Clear Cell Follicular Adenoma of the Thyroid: A Case Report
Torill Sauer, M.D., F.I.A.C., and Reidar Olsholt, M.D., Ph.D.

A case of clear cell follicular adenoma of the thyroid is presented. The patient presented with a single, hyperactive nodule in the right lobe. The cytologic features include cellular smears with numerous disrupted cells and a granular background. The cytoplasm was abundant, pale grayblue vacuolated or granulated, but not clear. Thyreoglobulin was demonstrated both histologically and ultrastructurally, confirming the follicular-cell derivation of the tumor. Ultrastructurally, the cytoplasm was filled with empty, membrane bound vacuoles. The clear cell change might represent an artifact of formalin fixation and/or the paraffin embedding procedure. Diagn Cytopathol 1996;15:124-126.

Key Words: Clear cell; Thyroid; FNAC

Follicular lesions are common findings when investigating thyroid nodules by fine-needle aspiration cytology (FNAC). Histologically they may represent a cellular nodule in a goiter, a follicular adenoma, or a carcinoma. Several variants exist as to growth pattern (follicular, trabecular, solid) and cell types (common, oxyphilic, and clear cell type).

Clear cell changes of the cytoplasm may occur in areas of both follicular and papillary tumors, but pure clear cell differentiation is unusual. Chronic TSH overstimulation has been suggested as a cause for this change due to hypertrophy and dilation of mitochondria or hypertrophy of the Golgi apparatuses.

Accumulation of glycogen, lipid, and thyroglobulin has also been described. Other clear cell tumors such as metastatic renal cell cancer, parathyroid tumors and hyperplasias, and clear cell variant of medullary carcinoma may mimic a primary follicular-derived tumor, both cytologically and histologically, and demonstration of intracellular thyroglobulin is essential for diagnosis.

We present a case of clear cell follicular adenoma of the thyroid and demonstrate the cytologic features of this tumor.

Clinical History
A 47-yr-old female presented at the ENT outpatient clinic of Ullevaal Hospital with an asymptomatic, palpable nodule in the right thyroid lobe. The lesion was aspirated. The cytologic findings were consistent with a follicular tumor.

A scintigramm (using the isotope 99mTc-pertecnetat) of the thyroid revealed an enlarged right lobe with a hyperactive nodule occupying most of the lobe. The surrounding thyroid tissue and the left lobe was partly suppressed. The patient had normal thyroid function with FT4 and TSH within normal range.

Because the cytologic diagnosis was consistent with a neoplasm, a right thyroidectomy was performed. Histology showed a clear cell follicular adenoma. Follow-up has been uneventful.

Cytologic Findings
The smears were cellular with partly disrupted cells, numerous naked nuclei, and a finely granular background. Sheets and follicular clusters were loosely cohesive with occasional overlapping of nuclei (Fig. 1). Stromal fragments containing branching blood vessels and attached epithelial cells were seen. Nuclei were uniformly round and 2-3X the size of an erythrocyte. The chromatin structure was homogenous. A single, round and medium-sized nucleolus was apparent. The cytoplasm was abundant, pale grayblue, with different sized vacuoles in the Giemsa-stained smears and finely granulated in the Papanicolaou-stained smears (Fig. 2). Colloid material was not seen. Based on these findings, a primary diagnosis of follicular tumor of the thyroid was given.

Histologic Findings
Thyroidectomy specimen revealed a 2.2 cm diameter tumor. A thin rim of compressed, normal thyroid tissue
surrounded the lesion. The tumor was well circumscribed with a smooth, thin capsule and a rather soft consistency. The cut surface was pale brown and homogeneous. Microscopically the pattern was mostly solid, but with areas of follicular growth. The cells were large with a clear cytoplasm (Fig. 3). There was no evidence of vascular or capsular invasion. The tumor cells stained positive for intracytoplasmic thyroglobulin (Fig. 4) (APAAP method with a fast red substrate).

Ultrastructurally, the cells were dominated by closely lying, membrane bound, empty vacuoles (Fig. 5). Neuroendocrine granules were not found. EM immunostaining for thyroglobulin showed positivity in moderate electron-dense globules of the common follicular cell type. Acinic structures containing colloid revealed thyroglobulin positive granules within the colloid (Fig. 6).

Fig. 1. Loosely cohesive epithelial cell clusters; abortive follicular structure (arrowheads) and fragile cytoplasm (PAP stain; magnification ×250).

Fig. 2. Finely vacuolated cytoplasm (Giemsa stain; magnification ×500).

Fig. 3. Mainly follicular growth pattern; abundant clear cytoplasm (H&E stain; magnification ×250).

Fig. 4. Positive cytoplasmic staining for thyroglobulin (APAAP stain with fast red substrate; magnification ×250).

Fig. 5. Ultrastructural empty membrane bound cytoplasmic vacuole; in between normal appearing mitochondria (magnification ×5,700).
Fig. 6. Thyroglobulin positivity within colloidal material in a follicular lumen (magnification \( \times 9,100 \); EM immunostaining with colloidal gold).

Discussion

Cytomorphologically this lesion was a follicular tumor, and except for the consistency of the cytoplasm, was reminiscent of an oxyphilic cell variant. Instead of the dense, granulated cytoplasm of oxyphilic cells, the cytoplasm was pale granulated or vacuolated. These features are the same as reported by Jayaram\(^7\) in two cases of clear cell follicular carcinomas. Here also, the cytoplasm was vacuolated and not clear. The clear cell appearance of histologic specimens might therefore represent an artifact of formalin fixation and/or the paraffin embedding procedure.

Ultrastructurally, empty vacuoles were found, consistent with degenerative changes. The specific nature of the vacuoles could thus not be established. Glycogen or lipid accumulation was not present. Thyroglobulin was demonstrated both histologically and ultrastructurally, though not accumulated. In addition, the scintigraphic finding of a hyperactive nodule, confirmed the follicular-derived origin of the tumor cells.

Parathyroid lesions, medullary carcinoma of the thyroid, and metastatic renal cell carcinoma may all present with a dominant clear cell pattern. They may show several cytologic characteristics reminiscent of follicular thyroid lesions, such as microfollicular pattern, colloid-like structures and tissue fragments with branching vessels. Usually they have a much coarser and irregular nuclear chromatin pattern,\(^8-11\) but demonstration of thyroglobulin is essential in order to differentiate a follicular cell derived tumor from these lesions. This might mainly represent a problem in histologic specimens, though, as the clear cell changes are not appreciated in cytologic smears.

Acknowledgments

The authors are grateful to Dr. Fredrik Skjøtten for supplying the ultrastructural pictures, and Dr. Vibeke Engh for reviewing the manuscript.

References