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Poorly Differentiated Carcinoma of the Thyroid Retrospective Clinical and Morphologic Evaluation

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Five thyroid carcinomas showing clinically aggressive biologic behavior were retrospectively reviewed to evaluate the possible presence of morphologic differences from conventional thyroid carcinomas. They were originally diagnosed as follicular carcinomas, medullary carcinoma, papillary carcinoma, and mixed papillary and medullary carcinoma. There were three males and two females. The age at the time of initial diagnosis ranged from 36 years to 67 years (mean 56 years). The size of the tumor varied from 4.5cm to 10cm (mean diameter 7cm). One patient died of brain metastasis four years after the initial therapy and the other four patients are still alive with local recurrences and/or metastases to bone, spinal cord, lung, and buttock. Histologically these lesions are categorized into two different groups: insular variant and columnar cell variant. Insular variant was characterized by well-defined nests (insulae) that are composed of small, uniform cells, frequent tumor necrosis, and hyalinization of the stroma. Columnar cell variant was characterized by tall columnar cells with marked nuclear statification. All five cases stained positively for thyroglobulin and negatively for calcitonin. With the above clinical and histopathological findings, we interpreted these lesions as a poorly differentiated carcinoma, biologically in an intermediate position between well differentiated and anaplastic carcinomas. The rapid and often fatal outcome associated with these variants of poorly differentiated carcinoma warrants aggressive treatment at the time of diagnosis.

Key Words: *Thyroid gland tumor, Poorly differentiated carcinoma, Insular variant, Columar cell variant*

INTRODUCTION

Except for the carcinomas of C-cell origin, malignant tumors of the thyroid follicular cells have traditionally viewed as either the well differentiated type composed of papillary and follicular carcinoma or the anaplastic type. Although vast majority of patients with well differentiated carcinoma have an excellent prognosis regardless of the types of treatment used, there are a few patients who exhibit rapid and fatal outcome despite proper treatment.

There is growing evidence for the existence of a group of tumors that fall in between well differentated and undifferentiated carcinoma, both in terms of morphologic appearance and in biologic behavior (Langhans, 1907; Sakamoto et al., 1983; Carcangiu et al., 1984; Rosai et al., 1985; Evans, 1986; Flynn et al., 1988; Sobrinho-Simoes et al., 1988).

This report describes five cases of thyroid carcinoma which have recently been reexamined and revised

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as poorly differentiated carcinoma.

In this report, we reemphasize the previous authors' opinion that this type of lesion be classified as a separate entity and carries worse biologic behavior compared to the conventional well differentiated carcinoma of the thyroid.

MATERIALS AND METHODS

Five cases of thyroid carcinomas experienced at Seoul National University Hospital during the period of five years from 1984 to 1988, which had unusal behaviors in terms of patterns of metastasis and survival time were retrospectively reexamined to find out differential points between these unusual cases and other conventional well differentiated carcinomas.

Four of these cases (cases 1, 2, 3, and 5) were reexamined because the patients had a very unusual clinical course for either a follicular carcinoma or papillary carcinoma. Case 4 was originally diagnosed as medullary carcinoma, which was revised after careful histopathological analysis including congo red stain and immunohistochemical stain.

In addition to routine histopathologic analyses, immunohistochemical studies using anti-thyroglobulin and anti-calcitonin antibodies were done to clarify the characteristics of cells or origin. Immunohistochemical studies were performed on 5μm thick formalin-fixed paraffin embedded tissue sections using the biotin-streptavidin method. The sections were incubated overnight in humid chamber with the primary antibody (polyclonal goat antirabbit antibody to thyroglobulin and calcitonin) followed by incubation with linking antibody (biotinylated goat anti-rabbit immunoglobulin) and labeling with peroxidase conjugated streptavidin.

CLINICAL SUMMARY

As shown in table 1, there were three males and two females. Patient's age at the time of initial diagnosis ranged from 38 years to 67 years. None of the patient had a history of exposure to radiation or chemicals.

All five patients initially presented with a neck mass of 10 to 28 years of duration, and one of them (case 1) had multiple bone metastases at the initial presentation. Initial therapeutic approach to these lesions consisted of total thyroidectomy supplemented with either radioiodine therapy or neck irradiation, subtotal thyroidectomy with or without radioiodine therapy, and lobectomy with isthmectomy.

All five patients developed recurrent or metastatic disease in the following sites,; residual thyroid or soft tissues of the neck (5 cases), cervical lymph nodes (3 cases), bone (3 cases), central nervous system (2 cases), lung (1 case), and buttock (1 case). One patient who developed brain metastasis died of the disease four years after initial therapy and the other four patients have been alive but with disease at the time of the last follow up (5, 2, 10, and 3 years after initial therapy).

Gross Features

These neoplasms were poorly encapsulated but rather well circumscribed from the adjacent thyroid tissue. These measured 4.5cm to 10cm in greatest diameter and the cut surfaces showed multilobulated yellow-gray appearance.

Microscopic Features

Light microscopic appearances of these tumors were categorized into two distinct groups; insular variant (3 cases) and columnar cell variant (2 cases).

As shown in table 2, the outstanding morphologic feature of the "insular variant" of poorly differentiated thyroid carcinoma was the well defined nests of tumor cells forming "insulae" (Fig. 1). These nests often had a geographic configuration, which were surrounded by a thin rim of hyalinized collagen and occasionally were separated from this fibrous framework by an artifactual cleft (Fig. 2). Diffuse sheet-like pattern, trabecu-

Table. 1. Clinical Summary

Case	Age/Sex	Duration (year)	Size (cm)	Local recurrence	Distant metastasis	Outcome (yr. passed after initial Tx.)
Case 1	63/M	15	6×3×3	+	Bone, Spinal cord	Alive with disease (5)
Case 2	60/F	25	10×5×3	+	Brain	Dead of disease (4)
Case 3	67/F	28	7×2×1	+	—	Alive with disease (2)
Case 4	63/F	10	4.5×3×2	+	Buttock, Bone	Alive with disease (10)
Case 5	38/M	Unknown	Unknown	+	Lung, Bone	Alive with disease (3)

Table 2.

Histopathologic Criteria of Poorly Differentiated "Insular" Carcinoma
insular/trabecular pattern
small size and uniformity of tumor cells
tumor necrosis
hyalinization of the stroma
peritheliomatous pattern

Table 3

Histopathologic Criteria of Poorly Differentiated "Columnar Cell" Carcinoma
thin fibrovascular stalks
tall columnar epithelium
nuclear stratification
absence of ground glass nuclei/psammoma bodies
high mitotic index

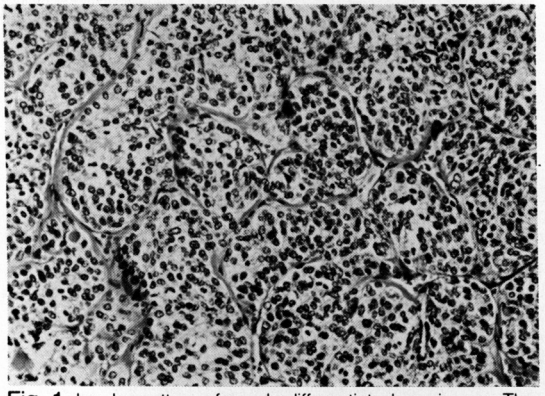

Fig. 1. Insular pattern of poorly differentiated carcinoma. The nests are predominantly solid (H & E, ×200).

lar (Fig. 3) or festoon-like configuration were present as a less constant feature. Small, round haphazardly distributed follicles indicating follicular differentiation were also present. In general, the neoplastic cells were relatively small and monotonous with little pleomorphism (Fig. 2). Mitotic figures were variable, but consistently found. Also identified in all three cases was tumor necrosis. In the areas of extensive necrosis, it appeared to spare the perivascular areas, resulting in a peritheliomatous pattern (Fig. 4). Angioinvasion was seen in one case.

As shown in table 3, the "columnar cell variant" of poorly differentiated thyroid carcinoma was characterized by a predominantly papillary growth pattern

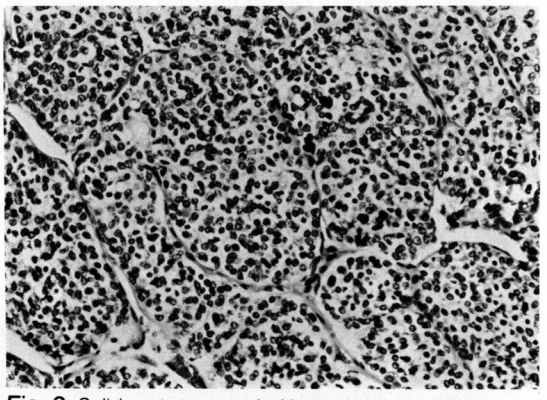

Fig. 2. Solid nests surrounded by artifactual clefts. Note the monotonous appearance with little pleomorphism (H & E, ×200).

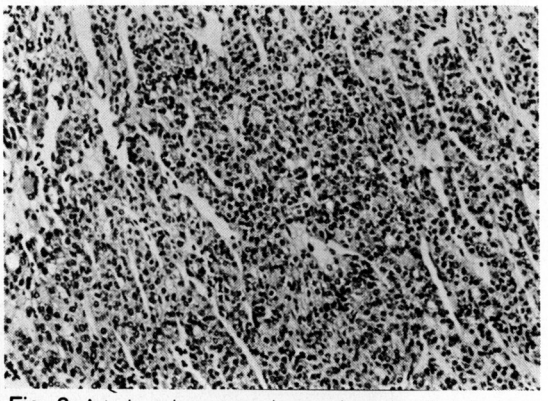

Fig. 3. A trabecular pattern is prominent in this field (H & E, ×200).

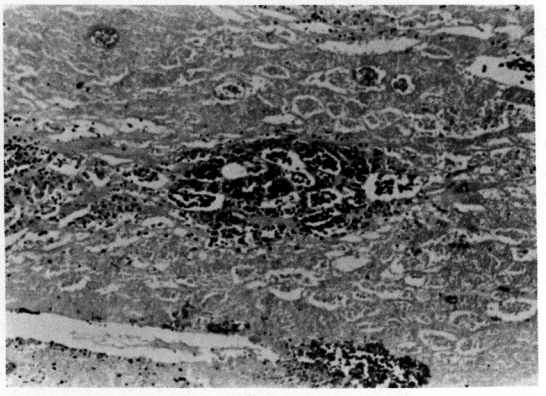

Fig. 4. Extensive necrosis resulting in a peritheliomatous pattern (H & E, ×200).

with tall columnar epithelium which showed marked nuclear stratification and frequent mitotic figures (Fig.

5). Even if the tumor cells had papillary structure, they lacked the characteristic histologic features of papillary carcinoma; crowded ground glass nuclei, intranuclear cytoplasmic inclusion, and psammoma bodies. In one case, there were small foci of solid sheets of spindle cells (Fig. 6). Capsular invasion was seen in both cases of the columnar cell variant.

All five cases were stained positively for thyroglobulin and negatively for calcitonin (Fig. 7A & 7B).

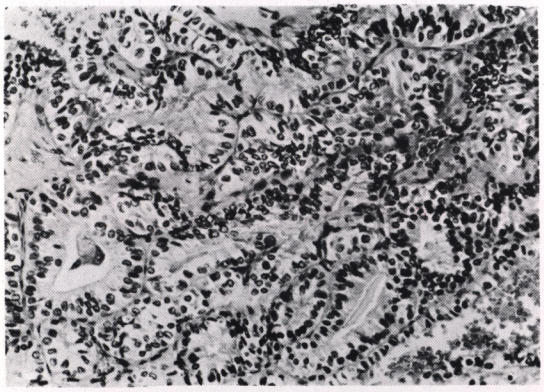

Fig. 5. Columnar cell variant of poorly differentiated carcinoma showing papillary architecture, tall columnar cells, and marked nuclear stratification (H & E, ×200).

DISCUSSION

Histopathologic grading of the well differentiated carcinomas of the thyroid has been of limited value in a small percentage of patients who will have an aggressive clinical course. The capsular and vascular invasion is a well known indicator for poor prognosis in follicular carcinoma (Lang et al., 1986). It is, however, not so easy to evaluate the presence of capsular or vascular invasion precisely in a reproducible way even

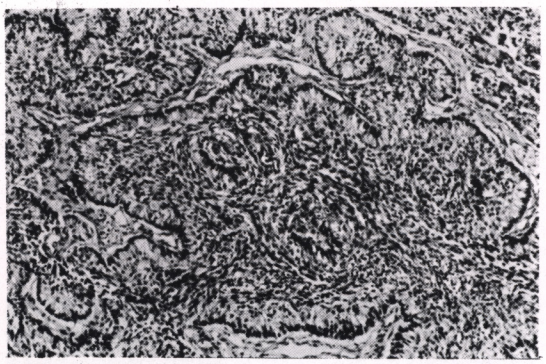

Fig. 6. Solid spindle-cell zone in columnar cell carcinoma (H & E, ×100).

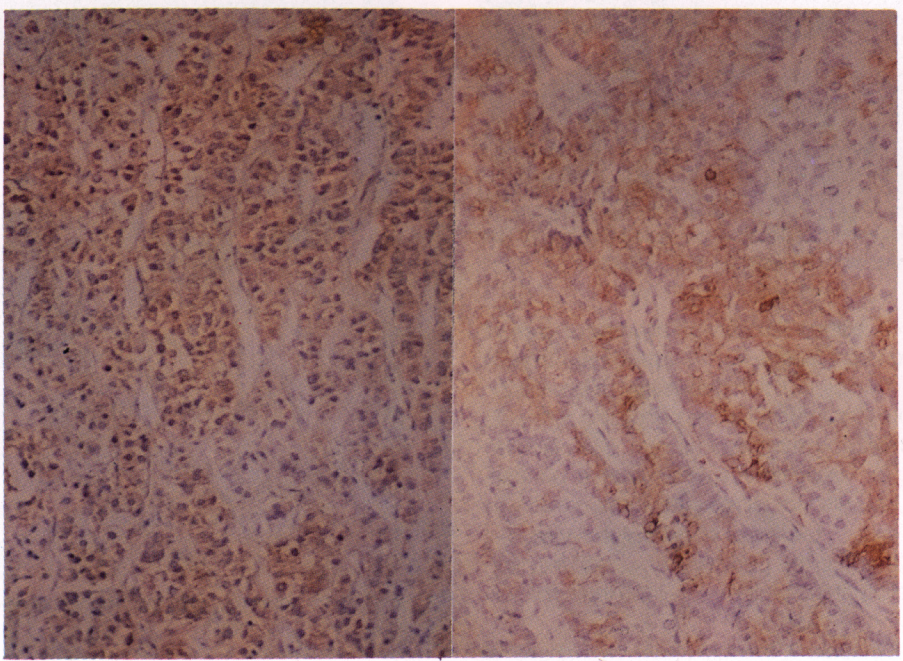

Fig. 7. Positive thyroglobulin stain in cytoplasm of tumor cells in insular variant (A, ×200) and columnar cell variant (B, ×200) of poorly differentiated carcinoma.

by the expert in thyroid pathology.

Instead, a few clinical parameters such as age, sex, tumor size, and initial extent of disease appear to be clinically more practical and valuable (Cady et al., 1985; Simpson et al., 1987). Present report deals with two histopathologic variants of poorly differentiated thyroid carcinoma situated morphologially and biologically in an intermediate position between the well differentiated and the undifferentiated carcinomas.

Carcangiu et al., (1984), who recently reported their experience of 25 patients with differentiated "insular" thyroid carcinoma, noted that this tumor probably was recognized in 1907 by Langhans (1907), who referred to it as "Wuchernde struma"; a proliferating thyroid neoplasm characterized by a striking nesting pattern, formation of small follicular lumina leading to a cribriform configuration, small size and uniformity of the neoplastic cells, and "peritheliomatous" arrangement of the tumor nests. The histologic features of the neoplasm are distinctive and quite uniform. Typically, the neoplasm is composed of large well defined nests of tumor cells that are reminiscent those of carcinoid tumors. The nests are round or oval, but sometimes geographic outlines, and are often sharply separated from the surrounding stroma by artifactually created clefts. They are composed of diffuse sheets of small and relatively monotonous cells. Another characteristic feature is the presence of necrosis, which occasionally results in a viable perivascular component imparting a peritheliomatous appearance. Mitotic figures are variable, but consistently present. In the series of Carcangiu et al, there were eight men and 17 women with an age ranged from 36 years to 76 years (mean, 55.7 years). All but two of the patients initially presented with the complaint of a thyroid mass, and the remaining two presented with bone metastases (pelvis and skull). The initial surgical treatment of the thyroid gland included total or near total thyroidectomy (20 patients), nodulectomy or lobectomy (4 patients), and incisional biopsy (1 patient). Five of the patients had clinical or radiologic evidences of metastasis at initial presentation. Only four of their 25 patients were found to be alive and free of thyroid disease at the time of last follow up (3, 6, 7, and 7 years after initial surgery) and the remaining 21 patients had recurrent or metastatic disease. Flynn et al. (1988) also reported four cases of poorly differentiated "insular" carcinoma of thyroid gland. In their series, all patients were women, with an age ranged from 27 years to 71 years. All except one patient (who initially presented with dysphagia) presented with neck mass. After subtoal to total thyroidectomy, three of the four patients have experienced local recurrence and all three patients have died as a result of their carcinoma within two years of diagnosis. The remaining patient was alive without evidence of disease one year after total thyroidectomy. A similar aggressive course was noted in our series, although the numbers of the cases were too small to be statistically significant. All three patients experienced local recurrences and two patients had distant metastasis (bone and spinal cord, and brain). One patient who had brain metastasis died of metastatic disease four years after initial operation.

The histologically distinctive carcinoma in all of these series exhibited very high rates of recurrence, metastases and mortality. This is the the reason why we think tumors of this type to be treated by a different protocol from that of conventional well differentiated thyroid carcinomas.

Neoplasia with similar features have been previously described (Meissner and Warren, 1969; Hedinger, 1974). For instances, Doniach (1978) described an "overtly invasive" type of follicular carcinoma characterized by a few follicles in the background of a predominantly solid pattern with numerous mitotic figures, and foci of necrosis; at the clinical level, this tumor had a tendency to local recurrence, and metastasized to lymph nodes, bones, and lungs. Franssila (1975) described a "solid subtype" of follicular carcinoma, composed of solid islets with partial follicular differentiation. Cabanne et al. (1974) divided their follicular carcinomas into a well-differentiated and a moderately or less differentiated (trabecular) type. Similarly, some so-called small cell undifferentiated caricinomas of the thyroid with "compact" architectures probably would be this insular carcinomas. Distinction from medullary carcinomas must not be a problem, because immunohistochemical studies of insular carcinoma reveal a positive reaction for thyroglobulin and negative reactions for calcitonin and carcinoembryonic antigen. Although areas of ordinary well differentiated carcinoma were associated in all of our cases, the larger part of the neoplasm were composed histologically of insular carcinoma.

Recently, Sakamoto et al. (1983) had proposed a very similar suggestion under the category of "poorly differentiated" thyroid carcinoma. However, their criteria for the diagnosis of this tumor were different from ours. They placed all the follicular or papillary carcinomas which exhibited solid, trabecular or scrrihous patterns in the "poorly differentiated" category. Therefore, in addition to insular carcinoma, there might be other histologic variants of thyroid carcinoma, which behave in a more aggressive fashion than typical well-differentiated follicular or papillary carcinoma.

One of these variants is "columnar cell carcinoma".

Evans (1986) reported two cases of "columnar cell carcinoma" in 34 and 47 year old male patients who died of tumor within two years of initial thyroid surgery. Since the clinical behavior did not ally with either papillary carcinoma or follicular carcinoma, he considered the columnar cell carcinoma as a separate type of thyroid carcinoma with a propensity toward an aggressive behavior. SobrinhoSimoes et al. (1988) had reported a similar case in a 60-year-old man who died of widespread metastases 5.5 years after the initial treatment. In our cases, both patients are alive but with multiple local recurrences and distant metastases despite adequate therapy. We agree with Evans (1986) and Sobrinho-Simoes et al. (1988) that this "columnar-cell variant"of poorly differentiated carcinoma is different from the "tall-cell variant" of papillary carcinoma described by Hawk and Hazard (1976), Tscholl-Ducommun and Hedinger (1982), and Johnson et al. (1988) which was characterized by a population of neoplastic cells having a height at least two times the width in an otherwise typical papillary carcinoma. The present cases, now called "columnar cell variant" of poorly differentiated carcinoma, do not fullfill the general criteria for a papillary carcinoma (large deeply grooved and pale nuclei, one cell layer, and psammoma bodies), and the patterns of metastasis and clinical behavior are also very unusual for a papillary carcinoma in general and should be regarded as an aggressive type of thyroid carcinoma.

In summary, these two types of lesions are better to be classified into poorly differentiated carcinomas and should be treated more aggressively.

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