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Sudha R. Kini

J. Martin Miller

Joel I. Hamburger

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Sudha R. Kini, MD,* J. Martin Miller, MD, and Joel I. Hamburger, MD*****

Fine needle aspiration biopsy is a simple and accurate means of obtaining a tissue diagnosis for a thyroid nodule. Our experience with 3,000 such biopsies and 242 surgically proven cancers has enabled us to characterize the cytologic presentations of the common "nodular" thyroid diseases. We can readily identify nodular goiter and papillary, poorly differentiated follicular, medullary, anaplastic, and metastatic cancers. Benign follicular neoplasms and well-differentiated follicular cancers cannot be separated with great accuracy, but useful predictions can be made. Care is required to recognize the cellular abnormalities of autoimmune thyroiditis and to diagnose the coexistence of this disease with malignant lymphoma.

In many parts of the world, fine needle aspiration (FNA) biopsy of the thyroid is recognized as a precise method of selecting thyroid nodules for surgical biopsy, but in the United States its acceptance has been slow. One impediment has been the pathologist's lack of familiarity with the aspiration cytology of various benign and malignant thyroid lesions. This paper, therefore, describes our observations on the cytopathology of the "cold" nodule of the thyroid, which are based on 3,000 fine needle aspiration biopsies and cytohistologic correlation with almost 600 thyroid lobectomies.

Material and Methods

The nodules included in this study had all been imaged with $Tc^{99}M$ pertechnetate or 123_I, and the nodule localized to an area of decreased function. Although most of the nodules were seemingly solitary or dominant, some diffusely abnormal glands were included if one particular area was suspicious because of its characteristics on palpation and/or its lack of function. Aspiration was performed with a 25 gauge needle and a 10 milliliter syringe. Depending on the vascularity of the nodule, 22, 20, or even 18 gauge needles were used. After the material obtained had been smeared on slides and immediately fixed with spray fixative, the smears were stained by the Papanicolaou technique. Usually six preparations were made, and several parts of the nodule were sampled.

Cytologic Findings

Specimens were considered satisfactory when at least two slides showed 8-10 follicular cell groups. Presence of histiocytes alone added no useful information, as they indicated degeneration but did not rule out carcinoma. The cytologic samples were reported as described in Table I.

Subacute thyroiditis (granulomatous thyroiditis)

The cytologic features include: 1) inflammatory cells, mostly lymphocytic; 2) large foreign body type, multinucleated giant cells, quite often in the vicinity of colloid or follicular epithelium (Fig. 1A); 3) epitheloid cells; and 4) follicular epithelium with or without atypical nuclei. Germinal center cells (follicle center) are not present.

We found no cases of acute thyroiditis and only one case of an abscess caused by Aspergillus fumigatus.

Lymphocytic thyroiditis (Hashimoto's thyroiditis or autoimmune thyroiditis)

The inflammatory component of Hashimoto's thyroiditis consists of lymphocytes, plasma cells, and lymphoid folli-

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* Department of Pathology, Henry Ford Hospital
** Department of Internal Medicine, Division of Endocrinology, Henry Ford Hospital
*** Associated Endocrinologists, Inc, Southfield, MI

Address reprint requests to Dr. Kini, Department of Pathology, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202

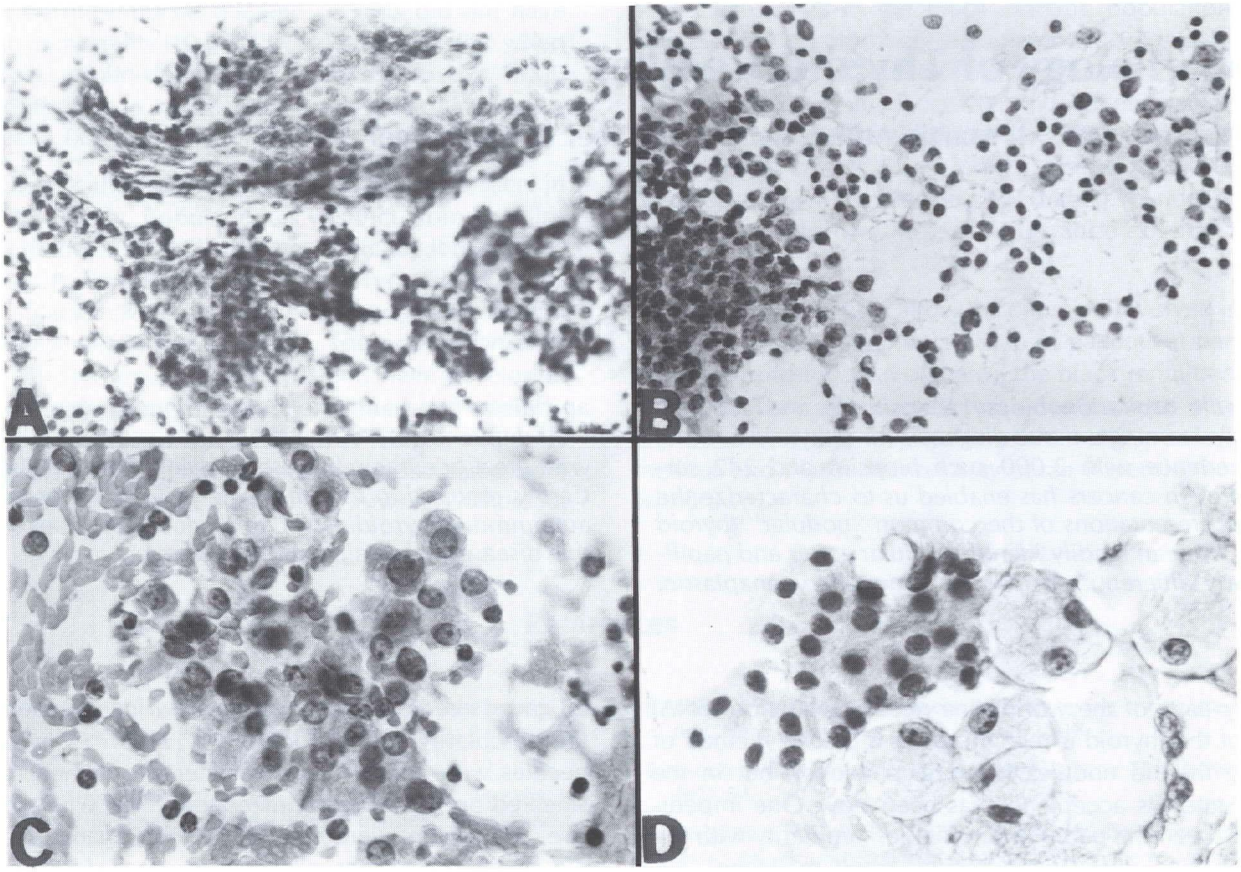

Fig. 1

A. Subacute thyroiditis: Multinucleated foreign body type giant cells and lymphocytes (X500). B . Hashimoto's (autoimmune) thyroiditis: Lymphocytes and plasma cells surrounding and obscuring follicular epithelium (X500). C. Hashimoto's thyroiditis: Hürthle cells and lymphocytes (X800). D. Benign follicular epithelium with uniform nuclei; note large degenerating follicular cells (X800).

cle center (germinal center) cells, e.g., the entire range of transforming lymphocytes to fully transformed lymphocytes (immunoblast) and histiocytes with phagocytized debris. Multinucleated giant cells may be present.

The epithelial component includes:

1) Hürthle cells, usually in tissue fragments with considerable nuclear atypia. This oxyphilic change can be extensive, forming Hürthle cell nodules, and thus can make cytologic diagnosis difficult.
2) Hyperplastic follicular epithelium with or without nuclear atypia. A folicular pattern is only rarely seen, and colloid is scant or absent altogether.

The epithelial cells are often surrounded by a mantle of inflammatory cells and even obscured by them.

The aspirates usually consisted of an admixture of lymphocytes, plasma cells, follicle center (germinal center) cells, and follicular epithelial cells, usually of the oxyphilic type with or without nuclear atypia (Fig. 1B-C). The epithelial tissue fragments were often surrounded and even obscured by lymphocytes and plasma cells. A follicular pattern in epithelial tissue fragments was rare. Colloid was usually not observed. The proportion of lymphoplasmacytic cells and epithelial components varied widely. When the former predominated, the diagnosis was usually made with no difficulty. However, a predominant epithelial component either of regular follicular cell type or oxyphilic type with few lymphocytes caused considerable difficulty in diagnosis, especially when the nuclear atypia was severe. Differential diagnoses included Hürthle cell tumors, follicular adenoma and carcinoma, subacute thyroiditis, and malignant lymphoma.

TABLE I
Categories for Reporting Fine Needle Aspiration of Thyroid

1. Unsatisfactory	Scanty cellular material or Follicular epithelium absent
2. Cancer cells not present: Benign cell population consistent with	Nodular goiter or Lymphocytic thyroiditis or Subacute thyroiditis
3. Abnormal: Cellular changes consistent with	Cellular adenoma or Hürthle cell tumor
4. Suspicious of cancer	Specify type
5. Diagnostic of cancer	Specify type

Nodular goiter (adenomatous goiter, colloid nodules)

The cytologic features of a nodular goiter are: 1) benign follicular epithelium; 2) follicular pattern, "honeycomb" sheet, or occasional papillary tissue fragment; 3) variable colloid; 4) macrophages, or multinucleated giant cells; 5) hemosiderin and calcific debris; and 6) Hürthle cell change.

Generally, we saw an admixture of follicular cells and colloid in varying proportions depending upon whether the goiter was hyperplastic or hyperinvoluted. In the hyperinvoluted stage, colloid is abundant, cellularity is usually low, epithelial nuclei are pyknotic, and degenerative changes are common. In the hyperplastic stage, just the opposite is true. The follicular cells were seen forming small follicles with a central lumen, sometimes containing colloid. When follicles were observed "en face," they had a characteristic honeycomb pattern with nuclei regularly spaced and with well-defined cell borders (Fig. 1D). Follicular cell nuclei in nodular goiter were generally uniform, the longest being about 8-10 μ. Their chromatin was finely granular and nucleoli were uncommon. An aspirate from a hyperinvoluted goiter usually yielded abundant colloid that stained bluish-green or orange when mixed with blood. The follicular cells were few, contained scanty cytoplasm and pyknotic small nuclei (Fig. 2A). Degeneration was a common phenomenon in nodular goiter with many macrophages with or without hemosiderin (Fig. 2B). Follicular cells undergoing degeneration appeared morphologically similar to macrophages because of their abundant foamy cytoplasm and could be differentiated from histocytes only by their cohesive nature and follicle formation. Hürthle cell change was frequently observed (Fig. 2C). Calcific debris was sometimes seen in nodular goiter.

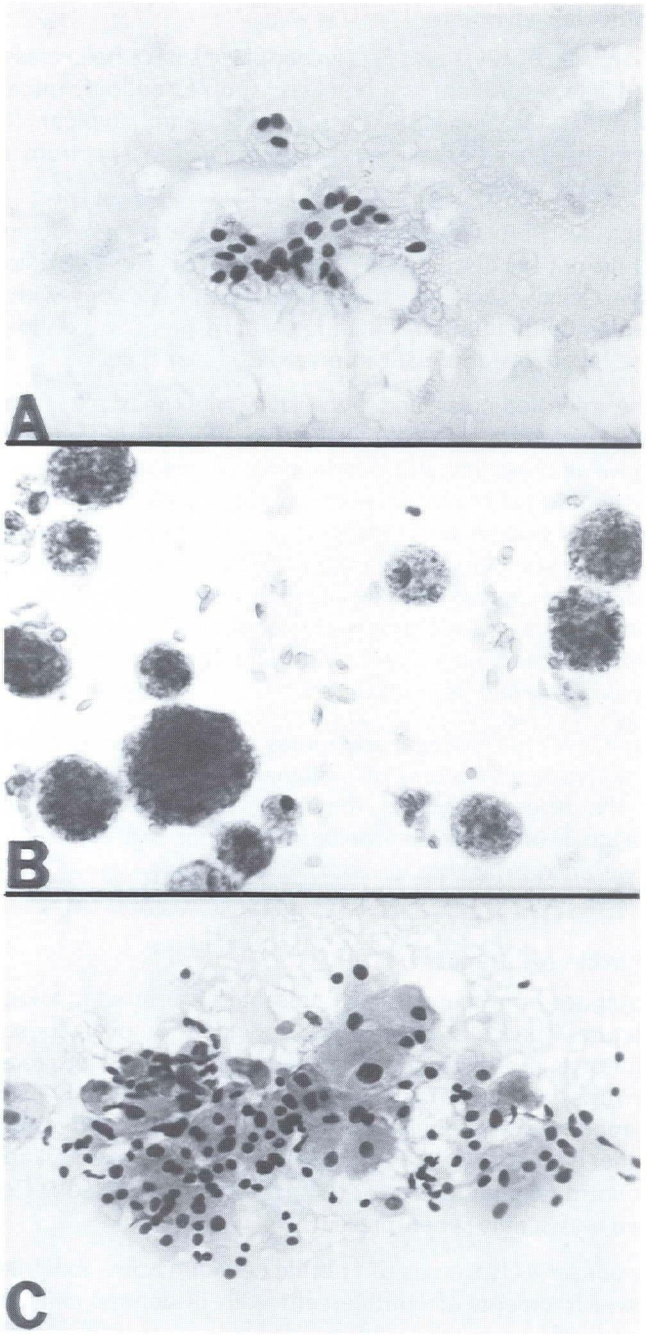

Fig. 2
A. Involutional goiter: Abundant colloid and pyknotic nuclei (X800). B. Hemosiderin containing macrophages (X800). C. Nodular goiter: Admixture of benign follicular cells and Hürthle cells (X500).

Follicular adenoma

Morphologically, these benign neoplasms have been classified into six different subgroups: simple, colloid, microfollicular, trabecular, Hürthle cell, and atypical (1). Cytologic samples accordingly presented a spectrum of morphologic features.

Aspirates from adenomas of the simple and colloid type could not be discriminated from those of nodular goiter. They usually showed varying degrees of cellularity with a benign epithelium forming a follicular pattern and colloid. The latter was abundant in macrofollicular types.

The microfollicular and trabecular adenomas almost always yielded a very cellular aspirate with tissue fragments showing crowding and overlapping of uniformly enlarged hyperchromatic nuclei with micronucleoli (Fig. 3A). A follicular pattern with or without colloid in the lumen was often present in the microfollicular type. Many of these cellular adenomas showed capsular and/or vascular invasion in the surgically removed specimen. Recognizing this type of adenoma is very important because its surgical excision should be considered.

Aspirates from atypical adenomas showed abundant cells with cytologic features of malignancy. Histologic sections of the resected thyroid, however, did not confirm the diagnosis of malignancy because capsular and/or vascular invasion was lacking.

Hürthle cell tumors

Aspirates from these lesions presented a distinct cytologic picture. The cells were large, polygonal or oval, loosely cohesive, mostly discrete, isolated, but also in sheets, loose groups, and with a follicular pattern (Fig. 3B). Their cytoplasm was granular, sometimes abundant, and stained either eosinophilic or cyanophilic. Nuclei were remarkably uniform, slightly eccentric with prominent nucleoli. Colloid was scanty when present.

In our series, six cases of Hürthle cell carcinoma exhibited tissue fragments of Hürthle cells with ill-defined cell borders with crowded, overlapped, and pleomorphic nuclei (Fig. 3C), in contrast to a monomorphic cell pattern that was usually observed in Hürthle cell tumors with noninvasive characteristics. Three cases diagnosed as Hürthle cell tumor turned out to be carcinoma when surgically excised specimens were examined. Needle aspirates from large non-neoplastic Hürthle cell nodules from autoimmune thyroiditis and nodular goiter could be mistakenly interpreted as Hürthle cell tumor. Most of these aspirates will show other features of the primary disease, e.g., a fair number of benign follicular cells. In nodular goiter (Fig. 3A), colloid will be present along with Hürthle cells, and in autoimmune thyroiditis, there is a polymorphic cell population comprised of lymphoreticular cells and follicular epithelial cells.

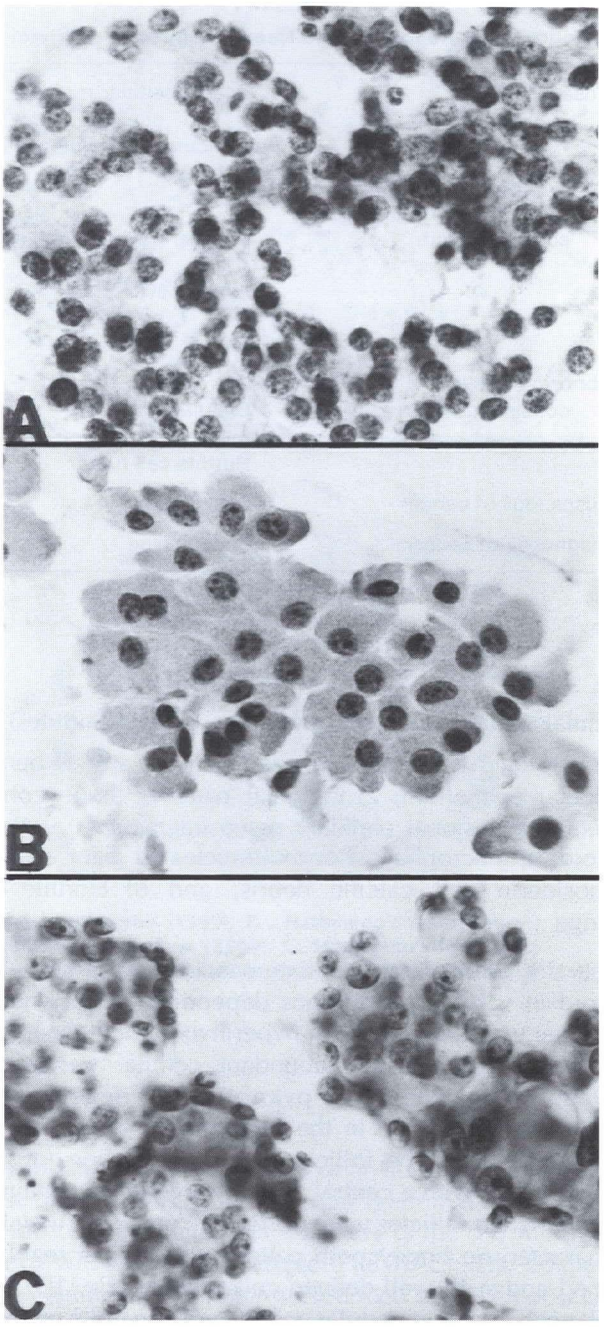

Fig. 3

A. Cellular adenoma: Note tissue fragments with follicular pattern; nuclei are uniformly enlarged, crowded, and overlapped (X800). B. Hürthle cell tumor with large polygonal cells with abundant granular cytoplasm and eccentric nuclei; note prominent macronucleolus (X800). C. Hürthle cell carcinoma: Tissue fragments of Hürthle cells with ill-defined cell borders and pleomorphic nuclei (X800).

Follicular carcinoma

The cytologic features in our preparations varied considerably depending on the differentiation of the carcinoma. On one hand, the aspirate presented cellular changes indistinguishable from those of a cellular adenoma, but, on the other, the diagnosis presented no difficulty because of obvious nuclear changes. The aspirates were generally cellular, composed of tissue fragments with or without follicular pattern. Colloid was usually scanty. Nuclei were considerably enlarged, hyperchromatic, with varying degrees of pleomorphism. Micro- and macronucleoli were common (Fig. 6A).

Papillary carcinoma

This most common malignant neoplasm of the thyroid offered the least diagnostic difficulty. Its cytologic features include: 1) papillary tissue fragments often with a branching pattern, smooth external contour, and peripheral palisading of nuclei; 2) tissue fragments with or without follicular pattern; 3) monolayered sheets of malignant cells; 4) psammoma bodies; 5) intranuclear cytoplasmic inclusions; 6) large, multinucleated foreign body type giant cells in the absence of degeneration; and 7) single or multiple micro- and macronucleoli. Individual cancer cells can be small, round, cuboidal to large polygonal with squamoid features. Cytoplasm is clear, scanty or foamy, or densely cyanophilic. Nuclei vary considerably depending on histological differentiation of the cancer. Chromatin are finely or coarsely granular.

The aspirates were usually very cellular and consisted of several small to large discrete and branching papillary tissue fragments; monolayered sheets of malignant cells, tissue fragments with or without a follicular pattern, psammoma bodies, and intranuclear cytoplasmic inclusions (Fig. 4).

When discrete, the cells were either cuboidal, large oval to squamoid, and rarely spindle-shaped. Their cytoplasm was either dense, cyanophilic or foamy, and varied in amount. Nuclei varied considerably in size and shape. In papillary tissue fragments, they were small, crowded, and overlapped, while in monolayered sheets or in the squamoid type, they were large and irregular. Micro- and macronucleoli were almost always present. Frequently, intranuclear cytoplasmic inclusions were seen (2-6). They appeared as sharp, single or multiple "halos" with a condensed rim of chromatin within the nuclei. Psammoma bodies were not a consistent feature of papillary carcinoma. These calcific, lamellated bodies were either basophilic, amphophilic, or golden brown surrounded by cancer cells (Fig. 4C). A nonspecific but frequently seen feature was large, multinucleated foreign body type giant cells. Degeneration in papillary tumors was not uncommon. Coexistent lymphocytic thyroiditis was seen in 10 of the 153 papillary carcinomas.

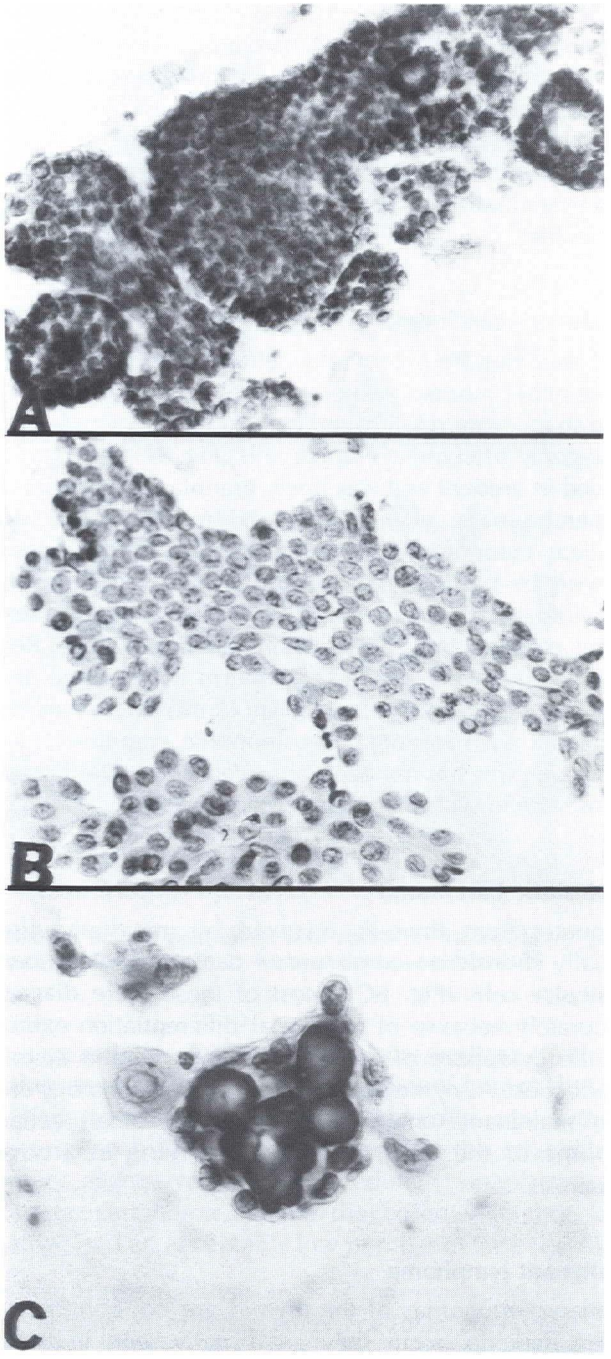

Fig. 4
Papillary Carcinoma
A. Papillary tissue fragments of cancer cells (X500). B. A monolayered sheet of cancer cells (X500). C. Psammoma bodies surrounded by cancer cells; note intranuclear cytoplasmic inclusions (X800).

Anaplastic carcinoma

The aspirates from anaplastic carcinoma showed malignant cells with extreme variation in size and shape. Depending on the type of carcinoma, they were either spindle or giant cell type (Fig. 6B). Their nuclei were hyperchromatic and irregular with coarse chromatin and multiple micro- and macronucleoli. This carcinoma presented no diagnostic difficulties.

Medullary carcinoma

The aspirates were generally cellular. The malignant cells were either monomorphic or pleomorphic, ranging in size and shape from small round cells to plasmacytoid, to large polygonal or spindle-shaped cells (Fig. 5). The cytoplasm varied in amount and was finely granular. The nuclei were hyperchromatic with micro- and macronuceloli. Intranuclear cytoplasmic inclusions similar to the ones observed in papillary carcinoma were very common. Amyloid often appeared as acellular dense material resembling colloid, and special stains such as Congo Red or Thioflavin T were needed to confirm its presence. In air-dried preparations, the cytoplasm of medullary carcinoma cells is known to contain eosinophilic granules (1, 7-10). However, this has not been observed in wet fixed preparations stained with the Papanicolaou method.

Metastatic carcinoma

Aspirates from thyroids involved by metastatic disease usually showed an admixture of cancer cells and benign follicular cells (Fig. 6C). Most of these were diagnosed accurately because of functional differentiation exhibited by the cytoplasm of cancer cells, e.g., keratin or mucin production. Also, the characteristic cytomorphology of certain malignant tumors (e.g., anaplastic small cell carcinoma of the lung) helped in arriving at a correct diagnosis.

Malignant lymphoma

Primary lymphomas of the thyroid are not common, but when they do occur they are usually seen in thyroids involved by Hashimoto's thyroiditis (5,11,12). Depending on the type of lymphoma, a monomorphic cell population is a characteristic cytologic feature of malignant lymphoma. The diagnosis can be very difficult on the fine needle aspirate. When the involvement was diffuse, the aspirates showed a dense population of lymphoma cells (Fig. 6D) without any epithelial cells or follicle center cells. When the involvement was focal, multiple aspirates from different areas of the nodule showed a pattern that varied from typical Hashimoto's thyroiditis to aggregates of lymphoma cells. Diagnosis from such aspirates was very difficult and was missed in three instances. Hodgkin's disease of the cervical lymph nodes extending into the thyroid gland was diagnosed in two cases because of characteristic Reed-Sternberg cells.

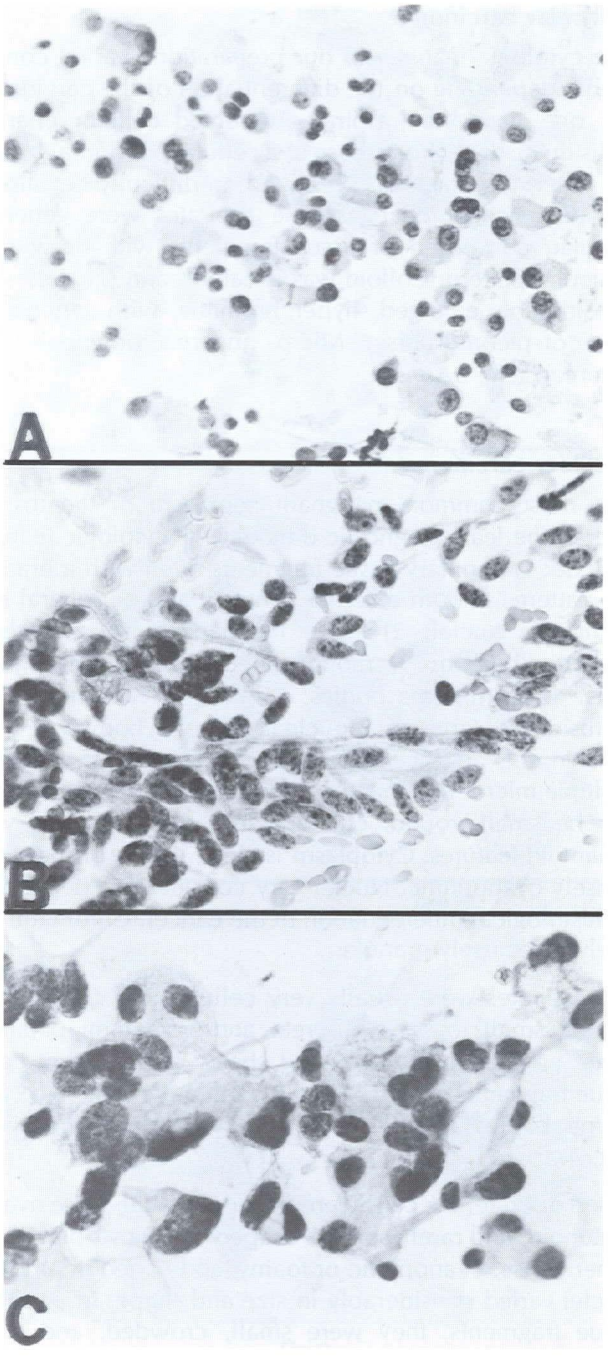

Fig. 5
Medullary Carcinoma
A. Pleomorphic tumor cells with plasmacytoid pattern (X500). B. Spindle shaped cancer cells (X800). C. Bizarre tumor cells (X800).

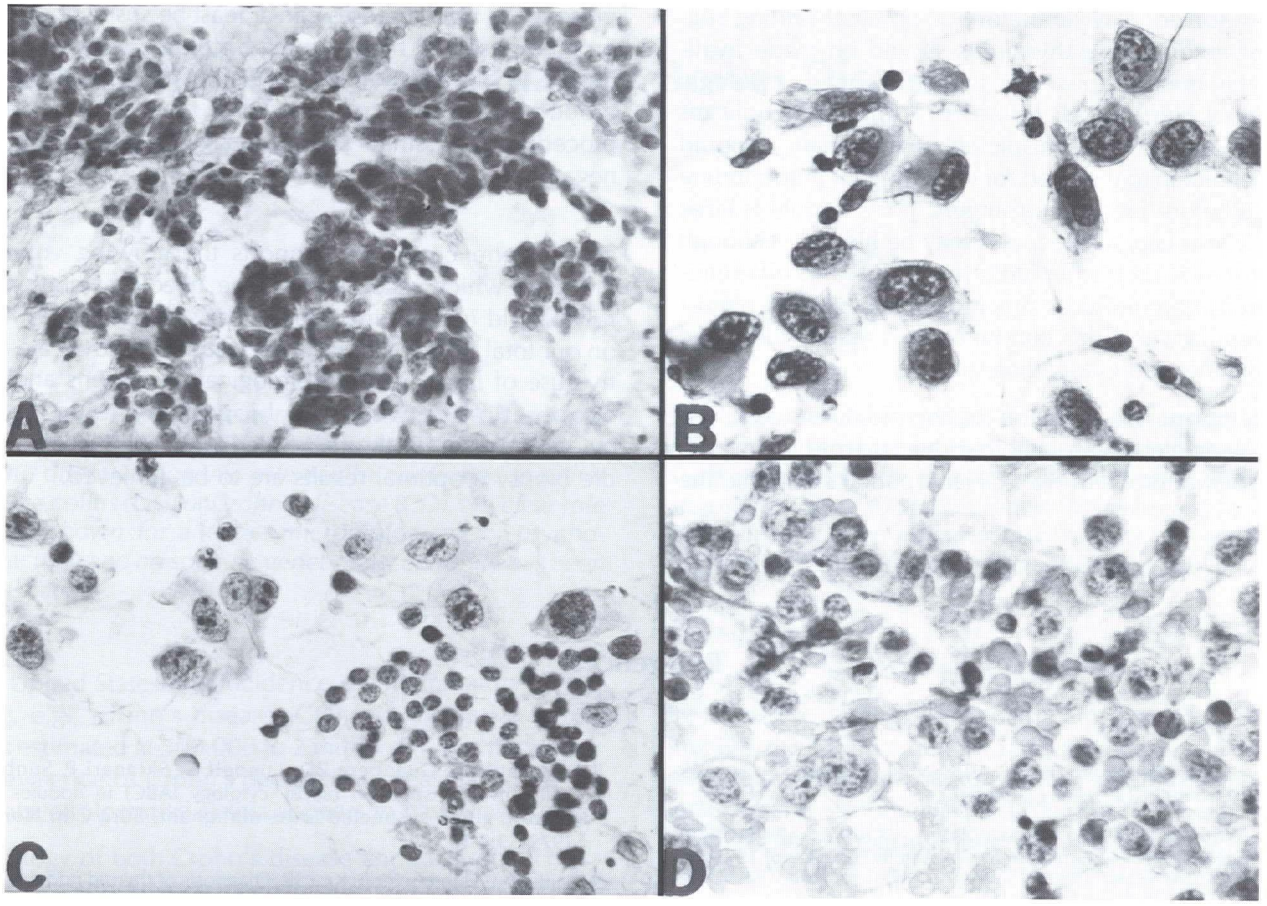

Fig. 6

A. Cellular aspirate from follicular carcinoma (X800). B. Anaplastic carcinoma: Bizarre giant tumor cells (X800). C. Metastatic carcinoma: Admixture of undifferentiated cancer cells and benign follicular epithelieum (X800). D. Malignant lymphoma: Diffuse histiocytic (X800).

Discussion

Fine needle aspiration of the thyroid is a common diagnostic procedure in European countries where air-dried smears prepared with May-Grunwald Giemsa stains are standard. The descriptive and illustrative literature, therefore, on the cytopathology of the thyroid has been based on this technique, which is not popular among American cytopathologists.

The European literature has provided few details on the specificity of common cytologic findings, the overlapping of patterns of benign and malignant lesions, and the diagnostic pitfalls to be avoided in cytologic diagnosis of thyroid disease. Such writers fail to focus on the primary purpose of fine needle aspiration biopsy of the thyroid, i.e., avoiding unnecessary thyroid surgery. Even after 20 years, there are reports listing large numbers of benign nodules which have been removed (8). Our primary purpose has been to refine diagnoses and promptly translate them into indications for surgery or for observation of nodules (4,9).

Selecting patients for observation or medical treatment requires great accuracy in the diagnosis of benign disease. Nodular goiter and autoimmune thyroiditis can both be diagnosed with rare false positives. On the other hand, papillary, aggressive follicular, medullary, anaplastic, and metastatic carcinoma can be diagnosed with rare false negatives and an acceptably low number of false positives.

The first of two problem areas is the overlap in the cytologic pattern of nodular goiter, cellular adenomas, and well-differentiated follicular carcinomas. The problem becomes more theoretical than practical if one simply acknowledges that it exists and that it cannot be solved with our present knowledge. These facts can then be incorporated into the evaluation plan for the management of thyroid nodules.

The second problem is mistaking cellular changes related to cytotoxic antibodies of autoimmune thyroiditis for those of neoplasia. Once again, if both the cytopathologist and the clinician are aware of the problem, it can be at least

partially resolved. Any laboratory or physical finding suggestive of autoimmune thyroiditis should be made available to the microscopist. On the other hand, cytologic diagnoses of Hürthle cell lesions or follicular neoplasms with small or moderate suspicion of malignancy should alert the clinician to the need for screening for autoimmune thyroiditis before prescribing surgery. If the nodule is large enough, a histological specimen may be helpful. Although the coexistence of Hashimoto's thyroiditis and differentiated thyroid carcinoma is not rare, the cancer is almost always papillary, and this combination is readily identified by the experienced cytopathologist.

When malignant lymphoma of the thyroid does occur, it is usually associated with autoimmune thyroiditis, which poses a special problem (13). Given optimal sampling, the presence of both diseases can at least be suspected and the problem resolved by obtaining histologic samples. A high degree of suspicion on the part of the cytopathologist will produce some false positives, but the additional biopsy procedure is a small price to pay for eliminating false negatives.

Our experience further supports the growing volume of literature which recommends fine needle aspiration as a reliable aid in selecting patients for surgical biopsy. Based on our total biopsy studies, we continue to advocate selective use of large needle histological specimens and close cooperation between the biopsy physician and the cytopathologist. Both are needed to supplement fine needle biopsy if optimal results are to be achieved.

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