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Lipid-Rich Follicular Carcinoma of the Thyroid in a Patient with McCune-Albright Syndrome

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A 41-year-old woman with McCune-Albright syndrome and a 2-cm thyroid nodule of ten years' duration presented for fine-needle aspiration, which yielded vacuolated clear cells with granular chromatin in pseudopapillary arrangement. The resected tumor showed 90% clear cells and 10% non-clear cells with capsular and vascular invasion. The cytoplasmic vacuoles in the clear cells were 3+ for oil red O stain in touch imprint cytology. Immunohistochemistry demonstrated thyroglobulin positivity in the nonclear neoplastic cells, whereas most of the clear cells were negative. Ultrastructural study demonstrated the gradual transition from protein synthesis to lipid synthesis as the neoplastic cells progressed from nonclear to clear. The study suggested that the lipid accumulation resulted from the uncontrolled fatty acid synthesis in the neoplastic cells rather than metaplasia. The karyotype of the tumor cells was normal, 46XX. Literature of lipid-rich thyroid neoplasms were reviewed.

KEY WORDS: Clear cell neoplasm, Cytology, Electron microscopy, McCune-Albright syndrome.

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In normal thyroid, oil red O stain for fat in adenolipomatosis has been reported to be positive in up to 50% of thyroid glands (1). This finding differs from lipid-rich cell neoplasms in which the abundant lipid droplets are localized intracytoplasmically (2). This entity is extremely rare; none of the 38 cases of clear cell thyroid neoplasms in the classic study of Carcangiu *et al.* (3) or the 17 fat-containing thyroid lesions found in the files of the Armed Forces Institute of Pathology (4) were lipid-rich cell

neoplasm. Such tumors have been documented only six times in Europe—three adenomas (5, 6, 7) and three carcinomas (8).

Lipid-rich cell neoplasms belong to the "clear cell tumor" category of thyroid neoplasms (9, 10, 11). According to Carcangiu *et al.* (3), clear cell change in thyroid neoplasms can be attributed to vesicle formation from massively dilated mitochondria or to the accumulation of intracytoplasmic substances, including glycogen, thyroglobulin, mucin, and lipid. Of the clear cell thyroid neoplasms, lipid-rich cell neoplasm is perhaps the rarest. The first case, involving a 2-cm lipid-rich follicular adenoma (an incidental autopsy finding) was reported from Germany in 1984 by Schröder *et al.* (5), who subsequently reviewed files of thyroid lesions over a 20-year period. Among 446 patients, there were three lipid-rich cell carcinomas of the thyroid, two follicular carcinomas, and one papillary carcinoma (8). Additional cases of lipid-rich cell follicular adenoma were reported by Tóth *et al.* from Hungary (6) and Ranaldi *et al.* from Italy (7). Table 1 summarizes the literature.

Clinical History

The patient was a 41-year-old white woman with McCune-Albright syndrome (MAS). She had symptoms of precocious puberty, café-au-lait spots, polyostotic fibrous dysplasia, and recurrent ovarian cysts. Fibrous dysplasia involving the skull and facial bones resulted in optic and acoustic nerve compression and chronic, severe head and facial bone pain. At age 31, she developed hypercholesterolemia and hypertriglyceridemia from membranous nephropathy. At age 34, she had a hysterectomy for atypical complex hyperplasia of the endometrium.

A thyroid nodule located at the middle of right lobe was initially noted in 1988 (patient age 31). A I^{123} radionuclide scan revealed slightly elevated uptake in a heterogeneous pattern. L-thyroxine ther-

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TABLE 1. Reported Cases of Lipid-Rich Neoplasm of the Thyroid

Source Year From	Schröder 1984 Germany	Schröder 1985	Schröder 1985	Schröder 1985	Toth 1990 Hungary	Ranaldi 1993 Italy	Current Case 1999 United States
Age/Sex	64 M	53 F	58 F	47 F	62 M	68 M	41 F
Size	2 cm	Not Reported	Not Reported	Not Reported	2 cm	1.3 cm	2.1 × 1.4 × 1.5 cm
Color	Pale grey (autopsy specimen)	Not Reported	Not Reported	Not Reported	Yellow-red	Yellow with red center	Yellow
Histology	Follicular adenoma.	Follicular carcinoma	Follicular carcinoma	Papillary carcinoma (but no clear nuclei)	Follicular adenoma	Follicular adenoma	Follicular carcinoma
Growth Pattern	Solid microfollicles (small foci)	Vacuolated clear cells	Vacuolated clear cells	Papillary	Small follicles	Cords Microfollicles Small follicles	*Solid small follicles, pseudopapillary
Cytology	Vacuolated clear cells	Vacuolated clear cells	Vacuolated clear cells	Oxyphil clear cells (Lipid at apex, mitochondria at basal location)	Vacuolated clear cells	Vacuolated clear cells	Vacuolated clear cells
Proposed Mechanism	Lipid metaplasia				Altered lipid metabolism not storage (different triglycerides)		Uncontrolled cytosolic fatty acid synthesis
Rest of Thyroid	Normal sized follicles				Nodular hyperplasia	Anaplastic carcinoma	
Other Disease	Disseminated rectal carcinoma	No metastasis or recurrence in 21 yrs	Vacuolated clear cells in lung & skin metastasis. Regress after surgery				McCune-Albright syndrome

M, male; F, female.

* Predominant growth pattern.

apy was initiated and continued for nine years. In 1995, a fine needle aspiration biopsy of the nodule was suggestive of a colloid nodule; however, cellularity was scant. As monitored by ultrasound, the nodule increased in size from 1.4 × 1.2 × 0.9 cm to 2.1 × 1.4 × 1.5 cm in three years. In 1998, the nodule was aspirated again, but this time the needle was guided by ultrasound and a cytopathologist was on-site for immediate assessment (12). A presumptive diagnosis of clear cell follicular neoplasm was made on cytology. The patient underwent a right lobectomy and isthmectomy two months later. Frozen section showed an encapsulated clear cell neoplasm. However, when the entire tumor was examined, vascular and capsular invasion were present. A completion thyroidectomy was done four days later. An I¹³¹ body scan six weeks after surgery was negative for functioning metastatic disease.

Cytologic Findings

All aspiration smears obtained from a 27-gauge needle were air-dried and immediately examined following Diff-Quik stain (Baxter Healthcare, Miami, FL) and Ultrafast Papanicolaou stain (Richard-Allan Scientific, Kalamazoo, MI) (13). The former stain showed pseudopapillary fragments of loosely cohesive vacuolated clear cells with enlarged (two to four times red blood cell size), round to oval nuclei in a background of scanty thin colloid. Within the same tissue fragment, the number of vacuoles ranged from none to numerous and the sizes of the vacuoles ranged from barely visible to almost the size of red blood cells, as illustrated in Figure 1A. The latter stain (Fig. 1B) revealed finely granular chromatin with and one to two small irregularly shaped nucleoli. Occasional vague nuclear grooves were present, but "orphan Annie eyed" clear nuclei (14) were absent.

Gross and Histologic Findings

The cut surface revealed a yellow, glistening tumor measuring 1.2 cm in diameter (Fig. 1C). Touch imprint cytology was 3+ positive for oil red O stain (Fig. 1D). The tumor was partially encapsulated with a major solid nest pattern composed of clear cells and minor follicular and pseudopapillary patterns composed of nonclear cells. Thick fibrous bands encircled the clear cells (Fig. 1, E-F), which are interspersed by occasional colloid-filled follicles composed of nonclear neoplastic cells (Fig. 1G). The clear cells and the nonclear cells shared the same nuclear features, hence the nonclear cells were considered neoplastic rather than entrapped normal follicular cells. In addition, there were small foci of pseudopapillary pat-

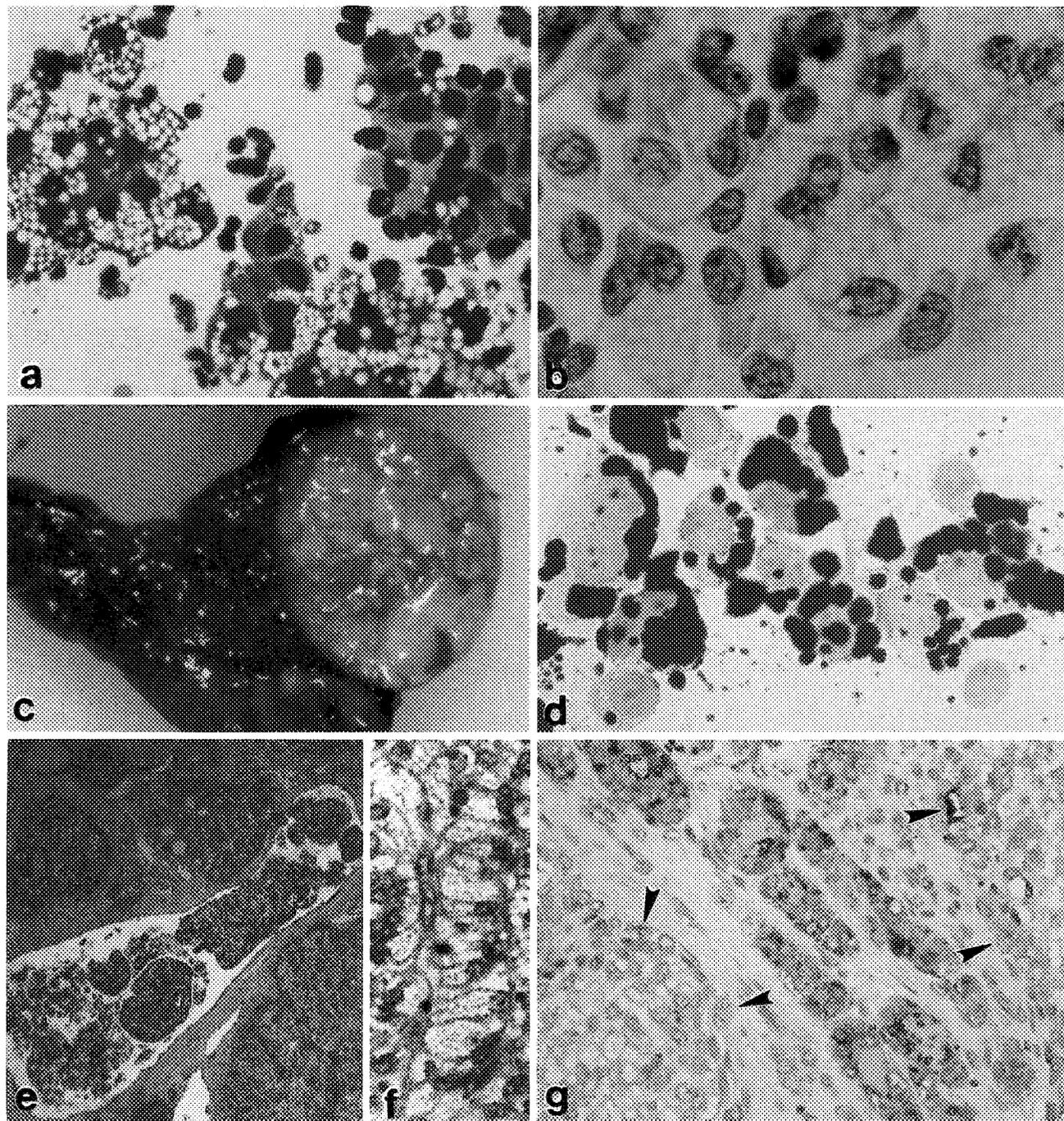


FIGURE 1. Composite photograph of lipid-rich cell carcinoma of the thyroid. **A**, the transition from lipid-poor neoplastic cells (*right*) to lipid-rich clear neoplastic cells (*left*) was seen in fine needle aspiration cytology. Barely visible minute lipid droplets are present in the cell in the middle of the photograph. (Diff-Quik stain; original magnification, 400 \times). **B**, neoplastic cells with round to oval nuclei with granular chromatin and one to two small nucleoli are observed in cytology. Their cytoplasm contains variable sized and a variable number of vacuoles. Occasional cytoplasmic vacuoles indent the nuclei. (Ultrafast Papanicolaou stain; original magnification, 1000 \times). **C**, sharply demarcated yellow glistening lobulated tumor, measuring 1.2 cm in diameter, bulging from the cut surface of the thyroid (gross photograph, 3.3 \times). **D**, intracytoplasmic lipid droplets ranging from barely visible to the size of red blood cells are demonstrated on the touch imprint cytology (oil red O stain; original magnification, 1000 \times). **E**, tissue section showing vascular invasion and predominantly solid growth pattern separated by thick fibrous bands. (hematoxylin and eosin stain; original magnification, 56 \times). **F**, close-up of the solid area show vacuolated clear tumor cells with round granular nuclei and lipid-filled cytoplasm (400 \times). **G**, thyroglobulin is expressed in the colloid-filled follicles composed of nonclear neoplastic cells, which are mainly present at the periphery of the solid nests of vacuolated clear cells. Only focal thyroglobulin positivity (*arrow*) is found at the periphery of solid nests of the lipid-rich clear cells, which comprised over 90% of the resected tumor. (Avidin-Biotin complex immunoperoxidase; original magnification, 100 \times).

tern, with a single layer of smooth contoured, peripheral, nonclear, columnar cells covering two to three layers of vacuolated clear cells wrapped along a core of small-caliber blood vessel. Extensive vascular (Fig.

1E) and capsular invasion was present, whereas a lymph node in the surgical specimen was negative for tumor. The remaining thyroid gland showed nodular hyperplasia.

Immunohistochemical Findings

The nonclear neoplastic cells were positive for thyroglobulin (DAKO, Carpinteria, CA; 1:50 dilution), whereas the clear cells were mostly negative for thyroglobulin, which was expressed only focally and faintly at the periphery of the clear cell nests (Fig. 1G, arrows). Negative immunostains performed included calcitonin, chromogranin, and synaptophysin.

Ultrastructural Findings

A neoplastic cell with minimal lipid droplets is shown in Figure 2A. The cytoplasm had numerous ribosomes and rough endoplasmic reticulum containing flocculent material, Golgi apparatus, mitochondria, and a few lysosomes. Some of the ribosomes were displaced from hydrophilic cytoplasmic space into lipid droplets (Fig. 2B). The fully-developed neoplastic clear cells were filled with lipid droplets,

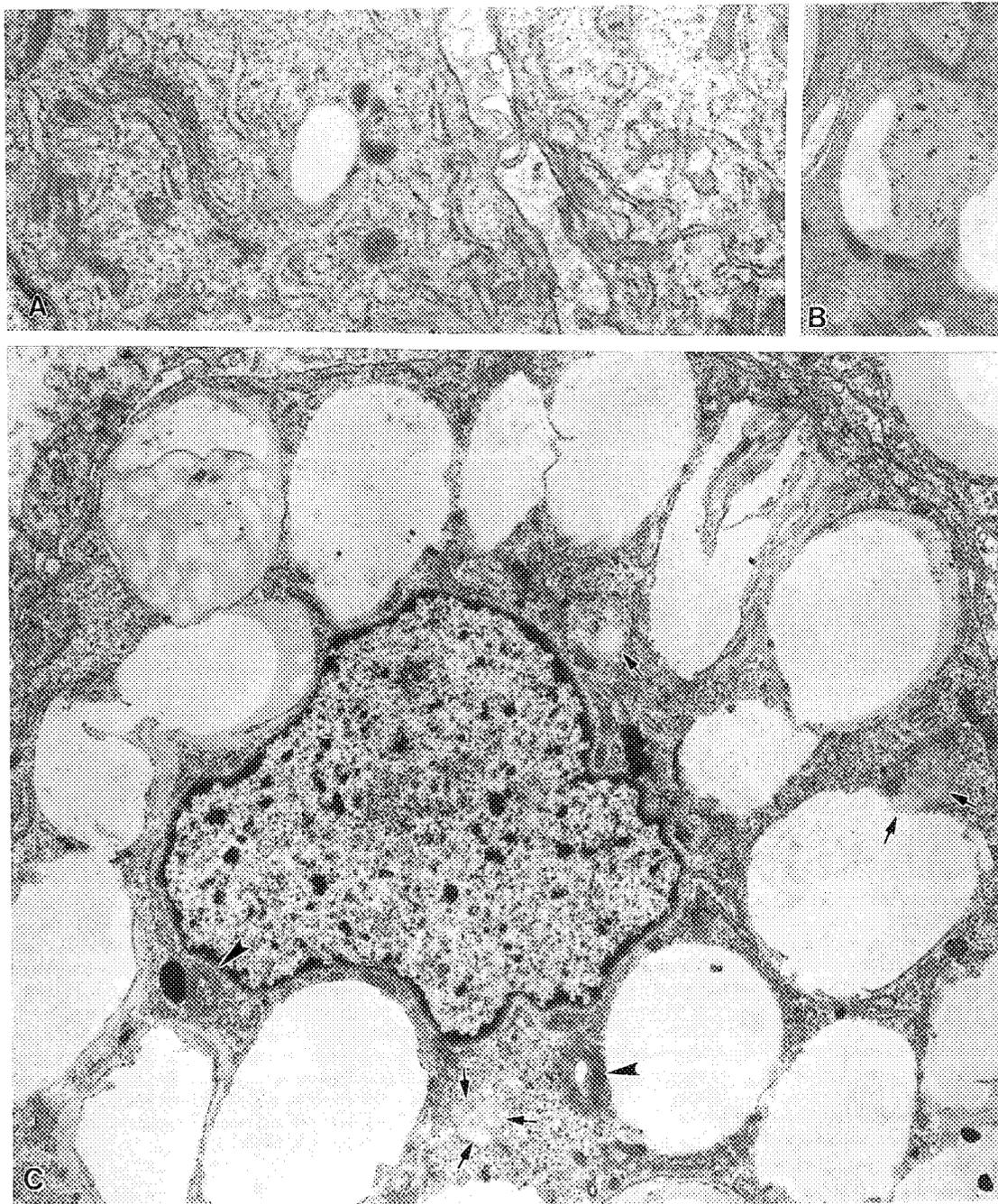


FIGURE 2. Electron photomicrographs of lipid-rich carcinoma of thyroid. **A**, neoplastic cell with rare lipid droplet has cytoplasm filled with ribosomes, rough endoplasmic reticulum containing flocculent material, and well-developed Golgi apparatus (original magnification, 15,750 \times). **B**, ribosomes are displaced from hydrophilic cytoplasmic space into a lipid droplet (original magnification, 10,000 \times). **C**, this neoplastic cell contains numerous lipid droplets, some of which coalesce. **Arrowheads** point to two compressed Golgi apparatus. **Small arrows** point to areas suggestive of cytosolic fatty acid synthesis before the formation of lipid droplets (original magnification, 10,000 \times).

which displaced other organelles into smaller cytoplasmic space and compressed Golgi apparatus (Fig. 2C, arrowheads). Areas suggestive of cytosolic fatty acid synthesis, before the formation of lipid droplets, were observed (Fig. 2C, small arrows).

Cytogenetic Findings

A diploid nucleus with normal karyotype with $46 \times X$ was found in the lipid-rich carcinoma of the thyroid.

DISCUSSION

During the on-site assessment, once the clear cells were aspirated, the possibility of metastasis from an occult renal primary was briefly considered and then dismissed. Although renal cell carcinoma cells may also contain lipid, the droplets are barely visible and typically have prominent nucleolus. Because the aspiration was guided by ultrasound, the presence of colloid was a significant finding. Clinically, the thyroid nodule had been developing for ten years, and it would be unlikely for renal cell carcinoma to remain silent this long. Histologically, the differential diagnosis of clear cell tumors included primary follicular-derived tumor, the rare clear cell medullary carcinoma, a parathyroid tumor, and metastatic renal cell carcinoma (9, 10). The positive thyroglobulin immunostain and negative calcitonin, chromogranin, and synaptophysin immunostains ruled out those possibilities.

Schröder *et al.* (5) hypothesized that metaplastic transformation of neoplastic cells was responsible for lipid-rich thyroid adenoma. By demonstrating the quantitative and qualitative differences among the triglycerides in lipid-rich thyroid adenoma, normal thyroid, and adipose tissue via chromatography, Tóth *et al.* (6) proposed altered intracellular lipid metabolism as the mechanism.

Our ultrastructural findings suggested that the neoplastic cells were actively synthesizing lipid, which displaced the organelles for thyroglobulin synthesis. It is known that fatty acid synthesis occurs in cytosol via acetyl CoA carboxylase. In lipid-rich neoplastic cells, this fatty acid synthetic pathway, for unknown reasons, was activated and out of control. The ultrastructural evidence of gradual transition from neoplastic cells filled with organelles known for protein synthesis to lipid-rich neoplastic cells, with these organelles squeezed into minimal space, suggested that the thyroglobulin synthesis was shut down, in part, due to the replacement of hydrophilic space by hydrophobic lipid droplets. Because sparse intracytoplasmic lipid droplets were reported as occurring in aging normal follicular cells (15), the increased lipid droplets in the neoplastic cells should be termed "change" rather than "metaplasia" as proposed by Schröder *et al.* (5).

The presence of MAS adds an interesting element to this case. Nodular or diffuse goiter with or without hyperthyroidism is the second most common endocrinopathy found in patients with MAS, but thyroid neoplasms have not been previously documented (16).

In summary, we report a case of lipid-rich clear cell follicular carcinoma of the thyroid in a woman with McCune-Albright syndrome initially evaluated by fine needle aspiration cytology and confirmed histopathologically. This is the seventh reported case of lipid-rich thyroid neoplasm and the fourth reported case of lipid-rich thyroid carcinoma. We believe the intracytoplasmic lipid accumulation resulted from the up-regulation of fatty acid synthesis in the neoplastic cells.

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