

Endocrine Pathology Society
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RECENT ADVANCES IN THYROID NEOPLASIA

PAPILLAE, NUCLEI AND ONCOGENES:
BACK TO THE DRAWING BOARD

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Several articles have been written over the years on the inter- and intraobserver variability among experts in the diagnosis of thyroid tumors.¹⁻⁵ These papers have brought up several important points, some of a general nature and others that specifically apply to the thyroid gland. In general terms, it seems that nearly every study that has been done testing concordance (or lack of it) among pathologists in lesions located in almost any site of the body has provided disappointing results. Some of the numerous examples that can be quoted are those on dysplasia in Barrett's esophagus,⁶ grading of prostatic carcinoma,⁷ grading of breast carcinoma,⁸ diagnosis of hydatidiform mole,⁹ and classification of thymic tumors.¹⁰ On first sight, these results make surgical pathology look like a subjective, arbitrary, unscientific discipline, and therefore many surgical pathologists don't like them. I still get occasional snotty remarks about a study of the kind I did many years ago on proliferative ductal lesions of the breast.¹¹ Yet, I doubt whether burying our head in the sand is the solution. Perhaps it is the nature of the beast, and nothing can be done about it.¹² As Vickery¹³ stated, some of the criteria on which we base those distinctions "may be indefinite and vulnerable to subjective morphologic interpretation." Or perhaps some of these studies will identify a specific problem that can be addressed.

The various thyroid studies above quoted mainly deal with the diagnostic significance of certain morphologic nuclear features (herein referred to as PTC-type nuclei) in the diagnosis of papillary thyroid carcinoma (PTC). It is obvious from the results obtained that some experts have a much lower threshold for the identification and/or diagnostic significance of PTC-type nuclei than others. It may be of some interest to briefly recount the evolution that PTC-type nuclei have had in thyroid pathology until reaching their presently exalted status. Originally, and for the many decades that followed its description, PTC was diagnosed primarily on the basis of the presence of papillae, hence its name. Then people began noticing that these tumors had peculiar nuclei, which looked empty or optically clear. Ronald DeLellis¹⁴ gave credit to Nancy Warner for drawing the amusing analogy between these nuclei and the eyes of Harold Gray's comic strip character, "Little Orphan Annie". Thus, the expression "Orphan Annie's eyes nuclei" became popular when referring to PTC, although the presence of papillae and other cytoarchitectural features (carefully listed and discussed in Vickery's authoritative review on the subject¹³) were still regarded as important criteria for the diagnosis of PTC. However, with the passing of the years, PTC-type nuclei rose through the ranks, so to speak, to become the paramount criterion for the diagnosis of PTC. At present, a thyroid tumor can have a papillary, follicular, solid, trabecular or cribriform pattern of growth; it can be composed of large, small, oncocytic, clear, round, spindle or columnar cells; it can be encapsulated, minimally invasive or widely invasive; in sum, it can have any of those features and more, but as long as it has PTC-type nuclei it is thought to be a PTC or one of its innumerable variants.

As a working hypothesis, the idea is appealing. After all, having a specific marker of any type has always been the dream of the diagnostic pathologist. However, if we are going to allow for PTC-type nuclei to have such an overriding discriminatory power, we better assure ourselves of the following:

- 1) That the criteria for the identification of the PTC-type nucleus are rigidly drawn and faithfully followed;
- 2) That thyroid lesions diagnosed as PTC primarily on the basis of PTC-type nuclei fulfill at least some of the traditional morphologic criteria of PTC;
- 3) That thyroid lesions diagnosed as PTC primarily on the basis of PTC-type nuclei behave as PTC, or at the very least that they have the behavioral properties of a carcinoma.

It is our impression that none of these essential provisos have been entirely fulfilled, and that this is the major reason for the uncertainties and misunderstandings that exist in the field. Let's look at each of these aspects:

1. The nature of the nuclear alterations associated with PTC.

It is somewhat misleading that the most common terms used to describe the nuclear changes that accompany PTC are “optically clear”, “ground glass”, and “Orphan Annie’s eyes”. In reality, the PTC-type nuclear changes can be divided into two major categories, both of still uncertain pathogenesis, which may or may not be related to each other: (1) The clearing itself, said to be due to the disappearance, fine dispersion or displacement of chromatin, resulting in a vesicular appearance of the nucleus; (2) A number of morphologic alterations of the nuclear membrane that seem to be the consequence of increased synthesis of this structure, which then folds into itself to lead to semilunar nuclear forms, a finely serrated contour, longitudinal grooves, and pseudoinclusions. It is our definite impression that the identification of these nuclear changes has become progressively liberal in recent years, both on the part of the “thyroid experts” and of pathologists at large. This is particularly true for the clear nuclei with a round to oval regular contour, which are not substantially different from the vesicular nuclei one sees in countless situations in all kinds of sites. To a lesser extent, this is also true for the nuclear membrane-related alterations. Thus, grooves, nuclear holes (sometimes referred to as “nuclear bubbles”)¹⁵, serrated nuclei and bonafide pseudoinclusions are often present in sites other than the thyroid, to the point that if one were to look for them with the same compulsion one exercises in thyroid lesions, one would find PTC-type nuclei almost anywhere. Parenthetically, this lack of specificity applies not only to pathology and biology at large, but also to the world of comic strips. The empty eyes were not an exclusive feature of Orphan Annie. Rather, they were a feature of several the characters that inhabited that cartoon !

2. The diagnostic significance of the PTC-type nucleus. Is it pathognomonic of PTC?

Let's assume that we have learned to disregard vesicular nuclei and nuclear bubbles, and that we are dealing with a thyroid lesion that contains nuclei which not only are totally clear, but which also exhibit one or more of the features resulting from nuclear membrane reduplication of the type above described. Is the presence of such nuclei, by itself, pathognomonic of PTC? Probably not. As we said above, practically nothing is pathognomonic in medicine, and these nuclei are not likely to be the exception. Vickery, in the already quoted review of papillary carcinoma written in 1983,¹³ stated that “the clear nuclear change, including occasional inclusions, is a very helpful guideline but not a specific criterion [for PTC]”. This obviously means that one needs to find additional features in order to substantiate a diagnosis of PTC. The analogy comes to mind with Reed-Stenberg cells vis-a-vis Hodgkin's lymphoma. For decades it was dogmatically stated that the former was pathognomonic of the latter. Then a seminal paper appeared from Henry Rappaport's group¹⁶

describing Reed-Stenberg-like cells in several other processes, both benign and malignant, both of lymphoid and non-lymphoid nature. Once this observation was accepted, the diagnostic criteria for Hodgkin's lymphoma had to be changed. The mere presence of cells looking like Reed-Stenberg cells was not longer enough. Rather, those cells had to be in the "appropriate cytoarchitectural background".

One could take a similar approach with PTC-type nuclei vis-à-vis PTC and regard the former as diagnostic of PTC only when found within the appropriate cytoarchitectural background. In the thyroid, this background means the presence at least some of the following features: a localized lesion (in the sense that it cannot be the entire thyroid, as in Hashimoto's thyroiditis); elongated, tubular-like follicles; homogeneous deep red intraluminal colloid; psammoma bodies; and dense fibrohyaline bands with a colloid-like appearance in between the neoplastic follicles, especially at the tumor periphery. It would be highly satisfying if one were able to go beyond this laundry list and specify how many of these features need to be present in order to render the background "appropriate". Unfortunately, no such model exists or is likely to. It is here where the strength and weakness of surgical pathology lies, in the sense that it is up to the surgical pathologist to decide in the individual case how many are "enough."

3. The clinical significance of the encapsulated well-differentiated thyroid nodule with a follicular pattern of growth (without capsular or vascular invasion) which contains some PTC-type nuclei. Does it behave as cancer ?

This type of lesion constitutes the majority of the cases I see in my consultation practice, and I suspect this is true for other thyroid pathology consultants. The way these lesions are interpreted ranges substantially, as most of the quoted studies demonstrate. Who is right? The question can be asked from a scientific (mechanistic) and from a practical (clinical) standpoint. Biologically, one could argue that since these nuclear changes are similar to those seen in blatantly invasive PTC, and since they have been correlated with the presence of RET mutations,¹⁷ they indicate the presence of PTC. To be sure, one cannot deny the possibility that these alterations are indeed the earliest manifestation of PTC, or at least a preneoplastic/dysplastic stage of the disease. However, from a clinical standpoint it is paramount to keep in mind that they practically never behave as cancer, in the sense that a conservative local excision (usually in the form of a lobectomy) will cure them permanently. Being this the case, why call them cancer and subject the patient to the overtreatment and mental anguish that such a diagnosis may elicit ? As Julian Huxley¹⁸ wisely stated in a lecture given at Sloan-Kettering Institute in the fifties, "Cancer (malignancy) must be defined operatively in terms of what the tumour cells do, not what they look like; otherwise the term ceases to have biological meaning".

The problem is to find an acceptable alternative. The Chernobyl Pathology group¹⁹ proposed the term "well-differentiated follicular tumor of uncertain malignant potential", borrowing from nomenclature used in the gynaecologic pathology field. Another possibility would be to adopt the terminology currently used for gastrointestinal stromal tumors (GIST)²⁰ and classify them according to their risk level (very low, low, intermediate, and high). I suspect that none of these proposals will be very palatable to surgeons, endocrinologists or nuclear medicine specialists, at least initially, but we need to work together to find an acceptable compromise and to avoid using the words "cancer" and "carcinoma" for this particular set of tumors.

One may argue that exceptionally these lesions will metastasize, thus proving that they are cancers after all.²¹ I don't think the argument is valid. To begin with, most of the reported cases had evidence of vascular and/or capsular invasion. Furthermore, we know that once in blue moon a morphologically typical pleomorphic adenoma of the parotid will metastasize,²² yet that fact does not make us view all mixed tumors as malignant. About 10% of adrenal pheochromocytomas metastasise, but we do use this fact to label the other 90% as malignant.

There is an interesting albeit somewhat dangerous experiment that any courageous pathologist interested in personally checking the above claim can perform. It consists in going back to the files of a Pathology Department and review the microscopic slides of the thyroid cases that had been diagnosed as follicular adenoma in any time period before 1980. Chances are that he will find a fair number of cases which today himself and/or a pathology expert would diagnose as the encapsulated follicular variant of papillary carcinoma on the basis of the presence of PTC-type nuclei and in the absence of capsular/vascular invasion. He should then get a follow-up on those patients. I predict he will find that practically nobody developed metastases from those tumors (some may have developed independent tumors in the contralateral lobe if originally treated by lobectomy, but that is another matter). I know of at least a group that has performed such a study, and this is exactly what they found.²³ Interestingly, the authors of that paper concluded that those patients may have been undertreated. Somebody else may have concluded just the opposite: that they were very lucky to have had the tumor diagnosed when they did, and that the treatment they had was just fine, thanks.

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**Oncocytes, Oxyphils
and Hürthle Cells**

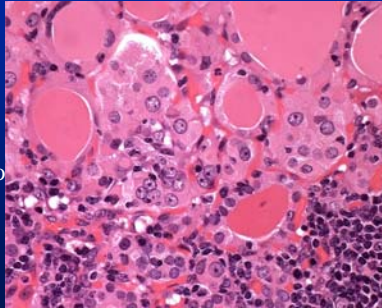
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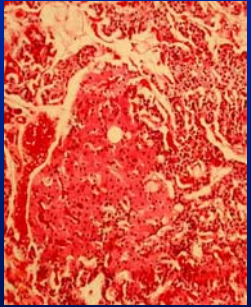
Hürthle (Askenazy) Cells

- Metaplastic change in follicular epithelium
- due to accumulation of numerous spherulated, dilated mitochondria



Oncocytes: Definition

- Epithelial cells with enlarged granular eosinophilic cytoplasm due to the accumulation of numerous, often spherulated, mitochondria
- Seen often in pituitary, parathyroid, thyroid, adrenal cortex, pancreatic islets



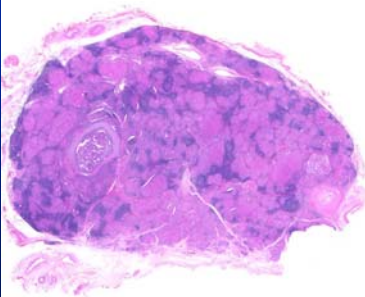
Oncoytic Change is Metaplasia

Metaplasia:

- An adaptive substitution of cells more sensitive to stress by other (related) cells better able to withstand the adverse environment
- Reversible

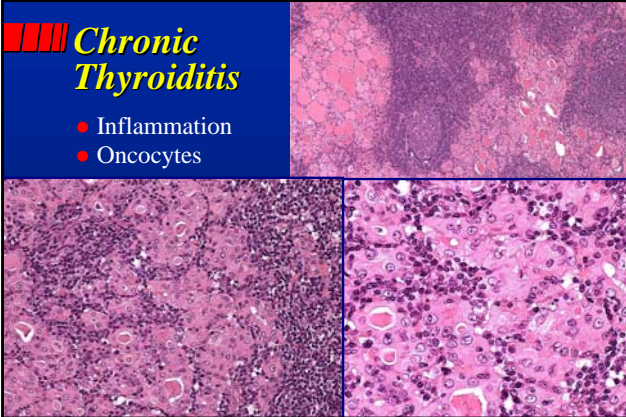
Chronic Lymphocytic Thyroiditis

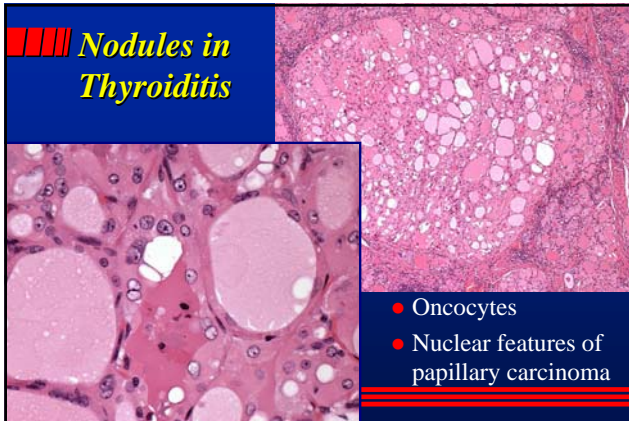
- Multiple variants
- Distinct clinical features
- Histological variants:
 - » ± oncocytes
 - » fibrosing variant

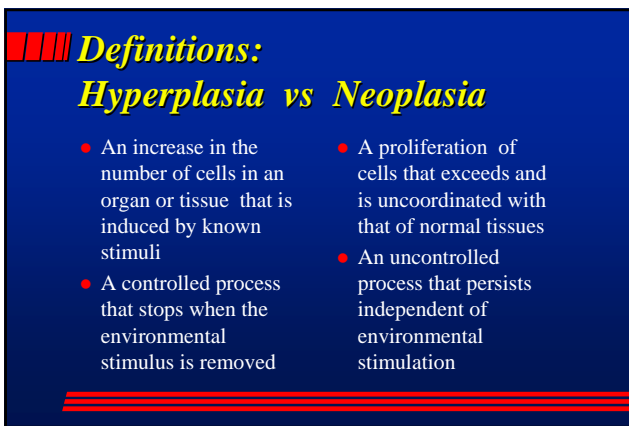


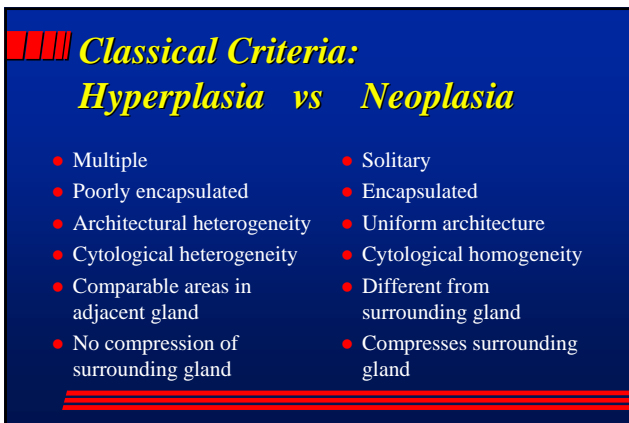
Chronic Thyroiditis

- Inflammation
- Oncocytes



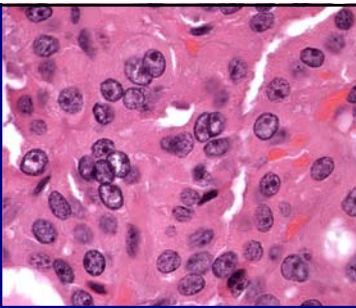




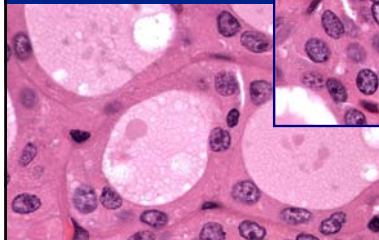


Oncocytes

- Nuclear features of papillary carcinoma



- Prominent nucleoli

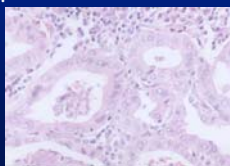
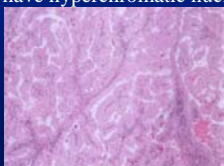


Hürthle Cell Nodules

- Hyperplasia
- Adenoma
- Papillary carcinoma
- Follicular carcinoma
- Medullary carcinoma

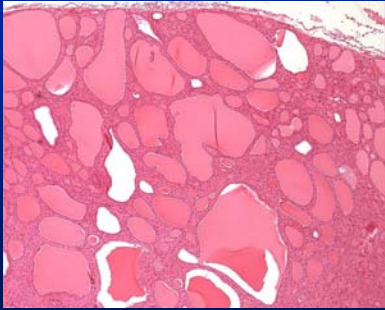
Oncocytic Tumors of Endocrine Tissues - Diagnosis

- Classify as for other lesions without oncocytic change
 - » Usually not difficult - capsular or vascular invasion, etc.
- Papillary Ca thyroid can be difficult because oncocytes have hyperchromatic nuclei!



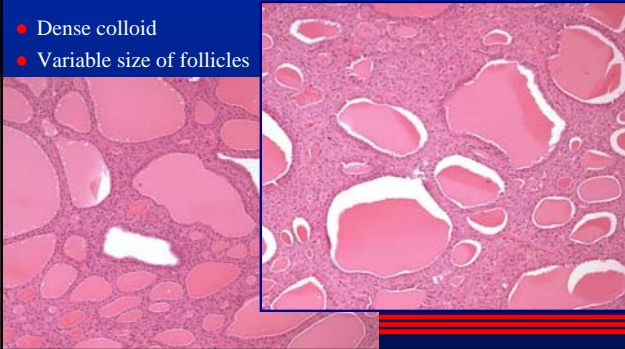
Oncoytic Follicular Neoplasm

- Macro- and microfollicular
- Dense colloid
- No fibrous capsule



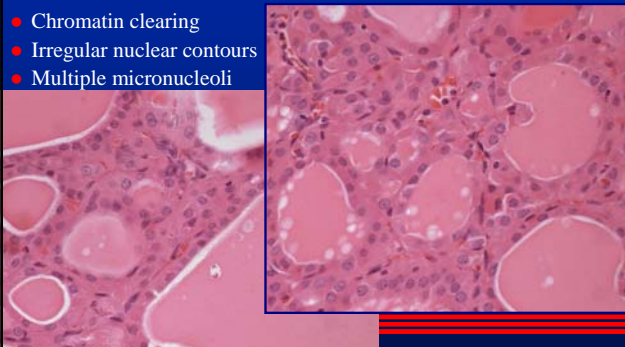
Oncoytic Thyroid Tumour

- Dense colloid
- Variable size of follicles



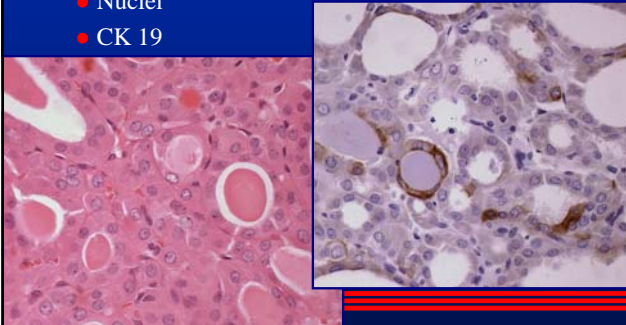
Cytology of Oncoytic Tumour

- Chromatin clearing
- Irregular nuclear contours
- Multiple micronucleoli



Markers of Papillary Carcinoma

- Nuclei
- CK 19



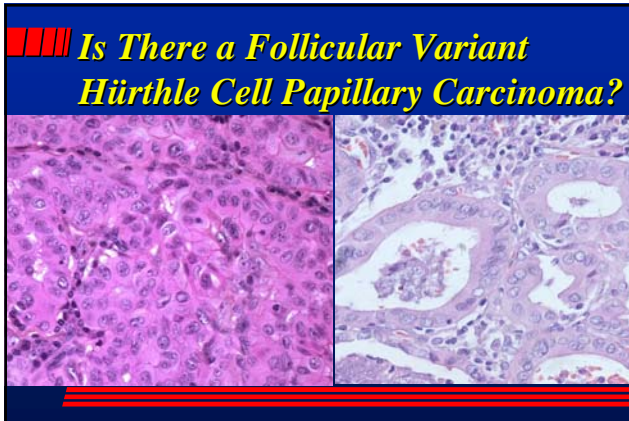
Hürthle Cell Tumors

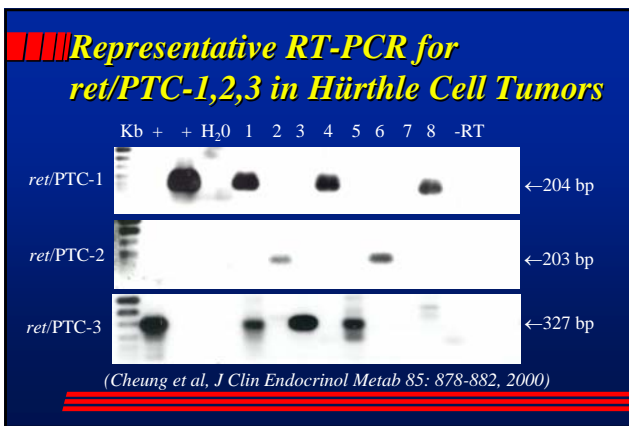
- Hürthle cell adenoma, Hürthle cell carcinoma
 - » distinguished by invasive behavior
 - » controversial because of unpredictable behavior
- Hürthle cell papillary carcinoma
 - » defined by papillary architecture

? Follicular Variant
Hürthle Cell Papillary Carcinoma?

Hürthle Cell Papillary Carcinoma







Molecular Basis of Hürthle Cell Papillary Carcinoma

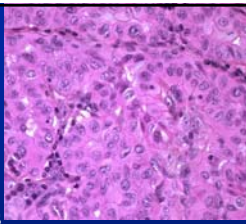
- ret/PTC identifies Hürthle cell tumors that have lymph node metastases
 - » allows distinction from Hürthle cell adenoma
 - » better prognosis than Hürthle cell carcinoma

(Cheung et al, J Clin Endocrinol Metab 85: 878-882, 2000)

mtDNA, GRIM19

- mtDNA somatic events
- Mutations in non-neoplastic and neoplastic oncocyctic cells
 - » Not specific to neoplastic transformation
 - » Associated with BRAF, ret/PTC etc
- GRIM19 (19p13.2) somatic and germline events

*Maximo et al Virchows Arch 2000,
Sobrinho-Simoes Int J Surg Pathol 2005*

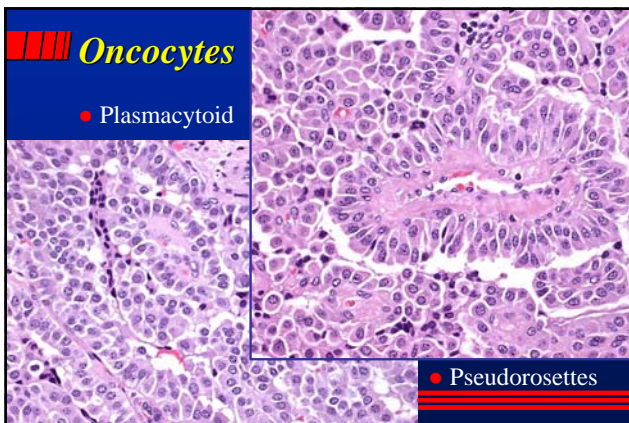


Oncocytic Tumour



Oncocytes

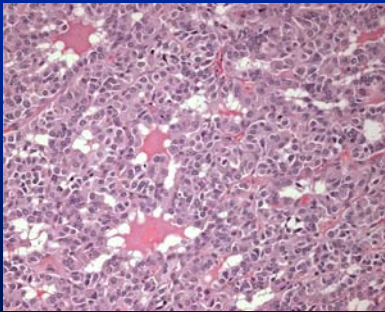
- Plasmacytoid



• Pseudorosettes

Oncocytic Tumour with Colloid

- Follicle formation
- Colloid with scalloping

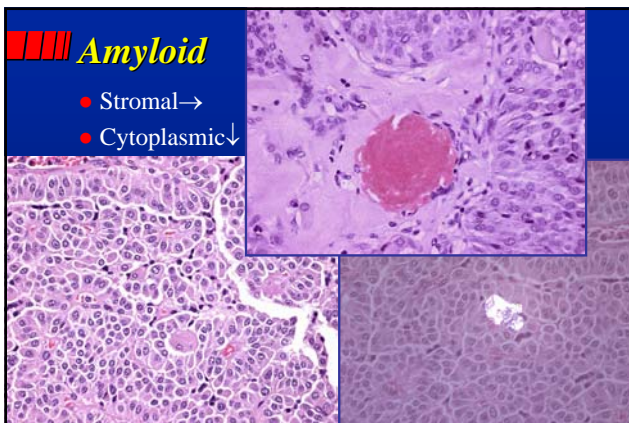


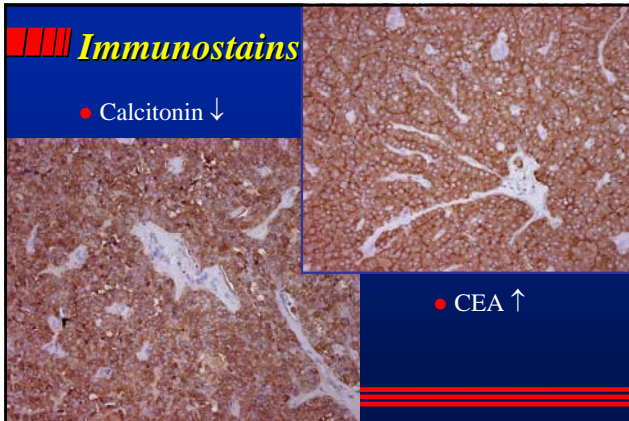
Medullary vs Follicular Carcinoma

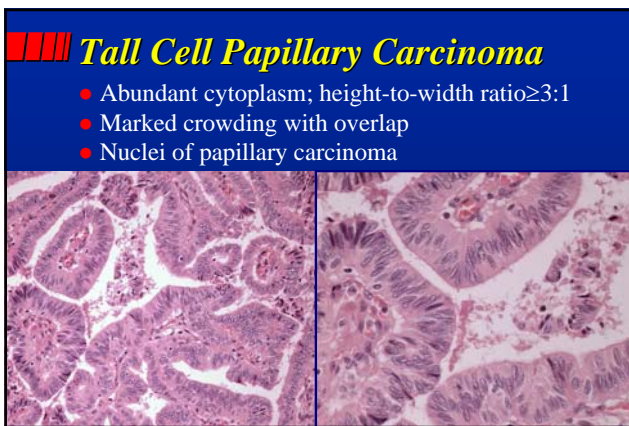
- Medullary carcinoma
 - » Usually has organoid architecture
 - BUT
 - » May trap follicles or may have true glandular pattern
 - » May even have papillary appearance
- Amyloid
- Immunohistochemistry
 - » Calcitonin/Chromogranin/CEA vs TG/TPO

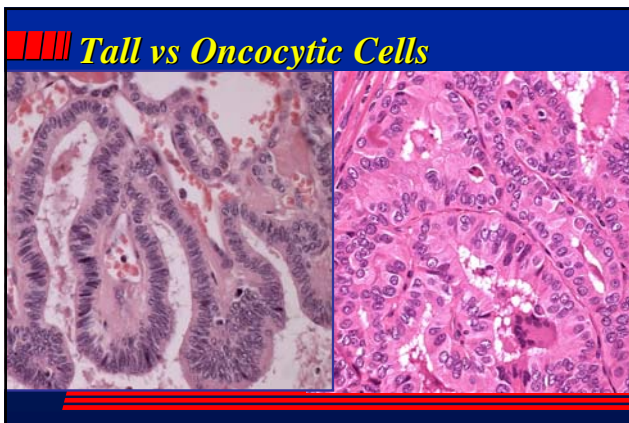
Amyloid

- Stromal →
- Cytoplasmic ↓









Summary

- Oxyphils are oncocytes
- They can be follicular epithelial cells or C cells in thyroid
- They may have a molecular basis
- They can form tumors, benign or malignant
- They may impact radioactive iodine uptake
- They are *NOT* a distinct cell or tumor type

TALL CELL VARIANT OF PAPILLARY THYROID CARCINOMA

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Papillary thyroid carcinoma is the most common endocrine malignancy and the most common malignant tumor of the thyroid gland. The majority of papillary carcinomas enjoy an excellent short-term and long-term prognosis with most patients surviving decades even in the presence of regional lymph node metastases. Occasional patients will demonstrate distant metastases usually to the lungs and this may present as lymphangitic spread or hematogenous metastasis. Less usual sites of distant metastases include bone, brain and liver.

Over the past 20 years a number of variants of papillary carcinoma have been described and their clinical and pathologic features reported. Many of these variants are histological curiosities and from a clinical standpoint do not impact patient prognosis or quality of life. Other variants are important to recognize because of their associations with non-thyroidal lesions; the best example of this is cribriform-morular variant which is associated with familial adenomatous polyposis of the colon.

Some types of papillary carcinoma are reportedly more aggressive than classic type. The one most frequently referred to in this regard is the tall-cell variant of papillary carcinoma.

Originally described in 1976 by the group from the Cleveland Clinic as a particularly aggressive thyroid cancer, several series have appeared in the literature which have recognized its clinical behavior. Unfortunately the pathologic definition of tall-cell variant has not been uniform. It should be defined by its cellular characteristics; these include abundant cytoplasm, which is often eosinophilic although not granular and the nucleus which is elongated and stratified cell to cell. The nuclei can but not necessarily always show all of the features of the so-called papillary carcinoma nucleus. Controversy has existed with regard to the amount of cytoplasm present and the configuration of the cell. In the 2004 WHO classification of endocrine neoplasms, tall-cell papillary carcinoma cells should be 2 times as tall as they are wide. In many examples of this carcinoma this definition is exceeded.

The pattern of growth of these lesions is frequently very papillary, and in some examples this is so florid as to assume a trabecular growth pattern. It is uncommon to see follicular differentiation in this tumor. The question that also has been controversial is "how much of a thyroid cancer should show the tall-cell pattern to be diagnosed as tall-cell variant?" Some authors have claimed 10%, 30%, or 70%. Again from the WHO classification, it should be at least 50%. In my experience tall-cell papillary carcinomas are frequently totally tall-cell in pattern.

Some pathologists prefer to include tall cell carcinoma as one of the poorly differentiated types of thyroid carcinoma. Since poorly differentiated thyroid carcinoma is still being defined, it is the feeling of many pathologists including myself that this is not appropriate at this time.

What about the aggressive behavior? Are these tumors clinically aggressive because they occur in older individuals (average age 55), because they show gross extrathyroidal extension from the thyroid, because they are large tumors (average size 4 centimeters or greater), or because they show vascular invasion?

Although most patients with this variant of papillary carcinoma present at somewhat older age than the average individual with papillary carcinoma, this lesion can occur in young individuals. It can also be of modest size and indeed anecdotal examples of tall cell micro-carcinomas with aggressive clinical behavior are known to exist. Is their behavior then related to extrathyroidal extension? Recently the group from Memorial Hospital in New York City has shown that this is also not true. In their report tall cell papillary carcinoma without extraglandular extension was shown to have a higher metastatic lymph node rate than classical papillary carcinoma without extraglandular extension. This was independent of age, sex or tumor size. In addition 6% of patients with tall cell papillary carcinoma without extraglandular extension developed distant metastasis while no classic papillary thyroid carcinoma in that series recurred at a distant site. In this same series it was noted that the median tumor size was 1.5 cm and indeed in one case a tumor that was less than 1 cm in diameter was associated with lung metastasis one year after diagnosis.

Another complicating factor and one which still deserves intense study are those cases in which metastases usually in lymph nodes show tall cell cytology but slides of the primary tumor are either totally classic pattern, follicular pattern or show very focal tall cell change. What is the prognosis of these patients? There are no studies which address the clinical impact of focal tall cell features in the primary tumor nor the presence of tall cell cytology in metastatic foci. Because of anecdotal cases it has become my practice to at least mention tall cell features in a comment on the pathology report of the thyroidectomy specimen, and to give an estimate of the percentage of tall cell histology that is present. Again from anecdotal experience, individual cases of progression of percentage tall cell histology from the primary site through nodal metastasis and subsequent recurrence and metastasis followed by the development of poorly differentiated and subsequently anaplastic carcinoma are known. Unfortunately the frequency of these events is not known and cannot at present be predicted.

The development of anaplastic carcinoma of a special subtype from the tall cell carcinoma has been reported and this lesion is so-called spindle cell squamous anaplastic carcinoma. In studying primary tumors in such cases one can not infrequently identify foci of extensive hemorrhage with a few spindle cells and an occasional cell resembling a squamous cell years before the development of the anaplastic transformation. Rarely examples of individual cell necrosis in these areas of hemorrhage may be seen.

Mitotic figures including abnormal forms may also be identified in tall cell variant even without these foci.

There have been several studies evaluating molecular factors in tall cell carcinoma which some authors feel may be responsible for its behavior. Thus, mutations in B-raf are found more commonly in tall cell variant than in classical or follicular variants of papillary carcinoma. (In fact in general papillary carcinomas with Braf. mutations show a higher frequency of extraglandular extension and regional node metastases than papillary carcinomas which are B-raf negative). The B-raf mutation in this subcategory of tumors gives rise to the hope that anti-B-raf targeted therapies may be effective in these patients.

In addition high expression of Muc1 which is amplified at the DNA level and overexpressed at the protein level in tall cell carcinoma as compared to classic and follicular variants may be associated with greater frequency of cellular disassociation and on-cogenic progression and therefore may contribute to the biologic behavior of this tumor.

From a clinical perspective the importance of recognizing tall cell variant papillary carcinoma which in my experience is under reported lies in the fact that tall cell carcinoma is overrepresented in series of papillary carcinomas which are refractory to radioactive iodine therapy. Indeed 20% of FDG-PET positive, radioactive iodine refractory tumors are tall cell variant. 88% of radioactive iodine refractory tall cell variants have extrathyroidal extension, another aggressive pathologic finding. Clearly tall cell variant is overrepresented in these incurable papillary tumors.

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TALL CELL VARIANT OF PAPILLARY THYROID CARCINOMA

BULLET POINTS

- Tall cell papillary carcinoma is under recognized and under reported.
- Tall cell papillary carcinoma is an aggressive form of thyroid cancer, even if it is gland contained.
- Molecular analysis of this tumor indicates a high frequency of B-raf mutations and this may lead to targeted therapies with anti B-raf agents.
- Tall cell papillary carcinoma is over represented in the subgroup of radioiodine resistant thyroid cancers.

TALL CELL VARIANT OF PAPILLARY THYROID CARCINOMA

KEY WORDS:

Tall cell papillary cancer, radioiodine resistance, Braf mutations,

Saturday, March 7, 2009, 8:30 PM, Boston MA
**2009 Endocrine Pathology Companion Meeting: "RECENT
ADVANCES IN THYROID NEOPLASIA"**

**POORLY DIFFERENTIATED CARCINOMA: FROM MORPHOLOGY TO
MOLECULAR DATA AND BACK.**

Mauro Papotti & Marco Volante, University of Turin, Torino, Italy

Definition and classification criteria - The term "poorly differentiated (PD) carcinoma" has been proposed twenty years ago to define a thyroglobulin-producing non-follicular, non-papillary thyroid carcinoma, having an intermediate behavior between well differentiated and anaplastic carcinomas (1-10). In the 2004 WHO classification of Endocrine Tumors (11), PD carcinomas have been introduced as a separate entity, and their recognition has been proposed on both architectural and high-grade cellular features. In fact, PD carcinomas have been defined according to both their non-follicular/non-papillary growth pattern, being trabecular/insular/solid (TIS) areas usually predominant, and their unequivocal high grade histology, with atypias, high mitotic count and necrosis. By definition, high grade variants (i.e. tall cell or columnar) of papillary carcinomas have been excluded from the PD tumor group. However, in the diagnostic practice the above mentioned criteria are still controversial and heterogeneously applied, some overlap therefore existing between other tumor categories: these include the solid variant of papillary carcinoma and well-differentiated follicular carcinomas with predominant solid/trabecular growth patterns.

A diagnostic algorithm for the diagnosis of PD carcinomas has recently been proposed, as the result of a consensus conference held in Turin, involving 12 pathologists from Japan, US, and Europe (12). An agreement was reached concerning the diagnostic criteria which were proposed as follows:

(1) presence of a solid/trabecular/insular (STI) pattern of growth in an otherwise malignant thyroid lesion. It is important to note that these different growth patterns are usually admixed in the same tumor, and to an extent not clearly settled for the diagnosis of PD carcinoma ("the majority of the tumor" is mentioned as a requirement in the WHO book) (12).

(2) absence of the conventional nuclear features of papillary carcinoma. One of the most common sources of disagreement in the diagnosis of PD carcinoma is represented by the solid variant of papillary carcinoma which is characterized by a solid/trabecular growth pattern, in the presence of the diagnostic nuclear features of papillary carcinoma. Since it has been demonstrated to bear a significantly better prognosis than PD carcinoma in the adult population (13), this tumor type should be kept separate.

(3) presence of at least one of the following features: convoluted nuclei; mitotic activity >3x10 HPF; tumor necrosis. Convoluted nuclei are defined as small round hyperchromatic nuclei with convolutions of the nuclear membrane, which are smaller and darker, with irregular ("convoluted" or "raisin-like") contours as compared to the typical nuclei of papillary carcinoma, but with only occasional grooves and loss of ground-glass appearance and pseudoinclusions. These changes are believed to reflect de-differentiation of the papillary carcinoma, with loss of many of its characteristic nuclear features, but preservation of the irregularity of nuclear contours. Concerning high grade features such as high mitotic activity and necrosis, they represent strong negative prognostic indicators in thyroid carcinoma (14,15). Therefore, the presence of at least one of those high-grade parameters was incorporated at a certain step of the proposed diagnostic algorithm. However, necrosis and mitotic activity (although present in most of the cases that were grouped as PD carcinomas) were not considered

patognomonic criteria by themselves, because they may also be recognised in otherwise well-differentiated carcinomas.

Molecular data - Since the original insular carcinoma description by Carcangiu and coworkers (3), both follicular and papillary derivations have been considered for PD carcinoma (6,8,16). To define PD carcinoma histogenesis, several molecular alterations have been investigated. TP53 mutations were described in a subset of PD carcinomas by different authors (17,18), and proposed as a molecular marker of thyroid tumor dedifferentiation and progression, despite the limited case series analysed. *Ras* point mutations were found in variable proportions of PD carcinomas and associated to prognosis, being N-*ras* mutations exclusively present in some reports (4,19) whereas K-*ras* more prevalent in others (20). Conversely, data concerning β -catenin mutations in PD carcinomas are controversial, having been detected in none (21) or in up to 32% (22) of the cases analyzed. Recent molecular evidence have shown that a link of PD carcinoma and papillary carcinoma exists, since activating BRAF mutations have been detected in a series of PD carcinomas having residual papillary carcinoma foci (23), but not in PD carcinoma cases lacking such morphological link to papillary carcinoma (24). RET/PTC1 rearrangements were also found in a small fraction of PD carcinomas having the nuclear features and/or (residual) foci of papillary carcinoma (25).

As a matter of fact, all the above mentioned molecular studies are difficult to compare due to the heterogeneous inclusion criteria. In this perspective, a collaborative study was designed with dr Y. Nikiforov (University of Pittsburg) based on a series of 63 PD carcinomas, re-classified according to the recently proposed diagnostic algorithm. *ras* point mutations were found as the exclusive molecular alteration in a subset of 23% of cases, being N-*ras* 61 codon mutation by far the most common. One single case arising from a tall cell variant of papillary carcinoma harbored a BRAF mutation. No RET/PTC or PAX8/PPAR γ rearrangements were found (*Volante, Nikiforov et al, manuscript in preparation*). Taken together, these findings and previous literature data support the hypothesis that PD carcinomas may de-differentiate from both well differentiated conventional follicular and papillary carcinomas, following a distinct molecular pathway involving *ras* molecular alterations that are alternative to the involvement of BRAF or RET/PTC for papillary carcinomas and PAX8/PPAR γ for follicular carcinomas.

Back to morphology - Molecular data are limited by the heterogeneous case series analyzed, but apparently identify *ras* alterations as the most common molecular signature in strictly re-classified PD carcinomas, depicting a peculiar molecular pathway in this tumor type as compared to well differentiated follicular and papillary carcinomas. Unfortunately, PD carcinoma of the thyroid has been heterogeneously defined and interpreted in the world. Nevertheless, large tumor series selected on the basis of structural and/or other morphological criteria showed that PD carcinomas have a distinct biological behavior, justifying the classification of these tumors into a separate group (also encompassing solid/trabecular oncocytic carcinomas). The call back to morphology is therefore meant to homogeneously classify thyroid carcinomas with poorly differentiated features, applying strict and reproducible diagnostic criteria. The recent Japanese study (26) aimed to investigate the prevalence and clinical significance of “three types of poorly differentiated carcinoma” as defined by Sakamoto (1), the WHO classification (11) and the Turin proposal (12), as well as of the tall cell variant of papillary carcinoma in a large series of thyroid cancers with papillary features, confirmed that different tumor groups are identified by the different inclusion criteria and showed that significant differences among the groups were also present in terms of survival, being cases identified according to the Turin proposal those associated to the worst survival rates.

Key words – Thyroid, poorly differentiated carcinoma, diagnostic algorithm, ras oncogene, solid insular growth.

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