Thyroid: Oncocytic tumors

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Identity

Note

Oncocytes (from the greek word "swell"), also known as Hurthle cells, oxyphilic cells or Askanyz cells, are characterized by abundant granular cytoplasm due to aberrant accumulation of mitochondria. The cause for the mitochondria accumulation is unknown. The increased number of mitochondria may be a compensatory to intrinsic defects in the energy production machinery of the cell. Cells that fit this basic description may be identified in a variety of non-neoplastic lesions as well as in the affected tissues of patients with mitochondrial myopathies. Tumors composed of oncocytes are not restricted to the thyroid gland and may arise in a variety of locations, most commonly in the kidney and salivary gland and may be benign or malignant.

Widely invasive oncocytic thyroid carcinoma
By convention, thyroid tumors are designated as oncocytic if at least 75% of their constituent cells can be described as oncocytes. In the context of the traditional classification of differentiated thyroid tumors of follicular cell derivation into follicular and papillary histotypes, the majority of oncocytic neoplasms represent a distinct subtype of thyroid follicular tumors. Papillary carcinomas, as well as a few medullary thyroid carcinomas, may also be oncocytic but for the purpose of this brief review, "oncocytic tumors" will refer to the follicular cell derived neoplasm that lacks nuclear features of papillary carcinoma. Thyroid oncocytic tumors are neoplasms composed by a majority of cells with the morphologic features of oncocytes.

**Classification**

**Note**

Oncocytic (Hurthle cell, oxyphilic cell, askanazi cell) adenoma: transcapsular and/or vascular invasion absent.
Oncocytic (Hurthle cell, oxyphilic cell, askanazi cell) carcinoma: transcapsular and/or vascular invasion present.

**Clinics and pathology**

**Etiology**
Unknown. The precise cellular derangements that lead to the abnormal accumulation of mitochondria in oncocytes and tumor development are obscure. Alterations of nuclear genetic material (marked aneuploidy) and of mitochondrial DNA are a feature of thyroid oncocytic tumors.

**Epidemiology**
The mean age at diagnosis was 43 years for adenomas and 52 for oncocytic carcinomas in a recent series. There is a female preponderance in both subgroups, with a female-to-male ratio of 8:1 in adenomas and 2:1 in carcinomas. Thyroid oncocytic tumors represent approximately 5-10% of thyroid neoplasms.

**Clinics**
Most patients with oncocytic neoplasms are euthyroid and present with a thyroid nodule. Secondary symptoms due to compression of the adjacent structures in the neck (e.g. dysphonia, dysphagia) may be present, particularly in patients with malignant tumors.

**Pathology**
Grossly, oncocytic adenomas are encapsulated, solid nodules with a characteristic brown cut surface. Secondary changes, including infarction and hemorrhage are common (particularly after fine needle aspiration), possibly as a result of the low tolerance to ischemia displayed by the oncocytes. Histologically, the follicular growth pattern is most common but cells may also be arranged in trabecular, solid sheets or papillary formations. The colloid is typically purple (amphophilic) rather than pink on conventional histology sections stained with hematoxylin and eosin. Oncocytes have round uniform nuclei with prominent nucleoli but may display scattered areas of marked nuclear atypia and anisonucleosis. The gross appearance of a minimally invasive oncocytic carcinoma is indistinguishable to that of an adenoma, while widely invasive oncocytic carcinomas are obviously invasive macroscopically and display pervasive vascular invasion with multifocal involvement of the thyroid gland. There are no reliable cytologic features which distinguish oncocytic adenomas from carcinomas and the only criteria for a diagnosis of malignancy is the identification of transcapsular and/or vascular invasion.

**Treatment**
Oncocytic adenomas are treated with a simple lobectomy or nodulectomy, which is curative but should not be enucleated, as an evaluation of their capsule is essential for the pathologist to determine whether the tumor is benign or malignant. Carcinomas are treated with total/subtotal thyroi-dectomy followed by radioactive iodide therapy. Oncocytic carcinomas tend to have lower iodide uptake compared with non-oncocytic cancers and are often therefore less responsive to radioactive iodide administration.

**Prognosis**
The extent of tumor invasion determines the prognosis in oncocytic carcinomas. Patients with widely invasive tumors (defined as having 2 or more foci of capsular and/or vascular invasion) have a mortality of approximately 50% with median disease specific survival of 7 years. Patients with minimally invasive carcinoma have excellent prognosis with no tumor recurrences or disease related deaths reported in a recent series. Extrathyroidal extension and nodal metastases are adverse predictors of survival after multivariate analysis in widely invasive oncocytic carcinoma.

**Cytogenetics**

**Cytogenetics Morphological**
Relatively few cases of oncocytic thyroid tumors have been studied by conventional cytogenetic analysis, usually in general reports dealing with chromosomal alterations of thyroid neoplasia. 42-47 chromosomes with structural and numerical changes have been demonstrated in one oncocytic carcinoma.

**Cytogenetics Molecular**
CGH: Chromosomal DNA unbalance and aneuploidy are present in 70-80% of oncocytic thyroid neoplasms. Chromosomal DNA gains (+5, +7, +12, +17, +19, +20) are more common than losses (-2, -9). Although aneuploidy is a feature of both oncocytic adenomas and carcinomas, sequential acquisition of numerical chromosomal changes (possibly beginning with trisomy 7) appears associated with tumor progression. Carcinomas tend to have more chromosomal gains and losses than adenomas and a statistical association has been demonstrated between the degree of aneuploidy and loss of differentiation, extent of tumor invasion, and recurrence.

**Genes involved and proteins**

**Note**
**Nuclear genes and proteins:** ATP production appears defective in oncocytic thyroid tumors but no specific alterations have been demonstrated in the nuclear genes which code for most of the proteins involved in the mitochondrial oxidative phosphorylation process or which control mtDNA replication. RAS mutations (frequently observed in follicular adenomas and carcinomas) and PAX8/9 rearrangement (frequently
observed in follicular carcinomas) are uncommon in oncocytic neo-plasms. A gene predisposing to the familial development of oncocytic thyroid neoplasms has been mapped at 19p13.2

**Mitochondrial DNA (mtDNA) and proteins:** The "common" mitochondrial DNA (mtDNA) deletion is a 4977 bp deletion frequently present in a variety of ageing human tissues. This deletion has been identified in 100% of oncocytic thyroid tumors but only at low level and in 20-30% of the non neoplastic thyroid parenchyma surrounding the tumor. Not only the prevalence but also the amount of the common mtDNA deletion is statistically higher in oncocytic thyroid tumors compared with non oncocytic ones. The proportion of mtDNA harbouring the common deletion appears to be higher in oncocytic carcinomas compared with oncocytic adenomas. Oncocytic tumors (benign or malignant) have a higher prevalence of mutations in the non coding displacement-loop (D-loop) region of their mtDNA compared with non oncocytic tumors. Although mutations have been identified in the coding portions of the mtDNA, these mutations do not appear different from those observed in thyroid tumors lacking oncocytic features. No specific alterations have been identified in the mtDNA genes coding for the components of the oxidative phosphorylation process.

**References**


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