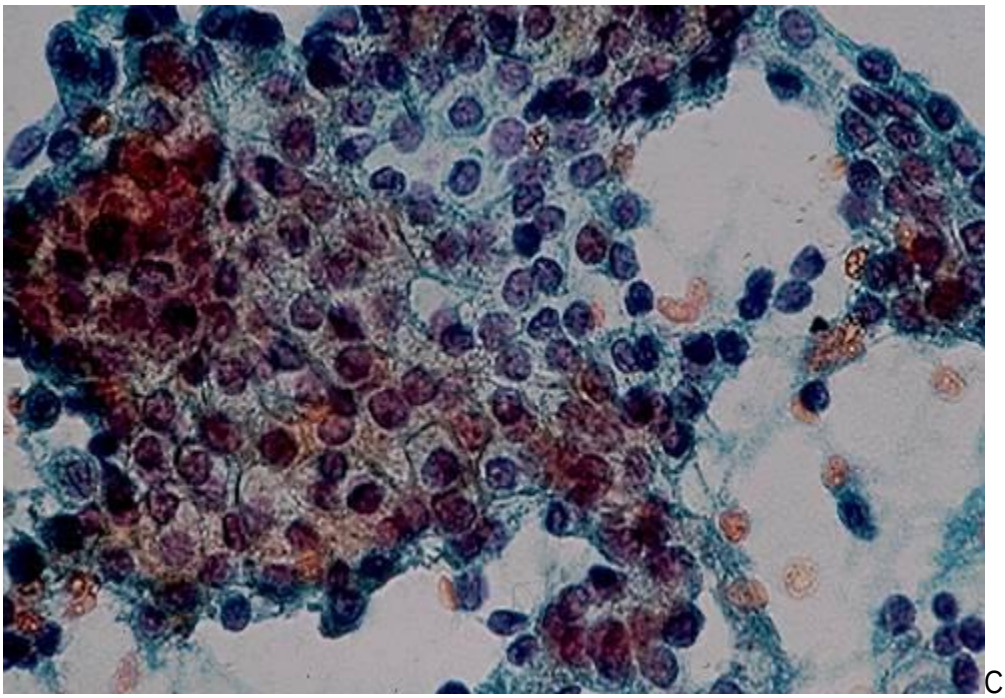
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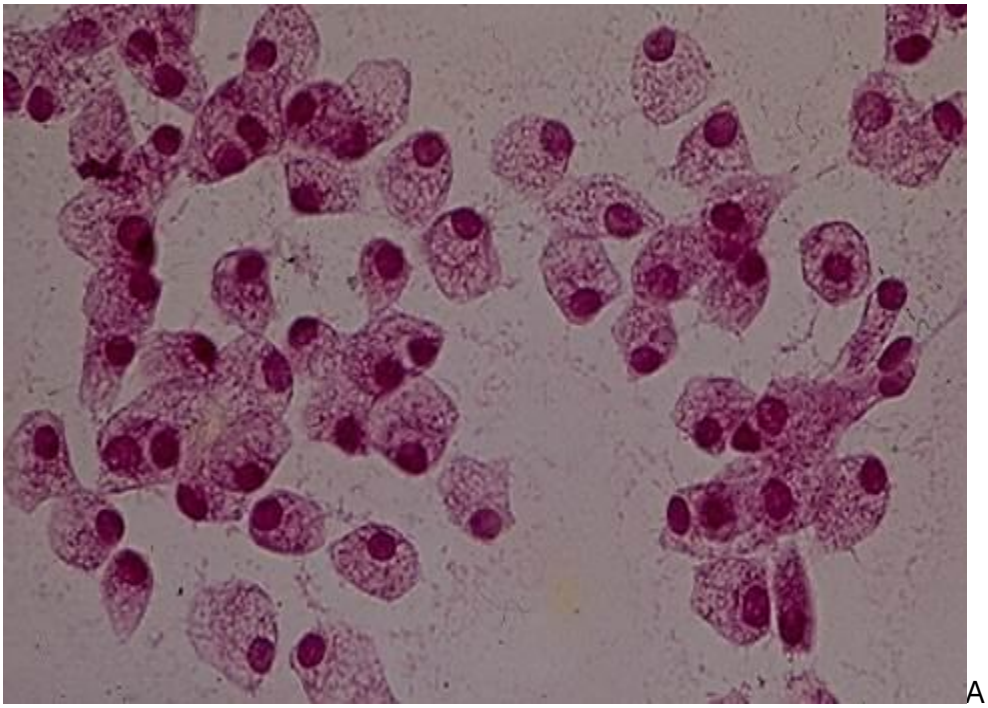
Fig.2.23. A. Histology of acinic cell carcinoma. (HE). B, C. An acinic cell carcinoma yields in FNA monolayered sheets of tumor cells with vacuolated cytoplasm in honeycomb pattern. (CP, Pap).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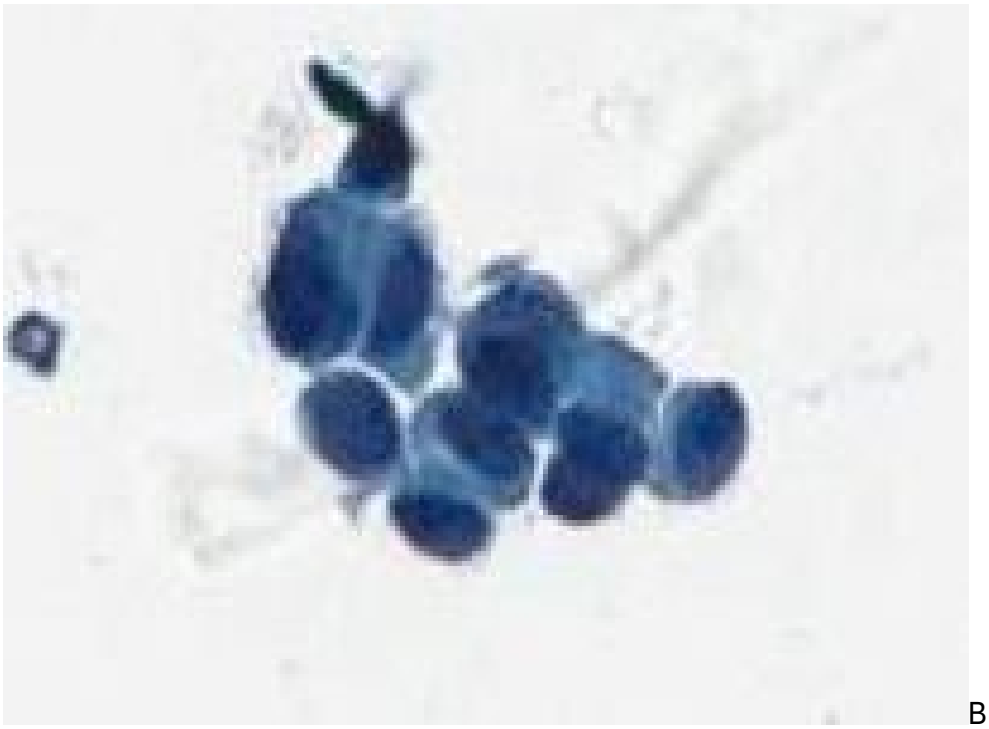
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Fig.2.24. A, B. Acinic cell carcinoma showing in FNA dispersed polygonal tumor cells with eccentrically located round nuclei and foamy cytoplasm (A. CP, HE; B. LBP, Pap)

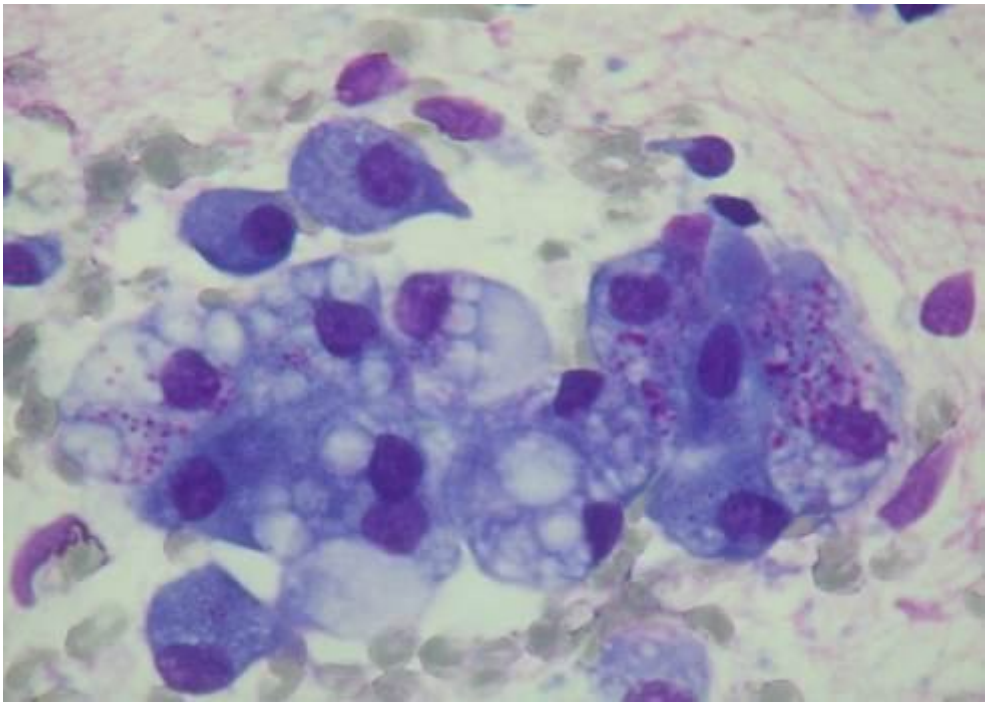


Fig.2.25. An aggregate of polygonal tumor cells with eccentrically located round nuclei, foamy or microvacuolated cytoplasm and metachromatic intracytoplasmic granules in FNA of an acinic cell carcinoma. (CP, MGG).

Mammary Analogue Secretory Carcinoma (MASC), a tumor whose histology and cytology overlap with those of an acinic cell carcinoma, has been recently described. MASC usually lacks intracytoplasmic zymogen granules but metachromatic granules may be present. The tumor has a papillary, cystic or solid lobular growth pattern without acinar arrangement. (Fig.2.26). Lesional cells are polygonal, often with markedly vacuolated cytoplasm. (Figs.2.27). Separation from acinic cell carcinoma may require ancillary IHC (MASC is positive for S100 and mammoglobin unlike acinic cell carcinoma) and/or molecular analysis (FISH reveals a characteristic t (12; 15) translocation).

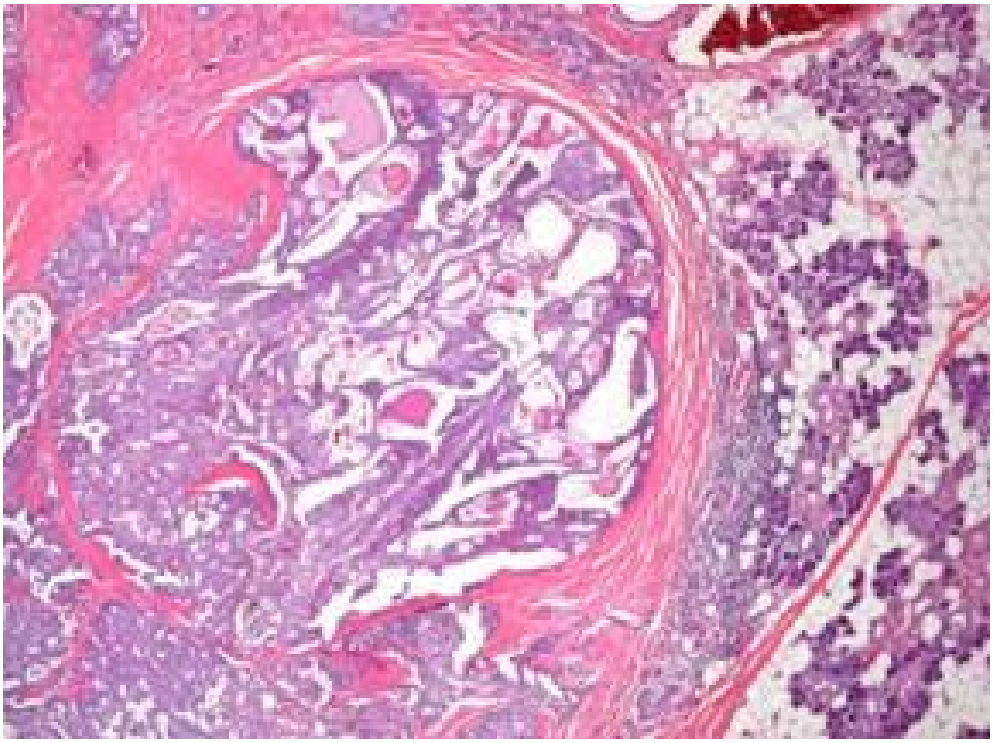


Fig.2.26. Histology of Mammary analogue secretory carcinoma of salivary gland. (HE)

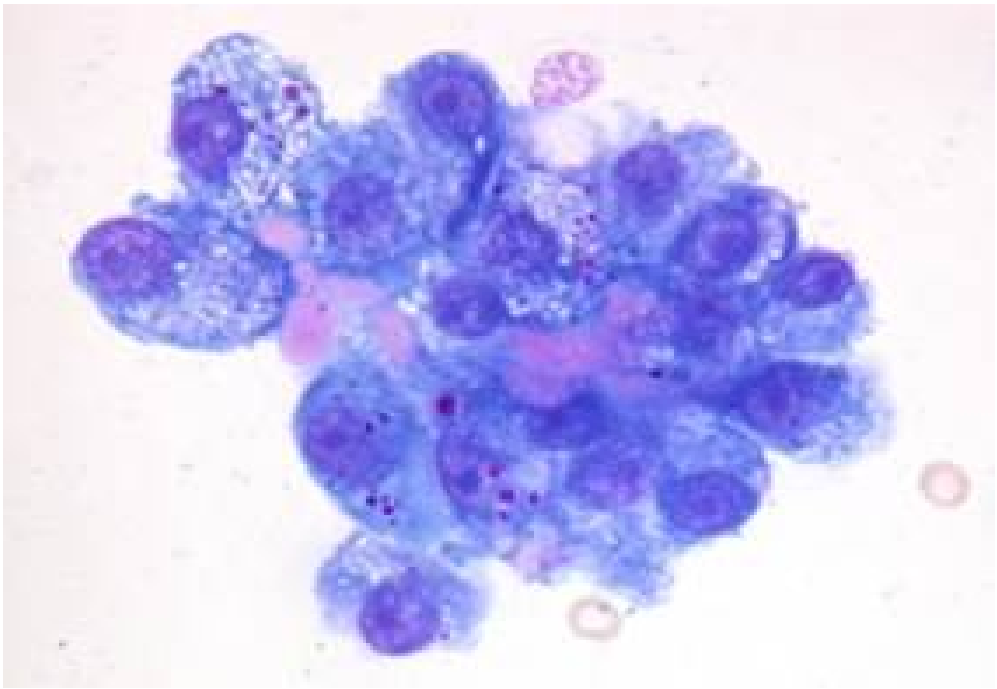
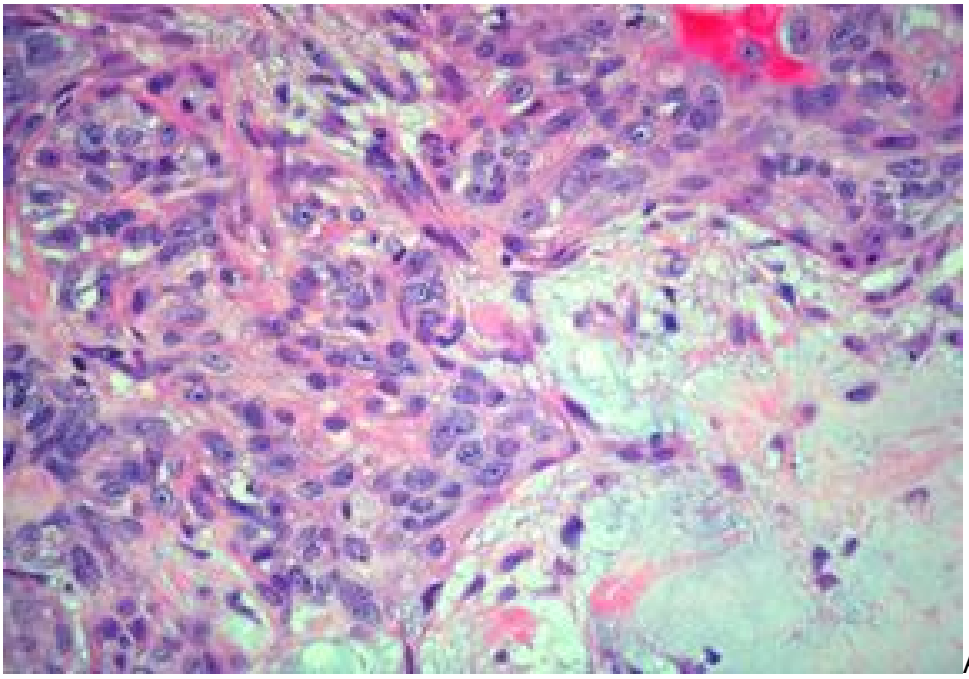


Fig.2.27. A cohesive aggregate of polygonal tumor cells with eccentrically located round nuclei, microvacuolated cytoplasm and occasionally metachromatic intracytoplasmic granules in FNA of a case originally reported as an acinic cell carcinoma but subsequently confirmed as a mammary analogue secretory carcinoma histologically. (CP, MGG)

Other carcinomas arising from the salivary glands are very rare and consist of adenocarcinoma, squamous cell carcinoma and undifferentiated carcinomas of large and small cell types. The cytologic manifestations of these cancers are similar to those of the same histologic types arising from other anatomic sites.

Other malignant tumors

Malignant mixed tumor has three histologic variants: (1) carcinoma ex-pleomorphic adenoma that is characterised by identifiable benign cellular elements of a pleomorphic adenoma and malignant epithelial cells that are commonly of glandular type, (2) tumor composed of both malignant epithelial and stromal cells, and (3) tumor with characteristics of pleomorphic adenoma but with distant metastases. The FNA of a malignant mixed tumor reflects its characteristic cellular components. (Fig. 2.28)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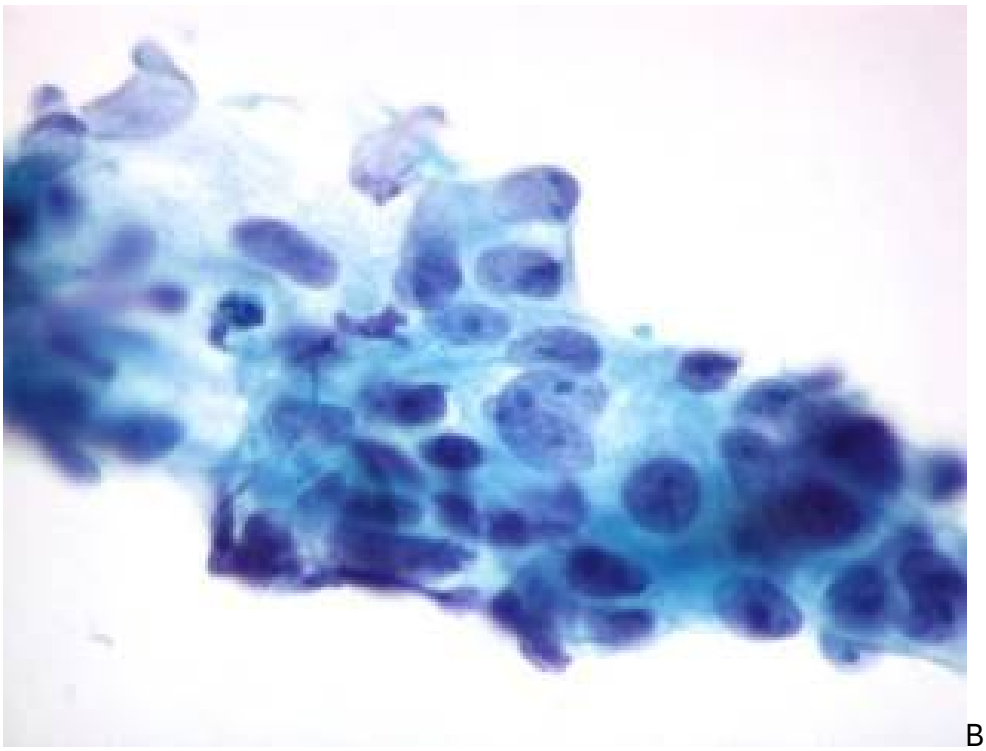

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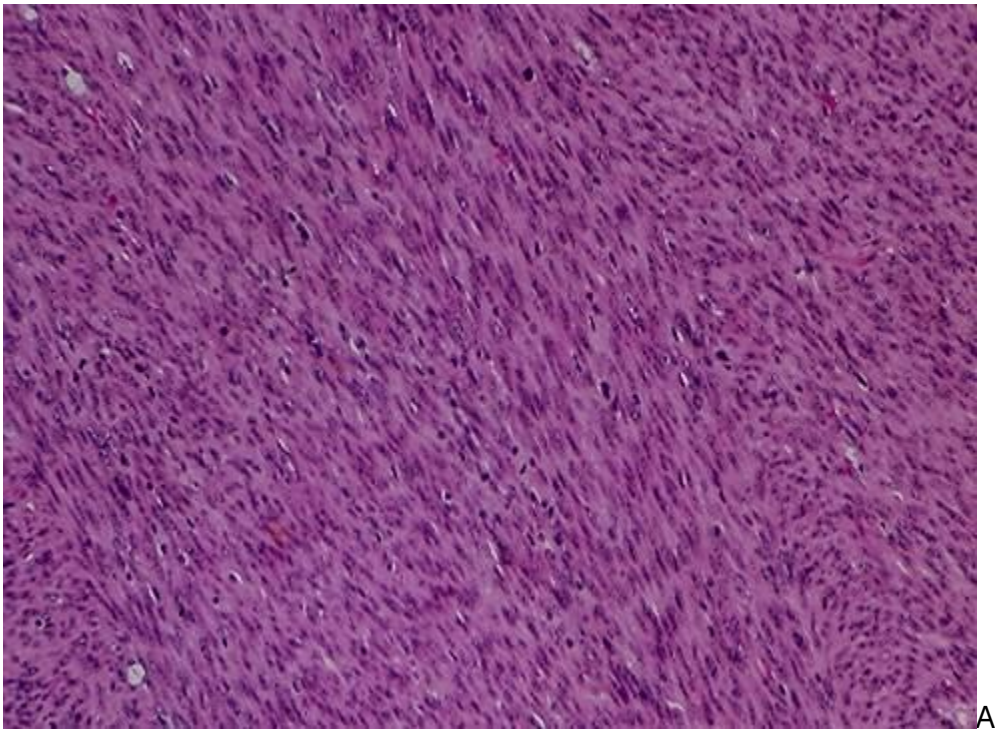
Fig.2.28. Carcinoma ex-pleomorphic adenoma. A. Histology showing an undifferentiated large cell carcinoma (left) arising from a residual PA with myxoid matrix (right). (HE). B. Tumor FNA showing a sheet of large malignant epithelial cells. (CP, Pap). Differential diagnosis includes other primary and metastatic large cell carcinomas in the salivary gland.

Malignant nerve sheath tumor is a rare tumor of the salivary gland. It is characterized histologically by malignant spindle or epithelioid cells arranged in solid pattern. It yields in FNA single and loosely clustered malignant cells with well-defined cytoplasm. Tumor cells with elongated “tails” may be seen. (Fig.2.29). Unlike benign nerve sheath tumors, S-100 protein is often only weakly positive.



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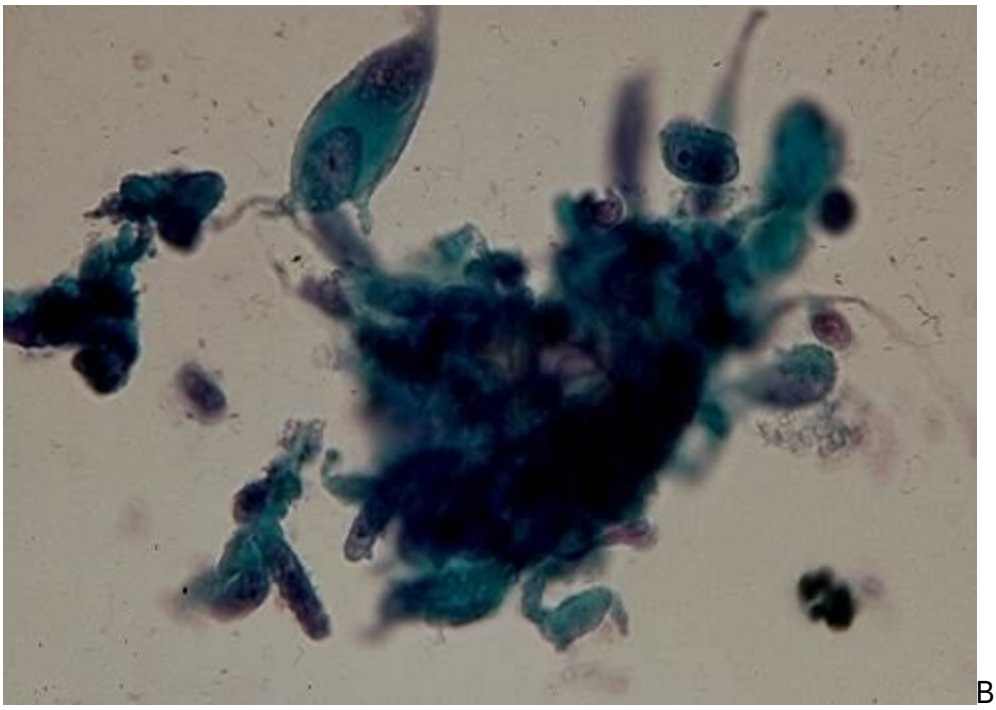

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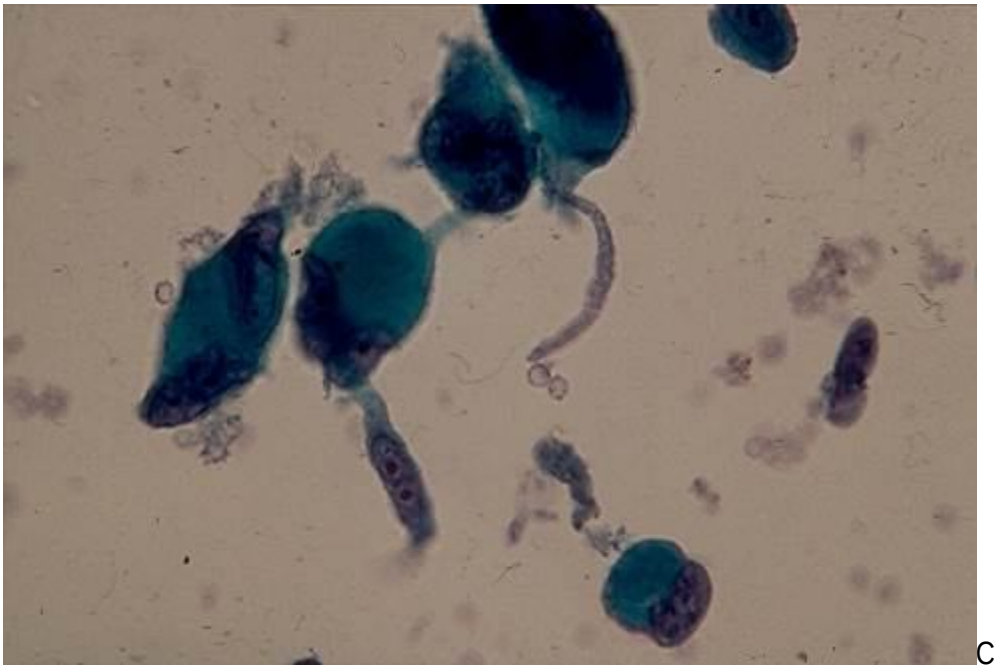
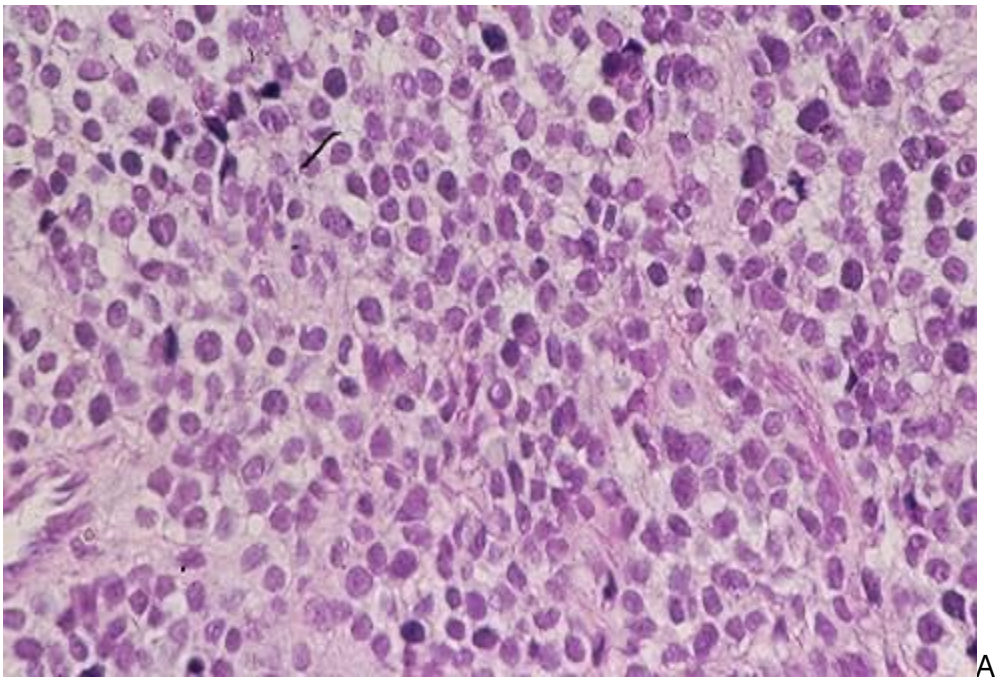
 C

Fig.2.29. Malignant nerve sheath tumor: A. Histology of the tumor. (HE). B, C. Tumor FNA showing in B a cluster of spindle cells with well-defined, thick cytoplasm, and in C isolated oval tumor cells with some showing cytoplasmic extension or tails. (CP, Pap).

Embryonal rhabdomyosarcoma is an exceeding rare tumor arising from salivary glands of oral mucosa. An example of embryonal rhabdomyosarcoma arising from the hard palate showing round tumor cells in syncytial sheets with empty round spaces mimicking an adenoid cystic carcinoma is illustrated below. (Fig.2.30). The excised tumor proved to be a rhabdomyosarcoma by IHC and electron microscopy.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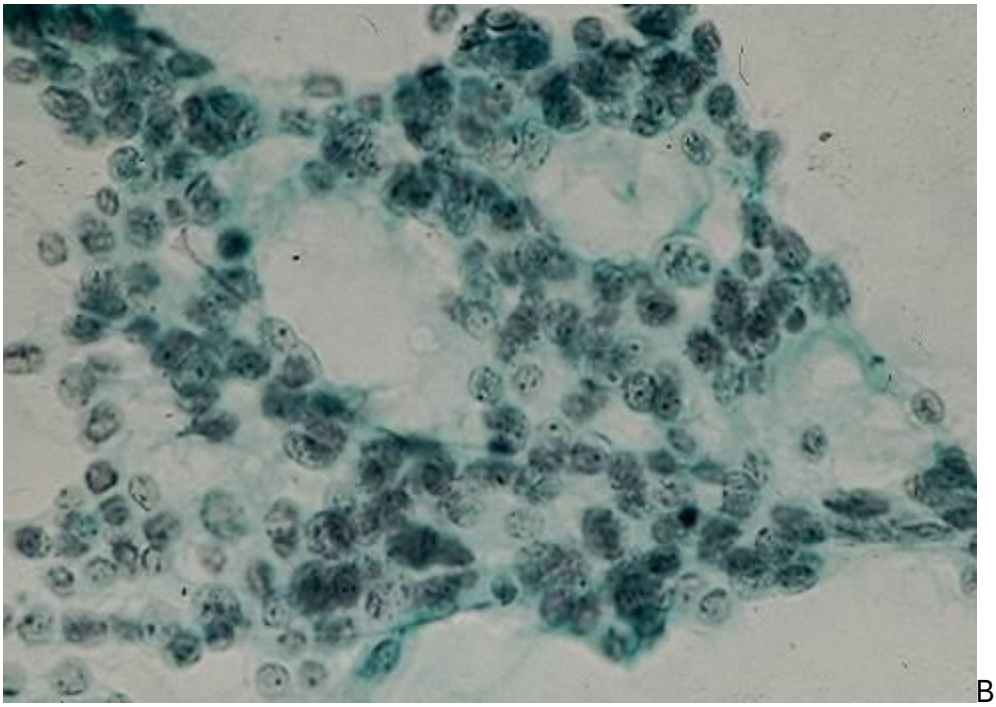
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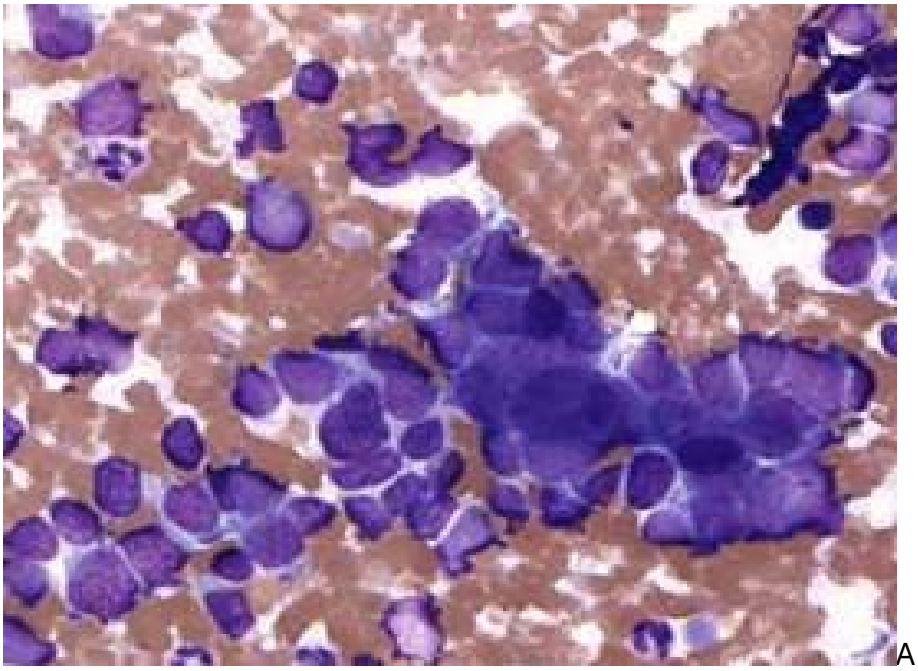
Fig.2.30. Embryonal rhabdomyosarcoma of hard palate: A. Histology of the tumor. (HE). B. Tumor FNA reveals a cohesive sheet of malignant small round cells. (CP, Pap).

Primary lymphomas of salivary glands are commonly of Non-Hodgkin types. These tumors may arise from a background of salivary gland with autoimmune chronic sialadenitis, usually in middle-aged women with Sjörgen syndrome.

Metastatic cancers to the salivary glands account for about 8% of all SGTs and commonly occur in 4-6 decades of life. Squamous cell carcinoma and melanoma are the most frequent metastatic tumors usually occurring in patients with a prior history of cancer in the head and neck area. Occasionally, metastases are from a lung or kidney cancer. Metastatic cancers should be considered the most likely possibility when the salivary gland tumor FNA reveals a squamous cell carcinoma, melanoma, high-grade adenocarcinoma or small cell carcinoma (Fig.2.31), although primary tumors of those types do rarely occur.



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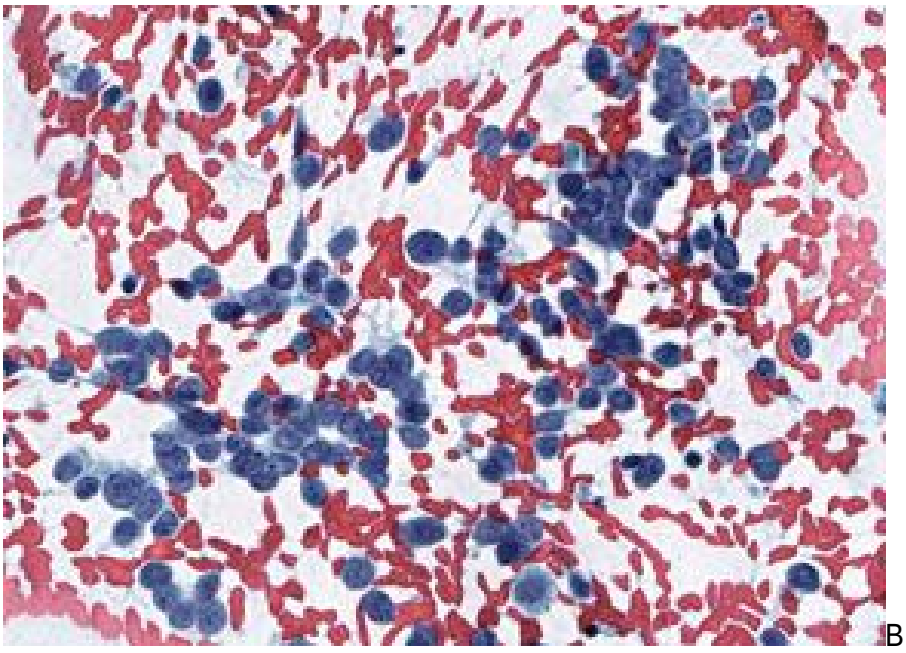

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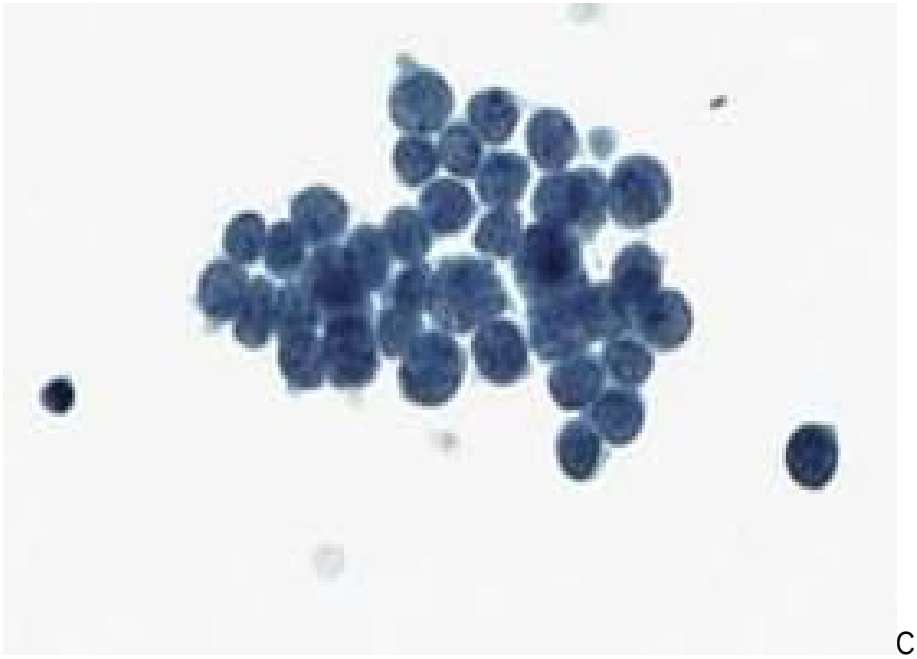
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Fig. 2.31. FNA cytology of a Merkel cell carcinoma (small cell carcinoma of skin) metastatic to parotid gland showing small tumor cells singly and in clusters with nuclear molding. (A. CP, MGG; B. CP, Pap; C. LBP, Pap)

Tumor-like lesions

Sialadenosis is a rare non-inflammatory lesion that is secondary to secretory dysfunction or metabolic disorders such as diabetes mellitus, thyroid insufficiency, alcoholism, sex hormone change... FNA in this case reveals only normal salivary gland cells.

Salivary gland duct cyst usually yields in FNA only benign cyst contents (watery clear fluid, foamy histiocytes, cholesterol crystals and perhaps a few mixed inflammatory cells). (Fig.2.32). Caution should be exercised when the cystic fluid is mucoid, even if hypocellular, as a MEC may be predominantly cystic and mucous cells may resemble histiocytes.

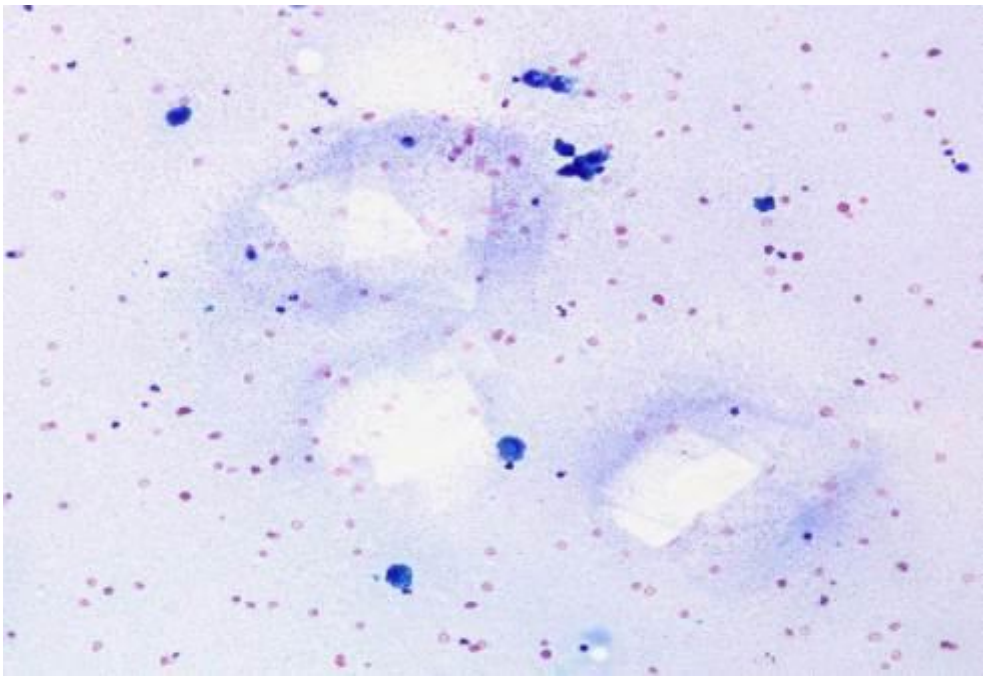


Fig.2.32. Non-specific cyst contents showing a few foamy histiocytes and cholesterol clefts. (CP, MGG).

Kuttner tumor or **chronic sclerosing sialadenitis** occurs most commonly in submandibular glands and is seen in patients in 40-50 years of age as a hard and usually painless well-circumscribed mass. The lesion may be the end stage of a chronic inflammatory process with fibrosis caused by lithiasis, radiation and disorder of salivary gland secretion.

Benign lymphoepithelial lesion is characterized by a bilateral or unilateral chronic inflammation of salivary and lacrymal glands. When the lesions are limited to these sites it may be classified as Mikulicz syndrome; if associated with a systemic collagen vascular disease it is classified as Sjörgen syndrome. The FNA cytology usually displays features of a follicular lymphadenitis with a polymorphous population of lymphoid cells. Normal salivary gland cells are usually not seen and only remnants of degenerated ductal epithelium are identified. (Fig.2.33).

Patients with Sjörgen syndrome are at increased risk for non-Hodgkin lymphoma, and this needs to be considered when examining the FNA material. The term “Mikulicz syndrome” is no longer used to describe enlargement of salivary and lacrymal glands secondary to leukemic, lymphomatous or amyloid infiltration, tuberculous infection or sarcoidosis.

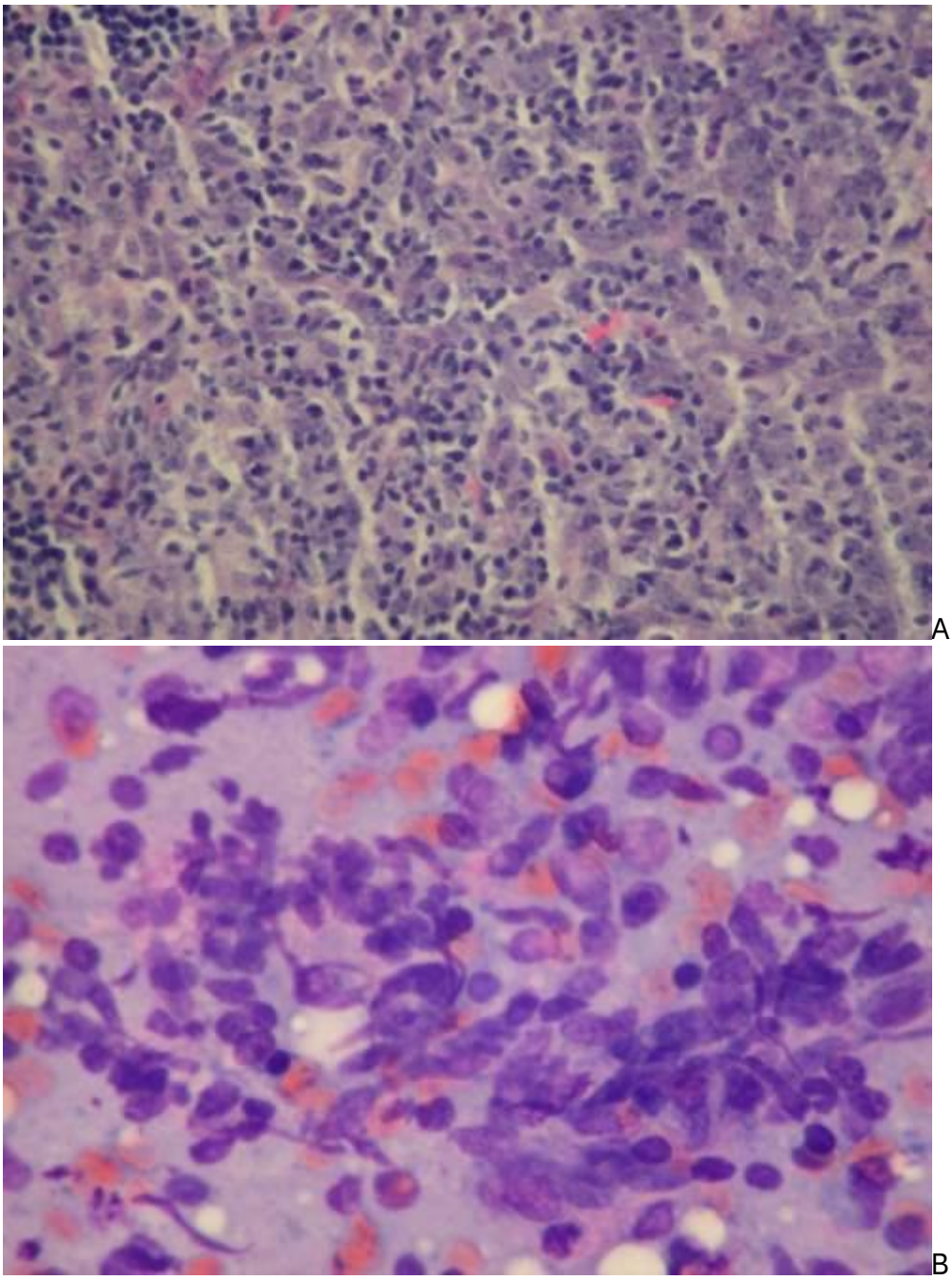


Fig.2.33. Histology (A) and FNA cytology (B) of a lymphoepithelial lesion of the parotid showing in both specimen an admixture of lymphoid cells and epithelial cells. (CP, DQ).

Diagnostic accuracy of salivary gland tumors

Kiijanienko et al. reviewed 18 large series of salivary gland tumors including their own and found that FNA of salivary gland tumors is a safe diagnostic procedure with no risk of tumor implantation along the needle tract, in contrast to open surgical biopsy that may cause extensive tumor spreading. It has a sensitivity varying from 62 to 98%, a specificity varying between 85 and 100% and an accuracy rate within 81 to 97%

range. For benign tumors a diagnostic accuracy of 92.5% has been reported. For salivary gland cancers a diagnostic accuracy rate of 65.7%, a false-positive rate of 3.3% and a false-negative rate of 11.9% have been documented.

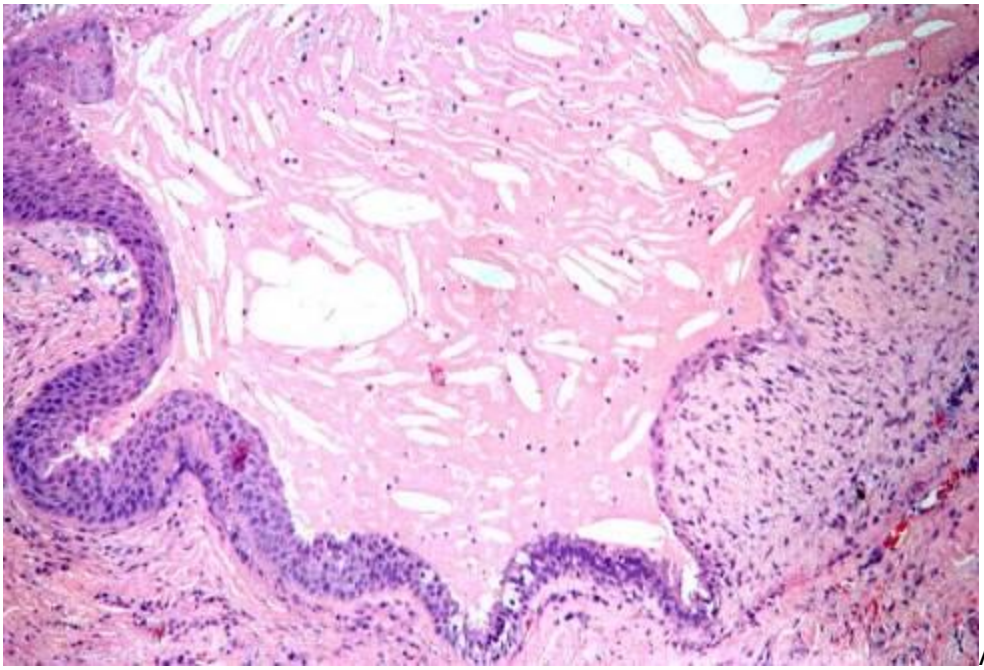
Cytology of salivary gland tumors is complex. It is possible to predict the exact tumor type with a high accuracy when unequivocal cytologic criteria are present. It should be born in mind that sampling error may lead to misinterpretation as there is an overlapping of histologic and cytologic patterns in several salivary gland neoplasms. However, exact tumor typing is not necessary at preoperative stage as it rarely influences management. When tumor typing is equivocal, it would be helpful to the surgeon if the cytopathologist offers a differential diagnosis with a preference, if possible.

II. Other Neck Mass Lesions

Cystic lesions

Six important cystic lesions of the neck are considered: thyroglossal duct cyst, branchial cleft cyst, thymic cyst, dermoid cyst, metastatic squamous cell carcinoma with cystic degenerative change and metastatic cystic papillary thyroid carcinoma.

Thyroglossal duct cyst is a congenital lesion arising from the thyroglossal duct that fails to disappear during the 6^{th} or 7^{th} weeks of fetal life. Most thyroglossal duct cysts are located on the midline of the anterior neck and is connected to the hyoid bone. A few are located laterally and rarely seen within the thyroid. Most lesions are encountered during childhood or adolescence. It is lined by either a squamous or columnar epithelium and thyroid follicle may be present in the cyst wall. (Fig.2.34). Rarely a cancer may develop from a thyroglossal duct cyst, and most of these malignant tumors are thyroid papillary carcinomas. The cyst yields in FNA benign cyst contents containing foamy histiocytes, anucleate squames and squamous cells, similar to the contents of a branchial cleft cyst. (Fig.2.35). Thyroid follicular epithelial cells are not seen, in most cases.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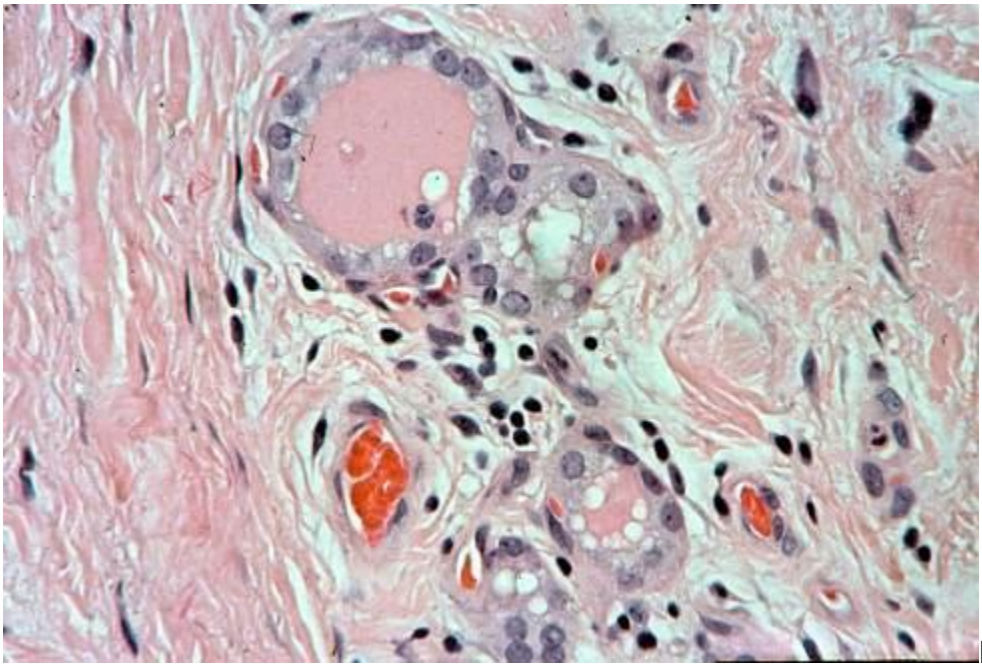
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Fig.2.34. Histology of a thyroglossal duct cyst: A. Cyst lined by a mature squamous epithelium with granular fluid containing histiocytes and cholesterol crystals. B. Cyst wall containing a few colloid-filled thyroid follicles. (HE)

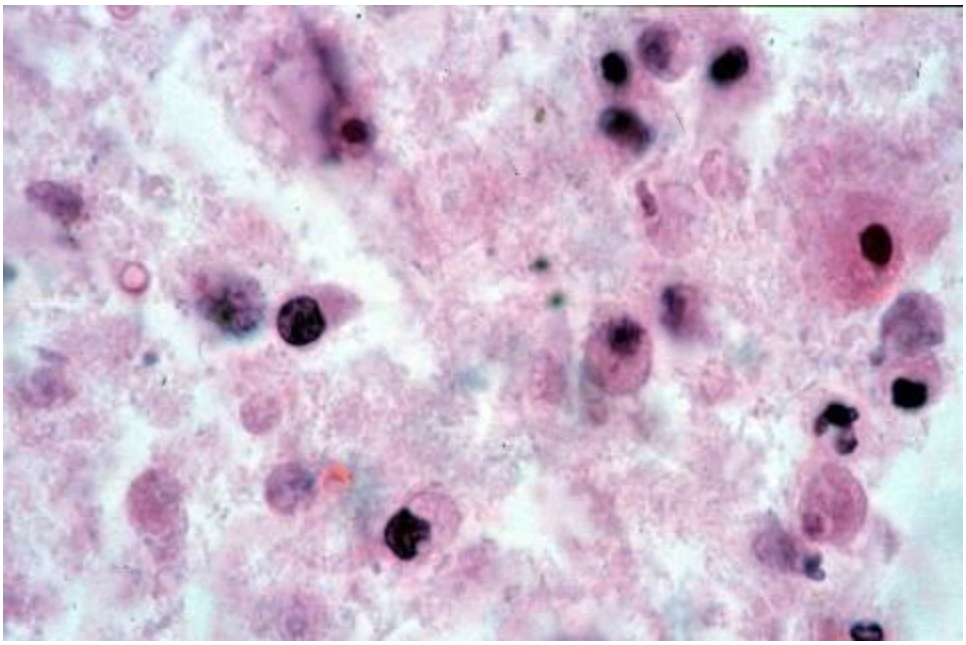
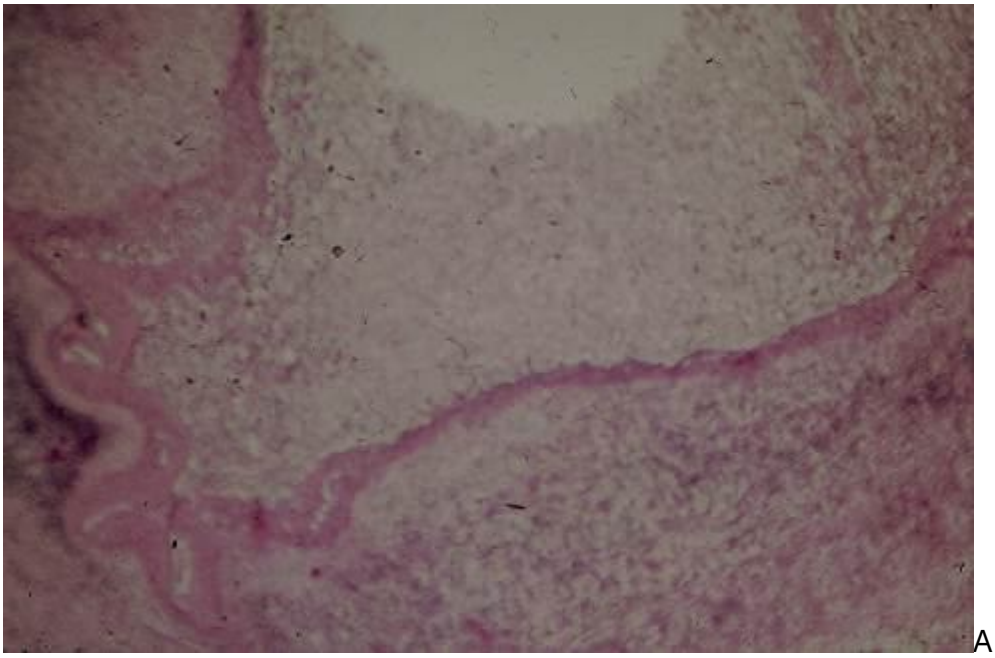


Fig.2.35. Thyroglossal duct cyst contents showing a few foamy histiocytes and necrotic debris. (CP, Pap).

Branchial cleft cyst is located lateral to hyoid bone. It is a congenital malformation developed from the branchial cleft (most commonly the second branchial cleft). Most of them are lined by a squamous epithelium and the subepithelium is heavily infiltrated with benign lymphoid cells with or without germinal centers. It shows in FNA anucleated, ghost squames and benign squamous cells. (Fig.2.36). Benign lymphocytes may be present. If the cyst is infected abundant polymorphonuclear leukocytes are noted and squamous cells with nuclear atypia may be encountered.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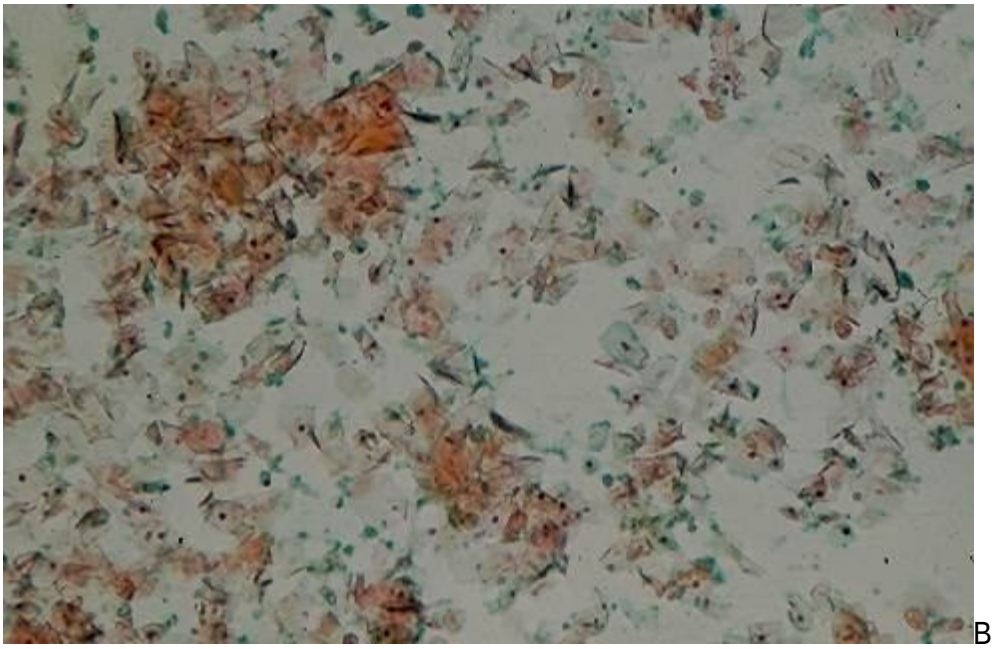
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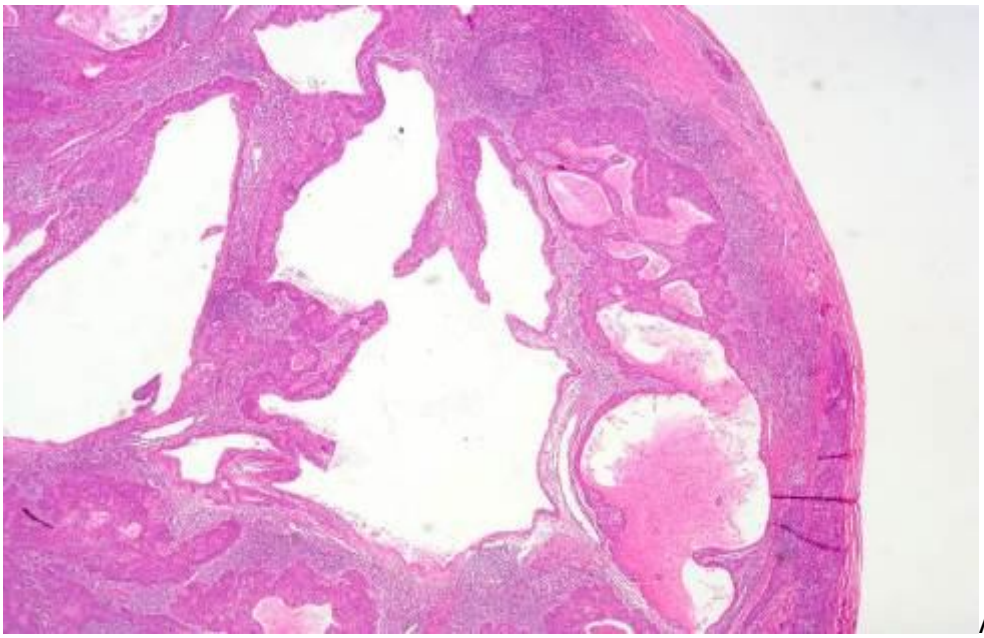
Fig.2.36. A. Histology of a branchial cleft cyst. B. FNA showing numerous anucleate squames and benign squamous cells. (CP, Pap).

Thymic cyst arises from remnants of the thymopharyngeal duct that fails to involute. It commonly occurs in the mediastinum and rarely in the neck. When it occurs in the neck it is most frequently located in the anterior cervical triangle and is readily mistaken for a branchial cleft cyst clinically. It is lined by a squamous epithelium and shows remnants of thymic tissue within its wall. The lesion yields in FNA abundant benign squamous cells and anucleated squames. Hassall corpuscles are rarely seen.

Cervical dermoid and epidermoid cysts are rare lesions that usually occur on the neck midline. The two lesions are lined by a squamous epithelium and differentiated from each other by the presence of skin appendages within the wall of the former. It shows in FNA abundant benign squamous cells and anucleated squames, similar to those of the 3 above-mentioned cysts.

Metastatic squamous cell carcinoma with cystic degeneration yields in FNA acute inflammatory cells, necrotic debris and atypical to frankly malignant squamous cells that are present singly, in clusters and sheets. (Fig.2.37). However, about 5% of cell samples have only benign appearing squamous cells, mimicking the aspirate of an infected branchial cleft cyst; and in patients over 40 years of age there should be a high level of suspicion for metastatic carcinoma. The primary tumor is not infrequently a small, undiagnosed occult cancer arising in the ipsilateral tonsil or base of the tongue that may require specialized diagnostic imaging techniques, biopsy or ipsitonsilectomy to detect.



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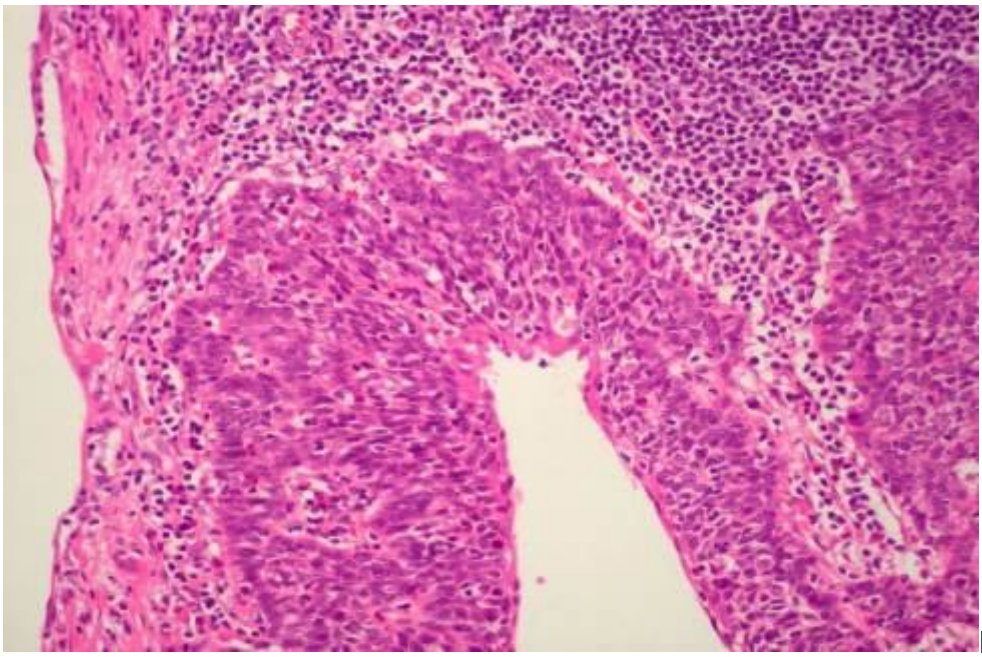

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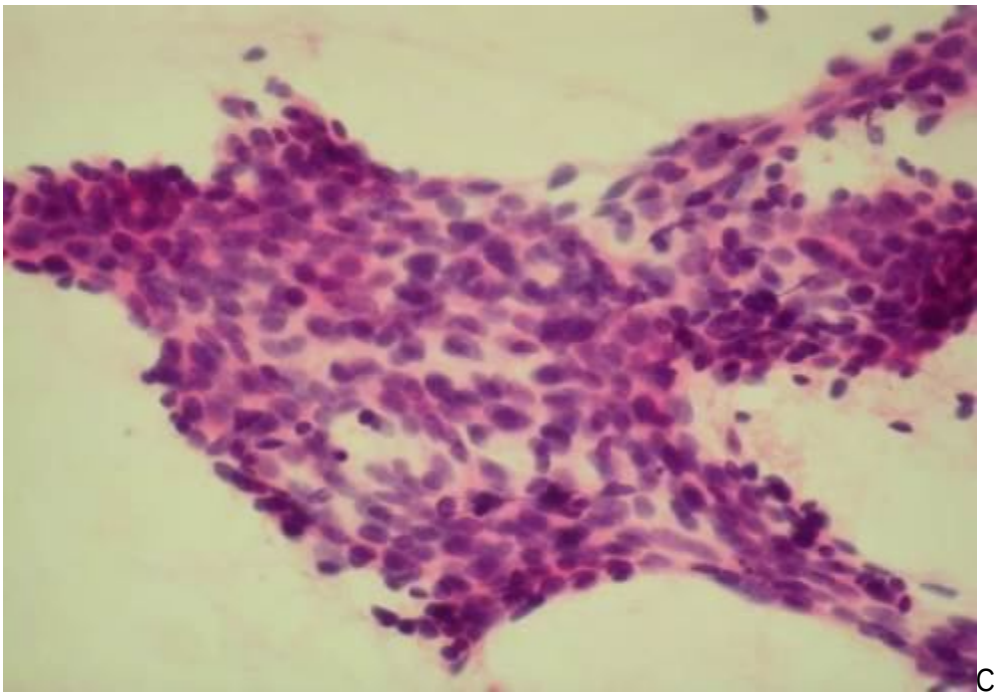
 C

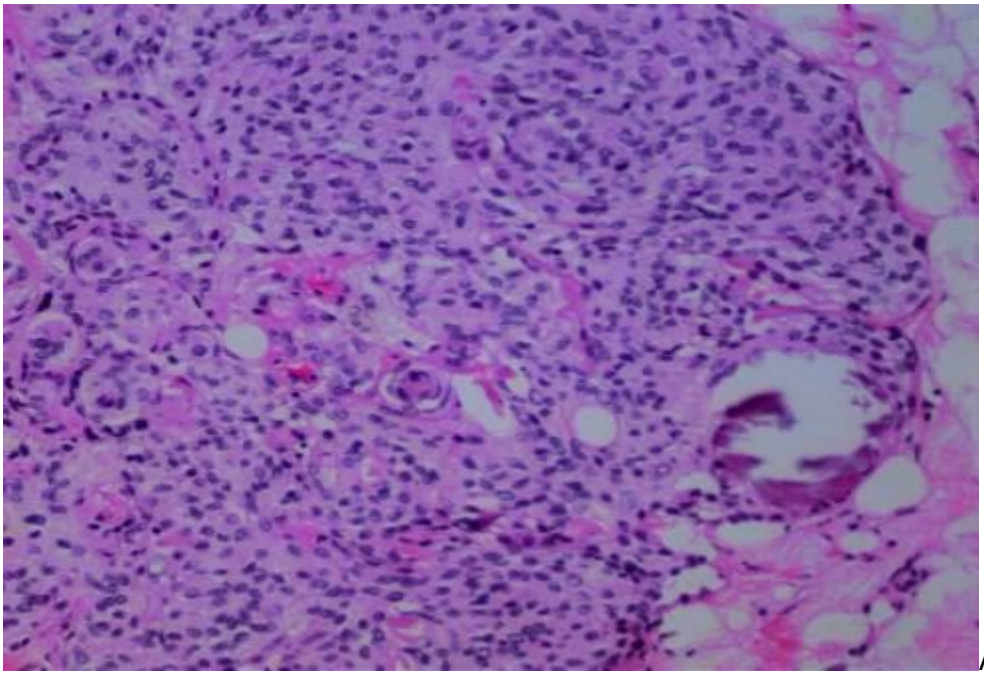
Fig.2.37. Metastatic squamous cell carcinoma to a cervical lymph node with marked cystic degenerative change: A and B. Histology of the lesion. (HE). C. FNA of the lesion showing a sheet of non-keratinizing malignant squamous epithelium. (CP, Pap).

Metastatic papillary thyroid carcinoma with marked cystic change accounts for about 1% of cases. FNA may reveal only a clear cystic fluid that shows only foamy histiocytes. It should be born in mind that epithelial cells in fluid usually round up and develop cytoplasmic vacuoles mimicking foamy histiocytes. Therefore, cellblocks should be prepared from all fluid samples to detect minute tissue fragments that may provide more information for correct diagnosis. A high index of suspicion is needed with a recommendation for clinical follow-up and repeat sampling if the lesion recurs. For illustrations the reader is refered to Chapter 1 on Thyroid. It should be kept in mind that salivary gland tumors such as PA, Warthin tumor, low-grade MEC, acinic cell carcinoma and papillary cystadenoma may show extensive cystic change and mimic a cyst clinically.

Meningioma

Primary extracranial meningioma is a rare tumor arising from the arachnoid cap cells located extracranially within nerve sheaths or vessels. It may originate from the sinonasal tract and it should be distinguished from an intracranial meningioma with extracranial/extraspinal extension. Clinically, epistaxis, nasal obstruction and facial deformity may be present. Rarely, it appears as a lateral cervical mass lesion. The tumor may measure up to 8 cm in greatest dimension with a mean of 3 cm. Histologically, it consists of a variety of histologic patterns, most commonly meningotheliomatous, that is characterized by lobules of cells with whorl formation,

indistinct cell borders and bland, oval nuclei with delicate chromatin. Intranuclear cytoplasmic inclusions and psammoma bodies are common. The tumor yields in FNA cohesive clusters of meningothelial cells with thin, defined cytoplasm and oval nuclei with finely granular chromatin and small nucleoli. Psammoma bodies are rarely observed. (Fig.2.38).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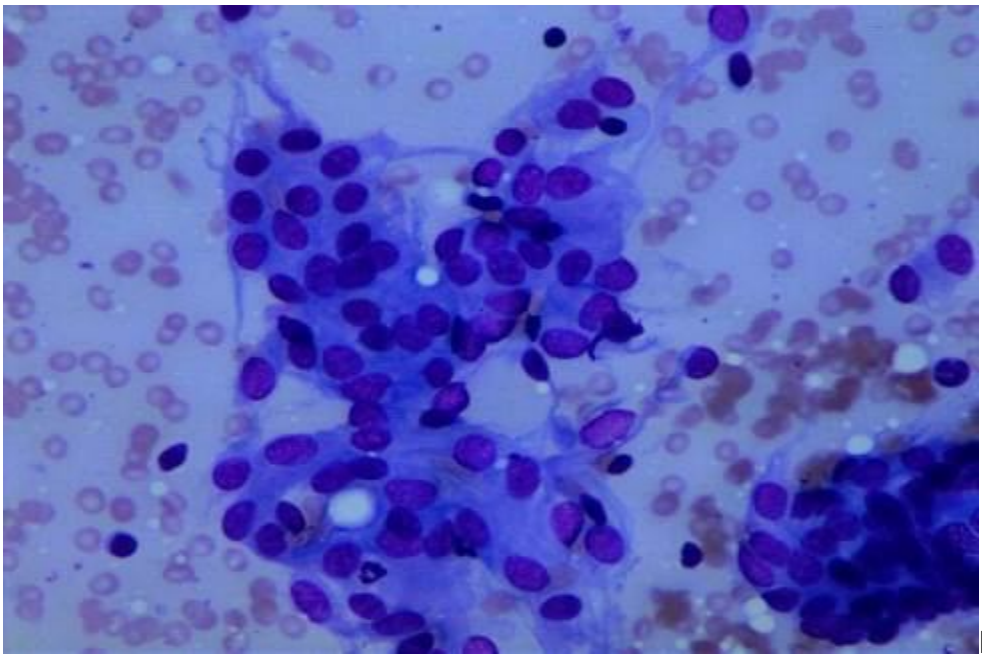
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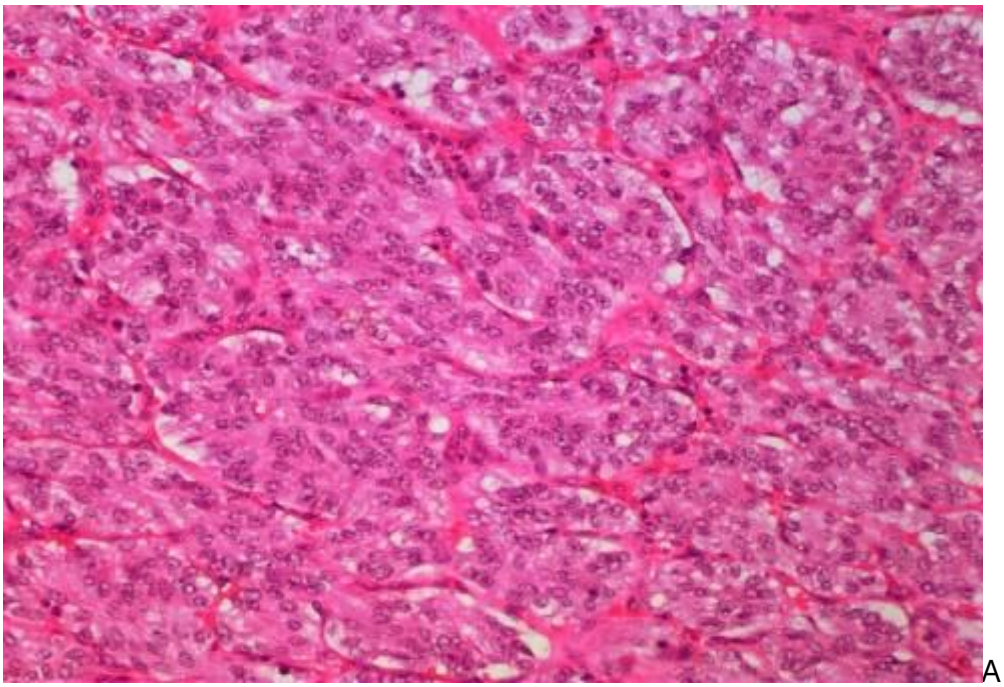
Fig. 2.38. Cervical meningotheliomatous tumor: A. Histology showing nests of tumor cells with a psammoma body. (HE). B. Tumor FNA showing a large sheet and a cluster of tumor cells with bland nuclei and thin, ill-defined cytoplasm. (CP, DQ).

Carotid body tumor

This neuroendocrine neoplasm is an uncommon and slow-growing lesion and it is the most common paraganglioma of the head and neck. The lesion occurs primarily in adults averaging 40-50 years of age. It usually presents as a lateral neck mass located deeply to the anterior border of the sternocleidomastoid muscle below the mandibular angle, measuring about 4 cm on average. It is rarely bilateral or associated with paraganglioma in other sites. Exceptional tumors are functional causing hypertension that is secondary to catecholamine secretion. Histologically, the neoplasm is highly vascular and consists of 2 types of cells, chief and sustentacular, arranged in a characteristic alveolar or Zellballen pattern. The chief cells are epithelioid in shape and contain catecholamine-bound neurosecretory granules. The supporting sustentacular cells are located at the periphery of the Zellballen and devoid of neurosecretory granules. The tumor yields in FNA pleomorphic cells with ill-defined granular cytoplasm and pleomorphic nuclei similar to cells aspirated from an adrenal pheochromocytoma. (Fig.2.39). Tumor cell nuclei have a finely speckled chromatin and generally lack visible nucleoli. On rare occasions, tumor cells arranged on ball-like cluster or Zellballen are observed. The tumor cell cytoplasm stains positively with neuroendocrine markers such as neuron-specific enolase and chromogranin antibodies. As excision is rarely complete tumor recurrence is common. Tumor recurrence is not an evidence of malignancy that is characterized only by metastasis. Malignant carotid tumors are very rare and indistinguishable from their benign counterparts histologically and cytologically.



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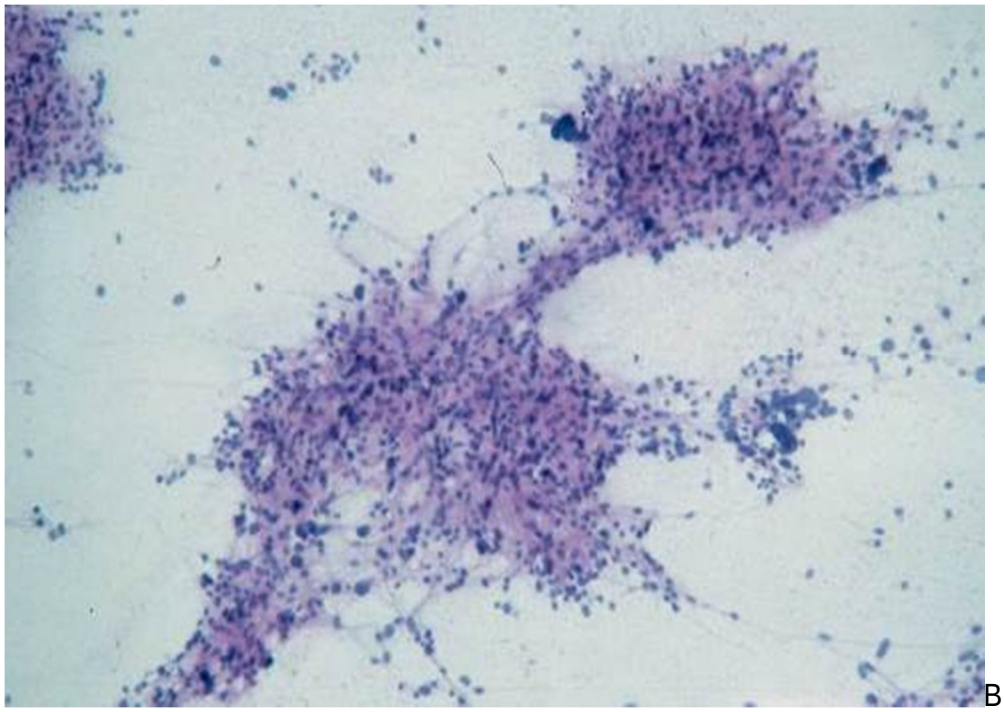

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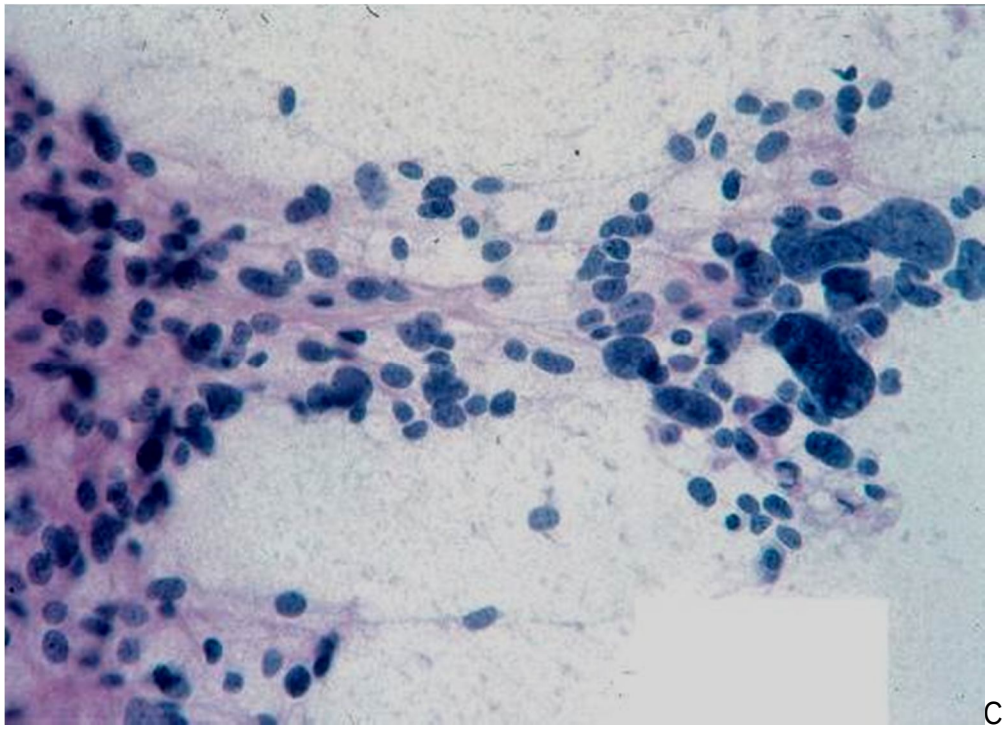

C

Fig.2.39. Carotid body tumor: A. Histology of the tumor showing nests of tumor cells separated by thin fibrovascular septae. (HE). B, C. Tumor FNA is cellular and shows ragged syncitial groups of spindle and epithelioid cells. The tumor cells display hyperchromatic nuclei and a moderate amount of eosinophilic cytoplasm. Bizarre giant tumor cells with degenerated nuclear changes are present. (CP, Pap).

Other tumors

Soft tissue tumors of different types may occur in the head and neck. Benign tumors are more common than the malignant ones. Among the benign tumors **lipoma** is the commonest. FNA of a lipoma reveals clustered benign fat cells. A **Merkel cell carcinoma** of the skin consisting of round tumor cells with neuroendocrine differentiation yields in FNA small, round tumor cells with hyperchromatic nuclei with nuclear molding and overlapping. (Fig. 2.40).

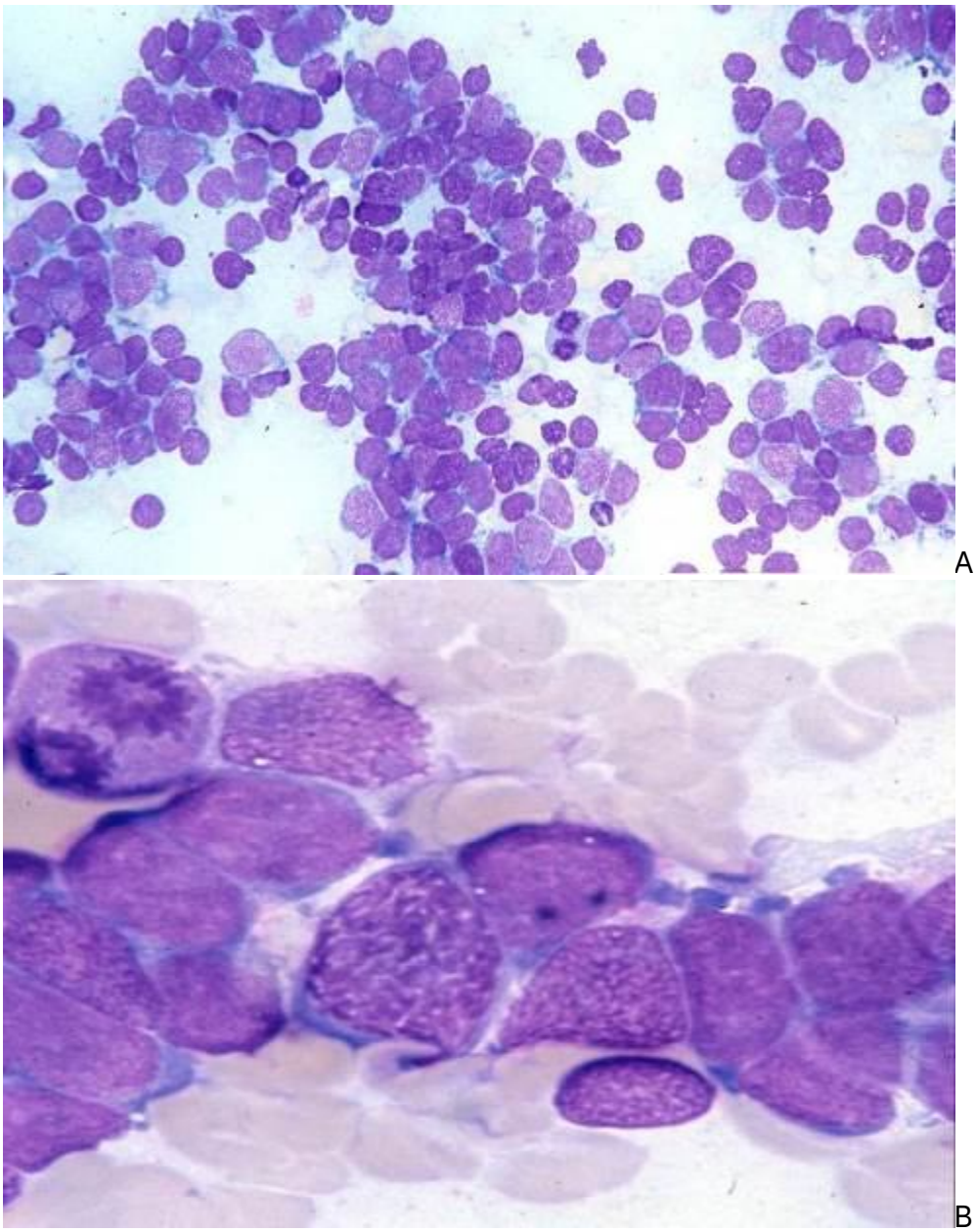

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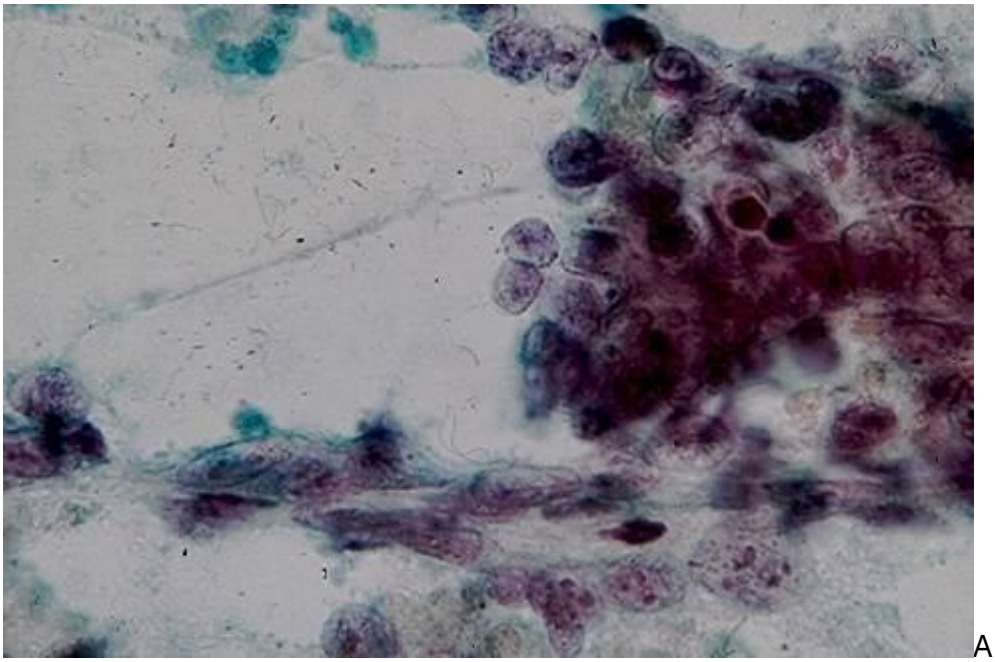
Fig. 2.40. Merkel cell carcinoma yields in FNA clustered round tumor cells with nuclear molding and overlapping. (CP, MGG).

Nasopharyngeal carcinoma

This is a poorly differentiated squamous cell carcinoma that is commonly associated with a marked lymphoid infiltration. It is more common in Asian countries and is related to Epstein-Barr virus infection. The primary tumor is often clinically occult and presents as a metastatic carcinoma to cervical lymph nodes of unknown primary. It shows in FNA undifferentiated malignant cells singly and in clusters. The tumor cells have a variable amount of pale, fragile cytoplasm with large vesicular, elongated or spindle nuclei with conspicuous nucleoli. (Fig.2.41). Rare keratinizing tumor cells may be seen. The tumor cells are positive for cytokeratin and Epstein-Barr virus associated nuclear antigens and negative for lymphocyte makers.

 A

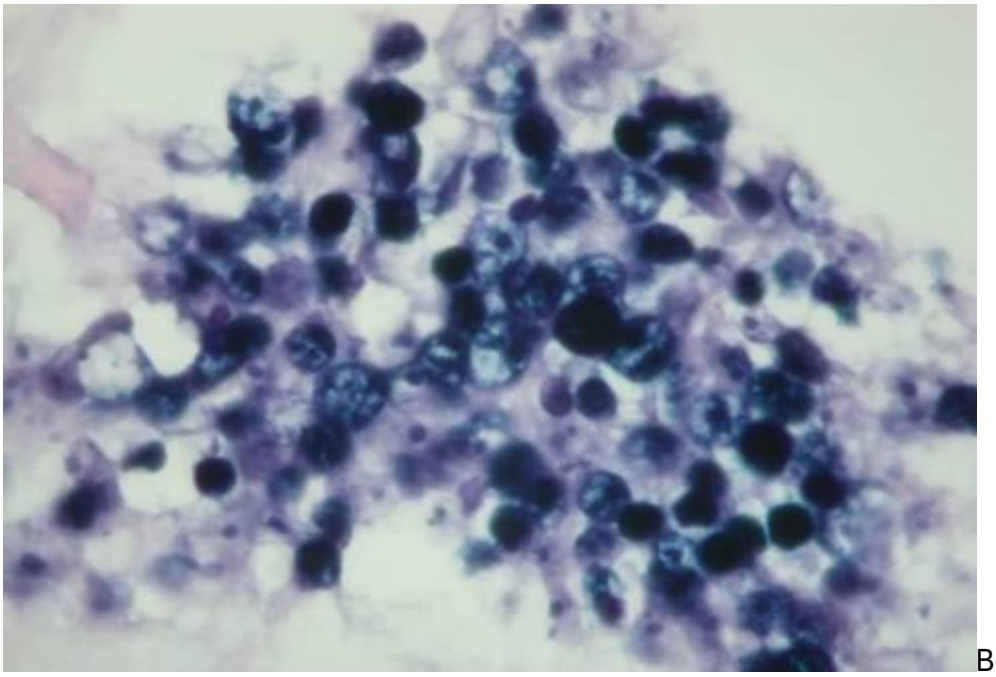

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Fig.2.41. A cluster of pleomorphic undifferentiated malignant epithelial cells with conspicuous nucleoli in FNA of a cervical lymph node with a metastatic nasopharyngeal carcinoma. (CP, Pap). B. Tumor cells showing a positive nuclear staining for Epstein-Barr virus RNA by in-situ hybridization.

Parathyroid tumors

Parathyroid adenoma may present as a lateral neck mass and rarely as an intrathyroid nodule. It may undergo cystic degenerative change with clear, acellular liquid contents with a high level of parathyroid hormone. A parathyroid adenoma is almost always solitary and associated with hyperparathyroidism (nephrolithiasis, osteitis fibrosa cystica and diffuse osteopenia). Histologically, a parathyroid adenoma is usually composed of cells with clear or granular cytoplasm and monomorphic round nuclei. (Fig.2.42).

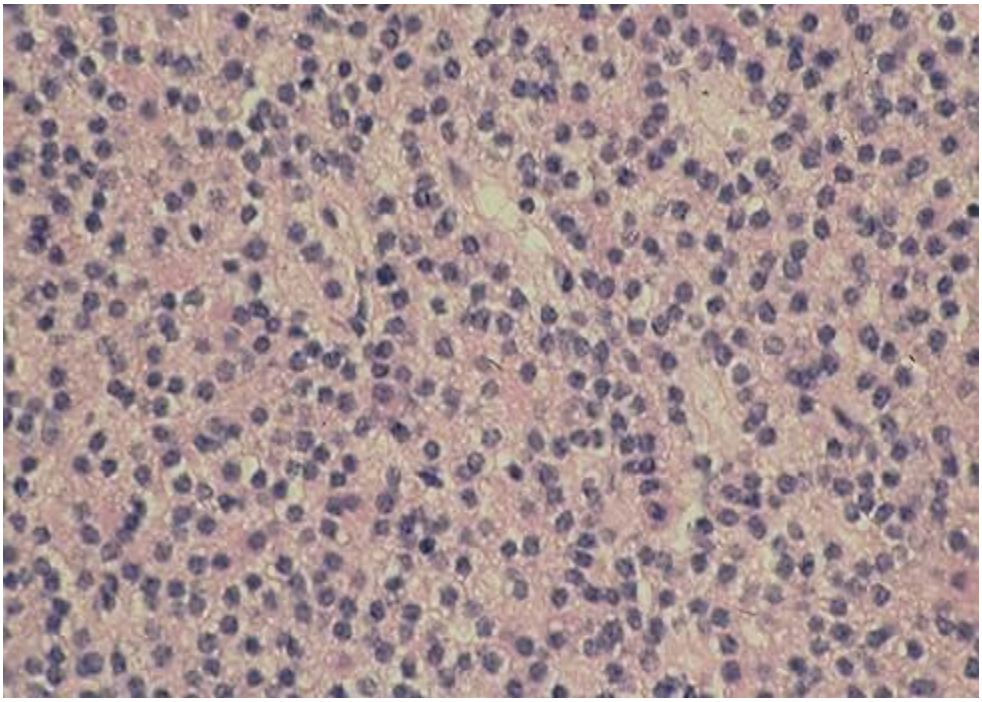
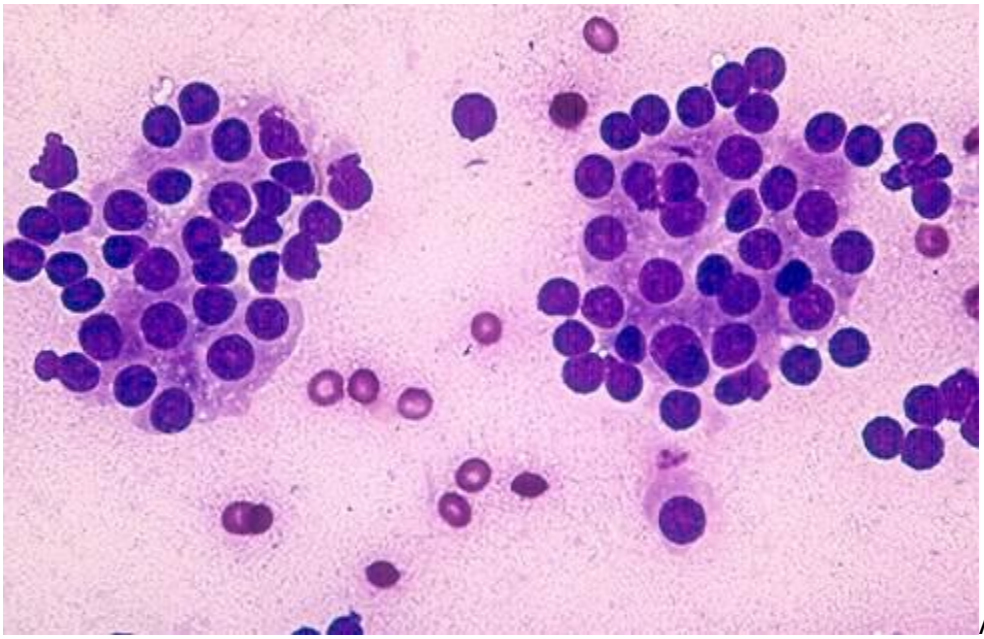


Fig.2.42. Histology of a parathyroid adenoma showing polygonal epithelial cells with round nuclei and granular cytoplasm. (HE)

Parathyroid adenoma usually yields in FNA abundant epithelial cells with scant, ill-defined cytoplasm and oval, bland nuclei arranged in acini and in syncytial sheets with nuclear crowding and overlapping. (Fig.2.43). Abundant bare tumor cell nuclei are commonly seen. Intranuclear cytoplasmic inclusions may be present in some tumor cells. A parathyroid adenoma FNA displays some overlapping features with those of a cellular microfollicular lesion or papillary carcinoma of the thyroid. Therefore, IHC staining of the tumor cells with parathyroid hormone and thyroglobulin antibodies is essential to differentiate a thyroid follicular lesion from a parathyroid neoplasm.



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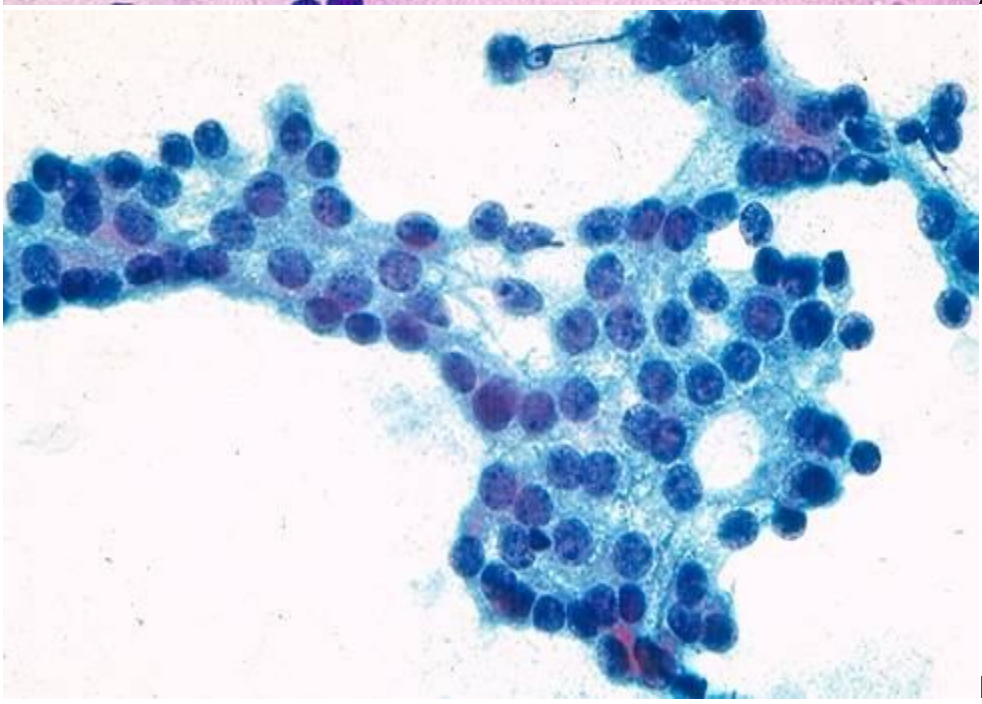


B

Fig.2.43. Parathyroid adenoma showing in FNA: A. Cuboidal epithelial cells in acinar arrangement. (CP, DQ). B. Epithelial cells in monolayered sheets with focal glandular spaces. (CP, Pap).

A parathyroid adenoma may consist of large pleomorphic oncocytic cells with bizarre nuclei. (Figs.2.44). IHC staining of the aspirated tumor cells with parathyroid hormone and thyroglobulin antibodies will be helpful for tumor typing.

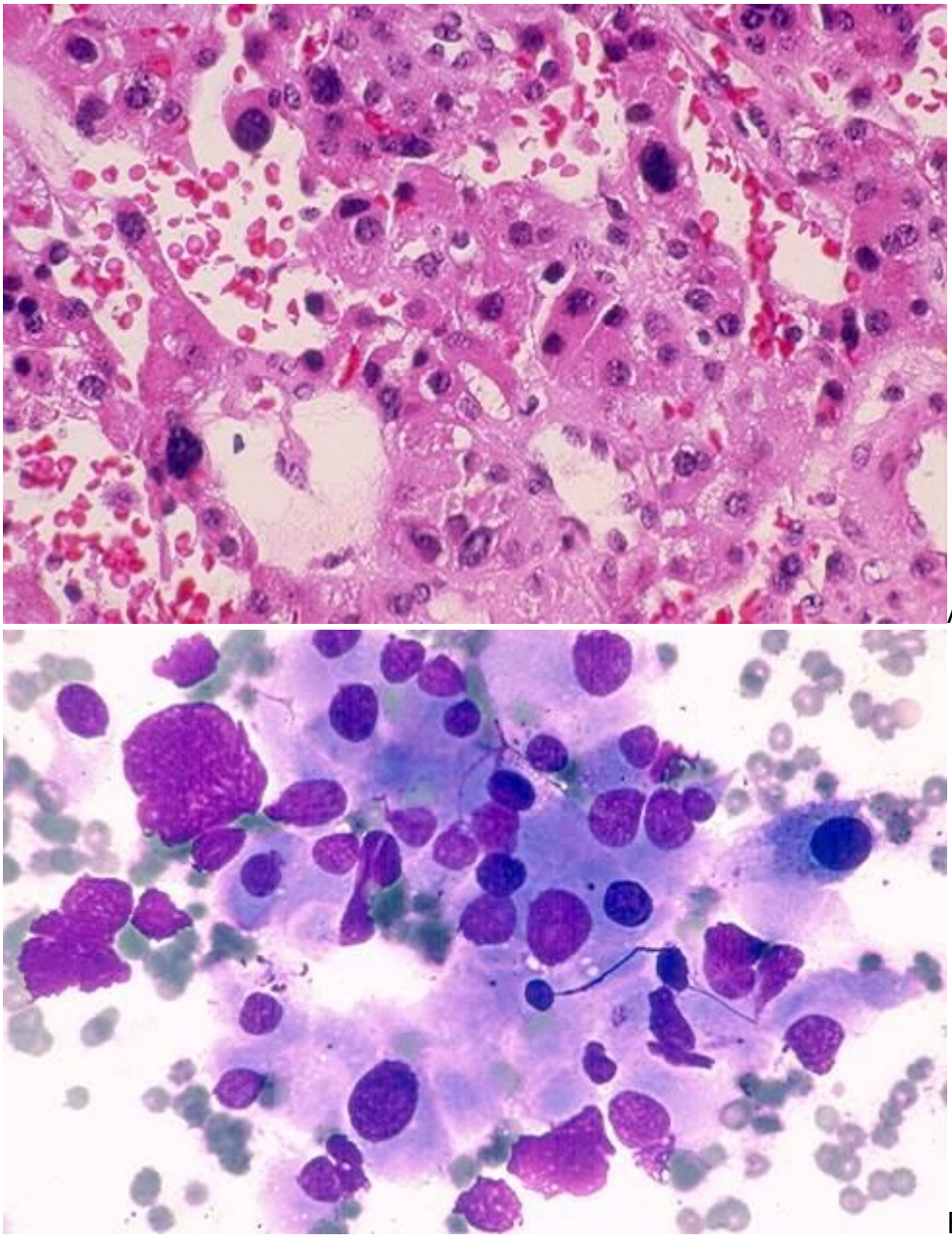
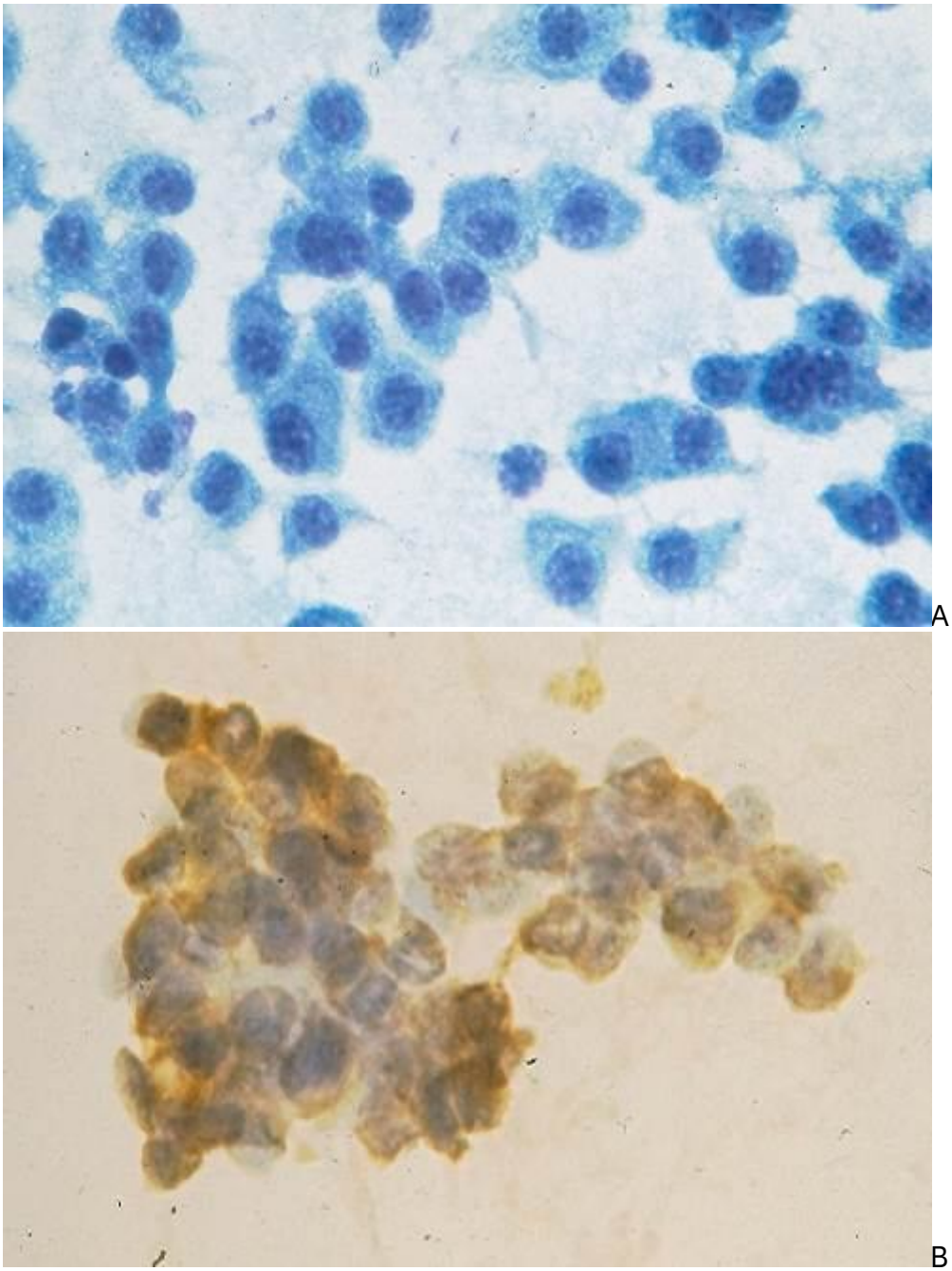


Fig.2.44. Parathyroid adenoma with oncocytic change: A. Histology of the tumor showing bizarre oncocytic tumor cells. (HE). B. Bizarre oncocytic tumor cells seen in the tumor FNA. (CP, DQ).

Parathyroid carcinoma is a rare tumor and most patients with parathyroid carcinoma have hyperparathyroidism. Asymptomatic non-functioning parathyroid carcinoma is uncommon. Histologically, a parathyroid carcinoma is usually composed of cells with clear or granular cytoplasm and little variation in nuclear size and shape. Bizarre tumor cells or tumor cells with oncocytic change may be present and mimic cells of an anaplastic carcinoma or oncocytic tumor, respectively. FNA of a parathyroid carcinoma

reveals dyshesive polygonal cells with enlarged, hyperchromatic nuclei, conspicuous nucleoli, and some tumor cells may have a plasmacytoid configuration. (Fig.2.45). A positive cytoplasmic staining of the tumor cell cytoplasm with parathyroid hormone antibody will confirm its parathyroid origin. Cases of parathyroid carcinoma showing cells mimicking a parathyroid adenoma or a low-grade thyroid follicular neoplasm has been reported.



A

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Fig. 2.45. FNA of a parathyroid carcinoma showing: A. Dyshesive and loosely clustered polygonal tumor cells with defined, granular cytoplasm and enlarged, hyperchromatic

nuclei. (CP, Pap). B. A cluster of tumor cells showing strong cytoplasmic reaction to parathyroid hormone antibody. (ABC).

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Chapter 3

Lymph nodes

Gia-Khanh Nguyen and Thomas Thomson

Fine needle aspiration for cytologic evaluation of enlarged lymph nodes was initially performed in 1911 by Grieg and Gray who identified trypanosomes to support their clinical diagnosis of sleeping sickness. In 1921 Guthrie documented a case of Hodgkin disease correctly diagnosed by FNA, and in 1930 Martin reported a large series of FNA of different anatomic sites including lymph nodes. Since then several papers documenting the utility of FNA in diagnosing enlarged lymph nodes have appeared in the literature. Lymph node FNA for cytologic evaluation now is practiced worldwide.

Indications and goals of FNA

Enlarged cervical lymph nodes are prime targets of FNA for cytologic evaluation. This diagnostic procedure is a safe, convenient, minimally invasive and economical method of clinical investigation. The goals of lymph node FNA include the identification of:

1- A reactive hyperplasia
2- An infection (bacterial or fungal)
3- A metastatic cancer
4- A Hodgkin or Non-Hodgkin lymphoma

The value of FNA in the cytodiagnosis of a Non-Hodgkin lymphoma (NHL) is controversial. Most investigators, including the writers, still think that an accurate diagnosis of NHL can only be made by histologic, cell maker and molecular studies of lymph node tissue, as cell marker studies of a small number of tumor cells may yield unreliable information leading to an incorrect tumor typing. However, several recently published studies have reported a high diagnostic accuracy rate of NHL by FNA coupled with cell marker and/or molecular studies. Since enlarged cervical lymph nodes are superficial, therefore they can be easily sampled by excisional or incisional biopsy under local anesthesia for tissue diagnosis. A primary cytodiagnosis of mediastinal, intraabdominal and retroperitoneal NHL by FNA and ancillary techniques is acceptable only in patients in whom a thoracotomy, mediastinoscopy or laparotomy to obtain tissue for histologic diagnosis are contraindicated. For metastatic cancer, the great advantage is that a lymph node FNA can, not only make a correct diagnosis, but it can avoid an ugly seeding of tumor cells into avascular planes and scarring that may be caused by incisional biopsy.

Contraindication and Complications of FNA

Bleeding disorders constitute the only contraindication for cervical lymph node FNA. Hematoma formation often occurs but it can be controlled by digital compression of the biopsy site. Focal lymph node infarction is observed in 4% of excised biopsied lymph nodes with prior FNA but it rarely interferes with histologic evaluation of the subsequently excised lesions. A pneumothorax may occur in FNA of a low cervical or supraclavicular lymph node.

Technical considerations

FNA of an enlarged lymph node is best performed by non-aspiration technique using a 23- to 25-gauge needle without a syringe. Dermal anesthesia of the overlying skin with 1 ml of xylocain is usually necessary as multiple samples will be taken to secure an adequate cell sample for routine cytologic evaluation and cell marker studies. A smear should be prepared and stained by the DQ technique to evaluate the cell sample adequacy. If an infection is suspected, an additional cell sample should be obtained for bacterial or fungal culture. Usually cell samples are either fixed in 95% ethanol or air-dried for staining by the Pap or DQ method, respectively. Additional materials should be obtained for cellblock preparation for IHC studies, if indicated. If a lymphoma is suspected a tissue biopsy with fresh tissue samples saved in RPMI solution, according to usual lymphoma protocols, for cell marker and cytogenetics studies.

Lymph node groups and their common pathology

Cervical lymph nodes are clinically divided into 9 groups, as outlined below. Lymphoma may involve any groups. These nodal groups are more commonly associated with certain pathologic conditions, according to Chen and her associates, as follows:

1. Preauricular: metastases from the face skin, scalp and parotid cancers.
2. Postauricular: usually inflammatory conditions of face skin, scalp and external ear or viral infection.
3. Submandibular: metastases from cancers of mouth floor, cheek, submandibular salivary glands, face skin, maxillary sinus and anterior tongue.
4. Submental: metastases from lip, mouth floor and nose cancers.
5. Jugulodigastric: metastases from cancers arising from oropharynx, submandibular salivary glands or tonsils.
6. Mid jugular: metastases from thyroid, larynx or pharyngeal cancers.
7. Lower jugular: metastases from cancers arising from thyroid, larynx or pharynx.
8. Supraclavicular: metastases from cancers arising below the clavicle (lung, breast, esophagus, stomach, ovary…) and occasionally thyroid.
9. Posterior cervical, lower and upper: inflammatory conditions or metastases from cancers of nasopharynx, face skin, neck or scalp.

Non-neoplastic lesions

Reactive hyperplasia

This is a common condition that is most often caused by viral infection in children and young adults, and it is less common in older adult patients. Cytologically, it is characterized by a polymorphic cell population consisting of lymphoid cells at various stages of transformation. Tangible-body macrophages are usually noted. (Fig. 3.1)**.** The hyperplastic lymphoid cells express both kappa and lambda light chains. Similar cytologic findings are seen in FNAs from a lymph node with Castleman disease or toxoplasmosis lymphadenitis, HIV-associated lymphadenopathy and dermatopathic lymphadenitis. In the case of a dermatopathic lymphadenitis, in addition to a polymorphic lymphoid cell population, a few melanin-laden macrophages are seen. A hyperplastic lymph node may consist predominantly of small lymphoid cells, and in this situation, cell marker studies, either by flow cytometry or IHC should be done to rule out a small-cell NHL.

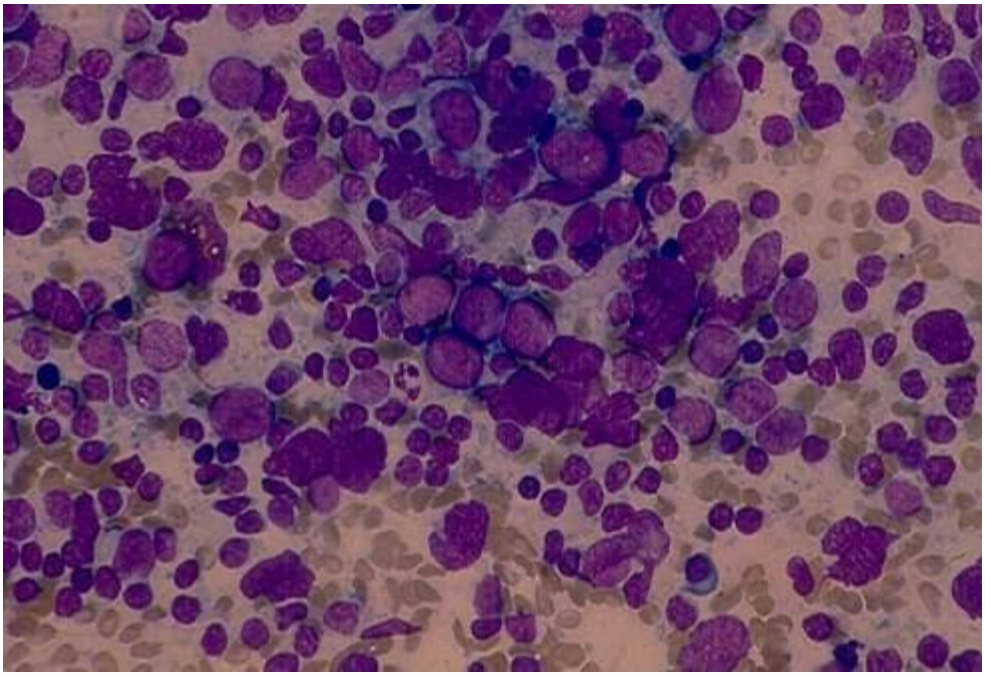


Fig.3.1. Reactive lymph node showing in FNA numerous lymphoid cells at different stages of maturation and a plasma cell. (CP, DQ).

Inflammatory/Infectious conditions

Sarcoidosis is a systemic granulomatous disease of unknown etiology affecting young and middle-age adults. A variety of tissues are involved but lung and lymph nodes in the neck and mediastinum are commonly affected. It is characterized in FNA by the

presence of granulomas containing C- , V- and boomerang-shaped epithelioid cells, multinucleated giant cells and lymphocytes. (Fig. 3.2).

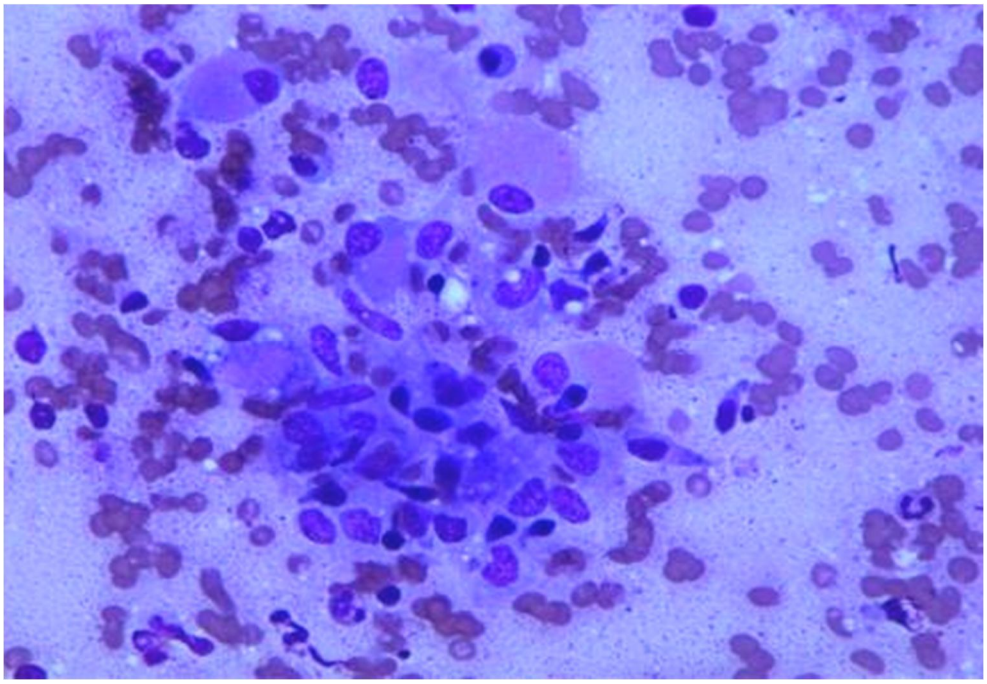
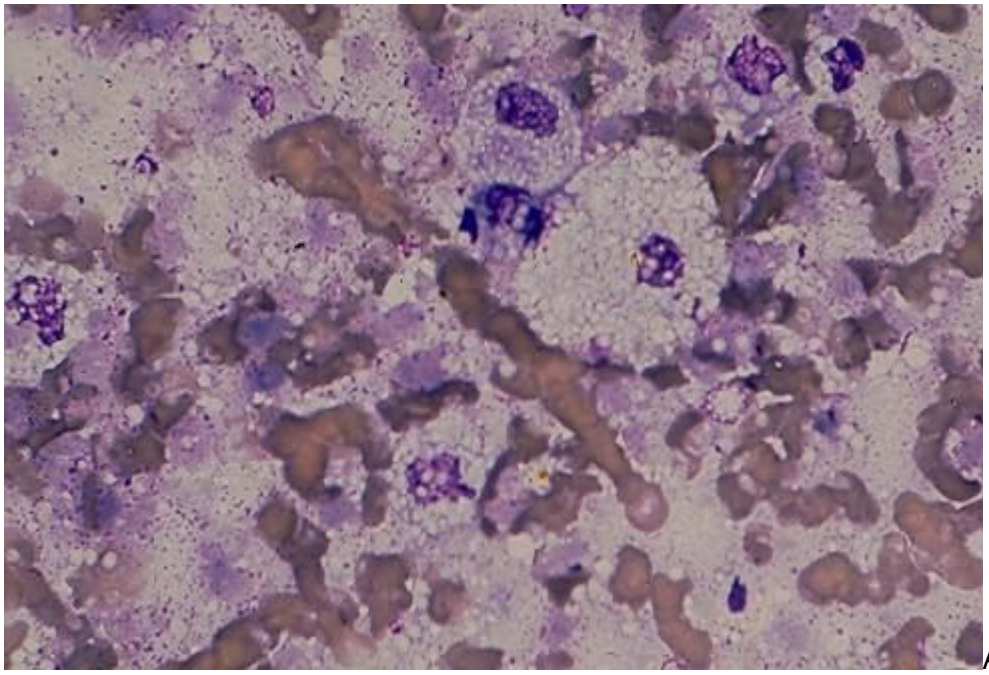


Fig.3.2. Lymph node with sarcoidosis showing in FNA a cluster of histiocytes and epithelioid cells. (CP, DQ).

Acute bacterial lymphadenitis yields in FNA purulent material and bacterial culture is the best means to identify the causative agent.

Fungal lymphadenitis occurs more commonly in AIDS victims and usually yields in FNA variable findings. Some show only purulent material and others may yield granulomas or abundant histiocytes admixed with other inflammatory cells. In other cases fungal elements admixed with inflammatory cells are seen. *Histoplasmosis capsulatum* and *Coccidioides immitis* may be seen in Pap-stained materials. (Fig.3.3). Histiocytes may show intracytoplasmic vacuoles containing microorganisms that are referred as “negative images”. These “negative images” are only observed in air-dried and Romanowsky-stained cytologic preparations and they are not seen in ethanol-fixed and Pap-stained smears. Fungal elements are best demonstrated by Gomori methenamin silver (GMS) or periodic acid-Schiff stain.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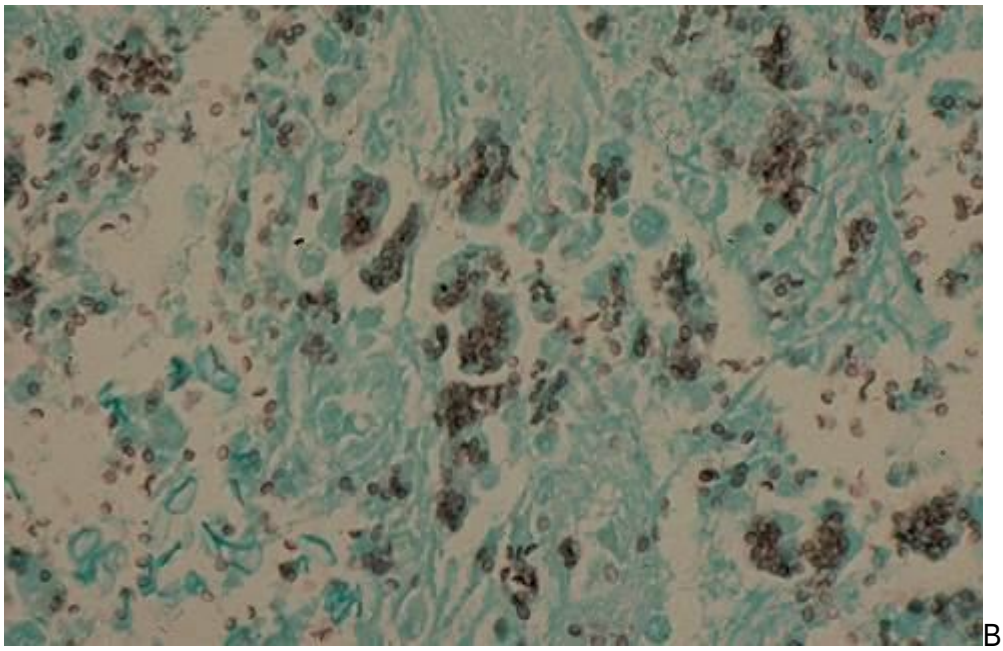
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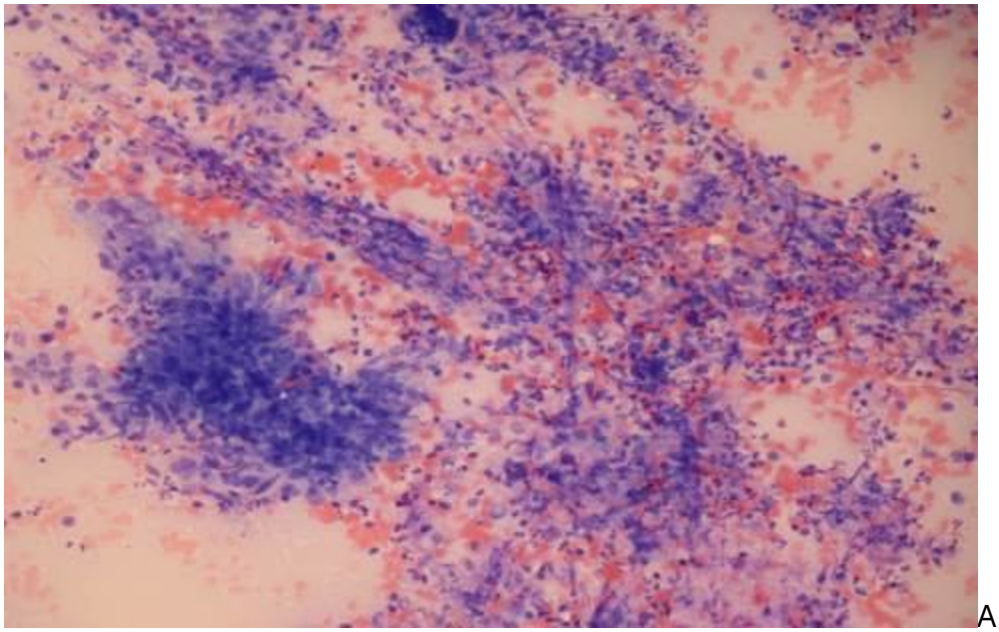
Fig.3.3. Histoplasmosis lymphadenitis. A. FNA shows numerous foamy histiocytes with vacuolated cytoplasm and “negative images” of organisms. (DQ) B. Cellblock section showing numerous fungal yeast forms within histiocytes. (GMS)

Cat scratch disease is the most common cause of chronic benign lymphadenopathy in North America and it is self-limited. Enlarged lymph nodes are tender and may be matted together. Early lesions begin with a monocytoid B-cell proliferation followed by necrosis and neutrophilic infiltratrion forming stellate microabcess. The causative agent

bacillus *Bartonella henselae* may be demonstrated by Steiner and Steiner staining method with variable results. Culture is the best way to confirm the disease.

Mycobacterial lymphadenitis is more commonly seen in people from third world countries. In North America mycobacterial lymphadenitis occurs mainly in immunocompromised individuals (eg. AIDS victims). It is characterized cytologically by extensive necrosis. Granulomas with epithelioid histiocytes, multinucleated giant cells of Langhans, neutrophils and intra- and extracellular bacilli may be seen. Acid-fast bacilli may be demonstrated by staining the FNA or cellblock sections with the Ziehl-Neelsen technique or acid-fast stain. (Figs.3.4 and 3.5).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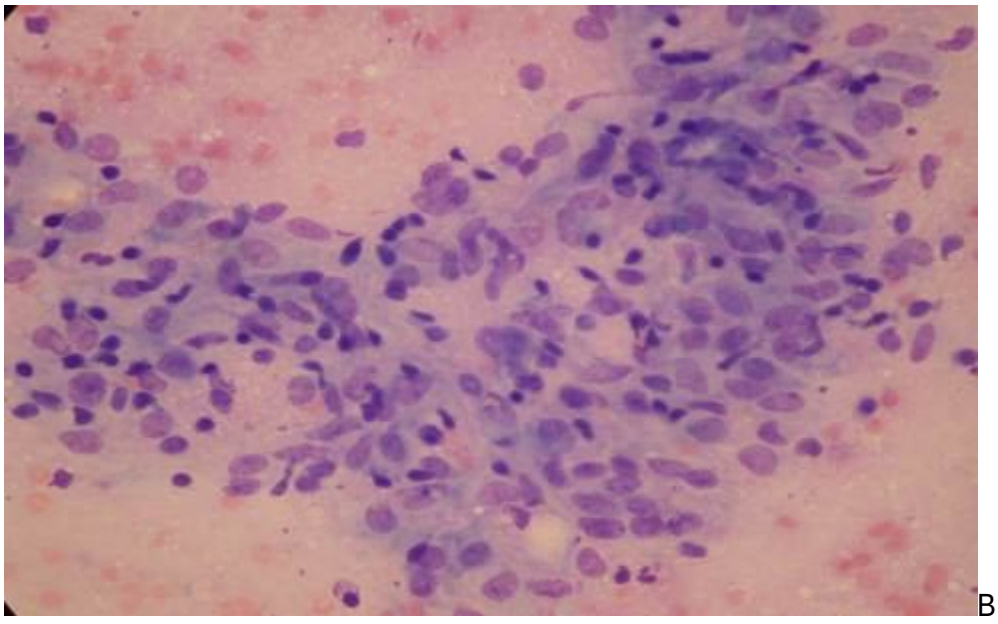
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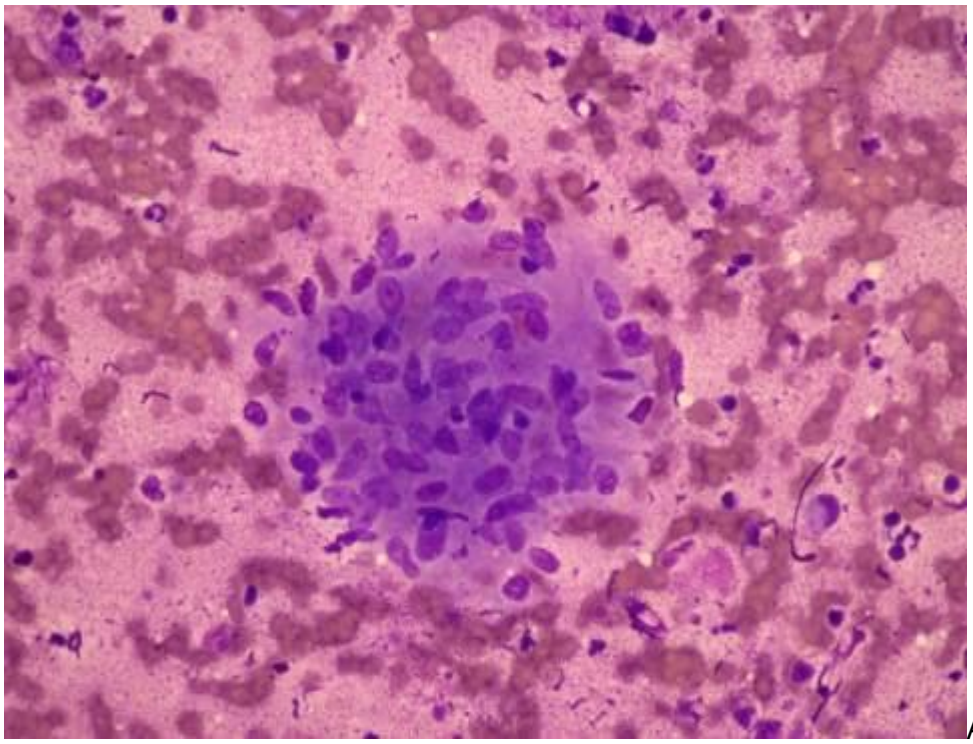
Figs.3.4. Tuberculous lymphadenitis showing in FNA: A. Large amount of necrotic debris admixed with clustered epithelioid cells and scattered polymorphonuclear leukocytes. (CP, DQ). B. A large cluster of epithelioid cells showing elongated, oval or curved nuclei and ill-defined cytoplasm. (CP, DQ).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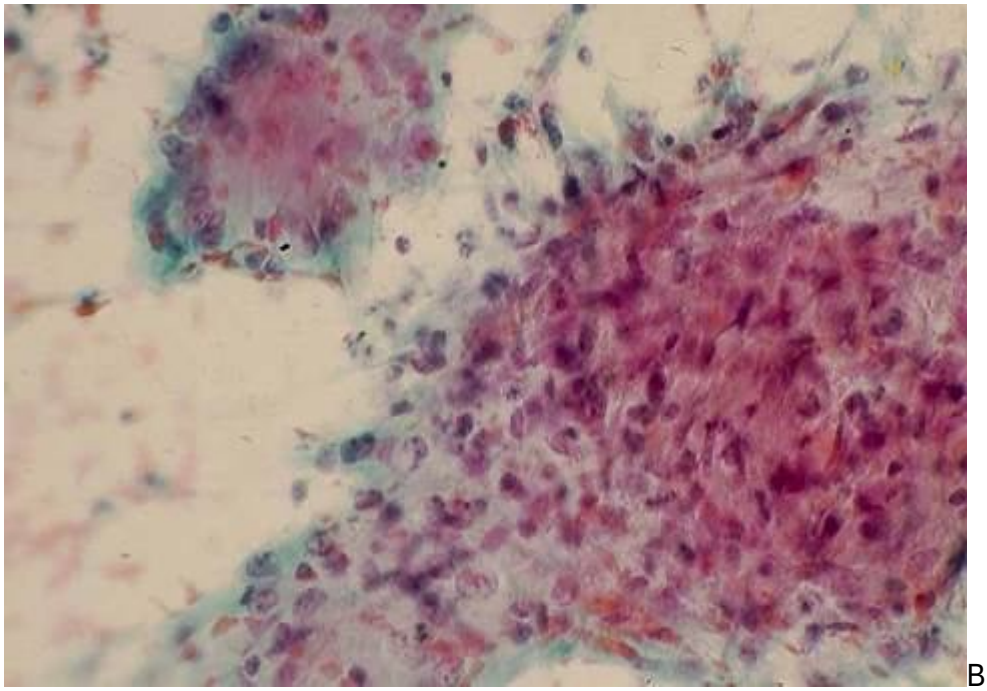
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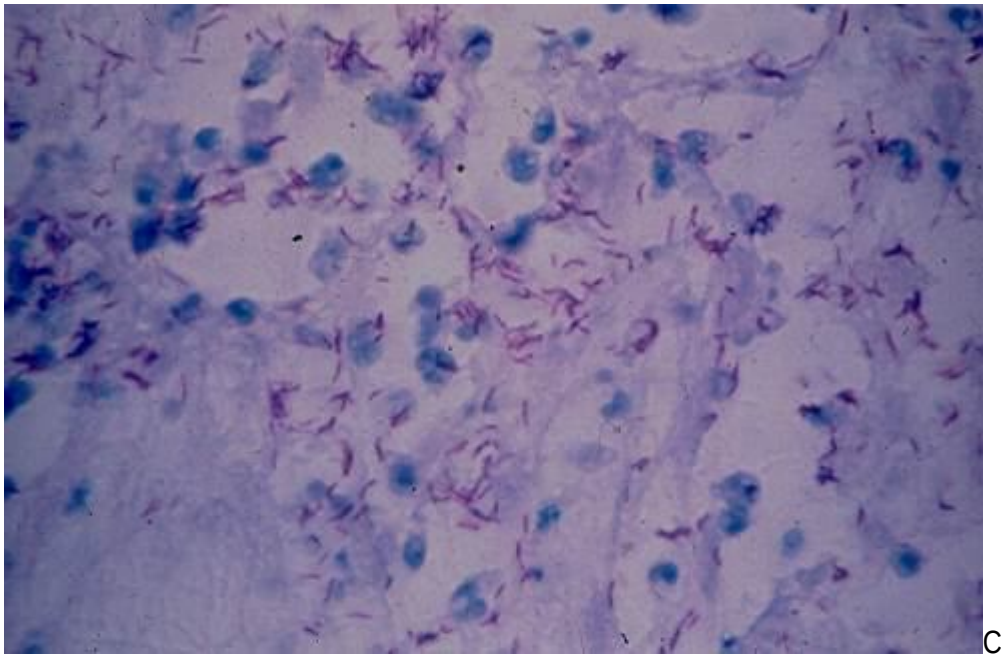
 C

Fig.3.5. Tuberculous lymphadenitis: A. A cohesive cluster of epithelioid cells forming a multinucleated giant cell of Langhans. (CP, DQ). B. Clustered epithelioid cells and a multinucleated giant cell of Langhans. (CP, Pap). C. Numerous acid-fast bacilli are present in a cellblock. (ZN, oil immersion).

Rosai-Dorfman disease is an uncommon disease involving mainly children and adolescents. It is characterized a bilateral, painless cervical lymphadenopathy associated with fever, night sweats and weight loss. In FNA small lymphocytes and histiocytes with emperipolesis (phagocytosis of lymphocytes by histiocytes) are noted. (Fig.3.6).

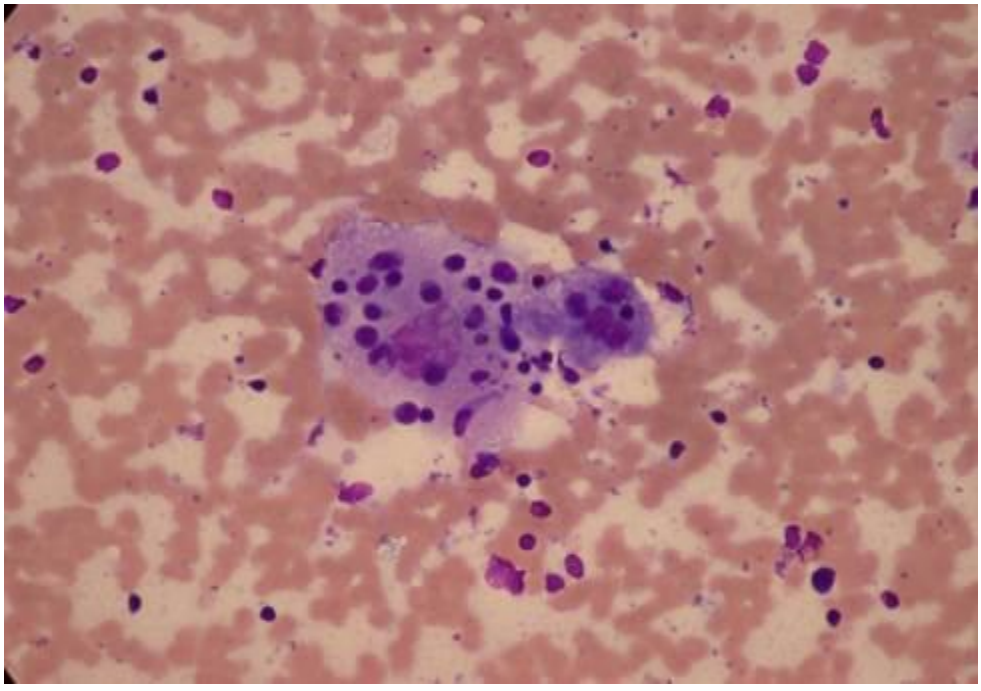


Fig.3.6. FNA of lymph node with Rosai-Dorfman disease showing large histiocytes with emperipolesis. (CP, DQ).

Kikuchi lymphadenitis is self-limited and occurs primarily in Asian countries. This is a necrotizing lymphadenitis affecting cervical lymph nodes with atypical peripheral lymphocytosis. The FNA of an affected lymph node reveals necrotic debris, phagocytic histiocytes with sharply angulated nuclei and increased number of immunoblasts. Neutrophils are absent.

Infectious mononucleosis is caused by the Epstein-Barr virus and spreads by person-to-person contact. Clinically, it is characterized by fever, malaise, pharyngitis, skin rash, peripheral lymphadenopathy and splenomegaly. Peripheral atypical lymphocytosis and a positive heterophil (Monospot) test are almost always present and diagnostic of the infection. By FNA numerous immunoblasts, abundant plasmacytoid lymphocytes and plasma cells are present. (Fig.3.7). Binucleated immunoblasts may mimick Reed-Sternberg cells and large immunoblasts may be mistaken for cells derived from a large-cell lymphoma. In difficult cases, an excisional biopsy of the affected lymph node should be done for histologic diagnosis.

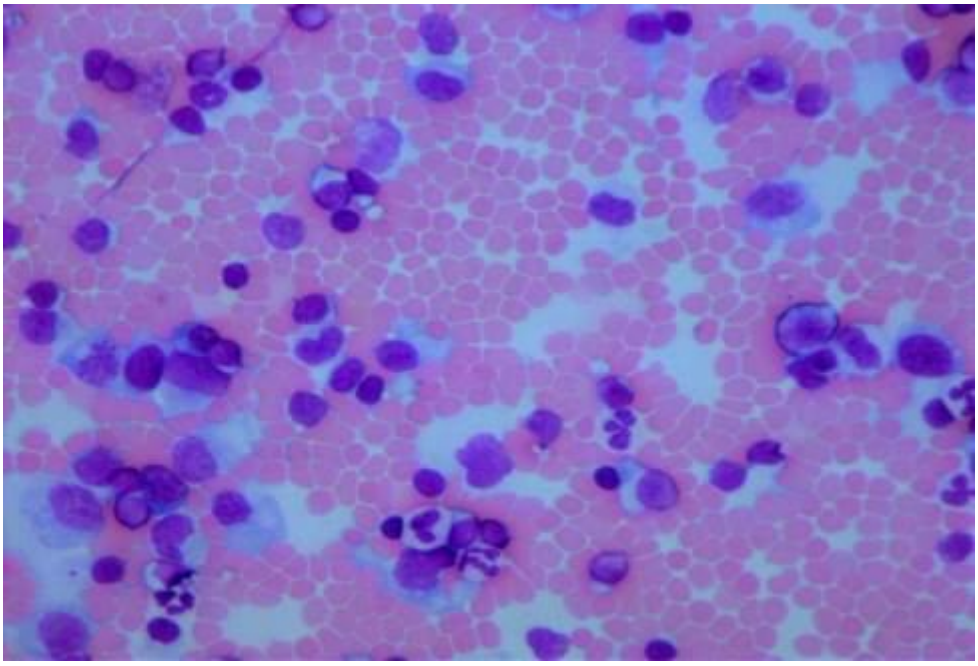


Fig.3.7. Abundant immunoblasts in FNA of a case of mononucleosis. (CP, DQ).

Lymphoma

It is the opinion of most authorities, including the writers, that FNA has severe limitations in making an initial diagnosis of Non-Hodgkin lymphomas (NHL) and that it

should not replace tissue biopsy for this purpose. It can be used to diagnose Hodgkin disease and recurrent or transformation of a known low-grade to a high-grade NHL.

Hodgkin lymphoma. A classic Hodgkin lymphoma yields in FNA small lymphocytes, eosinophils and Reed-Sternberg cells, classic and mononuclear variants. (Fig.3.8). Reed-Sternberg cells account for 0.1-10% of the total cell population, depending on the disease subtypes, being lowest in lymphocytic-rich type.

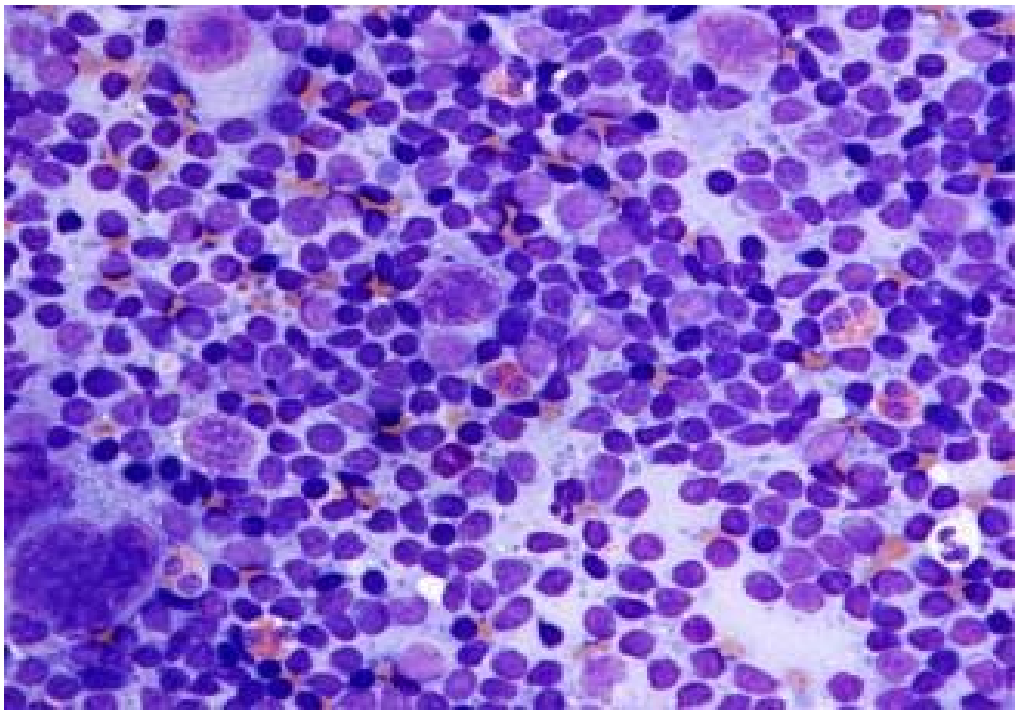
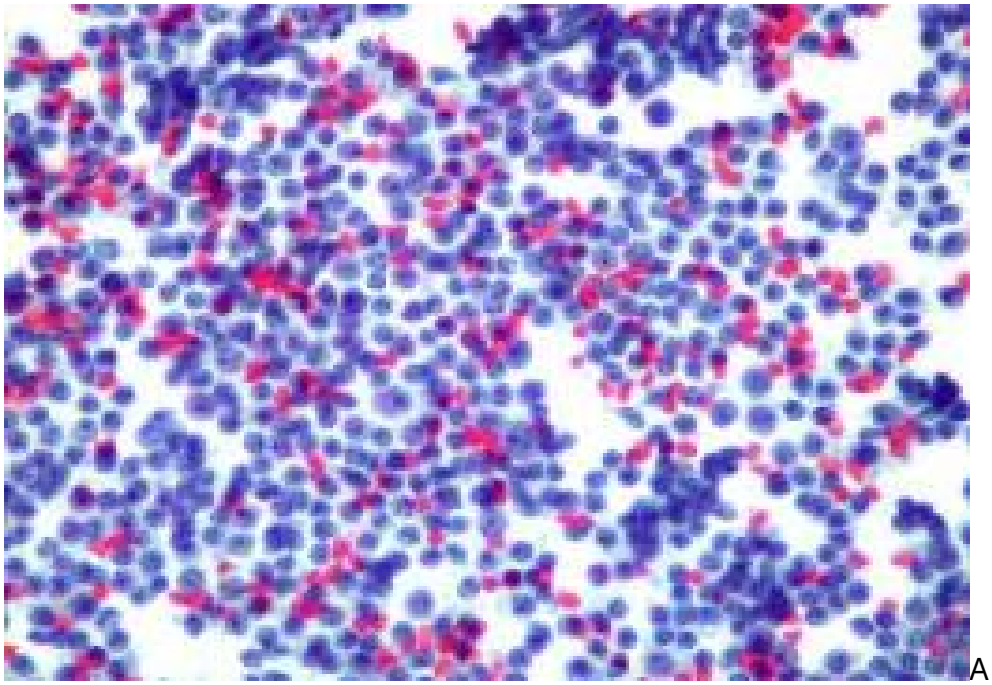


Fig. 3.8. Hodgkins Lymphoma. FNA reveals a polymorphous population of small to large lymphocytes, increased eosinophils and large Reed-Sternberg cells. (CP, MGG)

Non-Hodgkin Lymphomas are classified into B- and T-cell tumors, according to the recent WHO classification. About 90% of NHLs in the United States are B-cell neoplasms and about 10% are T-cell NHLs, while null-cell NHLs are very rare. A NHL is suspected if a monomorphic lymphoid cell population with or without abnormal forms is present in FNA. (Fig.3.9). When a NHL is suspected cytologically, the enlarged lymph node should be surgically biopsied for histologic, cell marker and/or molecular studies for a firm lymphoma diagnosis. The reader is referred to Chapter 5 in Dr. Nguyen's monograph on "Essentials of Abdominal Fine Needle Aspiration Cytology" for a more comprehensive discussion on the cytodiagnosis of NHL.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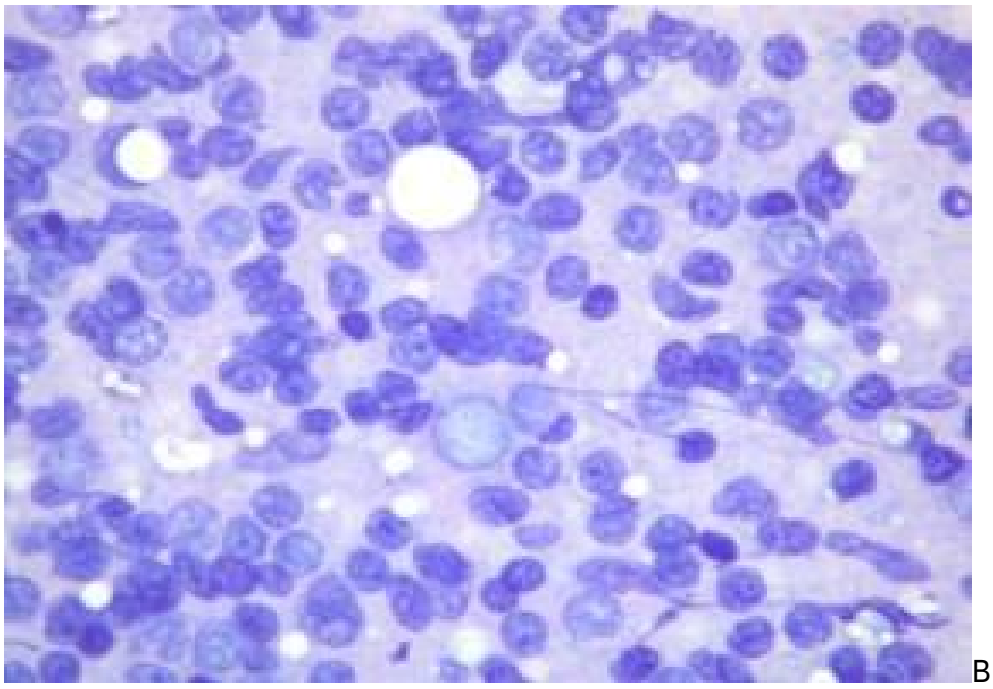
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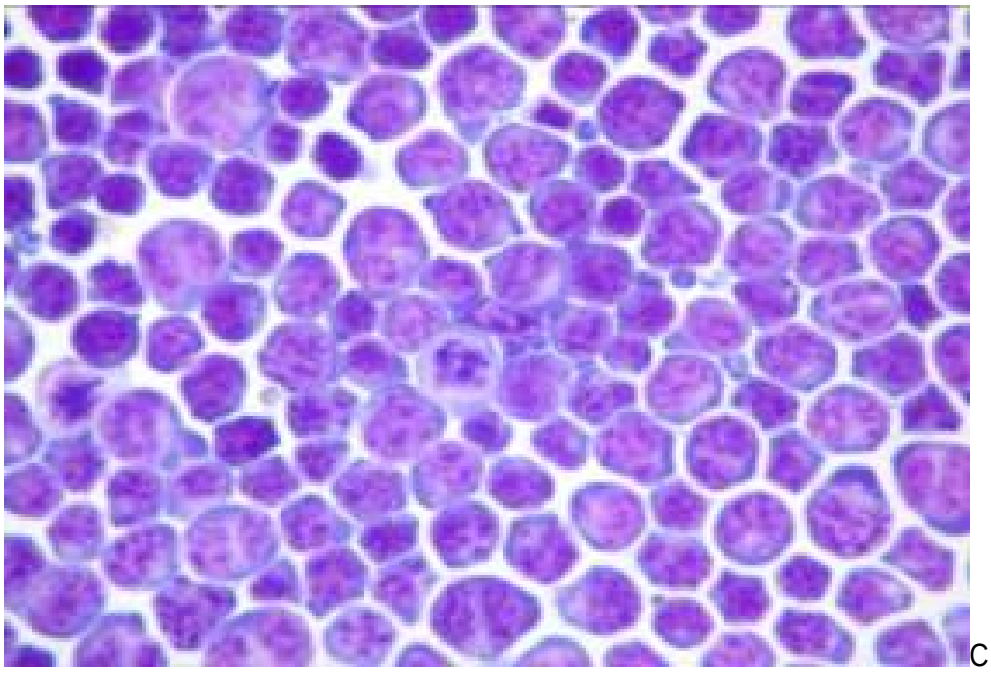
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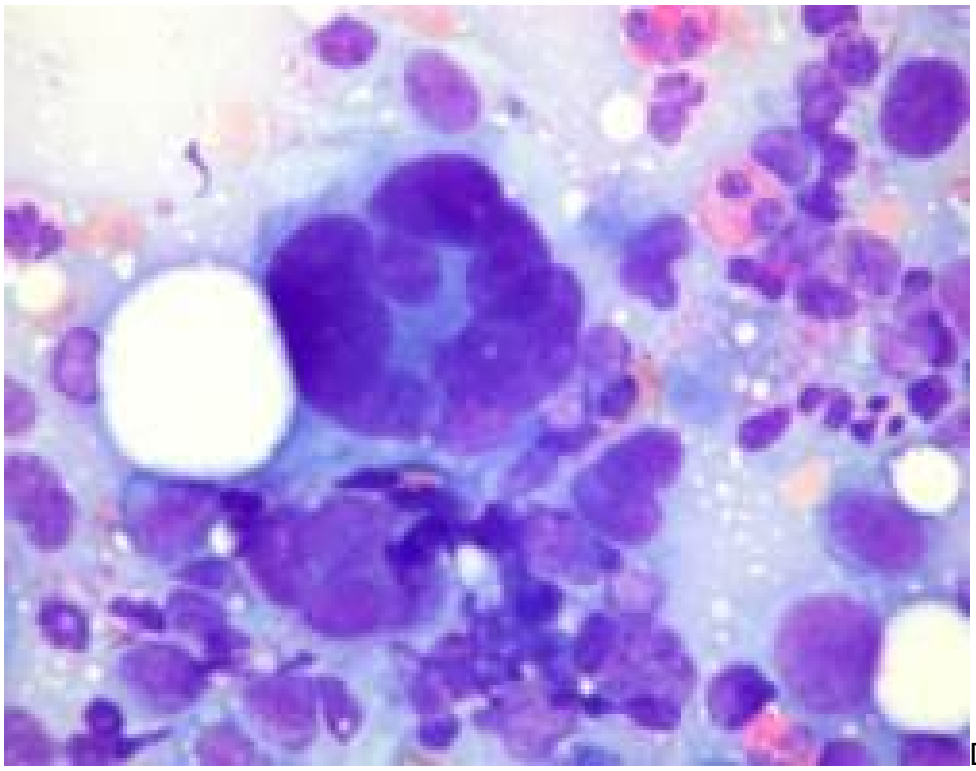
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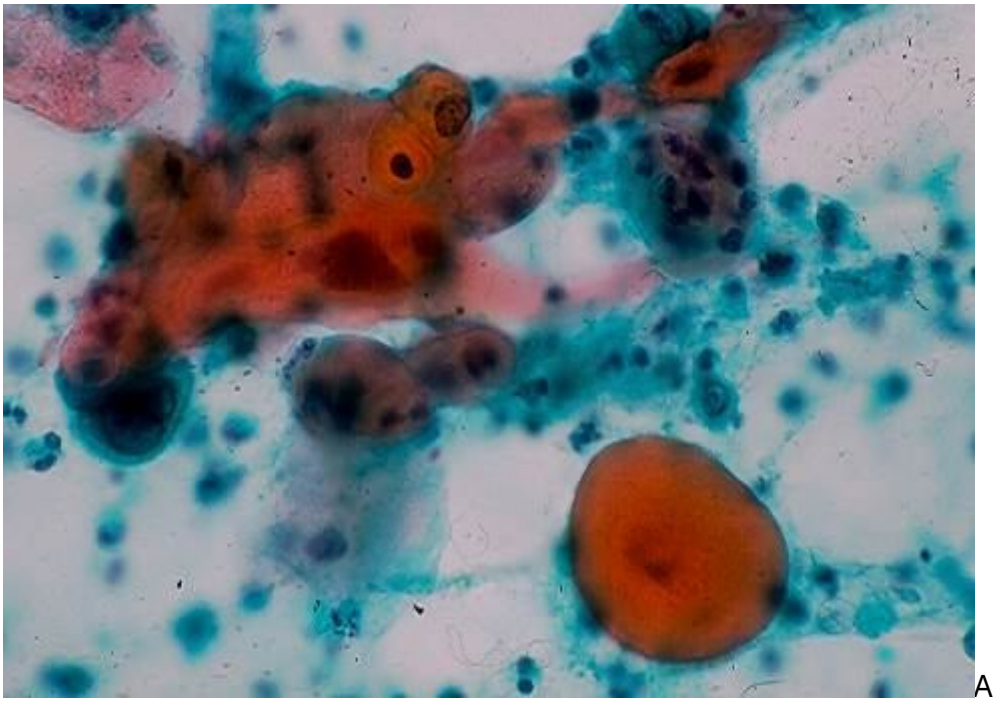
Fig.3.9. Non-Hodgkin Lymphomas. Suggestive cytodiagnostic features: A and B. Monomorphic population of lymphoid cells showing convoluted nuclei and scant cytoplasm. (CP, A, Pap; B, DQ). C. Relatively monomorphic population of polymorphous atypical lymphoid cells with increased intermediate sized lymphoid cells (centrocytes) and few small round lymphocytes. (CP, MGG). D. Presence of large and pleomorphic tumor cells without reactive lymphoid background suggesting an anaplastic large cell NHL. (CP, MGG)

Metastatic cancers

Carcinomas, sarcomas, melanomas arising from any body sites may metastasize to cervical lymph nodes. Among these tumors, carcinomas are the most common ones. In most instances the diagnosis of metastatic tumor to lymph nodes by FNA is not difficult because of the ease in differentiating "alien" cells from lymphocytes. Epithelial cells are usually seen in clusters or sheets as opposed to the dissociated arrangement of lymphoid cells. In patients with known primary malignant tumors, typing of a metastatic cancer to a lymph node is usually not problematic, as a comparison of needle aspirate material with primary tumor histologic sections is often available. However, when a metastatic cancer to a cervical node is the initial manifestation of a clinically occult cancer, cytologic features with or without adjunctive IHC studies of the aspirated tumor cells may be helpful in localizing the primary tumor.

Metastatic squamous cell carcinoma. The cytologic manifestations of a well- and poorly differentiated squamous cell carcinomas are different. A **metastatic well-differentiated squamous carcinoma** yields in FNA large keratinizing tumor cells with hyperchromatic nuclei, dense eosinophilic or orangeophilic cytoplasm with sharp cytoplasmic contours. Many single tumor cells are pleomorphic with polygonal, tadpole and fiber configurations and epithelial pearls may be seen. Tumor with extensive necrosis shows necrotic debris admixed with abundant polymorphonuclear leukocytes and rare tumor cells. (Fig. 3.10).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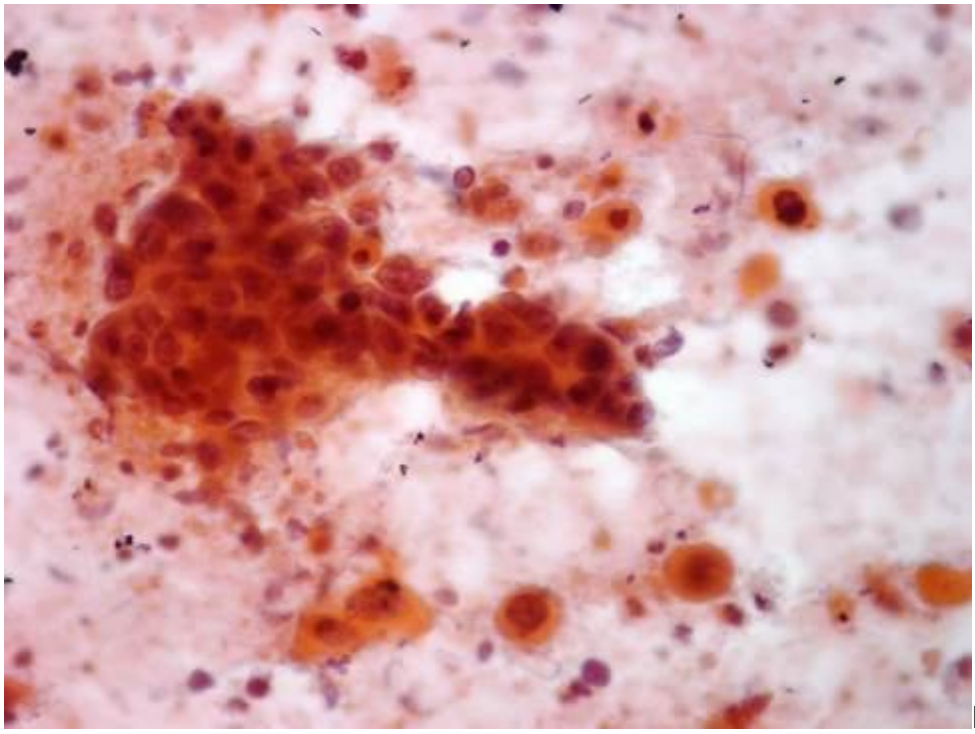
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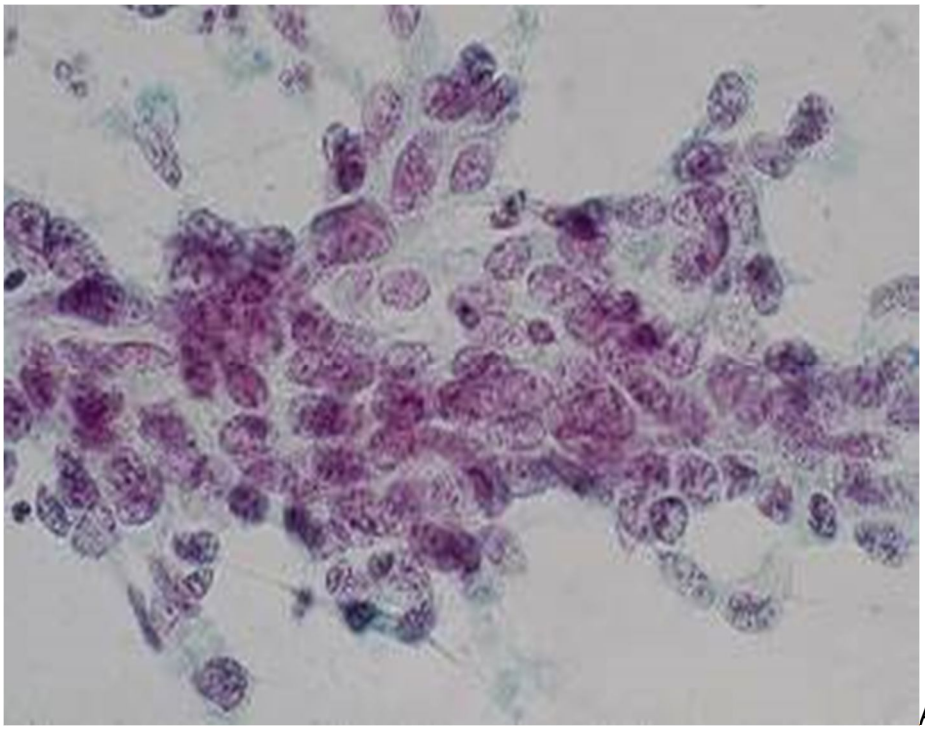
Fig.3.10. A, B. Well-differentiated squamous cell cancer showing in FNA keratinizing tumor cells with “hard” orangeophilic cytoplasm. (CP, Pap).

FNA of a **poorly differentiated squamous carcinoma** reveals non-keratinizing tumor cells that tend to occur in loose clusters or syncytia with crowded, overlapping nuclei. They are less pleomorphic than those of a keratinizing carcinoma and may display conspicuous nucleoli. Non-keratinizing, poorly differentiated squamous cell carcinoma of nasopharyngeal origin frequently presents with large metastases to posterior neck lymph nodes that yield in FNA single and clustered large malignant cells with prominent single nucleoli and scant cytoplasm. The tumor cells are positive for pankeratin and, in Asian patients, for Epstein Barr virus early RNA by in situ hybridization (EBER- ISH). (Fig. 3.11)



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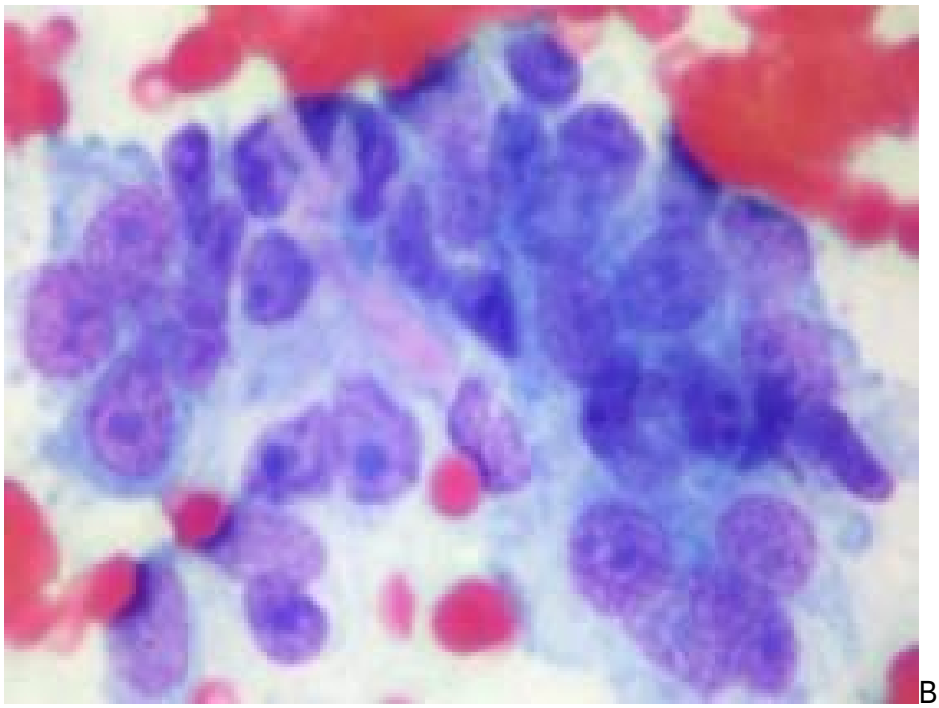

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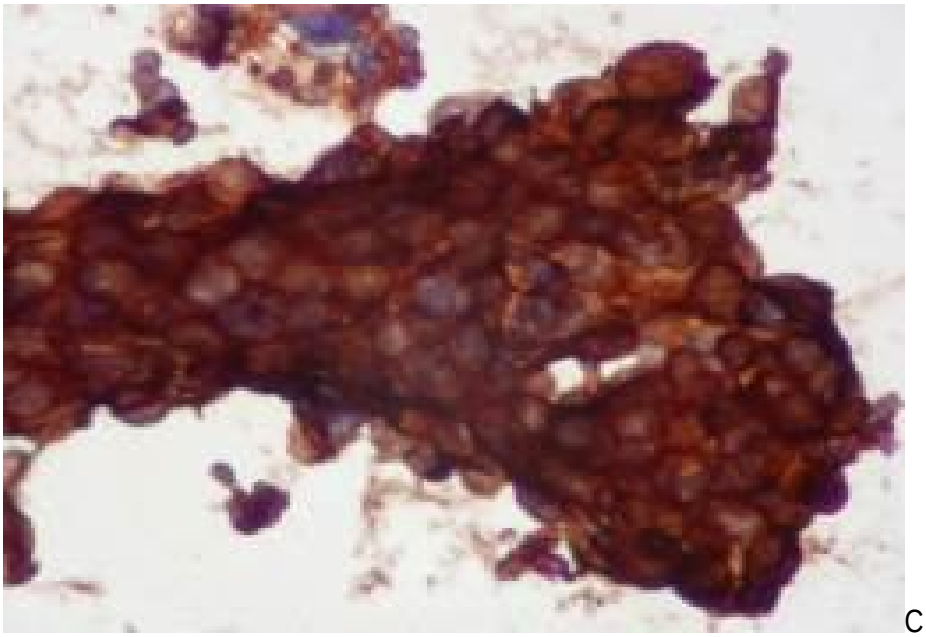
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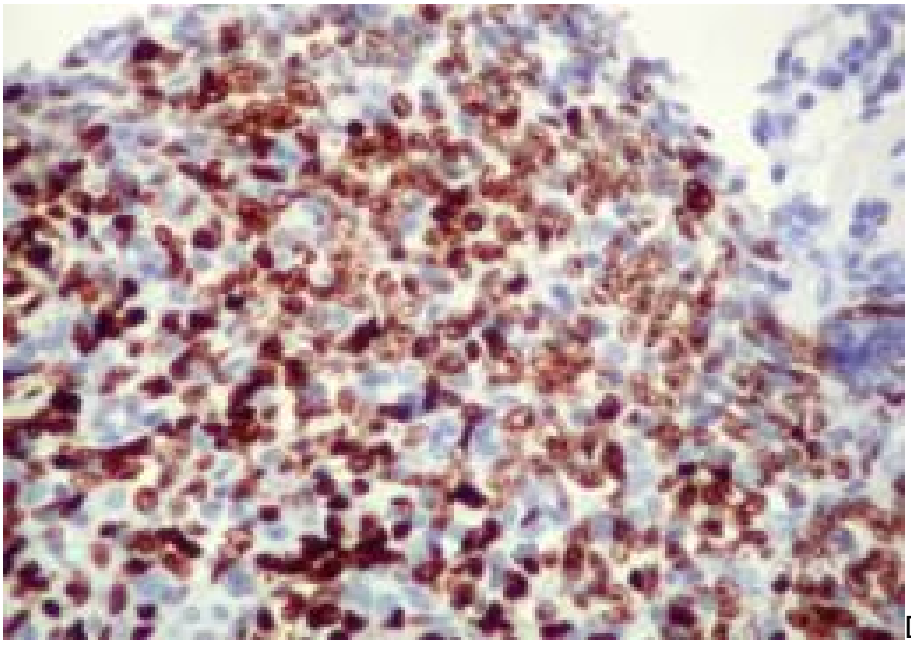
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Fig.3.11. Poorly differentiated squamous cell carcinoma. A, B. FNA shows syncitial clusters of non-keratinizing cancer cells with conspicuous nucleoli. (CP, A. Pap, B. MGG). C. Pankeratin immunostain confirms epithelial differentiation. D. Tumor tissue section with positive EBER-ISH suggests a nasopharyngeal origin.

Cytodiagnosis of a metastatic squamous cell carcinoma is not always straightforward:

1. In some cases of metastatic well-differentiated squamous cell carcinoma, the tumor cells may closely resemble benign squamous cells and the anucleated squames may mimic

material from an epidermal inclusion cyst or branchial cleft cyst. The presence of hyperchromatic, atypical nuclei and abnormal cell shaped is helpful for a more accurate diagnosis of a squamous carcinoma.

2. Extensive necrosis in a metastatic squamous cell carcinoma constitutes a diagnostic pitfall. The necrotic debris must be distinguished from that of tuberculous lymphadenitis. In the latter instance, necrotic material is granular and amorphous and may show fibroblasts, lymphocytes and epithelioid cells, whereas in metastatic carcinomas the necrotic material may contain many ghost tumor cells and rare viable tumor cells. A cell block or a repeat FNA is of diagnostic help in this situation. (Fig.3.12).

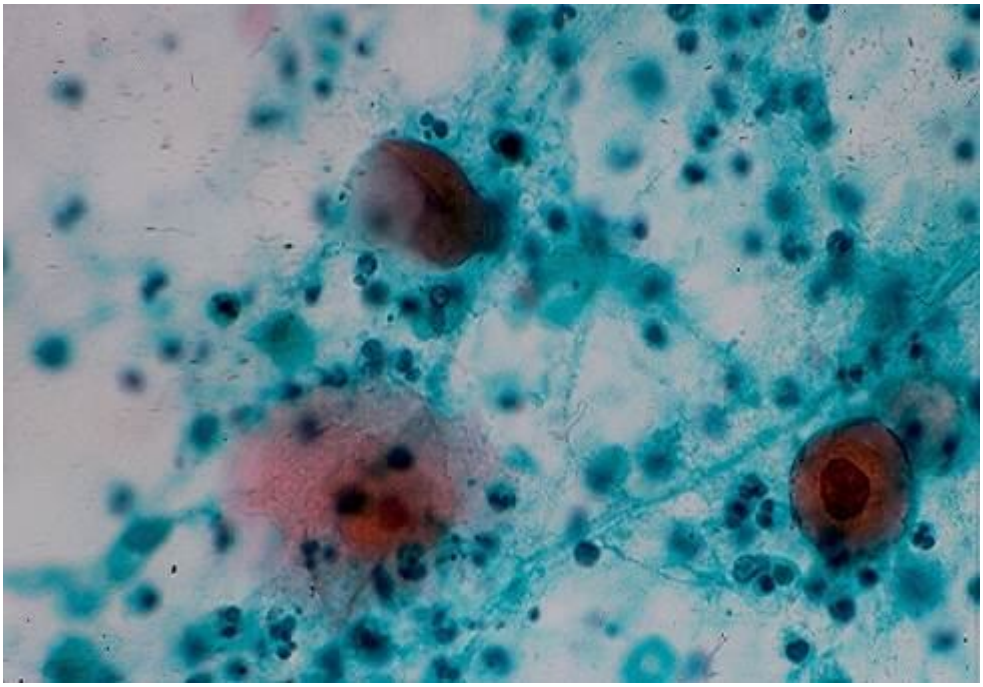


Fig.3.12. Single tumor cells admixed with necrotic debris and inflammatory exudate in FNA of an extensively necrotic metastatic squamous cell carcinoma. (CP, Pap).

Metastatic adenocarcinomas display in FNA certain characteristic cell patterns: monolayered sheets; 3-dimensional clusters; papillary and acinar or glandular formations. The individual tumor cells are cuboidal or columnar in shape, with central or basal nuclei, single or multiple prominent nucleoli and pale or vacuolated cytoplasm. (Fig.3.13).

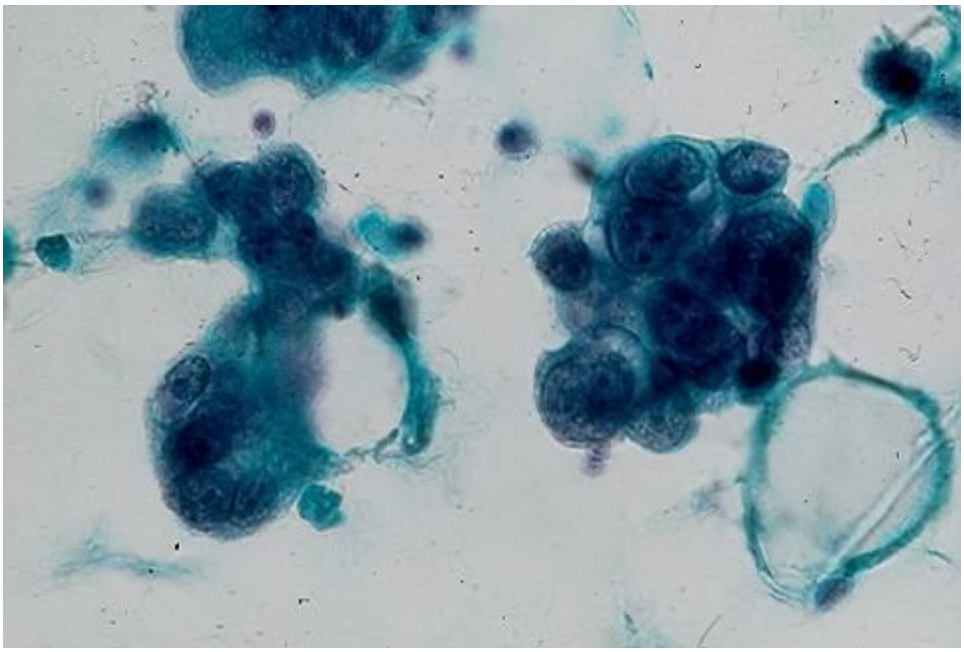


Fig.3.13. Tumor cell clusters from a metastatic bronchogenic adenocarcinoma. (CP, Pap).

Metastasis from a specific site can be recognized in some cases because of certain characteristic cytologic features. Papillary tissue fragments with or without psammoma bodies are most often associated with a thyroid or ovarian carcinoma. (Fig.3.14). A metastatic thyroid papillary carcinoma may produce a large amount of thick colloid containing scanty tumor epithelial fragments with nuclear grooves and intranuclear cytoplasmic inclusions.

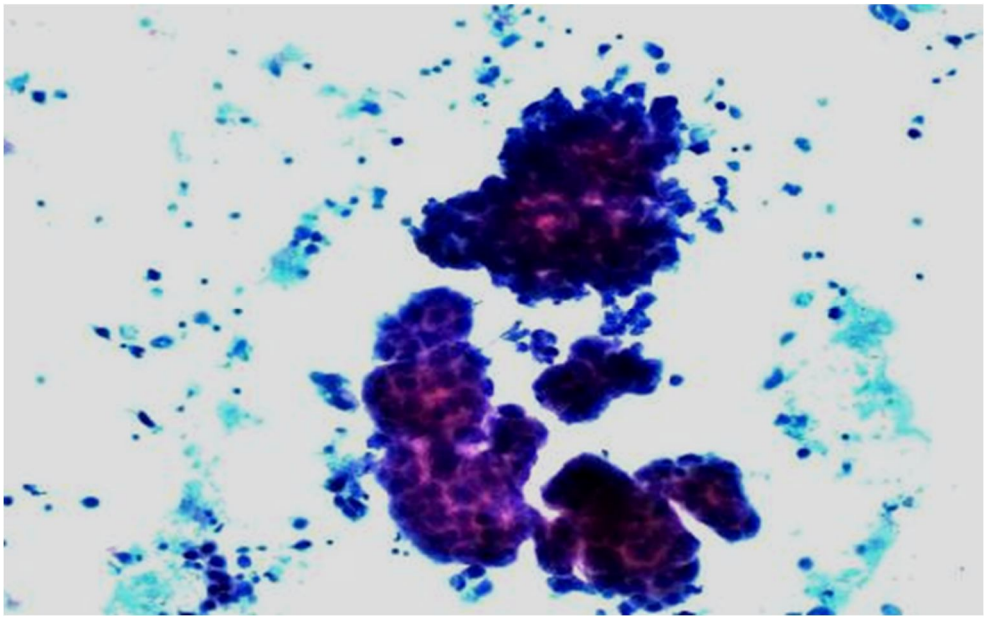
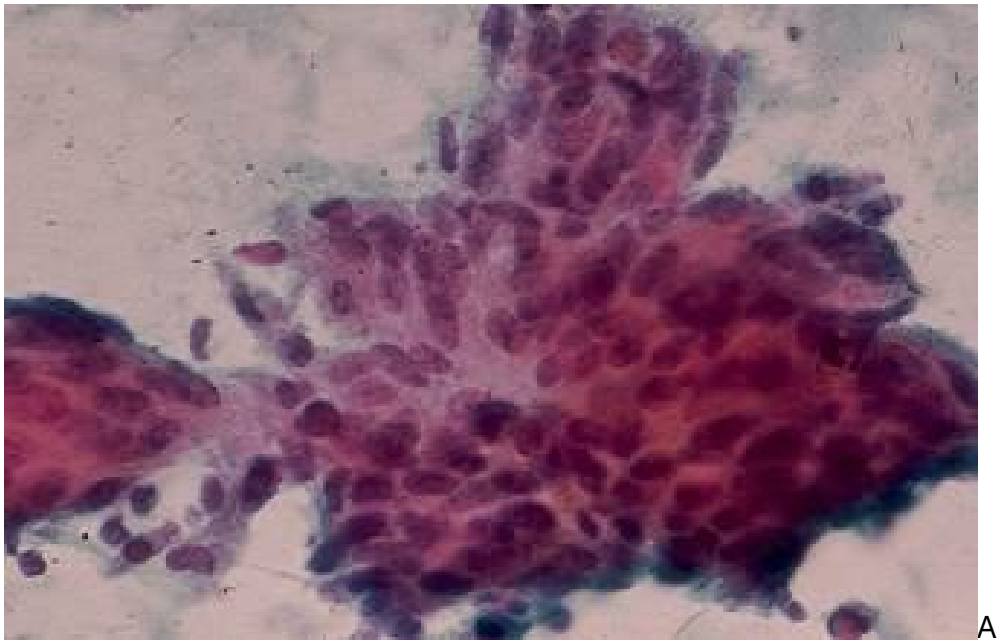


Fig.3.14. Papillary tumor tissue fragments from a metastatic ovarian papillary serous carcinoma. (CP, Pap).

Columnar cells with basal nuclei in picket-fence arrangement or arranged radially around a space are most commonly seen in a **metastatic colonic adenocarcinoma.** These tumor cells are CK7 negative and CK20 and CDX2 positive. (Fig.3.15). Malignant cells distended by a large intracytoplasmic mucinous vacuole with nuclei displaced to the periphery are typically associated with a gastric linitis plastica.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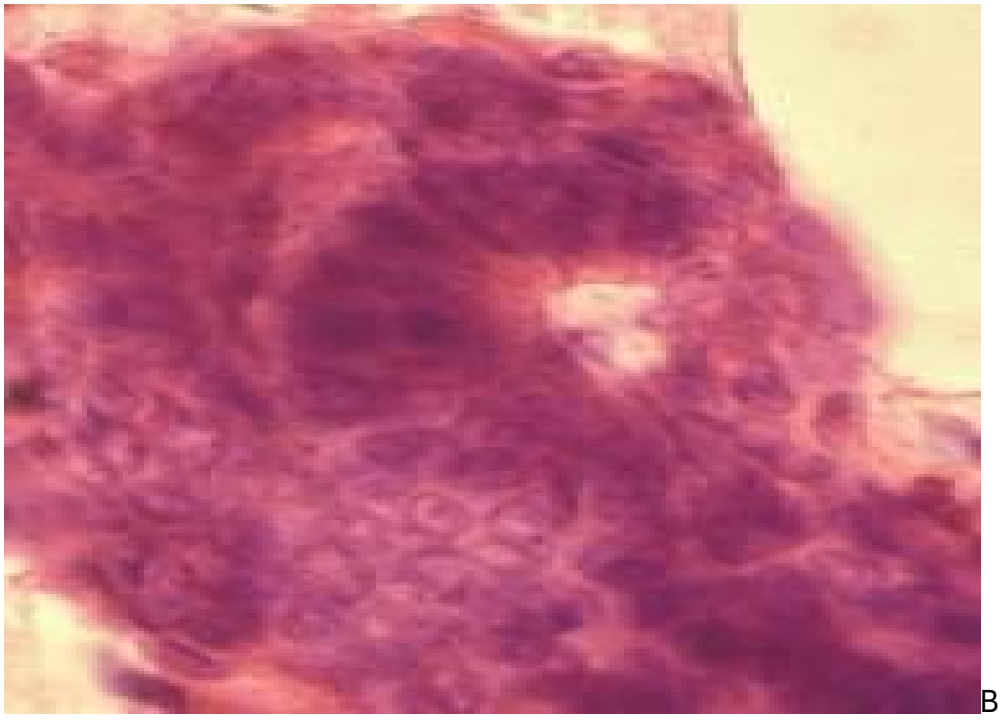
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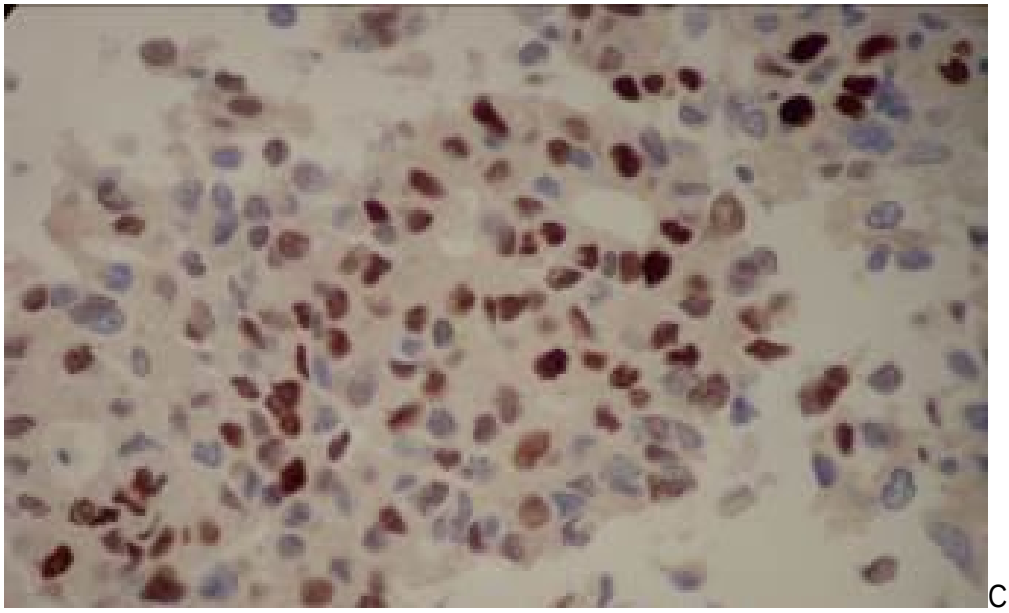
 C

Fig.3.15. Metastatic colonic adenocarcinoma. A, B. Tumor tissue fragments with nuclei in palisade or tubular glandular formation. (CP, Pap). C. Cellblock section showing a positive nuclear staining with CDX2 antibody. (ABC)

Cells from a metastatic **conventional renal cell carcinoma** have a clear or granular cytoplasm and are seen singly and in cohesive sheets. They react positively with cytokeratin, vimentin and renal cell carcinoma antibodies. (Fig.3.16).

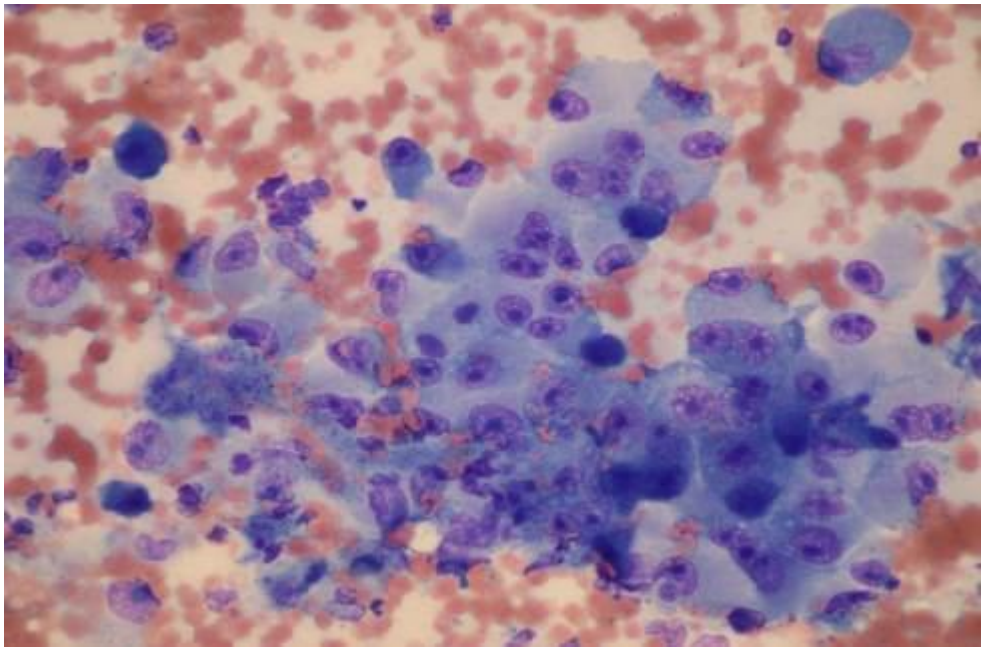


Fig.3.16. Single and sheets of tumor cells with clear or granular cytoplasm and prominent nucleoli from a metastatic conventional renal cell carcinoma. (CP, DQ).

Metastatic Anaplastic Carcinoma. FNA from a **large cell anaplastic carcinoma** reveals large neoplastic cells with a variable amount of cytoplasm and single or multiple prominent nucleoli. In some cases, multinucleated giant cells and spindled cells are seen. (Fig.3.17).

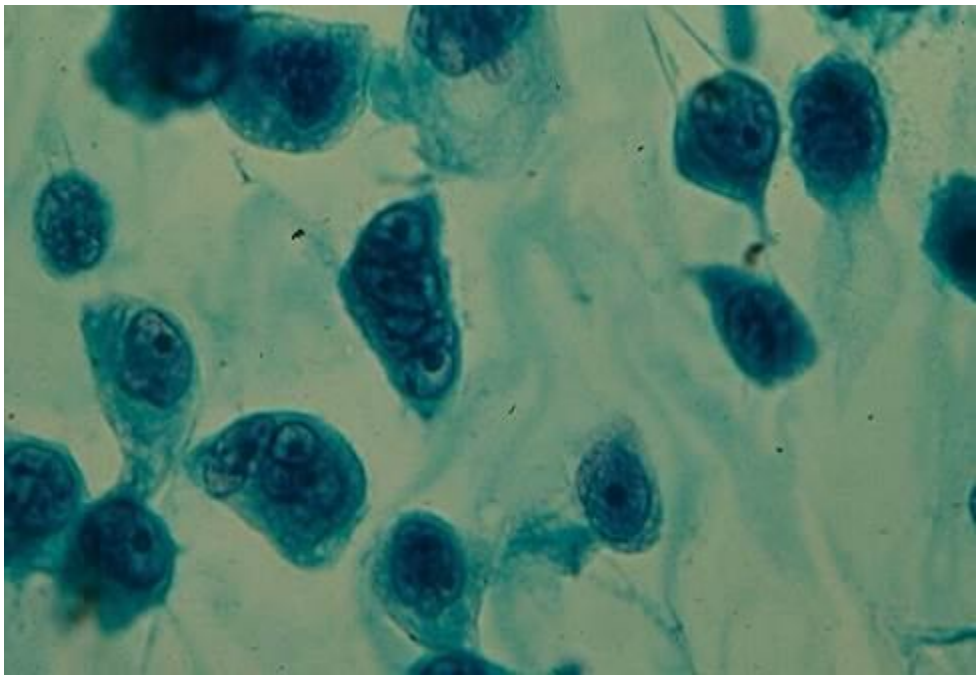


Fig.3.17. Metastatic bronchogenic large cell anaplastic carcinoma showing in FNA single large tumor cells with some cells displaying multiple nuclei with prominent nucleoli. (CP, Pap).

Small cell anaplastic carcinoma, most commonly originating from the lungs, shows in FNA small cells with rounded or angulated nuclei and scanty, ill-defined, basophilic cytoplasm. When the tumor cells are well preserved, the nuclei show "salt and pepper" chromatin and inconspicuous nucleoli. They tend to occur singly and in clusters with nuclear molding. Linear basophilic nuclear debris is frequently present. (Figs.3.18 and 3.19). Cells derived from a lung small cell carcinoma are NSE, chromogranin and TTF1 positive.

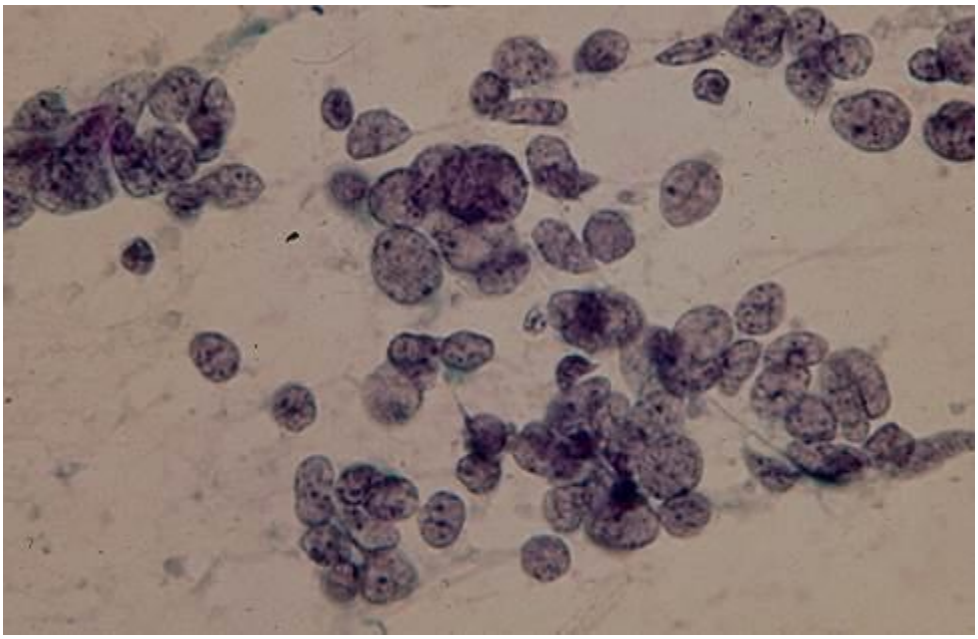
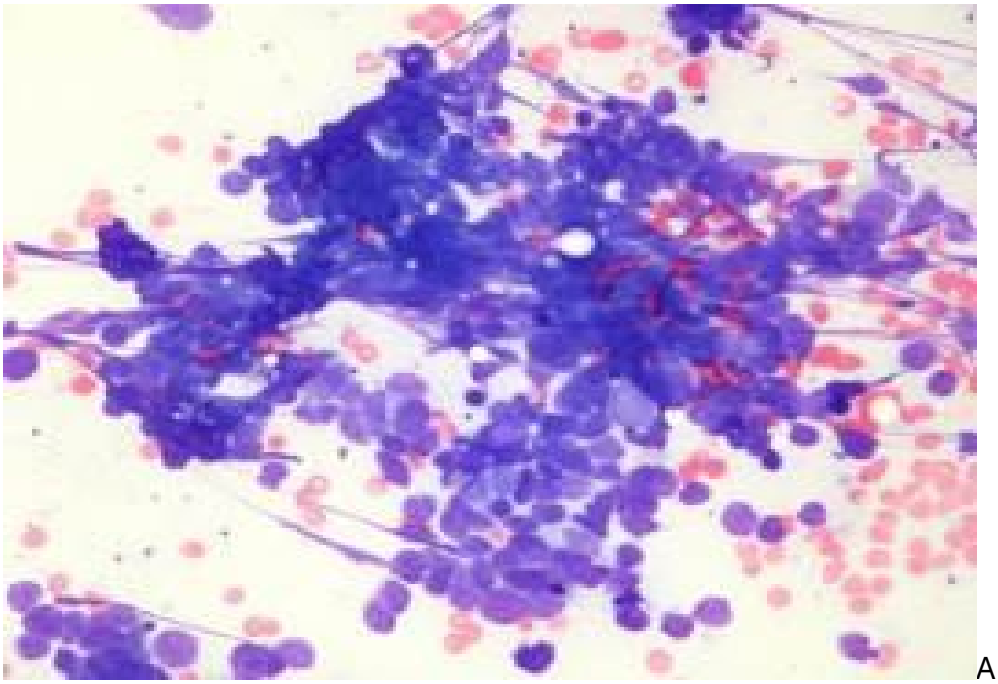


Fig.3.18. Metastatic lung small cell carcinoma showing single and clustered tumor cells with nuclear molding and “salt and pepper” chromatin pattern. (CP, Pap).



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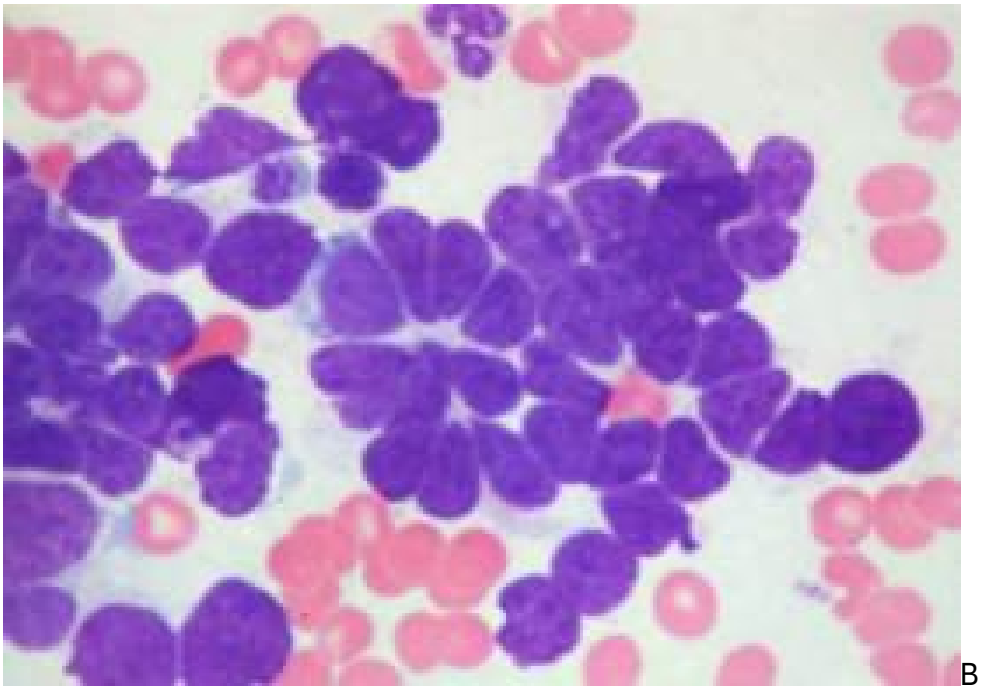
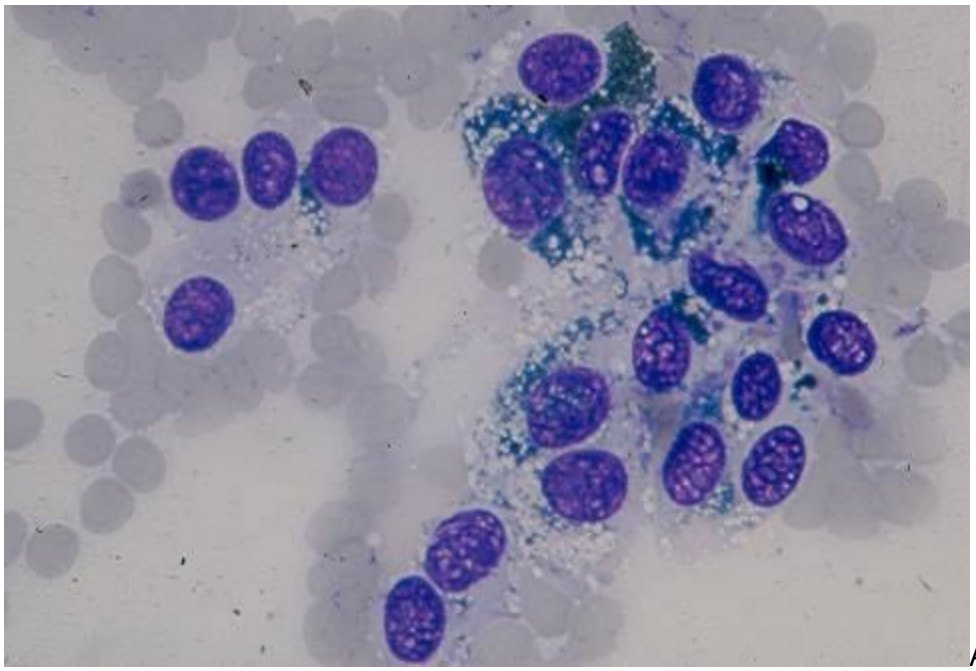
 B

Fig.3.19. A, B. Metastatic small cell anaplastic carcinoma showing single and clustered tumor cells with nuclear molding, pseudorosette formation and crush artifact. (CP, MGG)

Metastatic melanoma usually shows in FNA a mixture of different cell types and there is a distinct tendency for the tumor cells to be dissociated. The identification of intracytoplasmic melanin pigment is a useful aid in diagnosis. In most cases the epithelioid cells constitute the major component. They vary from small to large polygonal or plasmacytoid tumor cells with prominent nucleoli, well-defined cytoplasmic borders and variable amounts of granular cytoplasm. The nuclei are eccentrically located and may show intranuclear cytoplasmic inclusions. The spindle-shaped tumor cells have oval or elongated nuclei with prominent nucleoli and bipolar, slender cytoplasmic processes. The giant tumor cells are moderately pleomorphic large cells with single, double or multiple nuclei and macronucleoli. The cytoplasm is abundant and may show a glassy appearance. Intracytoplasmic melanin pigment granules may be observed in routinely stained melanoma cells. Staining of the aspirated tumor cells with S-100 protein, HMB-45 and melan A antibodies will be helpful for tumor typing. Rarely, tumor cell clusters with vascular transgression may mimic tumor tissue fragments aspirated from a thyroid papillary carcinoma. (Figs. 3.20 to 3.23).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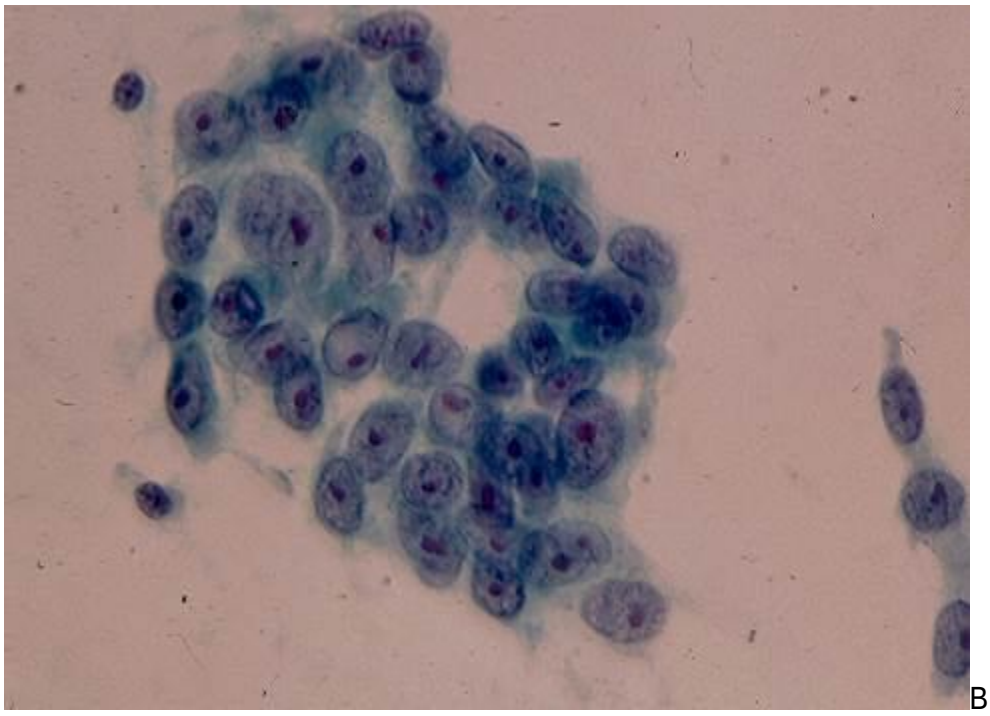
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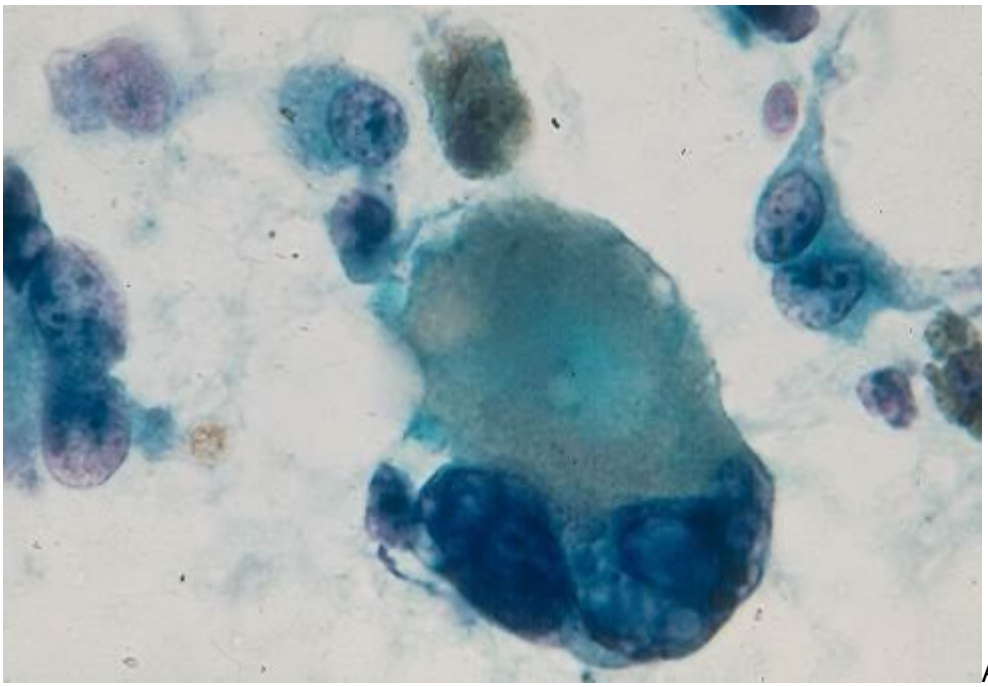
Fig.3.20. Two examples of metastatic melanoma: A. Loosely clustered melanoma cells with oval, bland nuclei and intracytoplasmic melanin pigment granules. (CP, DQ). B. Clustered melanoma cells with prominent nucleoli mimicking malignant glandular cells. (CP, Pap).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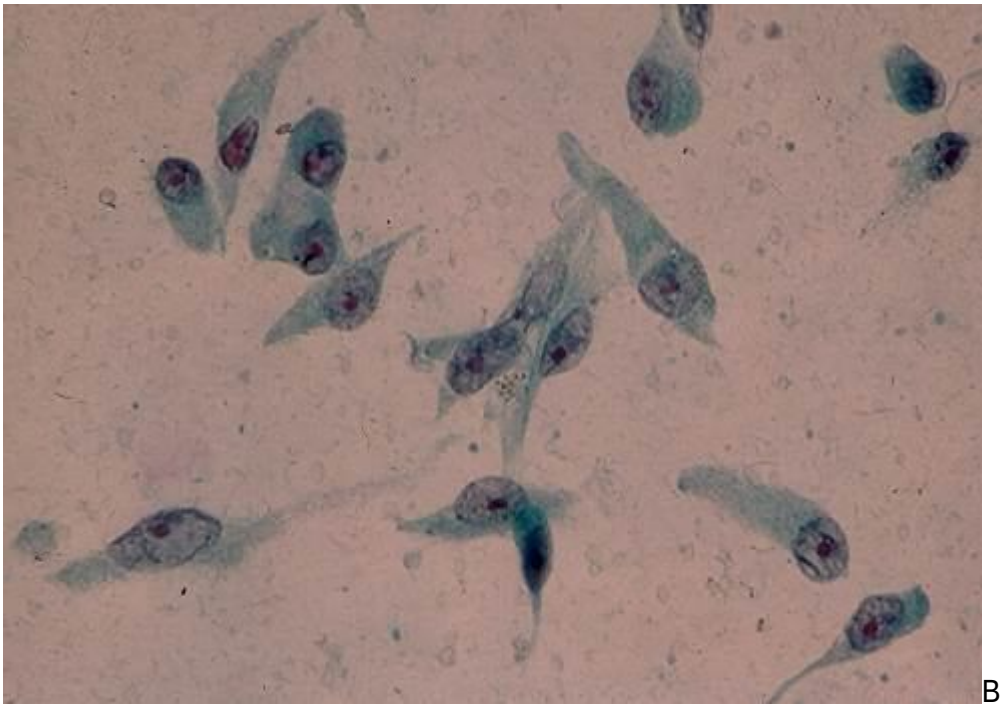
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Fig.3.21. Two examples of metastatic melanoma: A. Bizarre large single tumor cells. (CP, Pap). B. Isolated spindle-shaped malignant cells with prominent nucleoli. (CP, Pap).

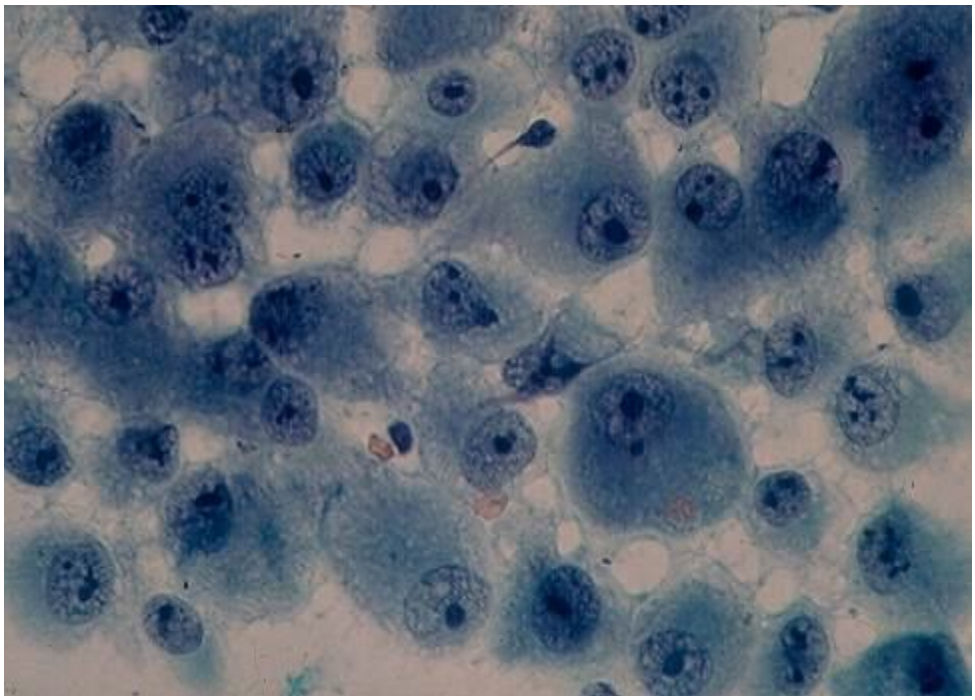
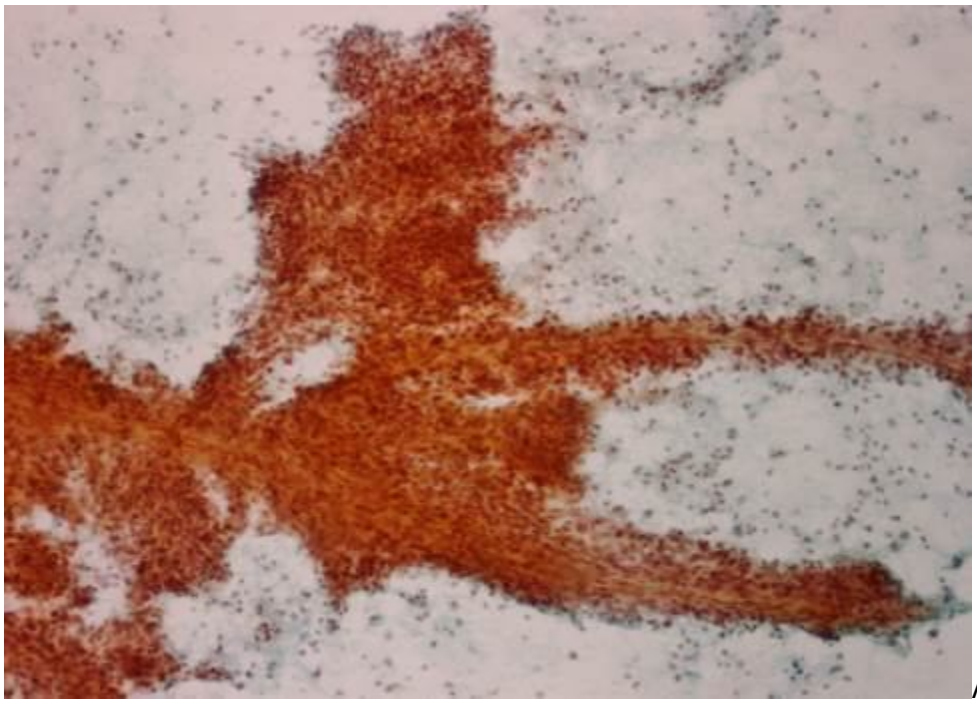


Fig.3.22. Metastatic melanoma showing tumor cells with plasmacytoid configuration and prominent nucleoli. (CP, Pap).



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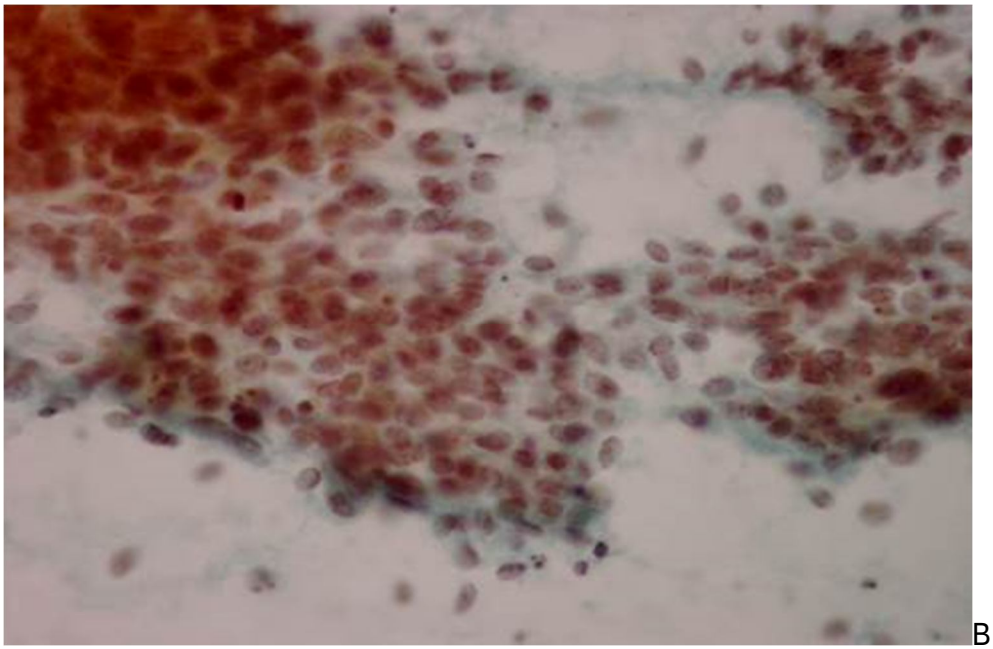
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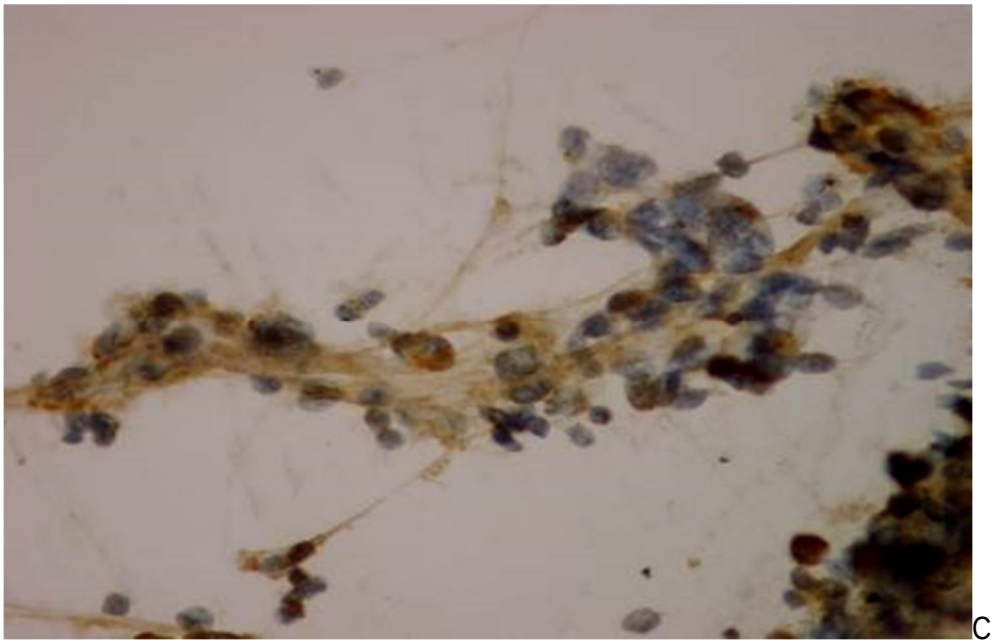
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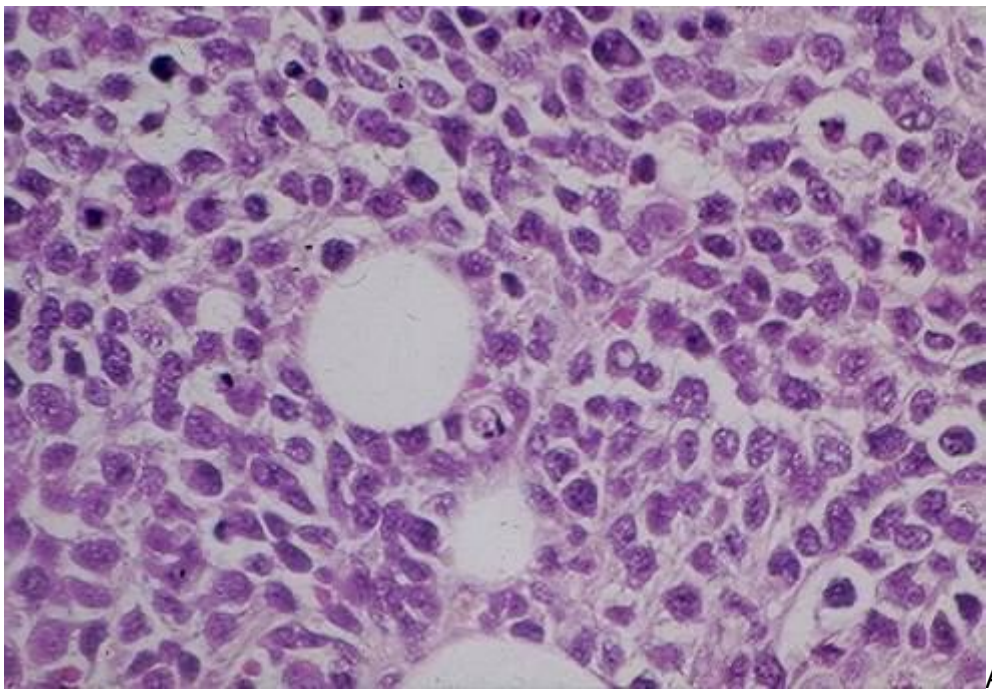
Fig.3.23. Metastatic melanoma: A, B. Tumor cell clusters with vascular transgression, mimicking papillary formation. (CP, Pap). C. Tumor cells with a positive cytoplasmic reaction to HMB-45 antibody. (ABC).

Olfactory neuroblastoma is a rare tumor arising from the nasal mucosa and may metastasize to cervical lymph nodes. FNA from a metastatic olfactory neuroblastoma usually shows small tumor cells with non-specific features. However when a glial fibrillary background is present a metastatic neuroblastoma can be suggested. (Fig.3.24). Cells from an olfactory neuroblastoma are negative for epithelial and positive for neuroendocrine markers.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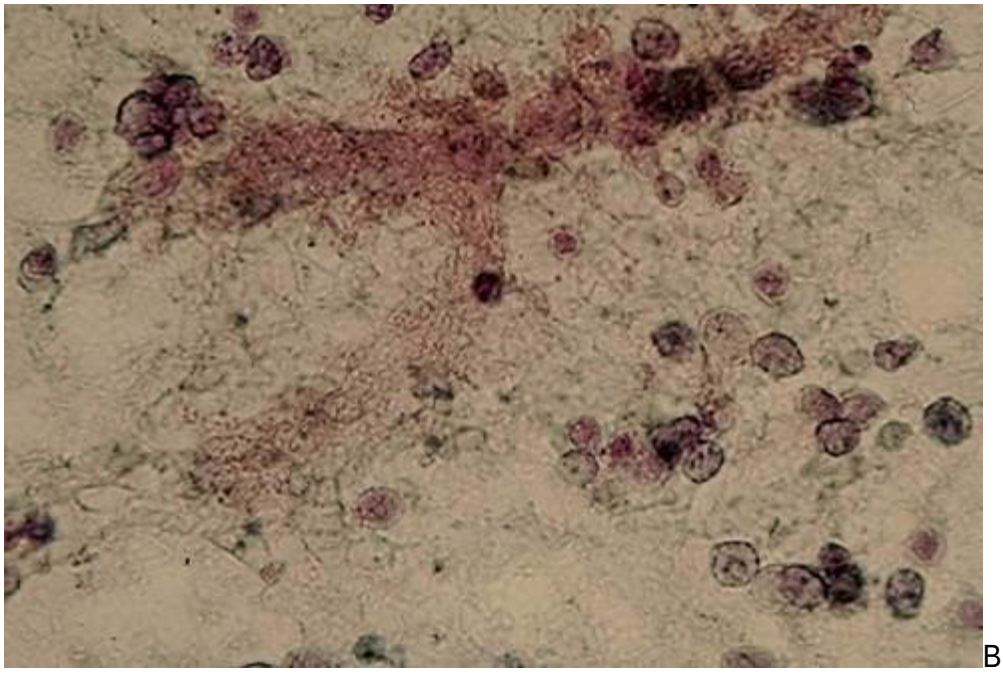
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Fig.3.24. Metastatic olfactory neuroblastoma: A. Tumor histology. (HE). B. Tumor FNA showing small tumor cells with scant cytoplasm in a glial fibrillary smear background. (CP, Pap).

Value of IHC in the work-up of a poorly or undifferentiated carcinoma of uncertain primary

IHC studies can be performed on routinely stained smears without prior destaining with an acetic acid-ethanol solution. However, best results have been obtained with formalin-fixed and paraffin-embedded minute tumor tissue fragments in a cellblock prepared from a lymph node FNA. Fixation of tissue fragments in ethanol may result in altered expressions of some cell makers that may mislead IHC interpretations. Final diagnosis should be made in conjunction with other clinical findings such as biochemical and diagnostic imaging data. Since malignant cells aspirated from a poorly differentiated lymphoma may mimic those from a poorly differentiated/undifferentiated carcinoma, melanoma, sarcoma and mesothelioma, staining of the tumor cells with some antibodies, such as leukocyte common antigen, S-100 protein, Melan A, HMB-45, AE1/AE3, CAM5.2, calretinin, MOC31 and vimentin antibodies, proves to be useful in classifying them into 5 broad categories: lymphoma cells, melanoma cells, sarcoma cells, mesothelioma cells and carcinoma cells. When carcinoma cells are identified, a coordinate staining of those cells with CK7 and CK20 antibodies will further classify them into different cell lines and additional expressions of other cell markers may further confirm the anatomic sites of the primary carcinomas, according to Dabbs:

1. CK7+/CK20+ cells may derive from an urothelial or ovarian mucinous carcinoma:

- Urothelial tumor cells express uroplakin III (UROIII), p63 and thrombomodulin.
- Mucinous ovarian carcinoma cells may sometimes express WT-1.

2. CK7+/CK20- cells may derive from a lung, breast, endometrium, endocrine and thyroid carcinoma or a germ cell tumor:

- Bronchogenic carcinoma cells express TTF-1, Napsin-A and CEA.
- Breast carcinoma cells express ER, PR and Gross cystic disease fluid protein fraction 15 and mammoglobin.
- Serous ovarian carcinoma cells express ER, WT-1 and Ber-Ep4.
- Endometrial carcinoma cells express vimentin and ER.
- Endocrine carcinoma cells express chromogranin, NSE and synaptophysin.
- Germ cell tumor cells are negative for EMA and positive for alpha-fetoprotein (Endodermal sinus tumor), beta-HCG (choriocarcinoma), CD30 and OCT4 (Embryonal carcinoma).
- Thyroid carcinoma cells are positive for TTF-1, PAX-8 and negative for CEA (Exception: medullary carcinoma cells express CEA).
- Epithelial mesothelioma cells express WT-1, CK5/6, calretinin and mesothelin.

3. CK7-/CK20- cells may derived from a squamous cell, prostatic, or renal cell or hepatocellular carcinoma:

- Squamous cell carcinoma cells are positive for CK5/6 and p63.
- Prostatic carcinoma cells are positive for PSA.

- Renal cell carcinoma cells react positively with PAX-8, vimentin and renal cell carcinoma antibodies.
- Hepatocellular carcinomas react with Hepar-1 and CK18 but not MOC-31.

4. CK7-/CK20+ cells may derive from a colorectal or Merkel cell cancer:

- Colorectal carcinoma cells are positive for CDX2, CEA and villin.
- Merkel cell tumor cells express chromogranin, synaptophysin and CK20.

Diagnostic accuracy

For lymph node FNA a non-diagnostic/unsatisfactory rate of 5-15% has been reported.

FNA can be used to diagnose Hodgkin disease, recurrent NHLs or a transformation of a known low-grade to a high-grade NHL. But its value in the primary diagnosis of NHLs is still controversial. For Hodgkin disease FNA has a lower sensitivity rate (48-86%) and a higher specificity rate (98-100%).

FNA cytology of lymph nodes is highly accurate in identifying metastatic cancers. It has a high sensitivity rate (91-98%), high specificity rate (95-99%) and high overall accuracy rate (94-97%).

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Chapter 4

Intracranial tumors

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Cytologic evaluation of crushed tissue samples from brain lesions was originally used by Cushing in the early years of 1930s to diagnose brain tumors during the course of his operations. Since that time, this diagnostic procedure has been sporadically practiced by pathologists as well as neurosurgeons, and has gradually been recognized as a useful adjunct to the frozen section diagnosis of brain tumors. With the current widespread use of stereotactic brain biopsies to obtain morphologic evidence of deeply-located and unresectable brain tumors prior to the institution of appropriate radiotherapy and chemotherapy, the crush preparation diagnostic method has become a routine adjunct to quick tissue diagnosis. The small size of specimens procured by stereotactic biopsy makes their histologic interpretation by frozen section challenging, and cytologic examination of crush preparations of minute brain tissue fragments that are unsuitable for frozen section preparation, has greatly increased the diagnostic accuracy of most intracranial neoplasms.

Biopsy technique, smear preparation and interpretation

Deeply located mass lesions of the brain are usually sampled by CT- or MRI-guided stereotatactic biopsy. No general anesthesia is necessary. A frame is commonly used to guide a cup forceps, spinal-type needle, side-cutting needle and 14-gauge core-needle. At the University of Alberta Hospital a side-cutting needle and a large syringe are used to aspirate the brain tissue samples. Tissues from the central part and at the periphery of the mass are sampled. A few cylindrical tissue fragments measuring about 0.1 cm in diameter and up to 1.5 cm in length and several minute tissue fragments measuring less than 0.05 cm in greatest dimension are usually obtained. These tissue fragments are put in normal saline and submitted to the pathology laboratory for frozen section diagnosis. A small tissue fragment measuring about 1 cubic mm excised from a larger tissue fragment or 2 to 3 minute tissue fragments measuring less than 0.5 mm in greatest dimension are gently crushed and smeared between two glass slides. The prepared smears are immediately fixed in 95% ethanol or formalin and stained with hematoxylin and eosin (HE) at the same time with the frozen tissue sections. For firm tissue fragments, touch or imprint preparations are made and stained with HE or by the DQ technique for cytologic evaluation.

Cytologic interpretation of crush preparations of brain lesions is challenging and requires not only a knowledge of brain tumor histopathology and cytology but also clinical information of the patient under investigation. A direct communication with the neurosurgeon who operates on the patient in difficult cases, will provide the pathologist with useful information to avoid errors in cytologic and histologic interpretations of brain lesions.

Diagnostic accuracy and difficulty

The diagnostic accuracy of brain lesions obtained by stereotactic biopsy depends largely on the team efforts of a neurosurgeon who biopsies the brain lesions and the pathologist who examines the tissue and cell samples. In general, the cytodiagnostic efficacy of crush preparations is higher than that of frozen section. Reported sensitivity rates of intraoperative cytologic technique varied from 76.6 to 96% and a correct cytohistologic correlation is obtained in over 90% of cases. On several occasions a high-grade astrocytoma or oligodendroglioma has been correctly diagnosed by crush preparation alone, as the biopsied tissue fragments are inadequate for frozen section diagnosis. Diagnostic difficulties are commonly encountered in cases of low-grade astrocytoma that display a smear pattern mimicking a reactive gliosis.

Normal brain

Normal brain tissue smears smoothly and evenly. The deep white matter of the cerebrum is characterized by a low cellularity, finely granular eosinophilic smear background, thin capillary blood vessels, thicker muscular vessels and scattered astrocytes and oligodendrocytes. These cells are easily identifiable as astrocytic nuclei are oval and show a finely granular chromatin and those of oligodendrocytes are smaller, round and hyperchromatic. The cytoplasm of both astrocyte and oligodendrocyte is ill-defined but fibrillar. The cerebral cortex, basal ganglia and hypothalamus are more cellular than the normal white matter and numerous neurons and glial cells are seen. Neurons commonly appear as large oval, naked nuclei with prominent nucleoli. An intact neuron has a triangular configuration and abundant cytoplasm. Corpora amylacea may be seen in material from elderly patients. Smears from cerebellar cortex contain numerous cells from internal granular layer admixed with Purkinje cells. The former shows round, small hyperchromatic nuclei and scant, ill-defined cytoplasm, and the later displays abundant cytoplasm with long cytoplasmic processes, large nuclei and prominent nucleoli. The cerebellar subcortical tissue is similar to the white cerebral matter cytologically. (Figs. 4.1 to 4.3).

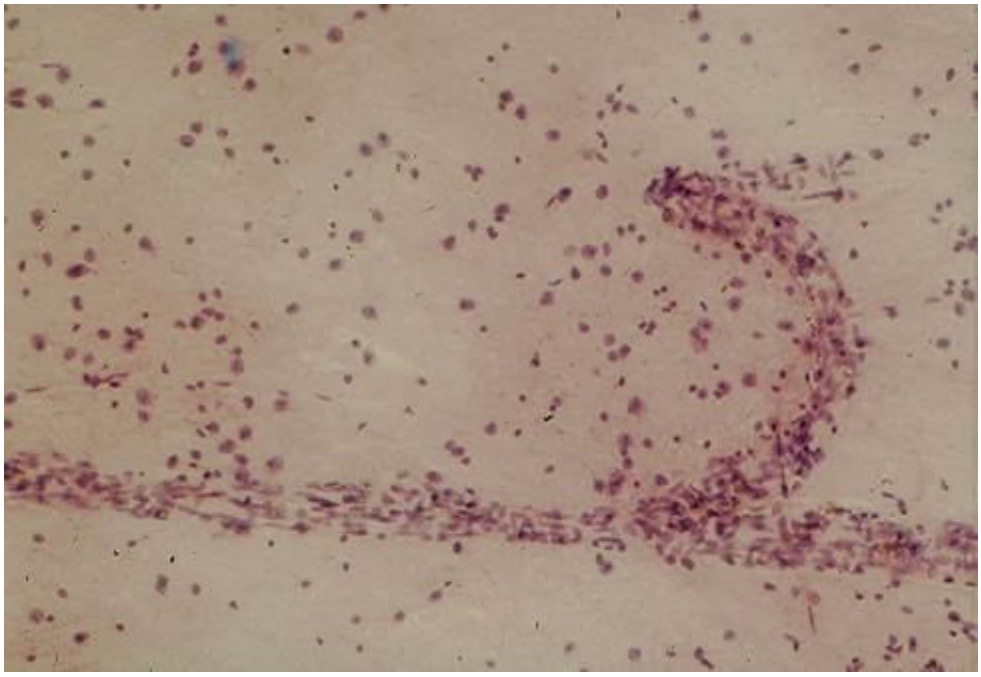


Fig.4.1. Normal brain showing neurons, glial cells and a thick branching blood vessel. (HE)

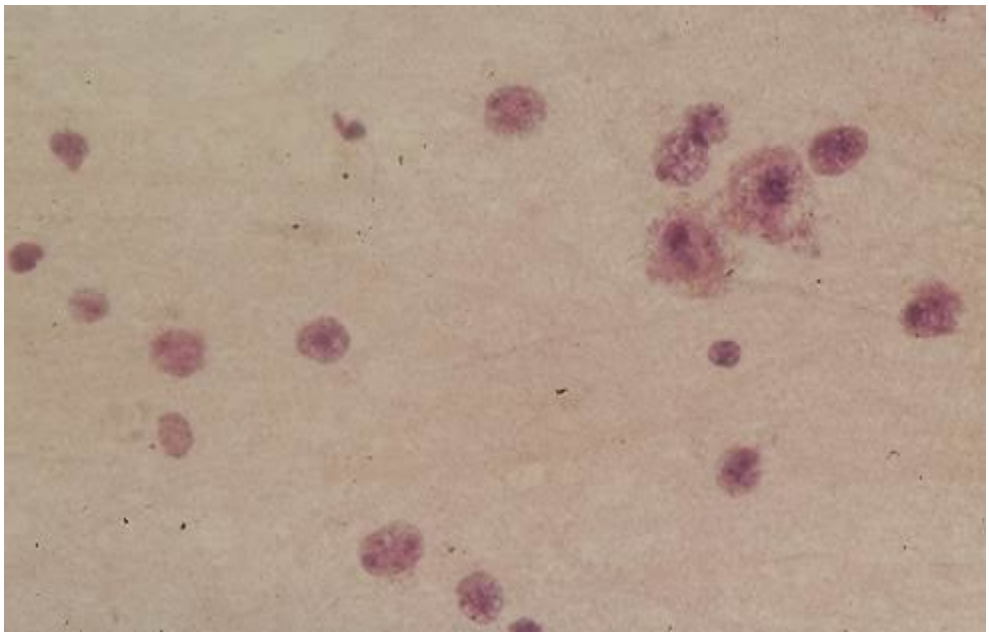


Fig.4.2. Normal brain tissue showing 2 large neuron nuclei with prominent nucleoli at right upper corner, large naked, round nuclei of astrocytes and small round nuclei of oligodendrocytes. (HE)

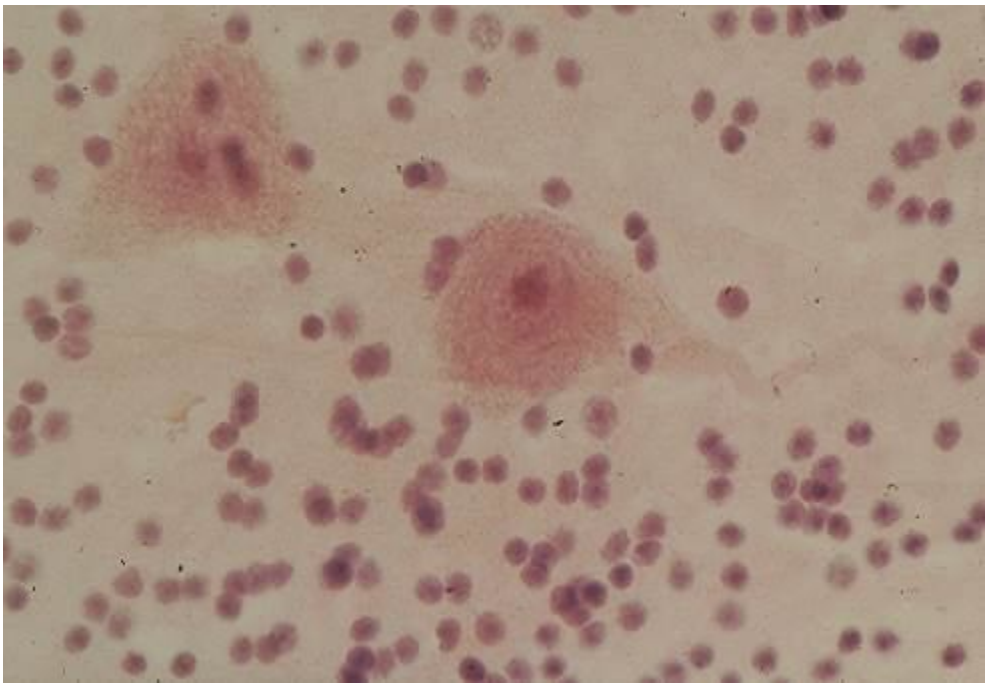


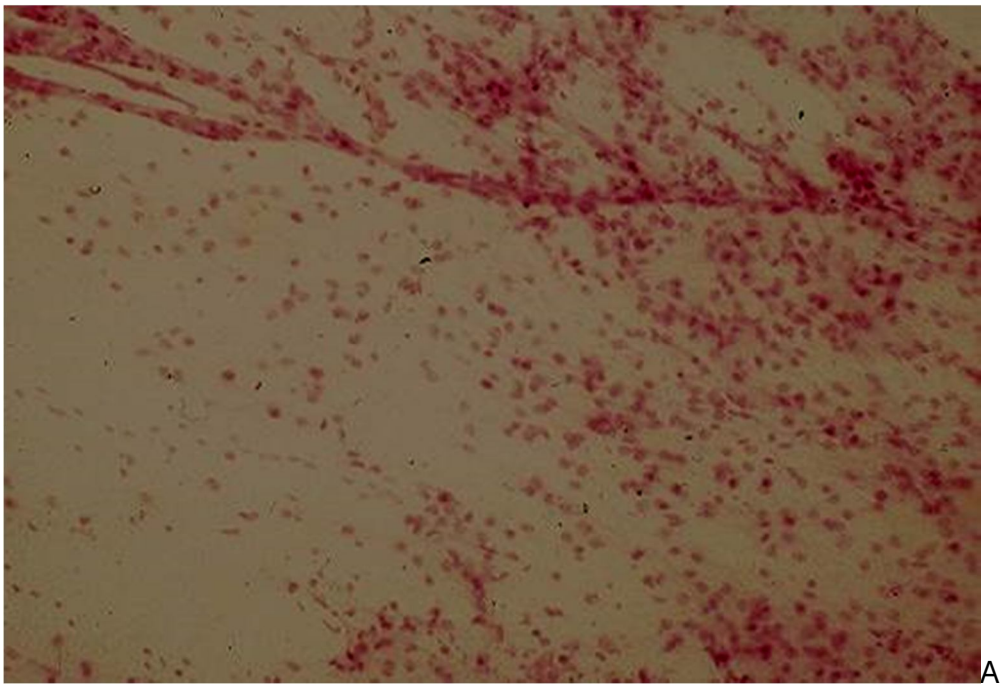
Fig.4.3. Normal cerebellum showing two Purkinje cells and several naked nuclei of inner layer cells. (HE)

Intracranial tumors

Tumors of neuroglia and choroid plexus epithelium

Astrocytomas account for 75-80% of all intracranial tumors and about 60% of all gliomas. Histologically, these tumors may be graded into 4 grades with grade I and grade II tumors being well-differentiated astrocytomas. Grade III tumor is an anaplastic astrocytoma, and grade IV tumor or glioblastoma multiforme is the most dedifferentiated tumor of the group. Grade I and II astrocytomas account for 25-30% and grade III and IV tumors for 50% of all astrocytomas, respectively.

In crush preparations, a correct diagnosis of a **well-differentiated astrocytoma** is difficult. Grade I astrocytomas are seen mainly in children and young adults and have the most favorable prognosis of all astrocytomas. The tumors resemble normal white matter cytologically. Grade II tumors have a diffuse growth pattern and patients with grade II tumors have an average life expectancy of 5 years. Grade II astrocytomas yield a more cellular material and may show slightly thick-walled blood vessels with marginated slightly atypical astrocytes. (Fig.4.4). **Pilocytotic astrocytoma** is a morphologic variant of grade I astrocytoma. It often occurs in the posterior fossa and is characterized cytologically by the presence of abundant bipolar cells with hair-like cytoplasmic extensions, Rosenthal fibers and, less commonly, eosinophilic granular bodies. (Fig.4.5).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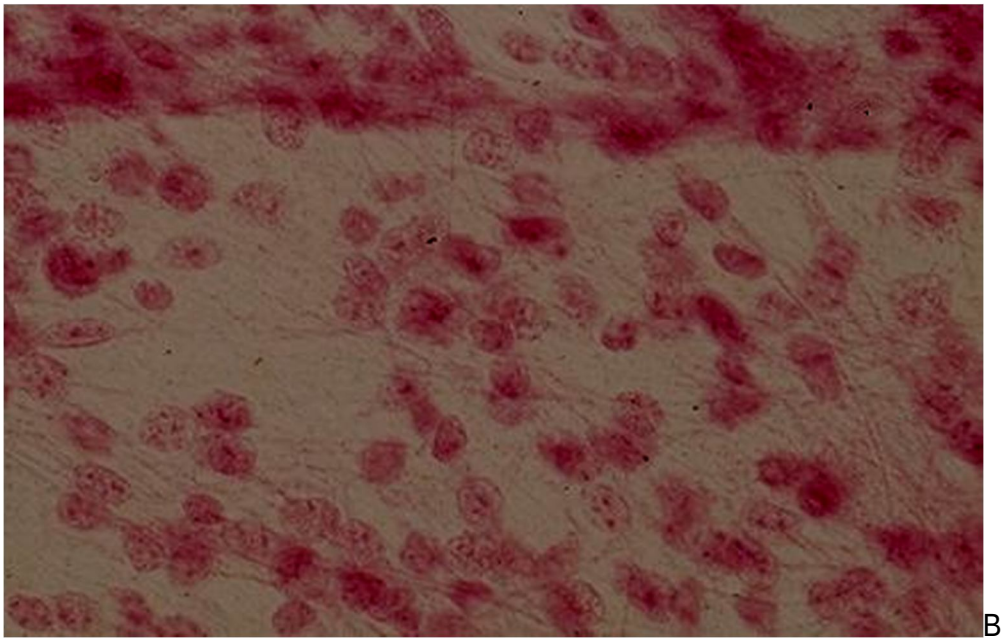
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Fig.4.4. Grade II astrocytoma showing abundant monomorphic tumor cells with scant cytoplasm and oval nuclei marginated around a thin-walled blood vessel. Note the glial fibrillary background. (HE)

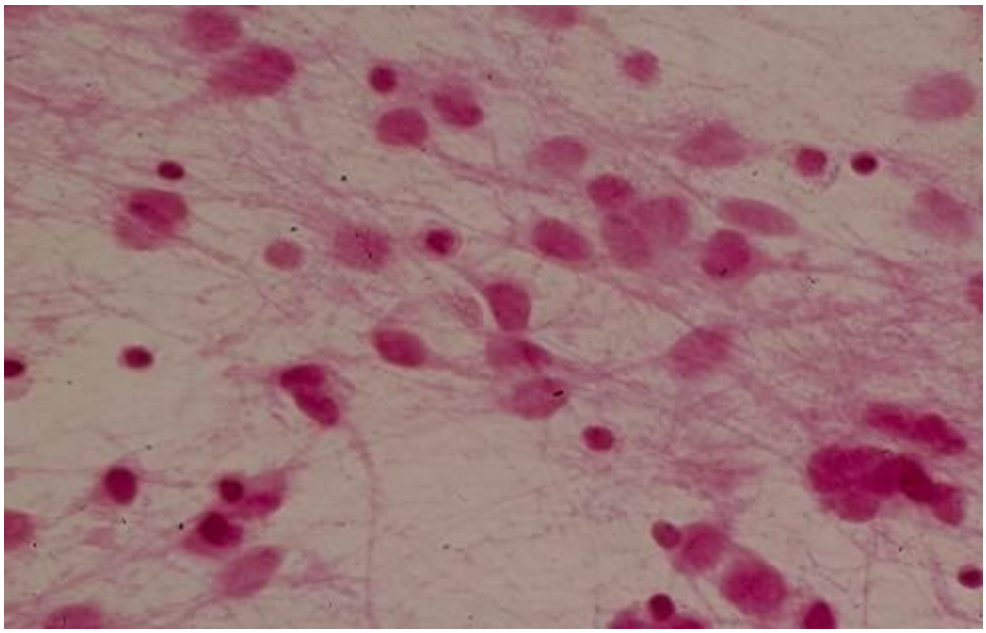
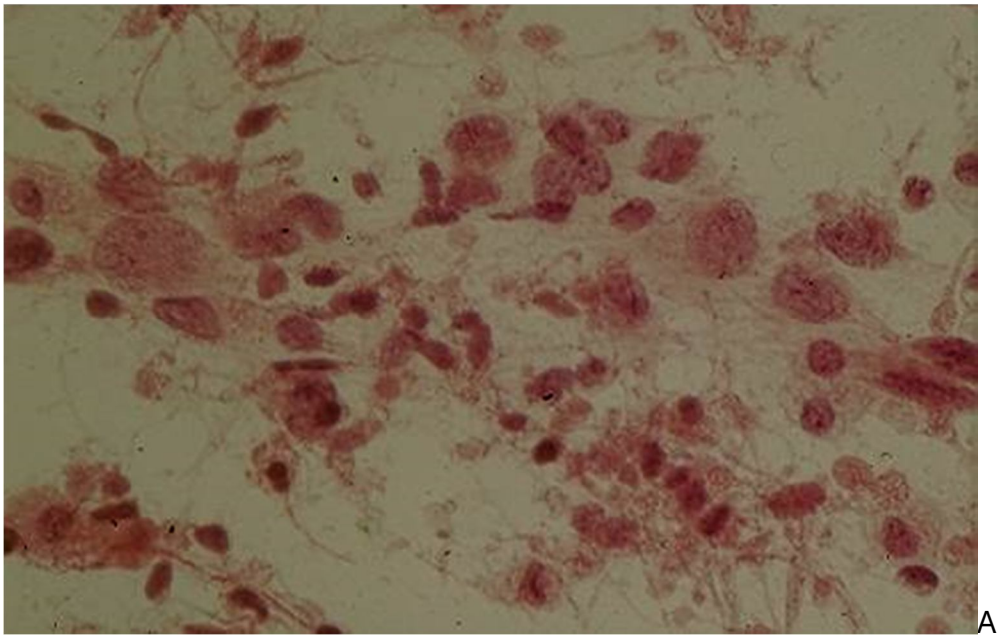


Fig.4.5. Pilocytotic astrocytoma showing monomorphic cells with hair-like cytoplasmic extensions and oval nuclei. An irregular, eosinophilic and granular body is seen at the lower right part of the figure. (HE)

Grade III or anaplastic astrocytoma is a rapidly growing neoplasm and patients with this tumor have an average life expectancy of 2 to 3 years. The tumor affects the cerebral hemispheres most commonly and it is easily identified cytologically. Smears prepared from the tumor tissue are hypercellular and show abundant pleomorphic malignant cells with many bizarre multinucleated large cells. (Fig.4.6). Proliferated, branching thick-wall blood vessels with marginated aggregates of tumor cells are commonly found.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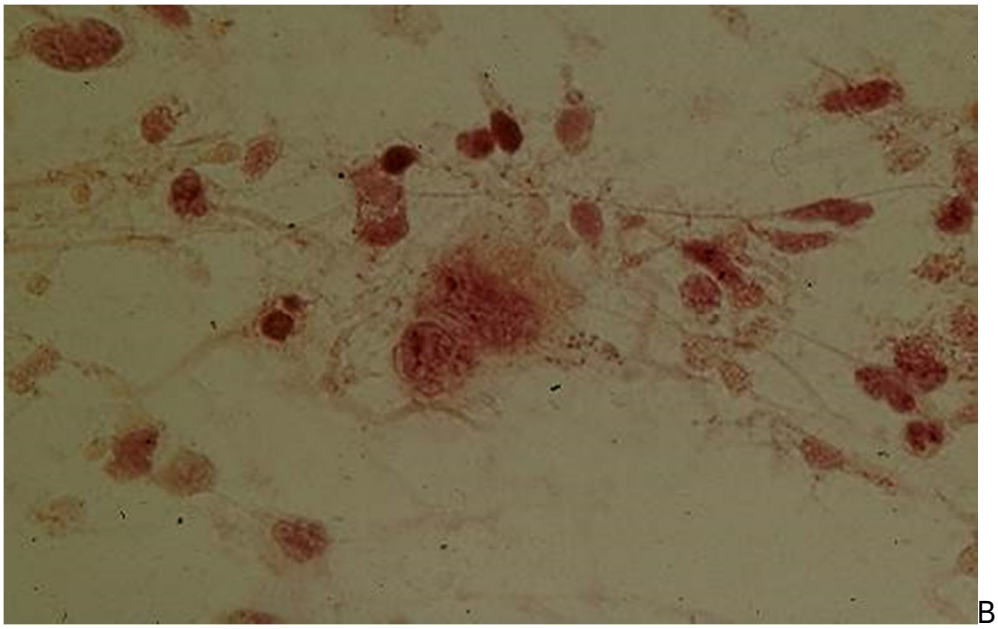

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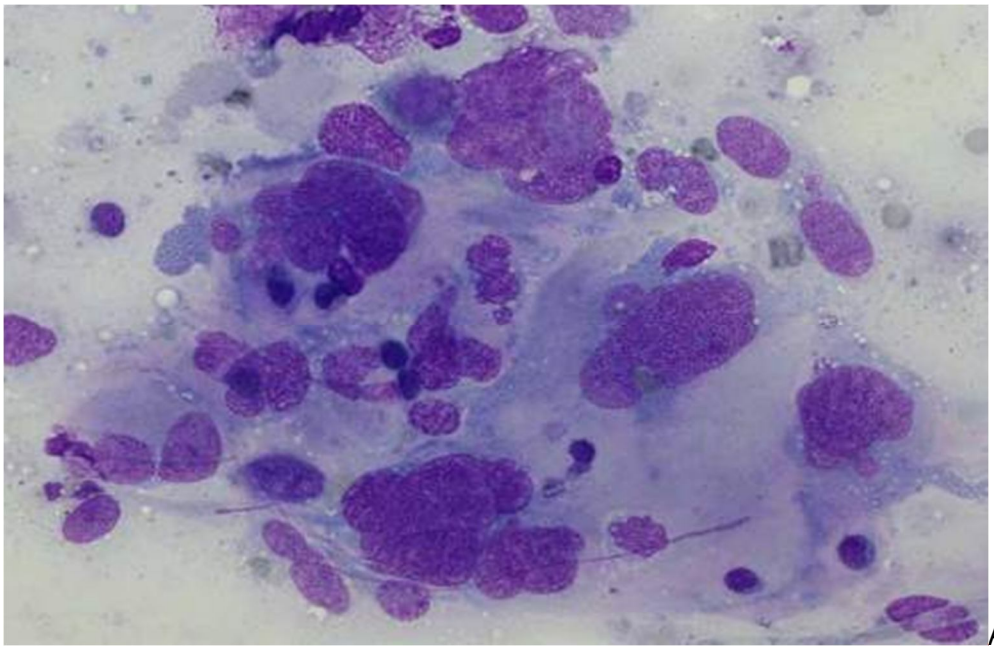
Fig.4.6. A and B. Anaplastic astrocytoma showing in a crush preparation smear pleomorphic malignant cells in a glial fibrillary background. (HE)

Grade IV astrocytoma or Glioblastoma multiforme accounts for about 40% of all primary brain tumors and affects most commonly patients over the age of 40 years. The tumor is highly aggressive and the patient's life expectancy is only 18 months on average. It is characterized by large, pleomorphic, bizarre tumor cells with several multinucleated giant tumor cells, numerous mitotic figures and proliferated vessels. (Fig.4.7).



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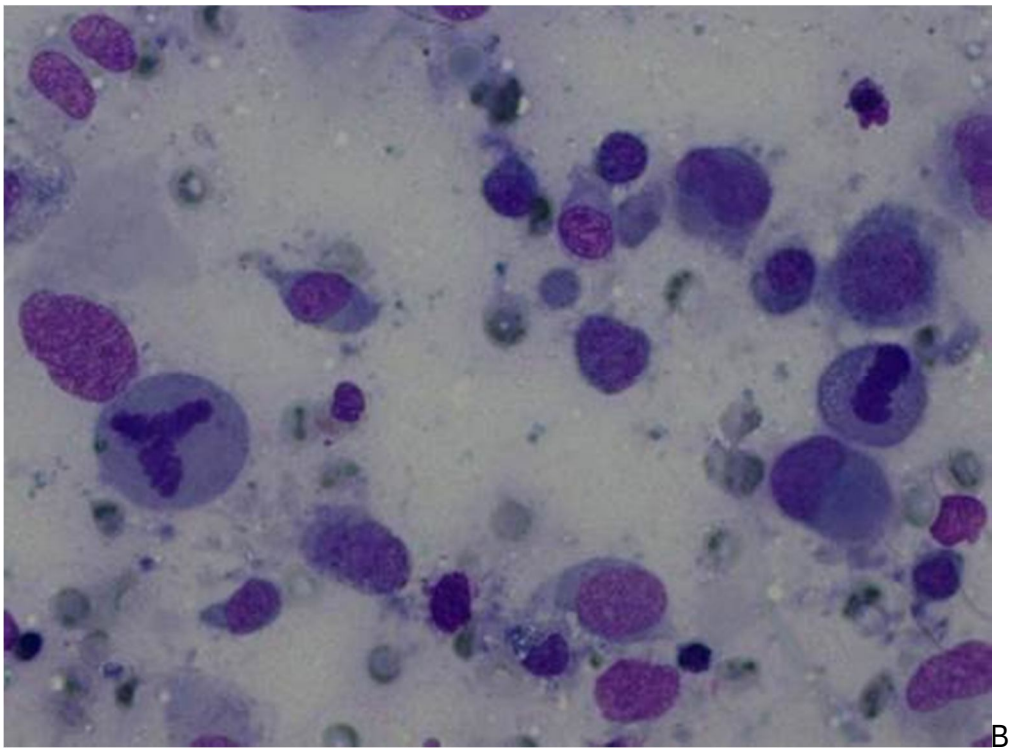

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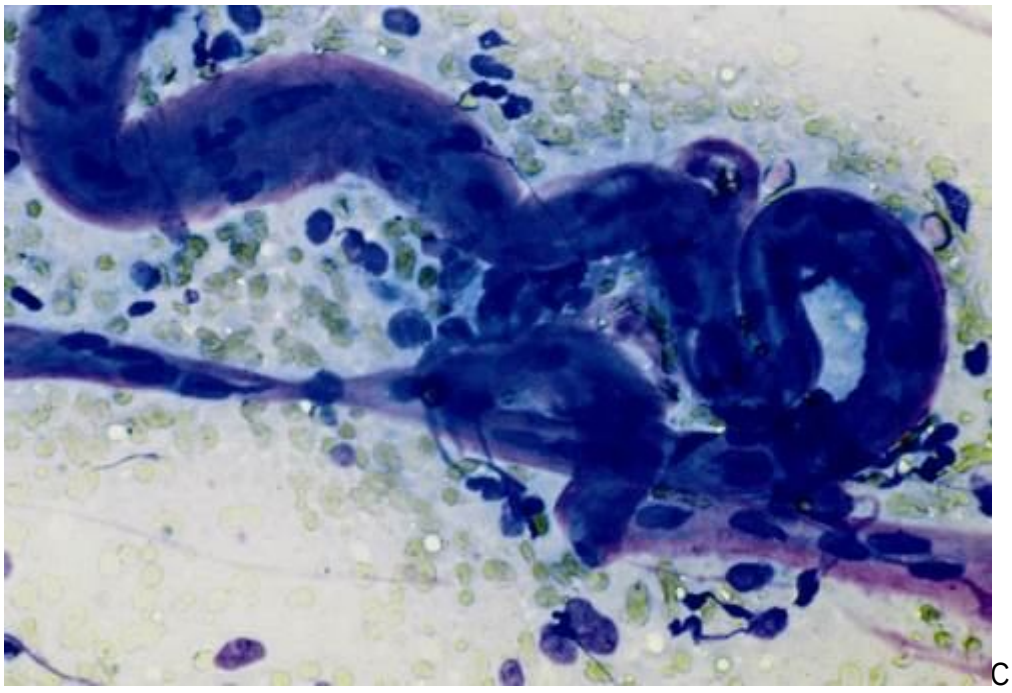


C

Fig.4.7. Cytology of a glioblastoma multiforme: A, B. Pleomorphic tumor cells with the larger ones showing multiple nuclei. A tripolar mitotic figure is seen in B. (DQ). C. A proliferated tortuous capillary blood vessel. (DQ). Courtesy of Dr. Y. K. Batoroev, Irskutsk, Russia.

Gemistocytic astrocytoma is a high-grade astrocytoma. It shows in crush preparations tumor cells with thick, abundant granular cytoplasm and eccentrically located nuclei. (Fig. 4.7).

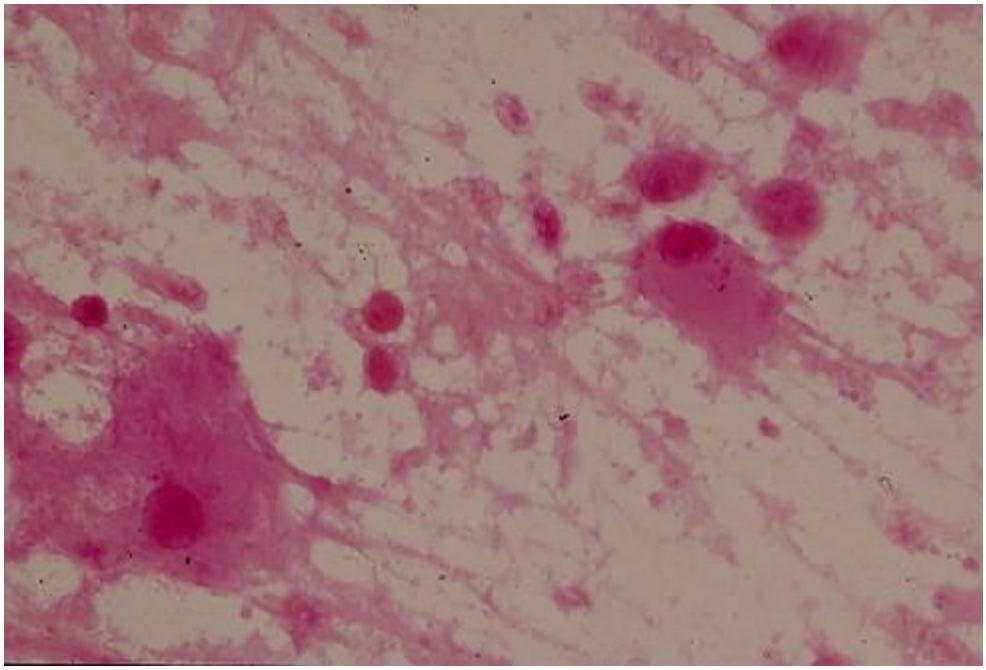


Fig.4.7. Gemistocytic astrocytoma showing large tumor cells with abundant, granular cytoplasm, cytoplasmic extensions and eccentrically located nuclei in a glial fibrillary background. (HE)

Oligodendroglioma accounts for 5-8% of all intracranial gliomas with a peak incidence in the 4^{th} and 5^{th} decades of life. In crush preparations of a low-grade oligodendroglioma abundant rounded tumor cells with slightly pleomorphic nuclei and scant cytoplasm are seen, and tumor cells arranged around round empty spaces may be observed. Perinuclear halo, as seen in tissue sections, may also be observed in cytologic preparations. (Fig.4.8). A high-grade oligodendroglioma shows more pleomorphic cells with variable and wispy cytoplasm. (Fig. 4.9).

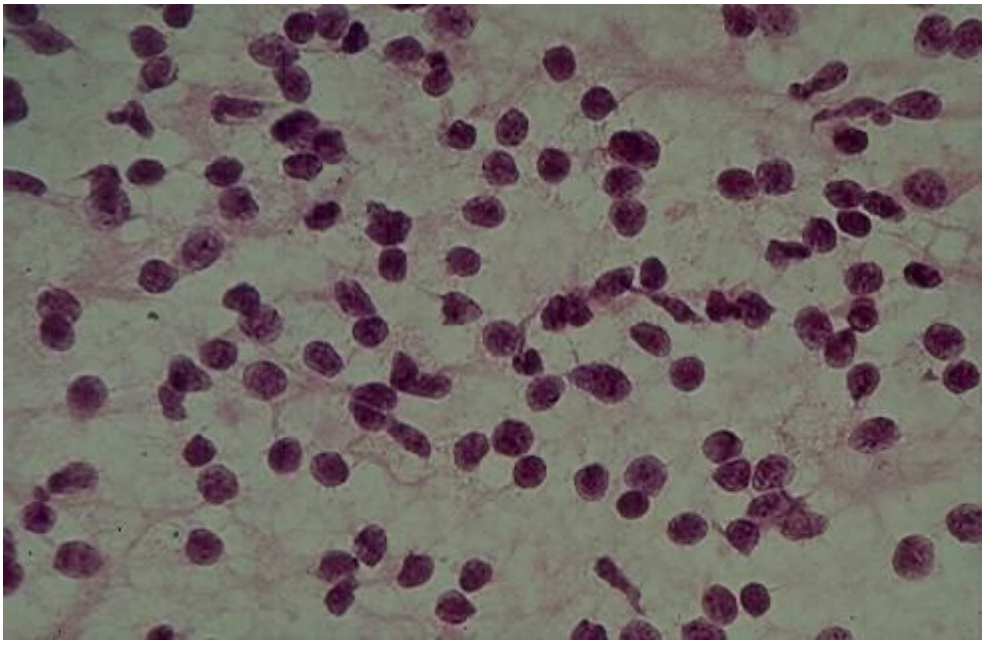


Fig.4.8. Low-grade oligodendroglioma showing slightly pleomorphic tumor cells with scant cytoplasm arranged around empty spaces in a glial fibrillary background. (HE)

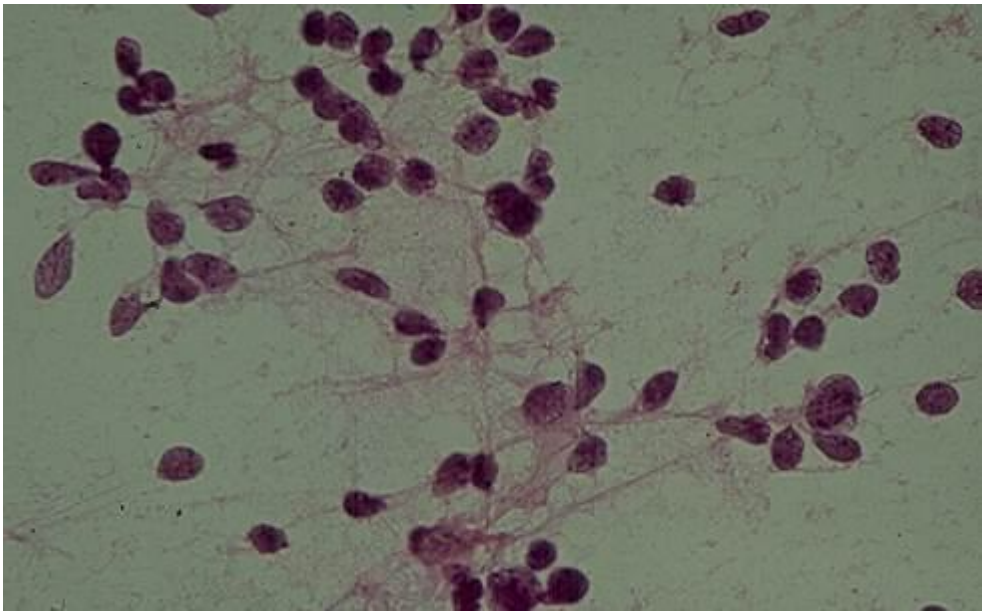
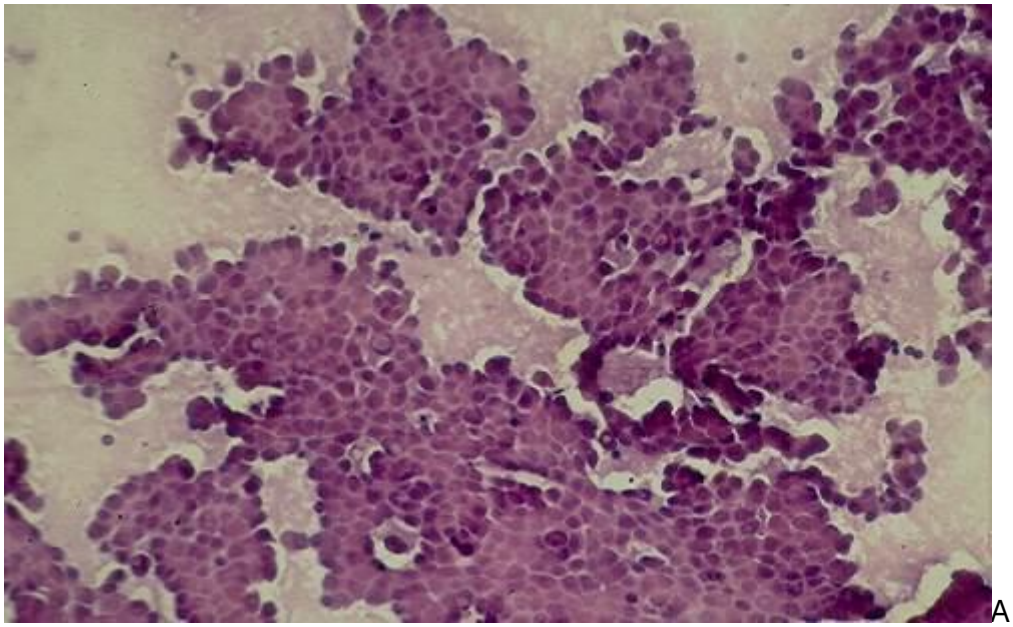


Fig.4.9. High-grade oligodendroglioma showing more pleomorphic tumor cells arranged around irregular empty spaces in a glial fibrillary background. (HE)

Ependymoma arises in the ventricular system and accounts for about 5% of all intracranial gliomas. In crush preparation an ependymomas is characterized by cuboidal or columnar epithelial-like cells in monolayered sheets or clusters. A papillary ependymoma with or without myxomatous change occurs almost exclusively in the conus medullaris or around the filum terminale, although rarely in the cerebrum, and it

is characterized by columnar cells arranged in sheets and clusters in a myxomatous smear background. (Fig. 4.10).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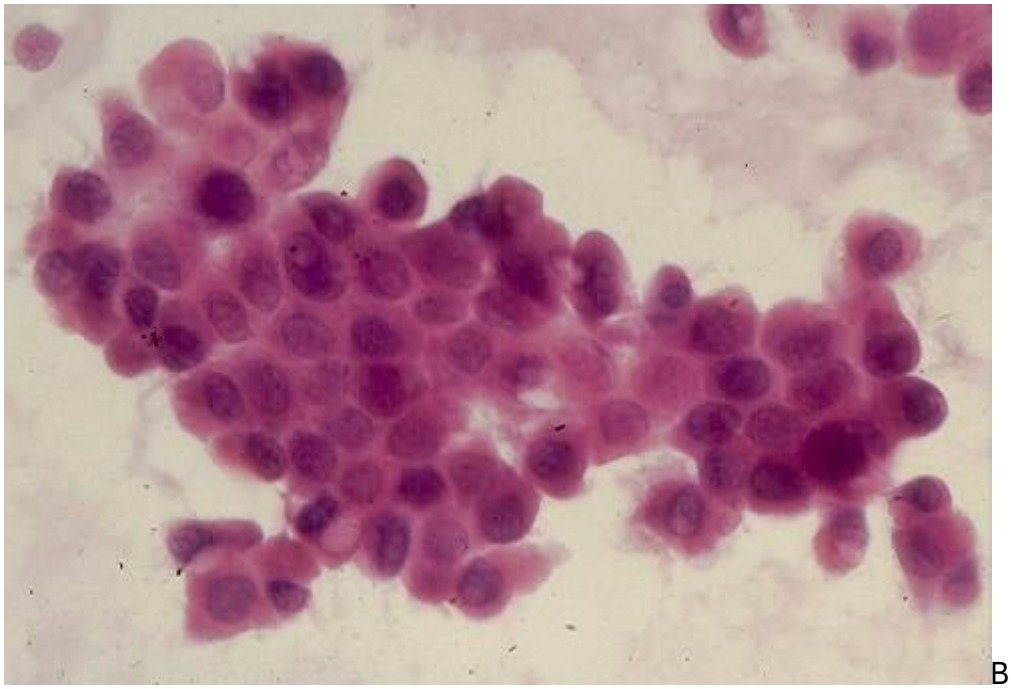

B

Fig.4.10. A,B. Ependymoma showing a monolayered sheet of benign appearing epithelial cells. (HE)

Medulloblastoma occurs most commonly in the first decade of life and accounts for about 6% of all intracranial tumors. It is most likely arising from cells of the external granular layer of the cerebellum and is located almost exclusively in the cerebellum. It

may occur sporadically or may arise in association with Turcot or Gorlin syndrome. In cytologic preparations a medulloblastoma is characterized by single and loosely clustered malignant cells with hyperchromatic, pleomorphic nuclei and scanty fibrillary cytoplasm. Tumor cell forming rosettes and nuclear molding may be seen. (Fig. 4.11).

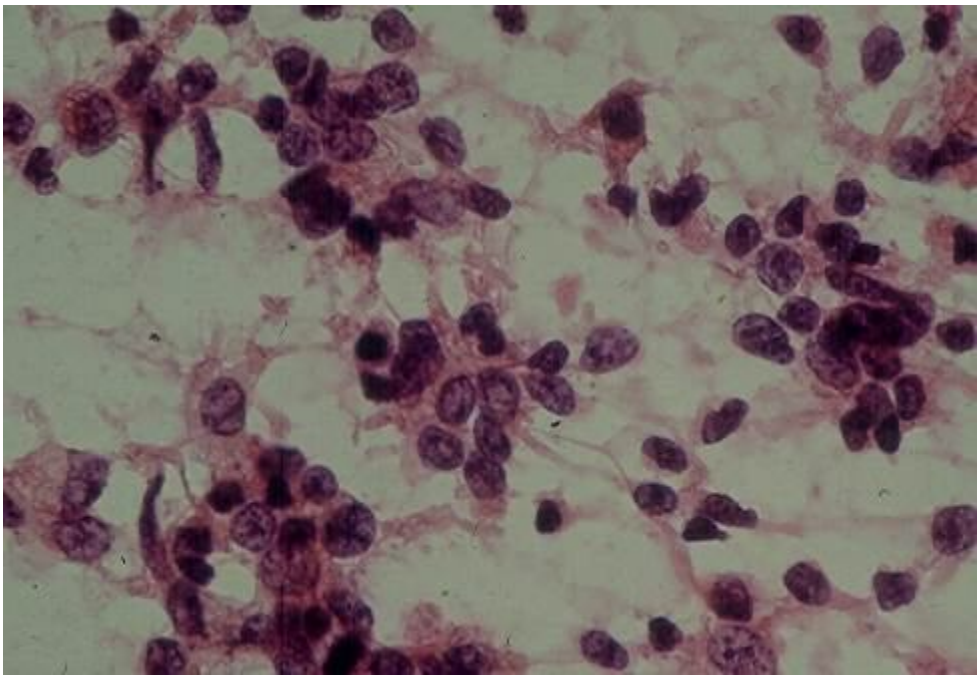


Fig.4.11. Medulloblastoma showing pleomorphic cells with eosinophilic cytoplasm and hyperchromatic nuclei forming rosettes in a glial fibrillary background. Nuclear molding in noted in some tumor cell clusters. (HE)

Choroid plexus papilloma and **carcinoma** are rare tumors and account for less than 1% of all intracranial gliomas. These tumors occur most commonly in the lateral ventricles of the cerebrum and are more common in young individuals during the first decade of life. In crush preparations these tumors are characterized by sheets and tridimensional clusters of oval or cuboidal cells with scant cytoplasm. (Fig.4.12). **Choroid plexus carcinoma** is a very rare neoplasm and characterized by single and clustered pleomorphic malignant glandular-type cells, indistinguishable from those of a metastatic adenocarcinoma.

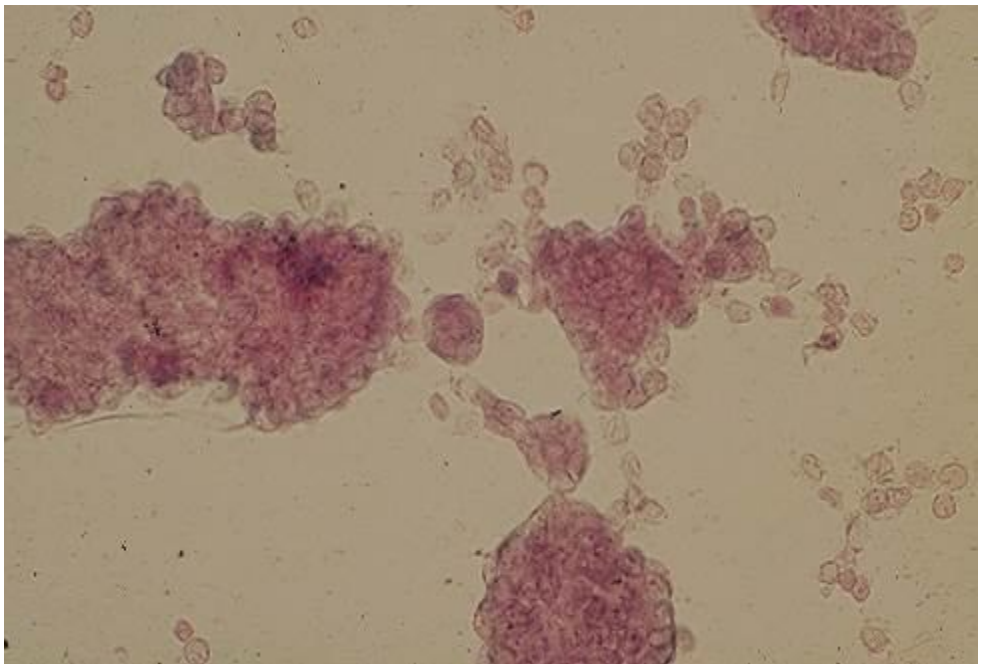


Fig.4.12. Choroid plexus papilloma showing cuboidal tumor cells with round, bland nuclei predominantly in large tridimensional clusters. (HE)

Metastatic cancers

Metastatic cancers to the brain account for 15-25% of all intracranial tumors. Primary tumors can arise from any anatomic sites with bronchogenic carcinomas being the most common primary cancers, accounting for about 65% of all metastatic cancers to the brain. Metastatic tumors to the brain are usually multifocal but may, on rare occasions, be solitary and mimic a primary brain tumor clinically and radiologically. In crush preparations the cytologic manifestations of metastatic cancers resemble those with the same histologic types sampled by FNA. (Figs.4.13 to 4.16).

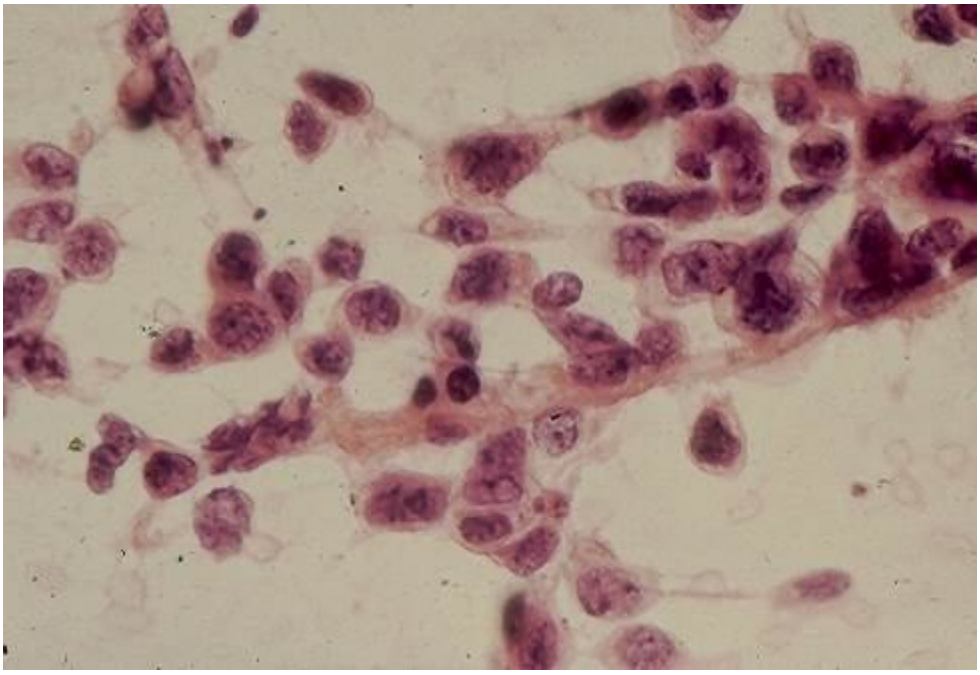


Fig.4.13. Dyshesive pleomorphic non-keratinizing malignant squamous cells from a metastatic squamous cell carcinoma. (HE)

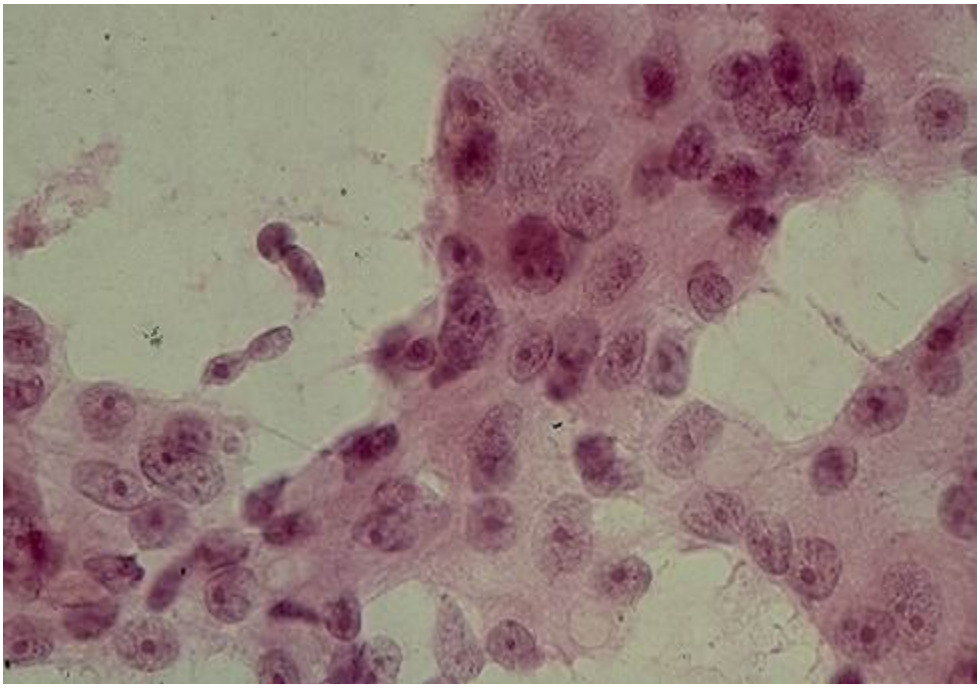


Fig.4.14. A sheet of malignant glandular cells from a metastatic adenocarcinoma. (HE)

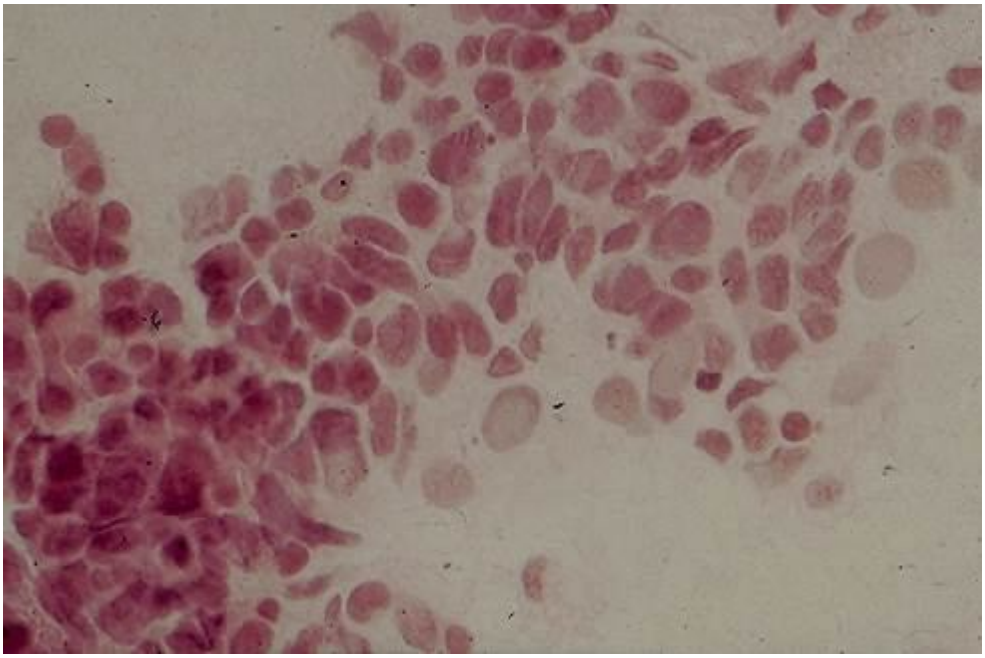


Fig.4.15. Metastatic small cell carcinoma showing tumor cells with scant cytoplasm and nuclear molding. (HE)

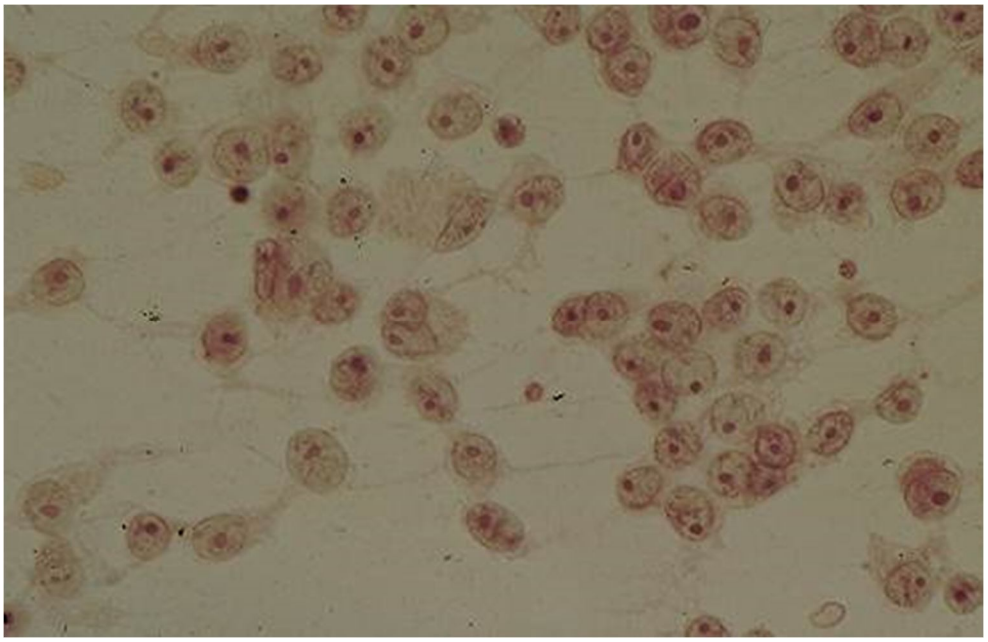


Fig.4.16. Dyshesive malignant cells with prominent nucleoli from a metastatic amelanotic melanoma. (HE)

Other tumors

Intracranial germ-cell tumor, craniopharyngioma, pituitary adenoma, lymphoma and chordoma and chondrosarcoma of the skull base may be mistaken as a deeply located glioma clinically and radiologically. These neoplasms have fairly distinctive cytologic patterns in crush preparations permitting their correct identification in the majority of cases. A **germ cell tumor** is characterized by single and loosely clustered large malignant cells with scant cytoplasm, prominent nucleoli. (Fig. 4.17).

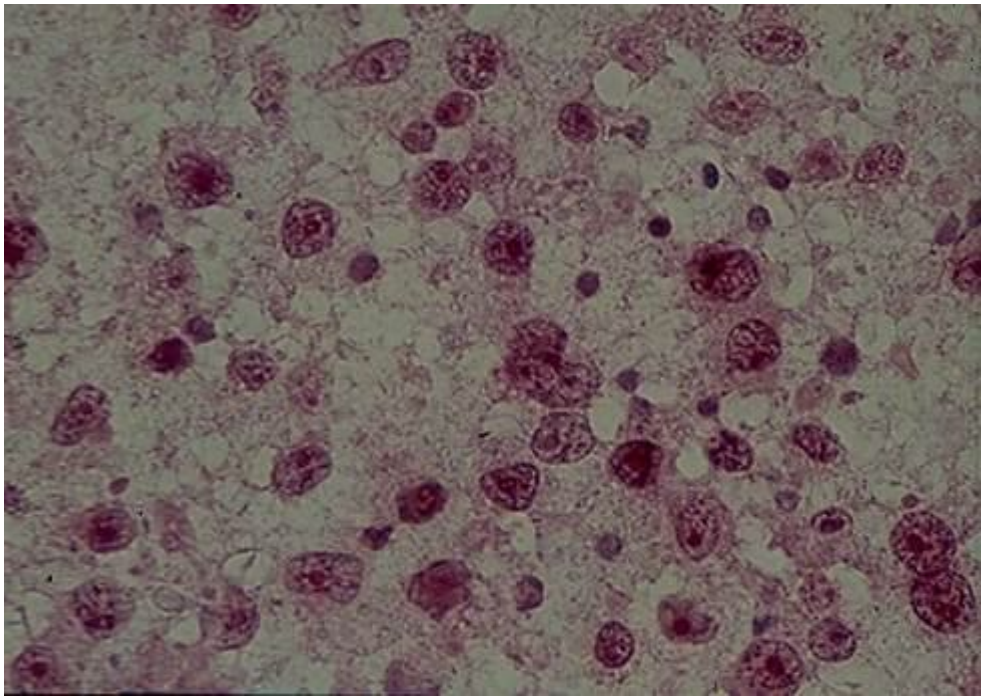
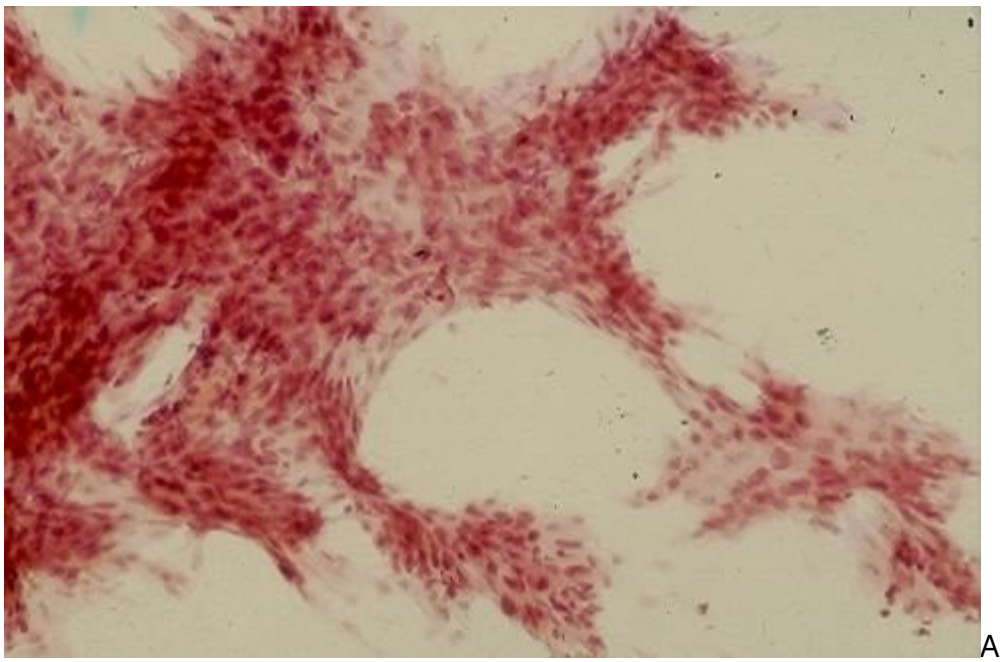


Fig.4.17. Germ cell tumor showing isolated tumor cells with ill-defined cytoplasm, large nuclei and prominent nucleoli in necrotic debris. (HE)

Craniopharyngioma shows in crush preparations fragments of benign squamoid epithelium admixed with cellular debris and squamous cell pearls. (Fig.4.18).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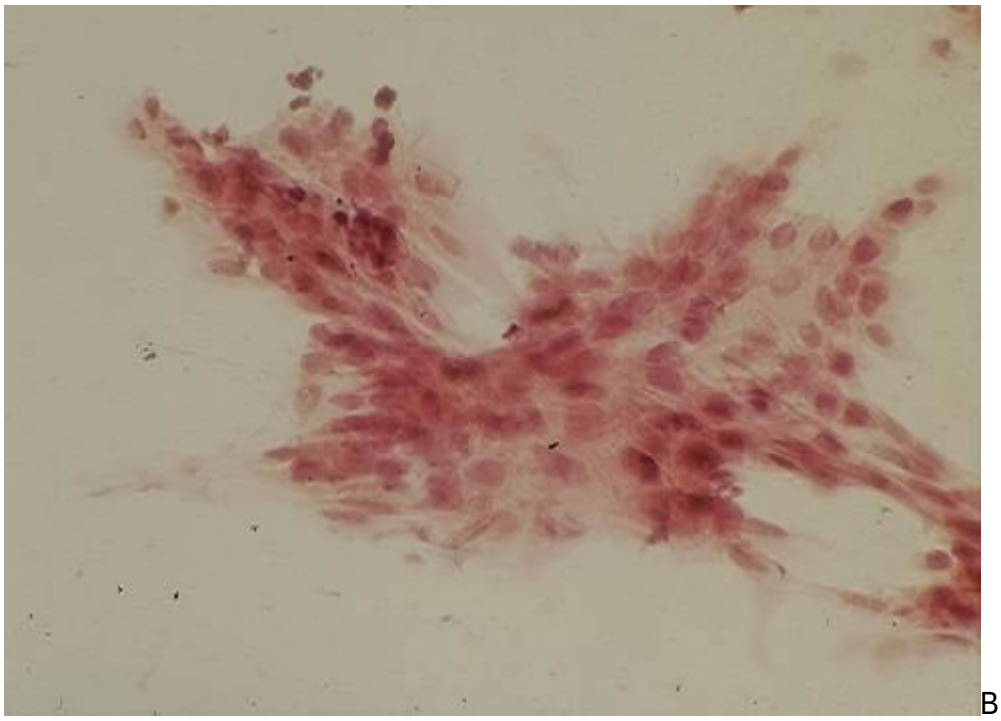
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Fig.4.18. A, B. Craniopharyngioma showing large sheets of benign squamous cells. (HE)

Pituitary adenomas show in crush preparations single cuboidal epithelial cells admixed with naked tumor cell nuclei, and no glial fibrillary smear background is noted. (Fig.4.19).

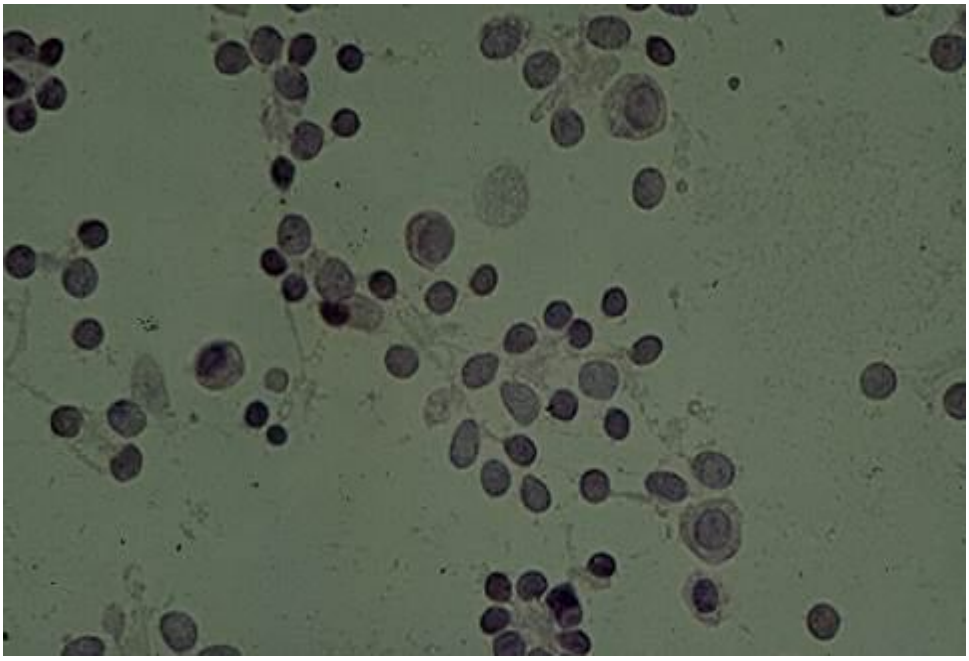

Fig.4.19. Pituitary adenoma showing abundant naked, oval tumor cell nuclei and a few cuboidal neoplastic cells with defined cytoplasm. (HE)

Chordoma is characterized cytologically by clusters of large cells with intracytoplasmic vacuoles (physallipherous cells). (Fig.4.20).

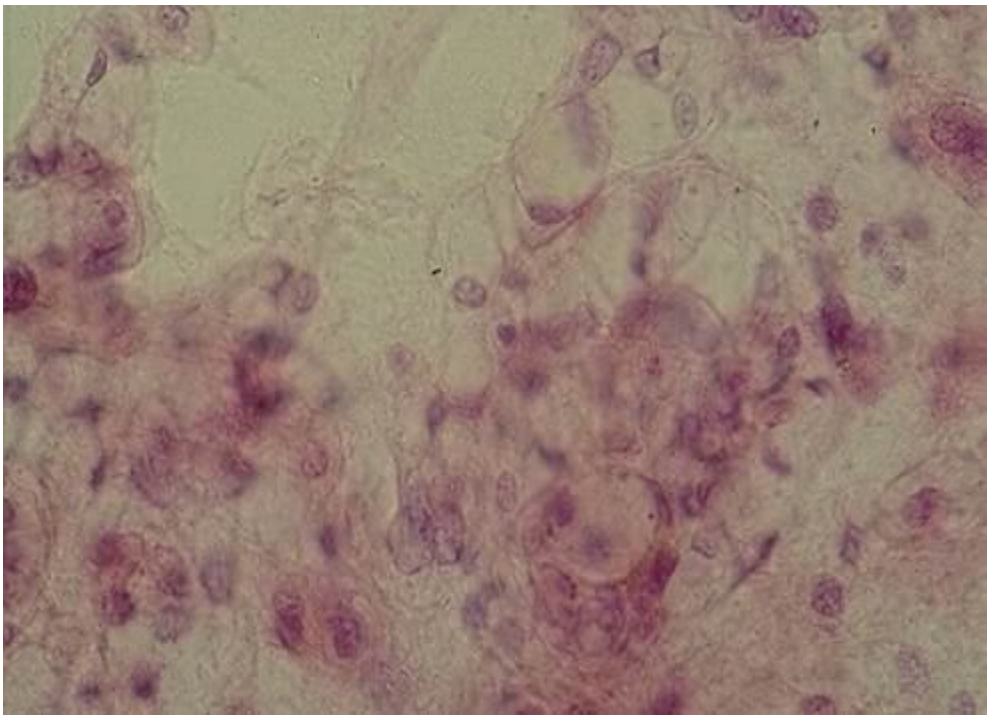

Fig.4.20. Chordoma showing clustered tumor cells with large intracytoplasmic vacuoles. (HE)

Chondrosarcoma arising from the skull base is characterized by single and clustered malignant cartilaginous cells with pleomorphic nuclei. (Fig.4.21).

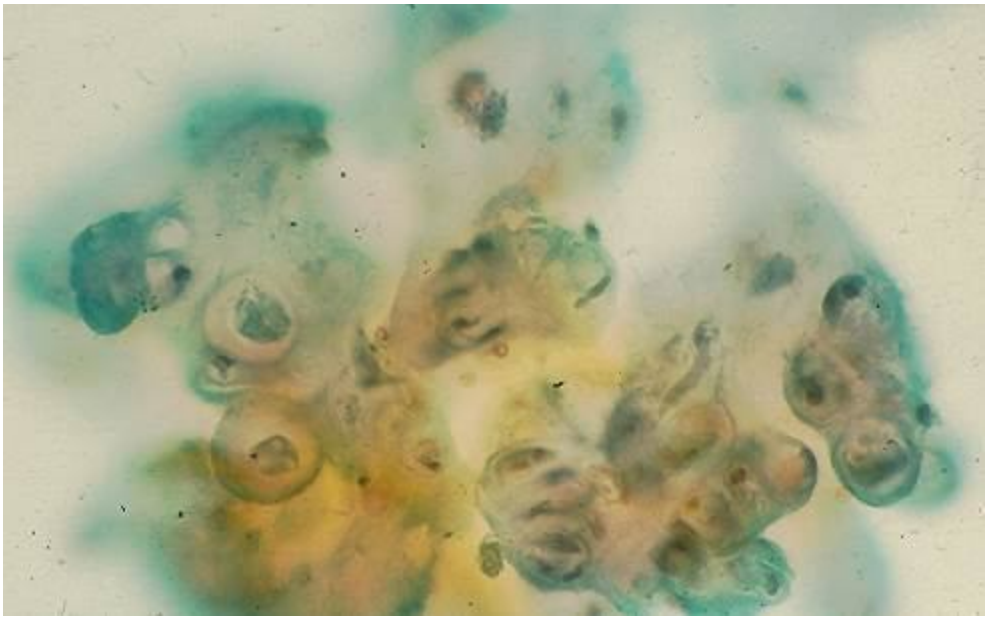

Fig.4.21. Clustered malignant cartilaginous cells from a well-differentiated chondrosarcoma. (Pap)

Meningioma and Schwannoma. Meningiomas account for 13-18% and schwannomas arising from acoustic nerves for about 8% of all intracranial tumors. With current diagnostic imaging techniques, a preoperative diagnosis of benign and some malignant meningiomas and schwannomas is possible in the majority of cases. However, in aberrant locations these tumors may mimic a glioma or a pinealoma clinically or radiologically, and therefore may be sampled by stereotactic needle biopsy. These tumors show in crush preparations distinctive cytologic features permitting their correct diagnoses in almost all cases. It is important to note that the smears lack a glial fibrillary background, as commonly seen in neuroectodermal tumors. (Figs.4.22 to 4.27).

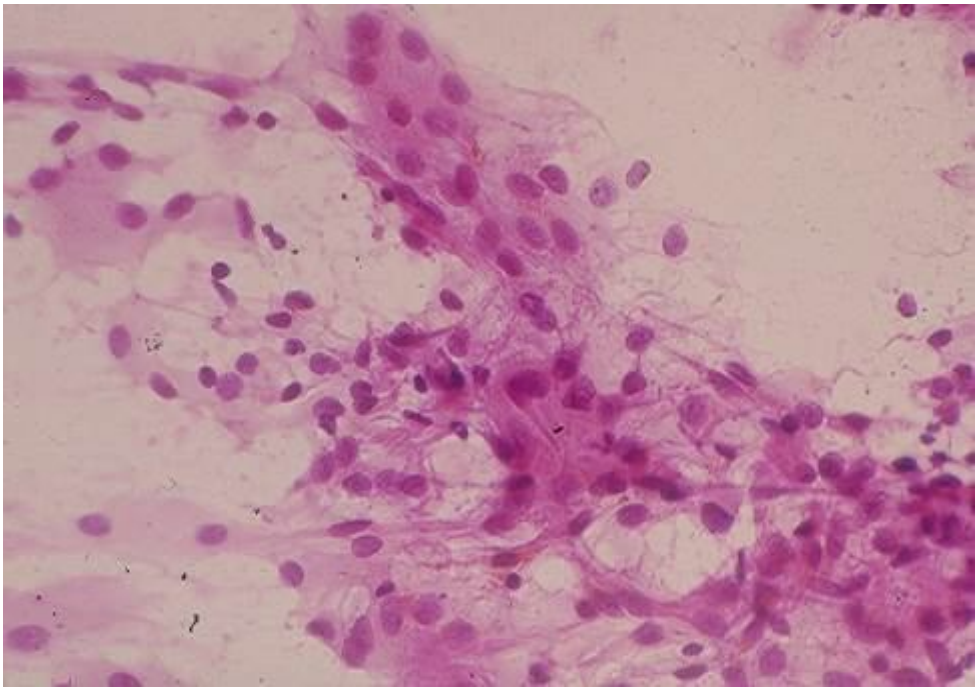

Fig.4.22. Meningothelioma showing cells with oval nuclei and abundant, ill-defined cytoplasm in sheets. (HE)

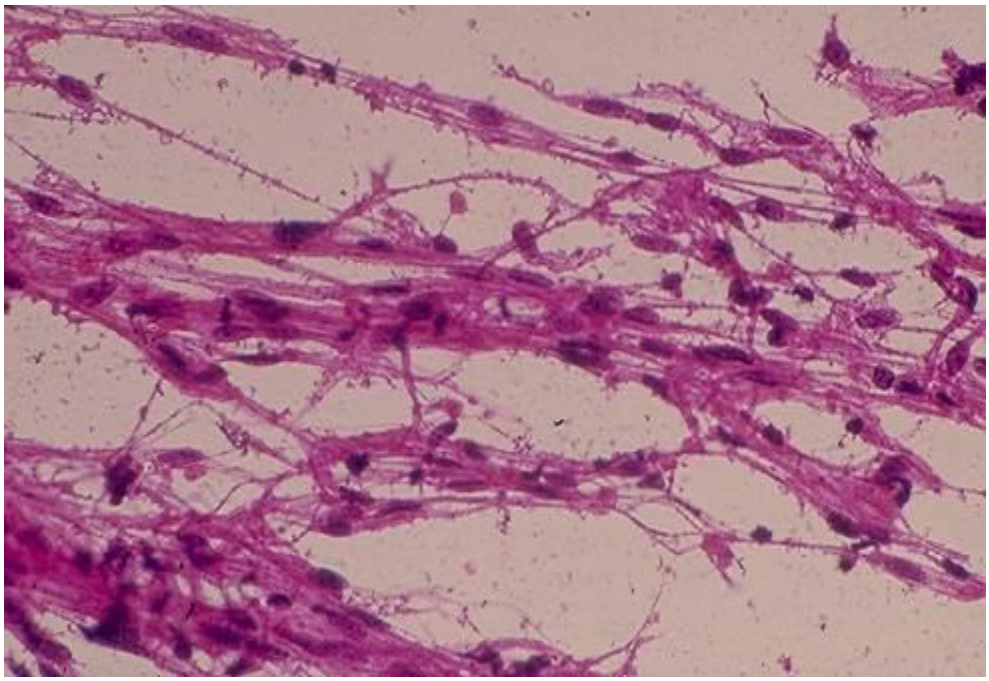

Fig.4.23. Fibromatous meningioma showing loosely clustered “wire-like” cells with elongated nuclei and scant cytoplasm. (HE)

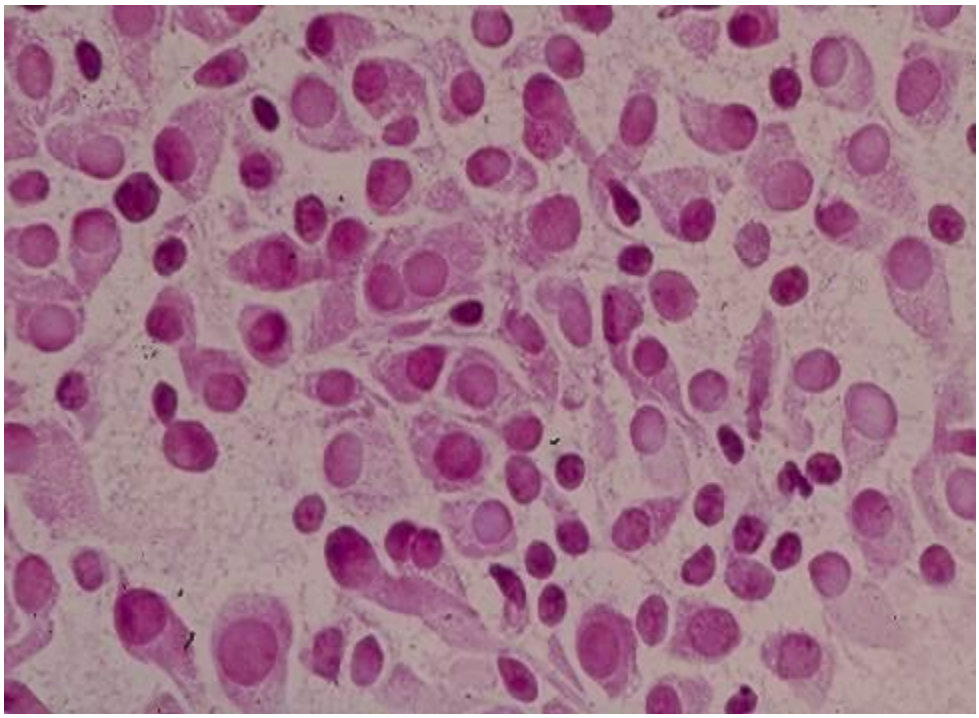

Fig.4.24. Dyshesive plasmacytoid cells from a malignant meningioma. (HE)

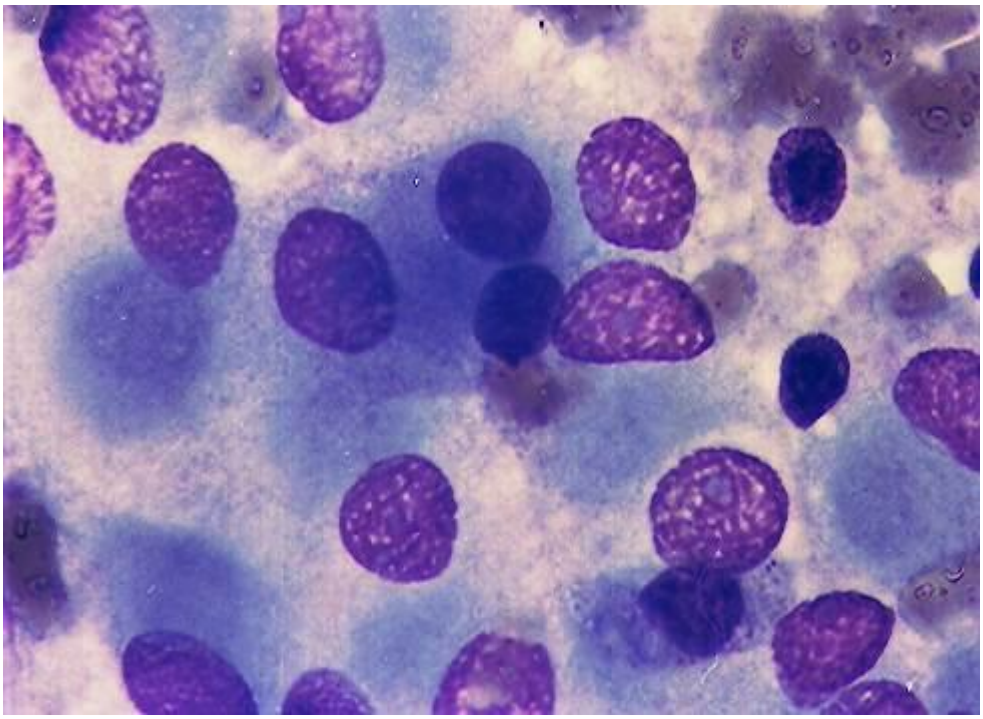

Fig.4.25. Imprint preparation from a rhabdoid meningioma showing single and clustered polygonal tumor cells with abundant granular, ill-defined cytoplasm, intracytoplasmic globular body and eccentrically located oval nuclei. (DQ). Courtesy of Dr. Yuri Batoroev, Irkutsk, Russia.

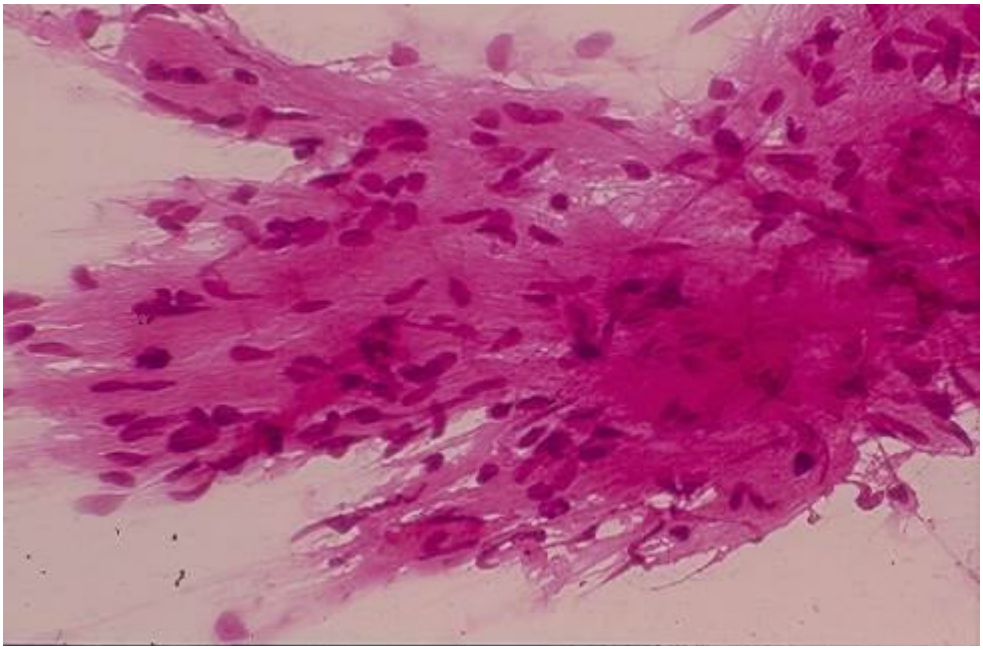

Fig.4.26. Schwannoma showing a thick fragment of tumor tissue with elongated nuclei in vague palisading arrangement. (HE)

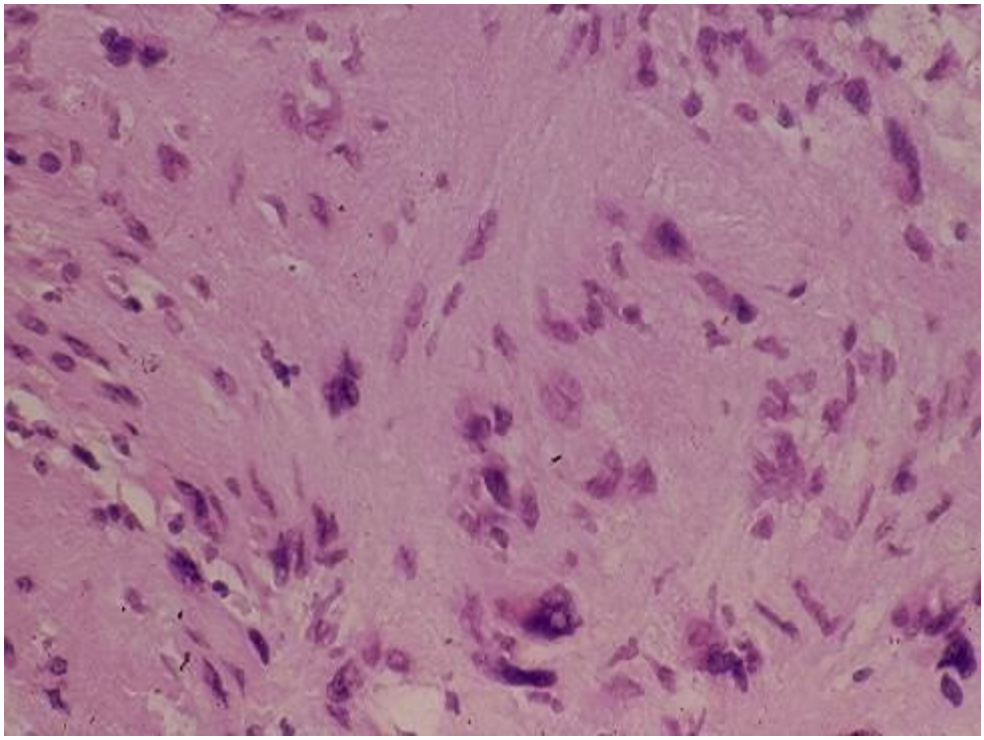

Fig.4.27. A thick crushed tissue fragment from an ancient schwannoma showing pleomorphic and hyperchromatic nuclei. (HE)

Diagnostic pitfalls

The majority of commonly encountered intracranial primary tumors display fairly distinctive cytologic features in crush preparations permitting their correct cytologic diagnoses. However, it should be kept in mind that classification of brain tumors is complicated and requires an extensive histologic examination with IHC studies, electron microscopic and even molecular studies. Common diagnostic pitfalls include:

1. Cells of a **medulloblastoma** may mimic those of the granular layer of the cerebellum and those of a Non-Hodgkin lymphoma. Cells derived from a Non-Hodgkin lymphoma commonly show nuclear indentation or protrusions that are not usually seen in medulloblastoma cells and that possess a scant cytoplasm without fibrillary background.

2. Pleomorphic malignant cells from a **grade IV astrocytoma** or **glioblastoma multiforme** can mimic cells of a metastatic anaplastic carcinoma to the brain.

3. **Reactive gliosis** may occur at the periphery of a neoplastic, inflammatory, vascular or degenerative lesion of the brain. Cytologically, reactive gliosis is cellular and may show slightly pleomorphic glial cells mimicking a low-grade astrocytoma. The presence of a heterogenous cell population consisting of oligodendrocytes and astrocytes usually

indicates a reactive gliosis. Astrocytes with gemistocytic change and inflammatory cells may be present. (Fig.4.28).

4. Radiation-induced brain necrosis, cerebral infarct, xanthomatous lesions, sarcoidosis, plasma cell granuloma, collagen vascular diseases and amyloidoma may mimic a brain tumor on CT scan. Tissues from these lesions may neither smear smoothly nor show malignant cells. However, reactive glial cells are commonly found, as well as other acellular or necrotic material. Blood vessels with thick hyalinized walls and hyperplastic endothelial cells may be observed from tissue samples from a radiation-induced necrosis.

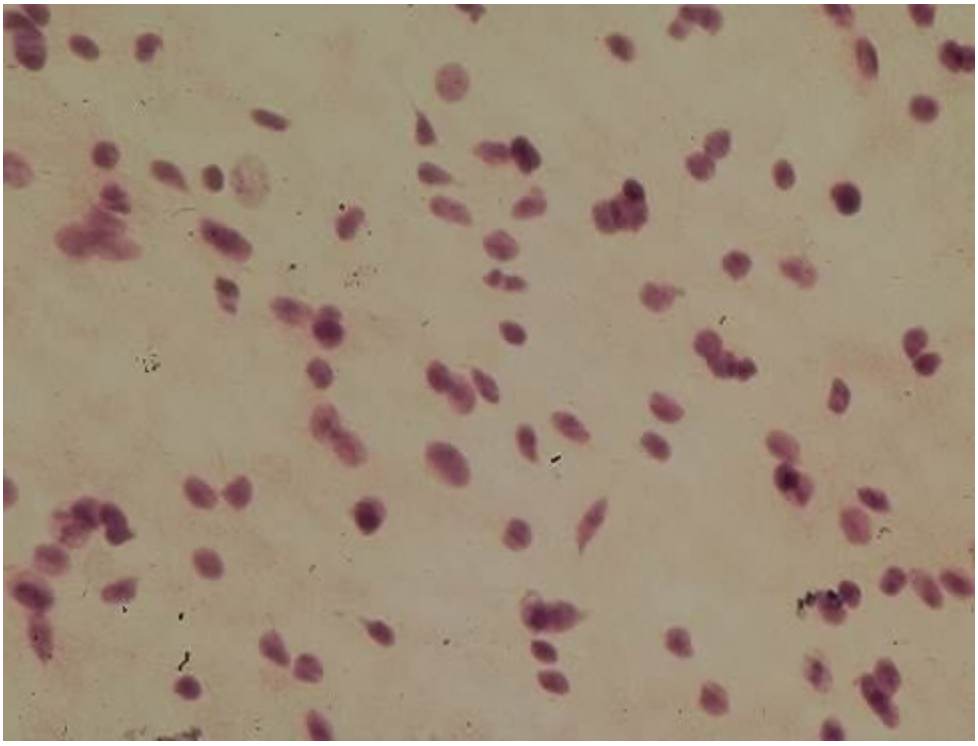

Fig.4.28. Reactive gliosis is characterized by a hypercellular smear with an admixture of oligodendrocytes and astrocytes. (HE)

Remark: This chapter is a modified version of the authors' article in Russian News of Clinical Cytology. 2004;8:23. The permission was kindly granted by Dr. N. Shapiro, Moscow, Russia.

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