Thyroid: Anaplastic (undifferentiated) carcinoma

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Identity

Note: Anaplastic (undifferentiated) carcinoma of the thyroid gland is a highly malignant tumor composed in part or wholly by undifferentiated malignant cells.

Clinics and pathology

Epidemiology

Anaplastic (undifferentiated) carcinoma of the thyroid gland is uncommon, accounting for less than 5% of all cases of thyroid carcinoma. The average age at diagnosis was 66.5 years, with a female to male ratio of 3.1:1 in one study of 70 cases.

Clinics

Most patients are euthyroid with a history of a rapidly enlarging neck mass. Sometimes, the tumor presents as a new-onset thyroid enlargement in a patient with longstanding thyroid nodule(s) or as the recurrence of a well-differentiated thyroid carcinoma. Tumor infiltration of surrounding structures results in secondary symptoms (dyspnea, dysphonia, dysphagia).

Pathology

Tumors are poorly defined, fleshy masses with areas of necrosis and hemorrhage. Microscopically they are composed of anaplastic cells with marked cytologic atypia and high mitotic activity. Tumor necrosis and vascular invasion are common. About one-third of cases of anaplastic thyroid carcinoma (ATC) have coexisting areas of well-differentiated thyroid carcinoma, supporting the hypothesis that ATC arises from well-differentiated thyroid carcinoma. Histologic patterns include spindle, giant and squamous cell types. Other patterns (e.g. angiomatoid, carcinosarcoma, lymphoepithelioma-like, adenosquamous) have been described. Undifferentiated (anaplastic) carcinoma of the thyroid must be differentiated from other high grade tumors with similar microscopic appearance originating from adjacent structures in the neck (e.g. larynx). Sometimes this distinction is only possible on clinical/anatomical grounds. Immunohistochemically, undifferentiated thyroid carcinoma is generally negative for thyroglobulin and calcitonin. Pankeratin and epithelial membrane antigen (EMA) are positive in about one-half and one-third of cases respectively. Vimentin is positive in about 90%, and epithelial membrane antigen is positive in about 30% of cases. Thyroid transcription factor-1 (TTF-1) staining is present in 0-50% of cases. Although immunostaining is negative for muscle-specific actin, Factor VIII-related antigen, and desmin, these markers can differentiate ATC from some soft tissue sarcomas with which they can be confused.

Treatment

No effective treatment modalities are currently available. A few patients with resectable disease have been reported to have long-term survival with aggressive multimodal therapy that included surgery, radiation, and chemotherapy. Current clinical practice emphasizes the use of multimodal therapy to achieve local disease control and stabilization of airway patency. Radiotherapy may be hyperfractionated and in combination with chemotherapy. Chemotherapy is usually doxorubicin-based or taxane-based combinations. Preclinical studies using human ATC
Anaplastic (undifferentiated) thyroid carcinoma is a highly malignant tumor composed of undifferentiated malignant cells. The inset in the left lower corner shows a magnified view of a cell in metaphase of mitosis.

cell lines show promise that new effective combinations including novel drugs will be found in the future.

**Prognosis**

Anaplastic (undifferentiated) carcinomas are highly aggressive neoplasms that are usually widely invasive at presentation. Regional and distant metastases are common, and about 75% of patients have distant metastasis in the course of their disease. Most patients die within 1 year of the diagnosis with a median survival of 3 to 6 months. The 5-year survival rate is around 5%, and the surviving cases are typically small tumors confined to the thyroid amenable to local resection.

**Cytogenetics**

**Cytogenetics morphological**

Anaplastic (undifferentiated) carcinoma represents not only morphologically but also in terms of somatic genetic alterations the extreme malignant form of thyroid cancer and as such it is characterized by complex chromosomal alterations. DNA aneuploidy is present in over 65% of the tumors.

**Cytogenetics molecular**

LOH: Allelic loss has been identified at 1q (40%), 9p (58%), 11p (33%), 11q (33%), 17p (44%), 17q (43%), 19p (36%), 22q (38%).

CGH: DNA unbalance can be demonstrated at a variety of chromosomal loci in 80% of undifferentiated carcinomas with a median number of chromosomal losses or gains of 10 per case with abnormal CGH profile. Gains were more common than DNA losses. Loss of chromosomal DNA was identified at 1p, 2q, 4q, 5q, 6q, 8p, 13q, 22q. Specific chromosomal DNA alterations (i.e. 3p13-14+, 5q11-31+, 11q13+) may be associated with the transition from more differentiated phenotypes to ATC.

CGH shows frequent gain of 20q, including the UBCH10 gene in 20q13.12, which may also be associated with progression of differentiated thyroid cancers to ATC.

Using microarray-based CGH with further fluorescence in situ hybridization (FISH) analysis, the MAP kinase phosphatase-8 (DUSP26) gene, which codes for a phosphatase that inhibits p38-mediated apoptosis, is shown to be amplified in ATC.
**Genes involved and Proteins**

**Note:** The genetic mechanisms involved with the development of anaplastic thyroid cancer are complex. Mutational inactivation of p53 has been identified in 70-80% of anaplastic carcinomas while H-Ras, K-Ras, or N-Ras activating mutations are present in approximately 50% of the cases. BRAF V600E mutation is found in 20% to 25% of cases. PTEN mutations are present in 6%. PIK3CA kinase domain mutations are found in 14%. PIK3CA gene copy amplification is present in 39%.

Aberrant Wnt/beta-Catenin signaling appears to be a distinctive feature of ATC since stabilizing mutations and/or aberrant beta-Catenin nuclear localization are present in 80% of ATC, beta-Catenin nuclear localization is accompanied by its cellular redistribution with marked decrease of the beta-Catenin membrane bound fraction.

ATC are characterized by increased cell replication and high Ki67/Mib1 proliferation index. Such is often associated with increased expression of Cyclin D1 and over-expression of Cyclin D1 can also be associated with poor differentiation of thyroid tumors. Aberrant Wnt/beta-Catenin signaling appears to be a distinctive feature of ATC since stabilizing mutations and/or aberrant beta-Catenin nuclear localization are present in 80% of ATC. beta-Catenin nuclear localization is accompanied by its cellular redistribution with marked decrease of the beta-Catenin membrane bound fraction.

Immunohistochemical staining of a tissue microarray of ATC showed the following: beta-catenin (positive in 41% of the cases), aurora A (41%), cyclin D1 over-expression and conversely by a fall in the CDK inhibitor p27. Transmembrane protein 34 (TMEM34) is down-regulated in ATC. It is not clear whether these changes represent the cause or (more likely) the effect of dysregulated cell differentiation and growth in ATC.

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