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 is 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 then 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 oncogenic progression and therefore may contribute to the biologic behavior of this tumor.

From a clinical perspective the importance of recognizing tall cell variant capillary 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,