Poorly differentiated ("insular") carcinoma of the thyroid gland
- Two cases report -

Poorly differentiated("insular") carcinoma of the thyroid shares insular, trabecular, and solid histological patterns that are different from those of papillary, follicular, medullary, and anaplastic varieties. This tumor is situated morphologically and biologically in the intermediate position between the well differentiated (papillary and follicular) and the totally undifferentiated (anaplastic) thyroid tumors. We report two cases of insular carcinoma of the thyroid, occurring in 39-year-old and 52-year-old women. Grossly, these cases showed a lobulated mass with fibrous septa. The histologic finding showed characteristic "insular" growth pattern with focal follicular or papillary areas. Thyroglobulin was demonstrated within cytoplasmic paranuclear vacuoles of the neoplastic cells. Calcitonin and amyloid were not demonstrated. The aspiration cytology showed high cellularity, low grade of atypia, presence of clusters, nests, and trabeculae of cells with poorly outlined cytoplasm. The ultrastructural finding showed primordial cells having cytoplasmic organelles such as rough endoplasmic reticulum, mitochondria, and free ribosomes. We believe that its separation from other types of thyroid carcinoma will lead to a more accurate estimate of its biologic behavior and a more appropriate therapeutic approach.

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Key Words : *Poorly differentiated carcinoma, Thyroid, Insular carcinoma*

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INTRODUCTION

Poorly differentiated ("insular") carcinoma is a rare, but distinctive, aggressive, and often lethal type of thyroid tumors composed of uniform cells in a characteristic insular architectural pattern. It is situated, morphologically and biologically, in the intermediate position between the well-differentiated (papillary and follicular) and the totally undifferentiated (anaplastic) thyroid tumors (1, 2). It was described originally by Langhans in 1907 under the term "wuchernde struma" and characterized by locally aggressive behavior and a typical architectural pattern with formation of large, round or oval nests of tumor cells (hence the term "insular" carcinoma). Herein we report two cases of insular carcinoma of the thyroid with cytologic, immunohistochemical, and ultrastructural findings with review of literature.

CASE REPORT

CASE 1. A 39-year-old woman was admitted to the hospital because of a palpable anterior neck mass mainly confined to the left side. The neck mass was found 20 years ago as a small palpable nodule. This mass had rapidly increased in size since 4 years ago. There was no history of radiation exposure.

On admission, physical examination revealed a huge anterior neck mass which was mainly confined to the left side of the thyroid. She had hypertension and complained a tingling sensation of left upper extremity and easy fatigue. Besides these complaints she appeared to be healthy. The laboratory data, including thyroid function tests, serum calcium and phosphate levels, were all within normal limits. An ultrasonograph revealed a markedly enlarged, heterogeneous thyroid gland with multiple nodules, suggestive of a multinodular goiter. A computed tomographic scan showed a large thyroid mass with severe tracheal deviation. Focal necrotic areas were noted. There was an enlarged perithyroidal lymph node considered to be nodal metastasis. Total thyroidectomy was done.

The left lobe of the thyroid was completely replaced to a huge pale-tan multilobulated solid mass with fish flesh appearance, measuring $12 \times 10 \times 6$cm in dimensions and weighing 400gm (Fig. 1a). The right lobe showed varying sized multiple nodules without infiltration of the tumor. Microscopic sections showed multiple foci of well

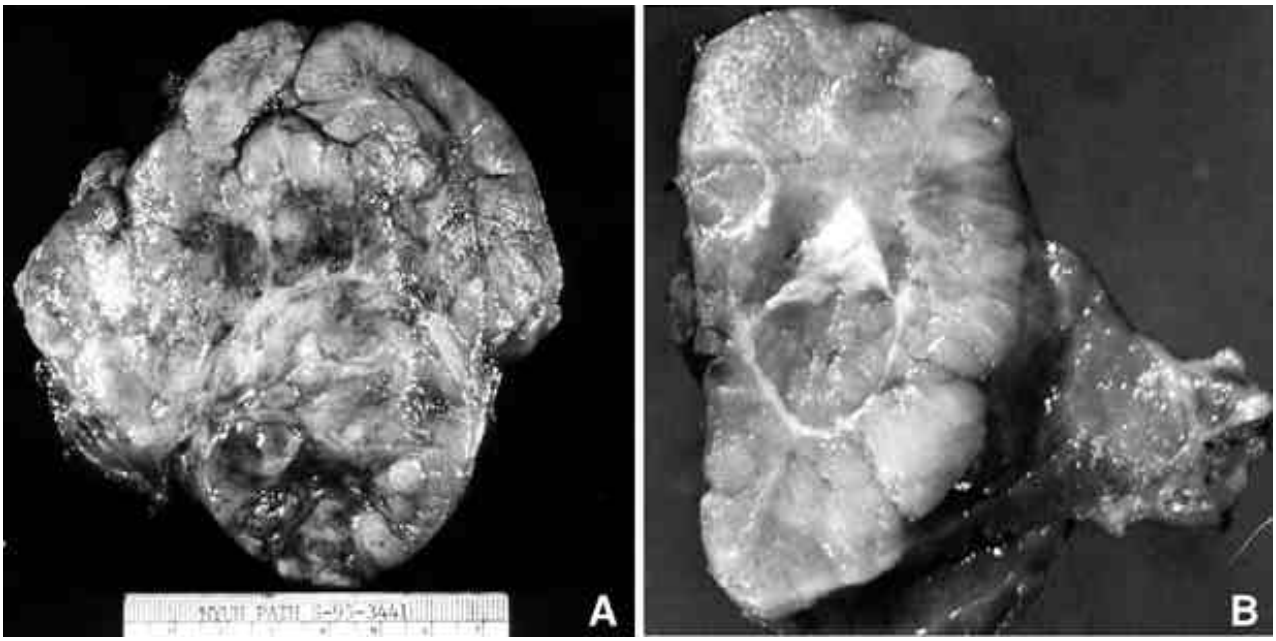

Fig. 1. The left thyroid was completely replaced by a huge pale-tan multilobulated solid mass with fish flesh cut surface(A). The right thyroid was nearly replaced by a lobulated tumor mass with a tan-brown solid cut surface(B).

defined nests and trabeculae composed of round or oval monotonous small cells with round nuclei and moderate amount of cytoplasm. There were areas of follicle formation. The round to oval tumor cell nests were separated by fine fibrovascular septae and artifactually created clefts. Within the nests, a microfollicular pattern was apparent. Mitotic figures were rarely encountered. There were necrosis and invasive foci of tumor cells in the blood vessels, lymphatics, and surrounding soft tissue. The residual thyroid tissue at the periphery of the tumor mass showed severe fibrosis and nonspecific thyroiditis. An adjacent lymph node showed metastatic carcinoma with an insular pattern. Immunohistochemically, thyroglobulin was demonstrated in the neoplastic cells, especially within cytoplasmic paranuclear vacuoles. Immunoreactivity for calcitonin was negative and Congo-red staining for amyloid was also negative.

On review of the aspiration cytology, the neoplastic cells were singly dispersed or arranged in small clusters and trabeculae showing some nuclear overlapping and microfollicular structures with scanty colloid (Fig. 2a). The background was bloody but no definitive tumor diathesis including necrotic cell debris was seen. Most of the cells were relatively uniform in size and shape with scanty cytoplasm. They showed mild pleomorphism and nuclear atypia, including nuclear enlargement and hyperchromasia. Nucleoli were inconspicuous. Rare mitotic figures were observed.

Electron microscopic study revealed relatively uniform tumor cells arranged in sheets or trabeculae, surrounded by thin collagenous stroma. Small luminal spaces contained thin colloid materials in which numerous microvilli are embedded. The cytoplasm contained abundant cytoplasmic organelles such as mitochondria, periluminal primary and secondary lysosomes, rough endoplasmic reticulum and free ribosomes. The tumor cells were connected by junctional complexes. The nuclei were uniform round and heterochromatic with marginal condensation. Some nuclei showed indentation or deep invagination with small prominent nucleoli (Fig. 3a).

CASE 2. A 52-year-old woman presented with a palpable mass in the right anterior neck. The mass had been progressively increasing in size during the recent six months. There was no history of prior radiation exposure. Physical examination revealed a painless movable mass in the right anterior neck. Thyroid function tests, serum calcium and phosphate levels were all within normal limits. An ultrasonograph revealed an enlarged heterogeneous nodule in the right thyroid gland and small multiple hypoechoic nodules in the left thyroid gland, consistent with a multinodular goiter. A radioiodine scan showed a large, hypofunctioning nodule, deforming the right thyroid. Total thyroidectomy was done.

The right lobe of the thyroid gland was nearly replaced by a lobulated tumor mass with a tan-brown solid cut surface without area of necrosis, measuring $4 \times 2.5 \times 2$cm in dimensions and 55gm in weight (Fig. 1b). The left lobe showed a vague nodular configuration. Microscopic section showed typical insular pattern or trabeculae

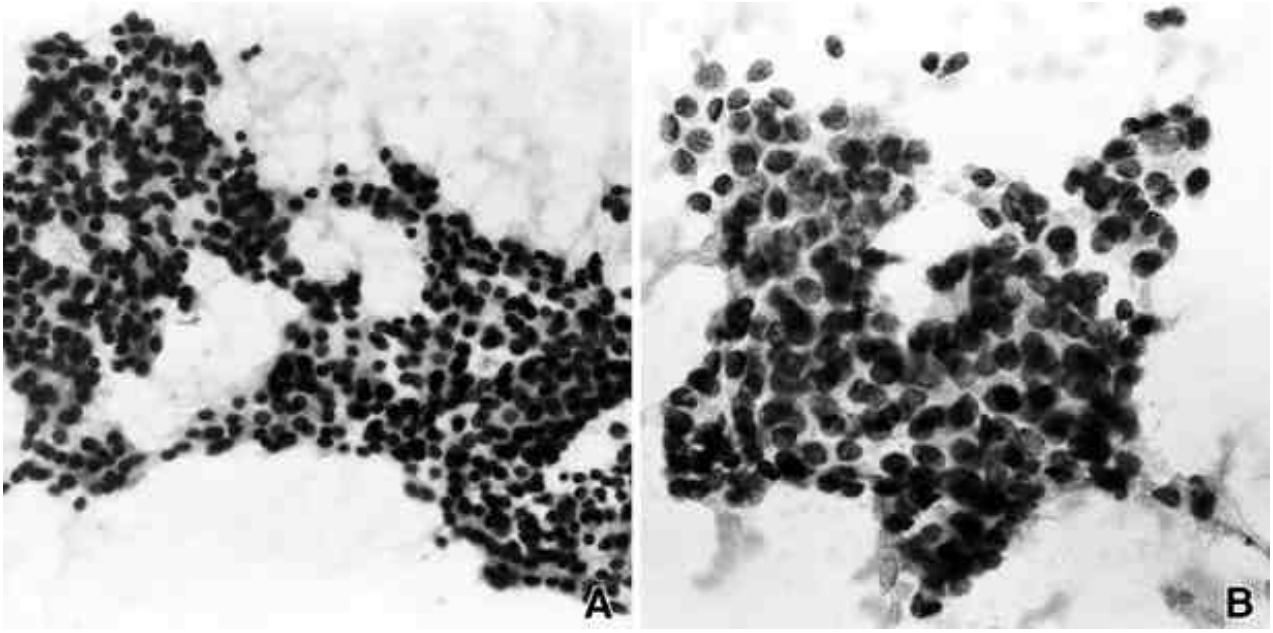

Fig. 2. The aspiration cytology showed the neoplastic cells arranged in clusters and trabeculae with microfollicular structures and scanty colloid (A : H&E, ×200). A cluster of tumor cells arranged in the insular pattern was seen. Vague microfollicular structures, fine ground glass chromatin, and nuclear grooves were noted (B : H&E, ×400).

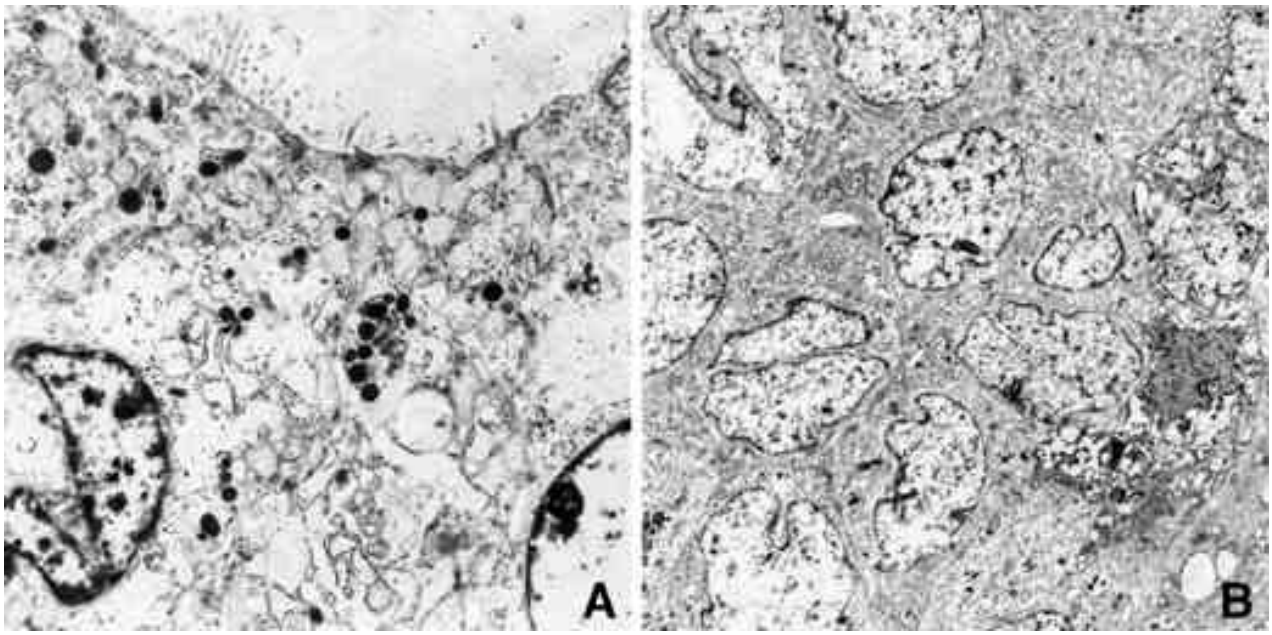

Fig. 3. Electron micrograph showed a small luminal space with numerous microvilli. The tumor cells were connected by junctional complexes (A : Original magnification, ×6,000). A solid arrangement of tumor cells were seen. Nuclear indentation and pseudoinclusion were noted (B : Original magnification, ×2,500).

of round or oval monotonous cells with round nuclei and scanty cytoplasm (Fig. 4). The tumor nests were separated by fine fibrovascular septae and clefts. The nuclei were mildly pleomorphic. Intranuclear cytolplasmic pseudoinclusions were inconspicuous. Mitotic figures were rare. Focal areas of fibrosis and calcification were also present. The tumor invaded blood vessels and lymphatics. But there was no metastasis in a perithyroidal lymph

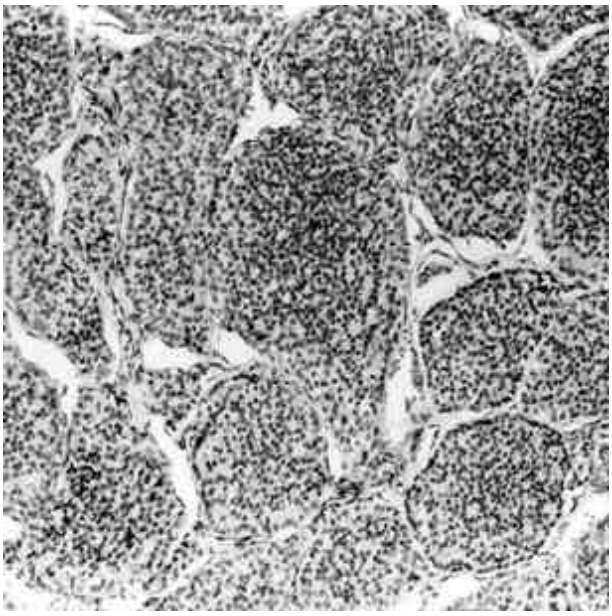

Fig. 4. Microscopic section showed a typical insular pattern of round or oval monotonous cells with round nuclei and scanty cytoplasm (H&E, x100).

node. The adjacent thyroid tissue showed features of lymphocytic thyroiditis, characterized by prominent lymphocytic infiltration with focal germinal center formation. Immunohistochemically, thyroglobulin was demonstrated in the neoplastic cells. Immunoreactivity for calcitonin and Congo-red staining for amyloid were negative.

The aspiration cytology revealed a few singly dispersed or cellular clusters of tumor cells arranged in the insular pattern. Microfollicular structures were noted at the periphery of tumor clusters. Most of the tumor cells were fairly uniform with scanty cytoplasm. Fine "ground glass" chromatin and occasional nuclear grooves were noted. Nucleoli were not prominent (Fig. 2b).

Ultrastructural study revealed solid or trabecular arrangement of uniform round cells. The tumor cells were joined by cell junctions and surrounded by well formed basement membrane. The cytoplasm possessed mitochondria, periluminal lysosomes, rough endoplasmic reticulums, free ribosomes, and focally aggregated glycogen particles. The nuclei had heterochromatin and an inconspicuous nucleolus. Nuclear indentation and pseudoinclusions were demonstrated (Fig. 3b).

DISCUSSION

Insular carcinoma of the thyroid is a relatively new histologic type of thyroid carcinoma, derived from follicular epithelium (3~6). In 1984, Carcangiu et al.(1) pointed out the worse prognosis of insular carcinoma than that of well differentiated carcinoma, such as papillary and follicular, but the better prognosis than that of anaplastic carcinoma. They first used the term insular thyroid carcinoma to emphasize the most characteristic histologic features of this neoplasm. The first description and illustration of this tumor were published in 1907 by Langhans, who described 16 cases of thyroid carcinoma using the term "wuchernde struma" (proliferating stroma). This lesion was characterized by a distinct nesting pattern, uniform cells and a "peritheliomatous" arrangement of the nests (1). These are now recognized by the World Health Organization as "uncommon poorly differentiated tumors with distinctive architectural features... associated with a worse prognosis" (7).

The age of patients with insular carcinoma of the thyroid at the time of initial diagnosis ranges from 34 to 76 years; the mean age is 55.7 years. The male : female ratio is 1 : 2.1-2.5. Twenty percent of the patients have distant metastases at initial examination (1, 8). The tumors measure from 1.5 to 11cm (mean, 5.9cm) and are growing in single nodule or multiple, firm, whitish nodules with irregular infiltrating margins within the thyroid parenchyme (9). In our cases, the patients' mean age was 45.5 years and both were female. There was lymph nodal metastasis in one patient. In our cases, one case was a lobulated, firm, tan-white mass, measuring 12 $\times$10$\times$6cm in dimensions, with irregular infiltrating margin. The other case was a solid tan-brown mass with lobulated appearance, measuring 4.0$\times$2.5$\times$2.0cm.

Microscopically, insular carcinomas are characterized by the formation of large or small, well defined nests (insulae) of tumor cells. These are round or oval, of generally smooth, but sometimes geographic outlines, often sharply separated from the surrounding areas by artifactually created clefts. The predominant pattern of growth is solid, but microfollicles are also commonly encountered, some of which contain dense colloid. The neoplastic cells are relatively small and monomorphous with only focal pleomorphism. The cells have a scant amount of eosinophilic cytoplasm and nuclei with smooth-to-slightly-irregular nuclear membranes, clumped chromatin, and inconspicuous nucleoli. Mitoses are present but in variable numbers. The pattern of growth is characteristically infiltrative. Foci of necrosis are frequent. The small necrotic foci tend to be located in the center of the insulae, whereas the larger ones are seen to spare the insulae situated around blood vessels, thus leading to a peritheliomatous appearance (1, 9, 10). Immunohistochemically, the tumor cells are positive for keratin and thyroglobulin. There is no staining with calcitonin or carcinoembryonic antigen. These immuno-

logic findings are supportive of a neoplasm arising from follicular epithelial cells and are inconsistent with medullary carcinoma - a neoplasm usually included in the differential diagnosis (11). In our cases, all histologic and immunohistochemical findings are compatible with those of insular carcinoma.

The cytologic features of insular carcinoma are not widely recognized, but some consistent findings were seen (2, 5). According to our experience and the literature, the main cytologic features are high cellularity, low grade of atypia, presence of clusters, nests, and trabeculae of cells showing microfollicular pattern and poorly outlined cytoplasm. It is important to define the cytologic criteria of insular carinoma of thyroid in order to recognize it preoperatively and plan aggressive surgery without respect to the extension.

On electron microscopic examination, the tumor cells have abundant cytoplasm with rough endoplasmic reticulum, numerous mitochondria and free ribosomes. Dense granular materials corresponding to thyroglobulin are observed in the lumina of microfollicles as well as in paranuclear globules in the tumor cells. The nuclei are round with homogeneously dispersed chromatin (9). In our cases, both the immunohistochemical staining and electron microscopic findings were supportive to confirm the follicular epithelial origin of this tumor.

Recently, Ashfag et al.(8) reported papillary and follicular carcinoma with focal or predominant insular component. They concluded that insular component within papillary and follicular carcinoma does not adversely affect the prognosis. They suggested that the worse prognosis in the series of Carcangiu et al.(1) may be related to the late presentation of disease rather than actual aggressive behavior. In our opinion, the separation of insular carcinoma from the other types of thyroid carcinoma would be needed for a more accurate estimate of its prognosis and more appropriate therapeutic approach.

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