Four Biopsy Cases of Medullary Carcinoma of the Thyroid Gland

Chotatsu TSUKAYAMA, Takako IWATA and Yoshimi YAMASHITA

First Department of Pathology, Yamaguchi University School of Medicine, Ube, Japan.

(Received March 3, 1977)

INTRODUCTION

Medullary carcinoma of the thyroid gland is sometimes associated with pheochromocytoma[1-4], Recklinghausen's disease[5], carcinoid-like syndrome[6-8] and also rarely with Cushing like syndrome[9]. Despite high incidence of regional lymph node metastasis, the tumor grows slowly and the patients with medullary carcinoma have usually a good prognosis by surgical treatment.

Microscopically, the tumor cells often form solid alveolar structures or represent sheet like growth. One of the most well-known characteristics is the presence of the amyloid substance in the stroma. However, all medullary carcinoma is not always associated with an amyloid deposition. Some investigators have demonstrated the argyrophilic granules in the cytoplasm of the tumor cells, emphasizing a diagnostic importance of them in medullary carcinoma[10,11].

We have experienced four cases of medullary carcinoma of the thyroid gland recently. One of them, lacking stromal amyloid deposition, showed a large quantity of granules in the cytoplasm as revealed by Grimelius staining. The others disclosed both the granules and amyloid in the stroma. Two of them were sisters and had a familial form. One of them, a younger sister, was associated with unilateral pheochromocytoma.

CASE REPORTS

Case 1. A 44 year-old woman had noticed a mass on the right cervical region without any previous symptom for 20 years. In December, 1975, an egg-sized tumor of the thyroid with elastic soft consistency was excised. It was clearly demarcated from the surrounding tissue (Fig. 6). Parathyroid glands were normal in size. She is now well without any

sign of recurrence. No obvious change of the serum electrolyte and B.M.R. have been observed after the operation.

Case 2. A 45 year-old man had noticed a painless nodule on the submandibular region since March, 1973. A nodule was removed and a diagnosis of metastatic cancer was made in August, 1973. Further physical examination after admission revealed an iron hard mass on the right lobe of the thyroid and other similar hard nodules around it. Thyroidectomy of the right lobe with excision of the surrounding lymph nodes was performed. Parathyroid glands were normal in size. He is now well although he has slight hoarseness after the operation.

Case 3. A 23 year-old female noticed a painless tumor on the right cervical region since December, 1975. Physical examination revealed the elastic hard and smooth-surfaced nodule in the right lobe of the thyroid gland. A thyroid scan demonstrated a circumscribed nodule 2 cm in diameter. Thyroidectomy with removal of swollen paratracheal lymph nodes was performed in August, 1976. After the operation a circumscribed tumor 0.5 mm in diameter in the left lobe of the thyroid was found, and the additional lobectomy on the left side was performed at the end of August, 1976.

This patient received adrenalectomy on the left in September, 1975, and histological examination disclosed pheochromocytoma.

Case 4. A 28 year-old female, an elder sister of case 3, noticed a painless tumor on the right cervical region since January, 1975. At the operation, the finger-tip sized tumor showed cystic degeneration and no adhesion to the surrounding tissue was noted. Enucleation of the tumor was performed in August, 1976.

MATERIALS AND METHODS

After embedding and sectioning as usual, specimens were stained with following procedures; hematoxylin-eosin, alkali Congo red for amyloid, Grimelius' method for the argyrophilic granules, reticulin staining, and Masson-Fontana stain for the argentaffin reaction.

MICROSCOPIC FINDINGS

Case 1. The tumor cells had oval or spindle shaped nuclei with the light cytoplasm. Neither nuclear aytpism nor mitosis was seen. The nuclear chromatin of the tumor cells was not so condensed and nucleoli were obscure. Some cells had pale brownish granules in their cytoplasm with hematoxylin-eosin stain. Proliferation of uniform tumor cells around

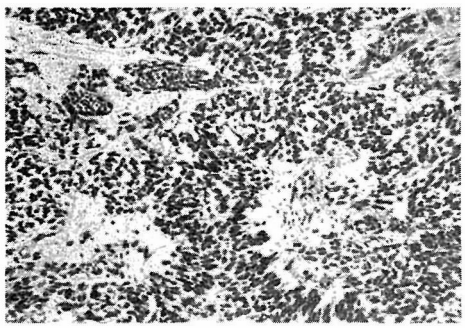

Fig. 1 Proliferation of the tumor cells around the blood vessels. (case 1) H.E.

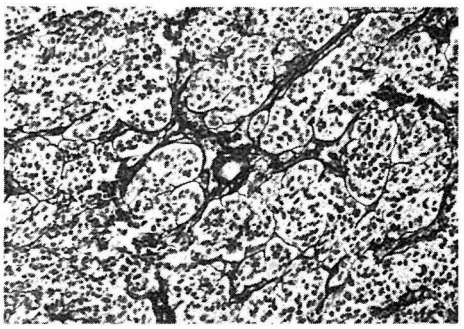

Fig. 2 reticulin staining. (case 1)

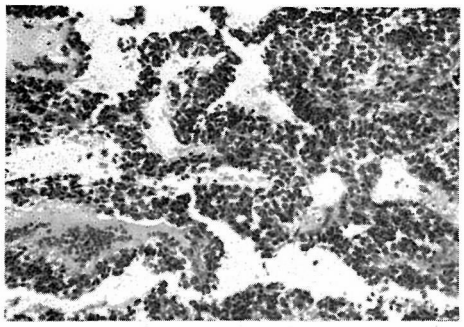

Fig. 3 Formation of lacunae with pseudopapillary appearance. (case 1) H E.

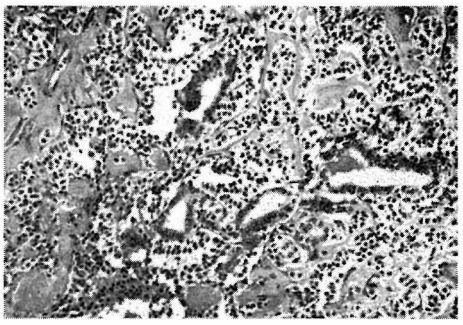

Fig. 4 Follicle-like structure. (case 2) H.E.

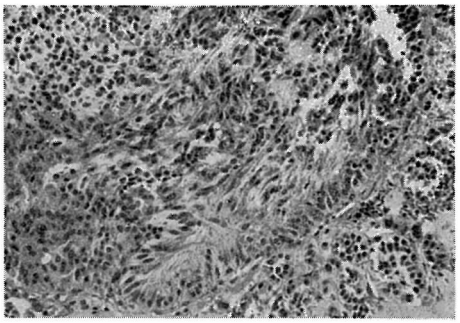

Fig. 5 Peripheral palisading of spindle shaped tumor cells. (case 2) H.E.

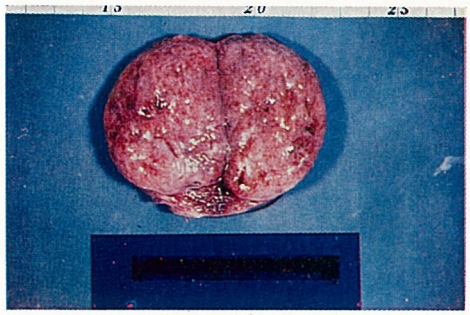

Fig. 6 Excised thyroid tumor. (case 1)

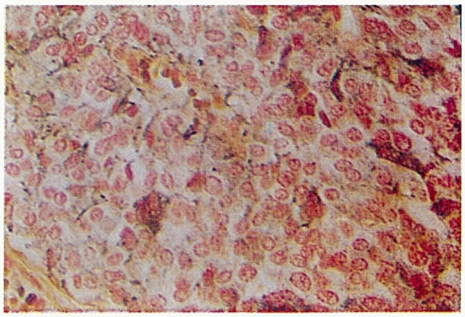

Fig. 7 Argyrophilic granules in the tumor cells. (case 1) Grimelius stain.

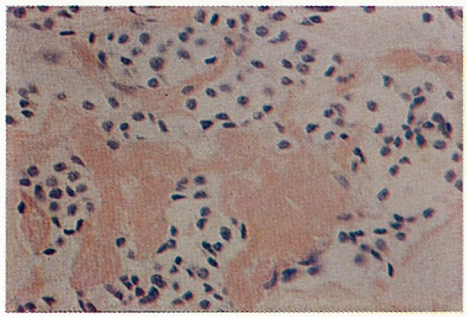

Fig. 8 Amyloid deposition in the stroma. (case 2) Congo red.

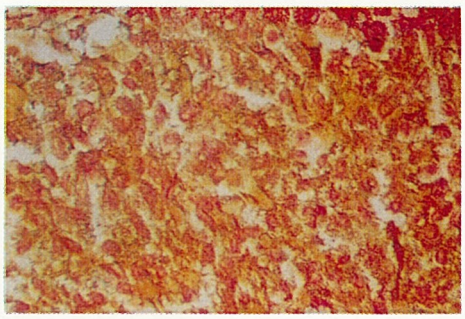

Fig. 9 Argyrophilic granules in the tumor cells. (case 3) Grimelius stain.

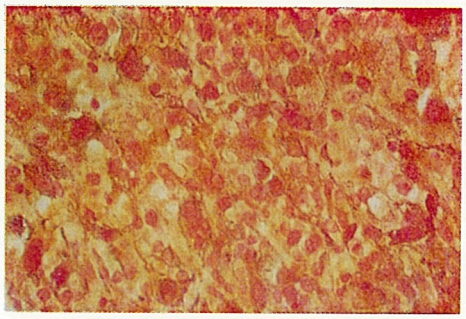

Fig. 10 Argyrophilic granules in the tumor cells. (case 4) Grimelius stain.

the blood vessels was appeared as if they were pericytic origin (Fig. 1). However, no penetration of reticulin fibers between individual tumor cells was observed (Fig. 2). In some areas, they did not show the perivascular proliferation but showed solid alveolar growth with thin fibrous connective tissue. No amyloid deposition could be identified throughout multisections of the tumor. Formation of lacunae, that gave a pseudopapillary appearance due to shrinkage of the tumor cells around the connective tissue stroma, was scattered (Fig. 3). No typical papillary structure as seen in papillary carcinoma of the thyroid was noted. Though a few normal thyroid follicles remained in the peripheral region of the tumor, no neoplastic follicle was observed. Even in hematoxylin-eosin staining, brownish granules could be identified in a small number of cells, and blackish brown granules were revealed in a large number of cells with Grimelius' method (Fig. 7). These granules were more numerous in the cells forming pseudopapillary appearance. Masson-Fontana staining revealed no argentaffin granules in any tumor cells.

Case 2. Round or oval tumor cells disclosed solid sheet growth. Some of them formed tubular or follicle-like structures (Fig. 4). In other place, solid growth composed of spindle cells with peripheral palisading was found (Fig. 5). The most characteristic finding was a deposition of homogenous eosinophilic substance in the stroma, which proved to be amyloid with Congo red staining (Fig. 8) and by its emitting green on the polarized light microscope. Calcification was scattered in the connective tissue stroma. The argyrophilic granules were found in many tumor cells in various amount. No tumor cells showed a positive reaction for Masson-Fontana technique.

Case 3. The tumor cells were rather uniform and oval in shape. The nuclear chromatin was not so condensed and nucleoli were visible in a few nuclei. The cytoplasm was eosinophilic. The predominant histologic architecture was similar to that observed in case 2. That is, sheets and solid nests of the tumor cells were separated either by thin fibrous septa or broad eosinophilic substance. Follicle-like structures were observed in a few places. Homogenous eosinophilic substance in the stroma was proved to be amyloid with Congo red staining and by the polarized light microscope. Grimelius staining demonstrated a large amount of argyrophilic granules in the cytoplasm of the tumor cells (Fig. 9). No positive reaction for Masson-Fontana staining was observed in any tumor cells.

Case 4. The tumor cells had oval or polygonal nuclei with eosinophilic and finely granular cytoplasm. The nucleolus was obvious in most tumor cells. A slight nuclear atypism was seen but mitotic figures were

scarce. In some areas, follicle-like structures were observed. Hemosiderin laden macrophages were noted in other places where degeneration of the tumor cells was present. The globules of eosinophilic substance, which were demonstrated as amyloid with Congo red staining and by the polarized light microscope, were seen. Grimelius staining demonstrated the argyrophilic granules in the tumor cells (Fig. 10). No tumor cells showed a postitve reaction for Masson-Fontana technique.

DISCUSSION

Medullary carcinoma of the thyroid gland was described as a specific clinicopathological entity by Hazard et al.[12] in 1959, who described that the tumor cells formed no characteristic cell arrangement or structure as seen in papillary or follicular carcinoma but accompanied by amyloid substance in the stroma. It usually takes a chronic clinical course and differs from the group of highly malignant anaplastic carcinoma which does not show any follicular or papillary differentiation. All 21 cases reported by Hazard et al. showed amyloid substance in the stroma, and, therefore, occurrence of amyloid in medullary carcinoma has been regarded as the most characteristic finding[12,13]. Absence of amyloid, however, does not necessarily deny the possibility of medullary carcinoma. Williams et al. also recognized three cases of the thyroid carcinoma which were very suggestive of medullary carcinoma, although there was no amyloid deposition[13]. Some investigators also describe medullary carcinoma without amyloid[6,11,14-17]. Gordon et al.[15] summarized the following variable histological criteria of medullary carcinoma of the thyroid in which amyloid could not be identified; 1. no follicular or papillary differentiation; 2. the micronodular pattern tending to be solid with scanty stroma; 3. areas composed particularly of spindle cells. The third criteria seems very important in our case 1, which is predominantly composed of spindle cells and shows no amyloid deposition. The similar case was reported by Ibanez et al.[8]

Besides amyloid, Hazard et al. noted the sheet like growth of the tumor cells, and mentioned it to be a basic pattern in medullary carcinoma. They also observed the structure resembling spindle cell sarcoma or carcinoid in other places. Tateishi et al.[11] observed four growth patterns such as solid alveolar, streaming, ribbon like or trabecular and rosette forming. In our cases, various growth patterns such as solid alveolar (case 1, 2, 3, 4), pseudofollicular (case 2, 3, 4) and peripheral palisading (case 2) were observed. In case 1, the predominant feature was the proliferation of the tumor cells around the small vessels and histological

architecture resembled carcinoid due to solid alveolar growth composed of monotonous spindle cells. Pseudopapillary appearance in case 1 resulted from shrinkage of the tumor cells are also described in some literature[12,13,15]. Thus, medullary carcinoma is characterized by its variegated growth pattern.

Tateishi et al. report that the argyrophilia of the tumor cells is more significant than the amyloid deposition[10,11]. In our series, three of four cases showed amyloid deposition, and positive argyrophilic reaction was observed in all cases. On the other hand, Williams described that only about half of 67 cases of medullary carcinoma disclosed the argyrophilia, and nearly all cases were associated with amyloid substance[13]. Therefore, it is not always accurate to diagnose medullary carcinoma only by silver staining. There is no hesitation, of course, to diagnose medullary carcinoma if amyloid is identified.

Concerning the origin of medullary carcinoma, Williams considered it to be a neuroectodermal origin with hereditary background[2], as medullary carcinoma often associated with pheochromocytoma or neural tumor[5]. He noted the resemblance of medullary carcinoma to the thyroid tumor of the rat arising from parafollicular cell, and observed the argyrophilic granules in both medullary carcinoma and dog thyroid tumor of solid type[18]. He described that various findings observed in medullary carcinoma would be easily explained if this tumor might have arised from the cell system other than the thyroid epithelium, namely, parafollicular cells. At present, medullary carcinoma is regarded by many investigators as derived from parafollicular cells[4,14,16,19]. Pearse found that amine and its precursor were uptaken and decarboxylized by parafollicular cell[20], and moreover, polypeptide hormone (calcitonin) was produced by them[21]. He considered them to be primitive entodermal in origin just like the islet cells of pancreas, pituitary corticotroph, intestinal enterochromaffin cell, and argyrophil cell of the stomach and intestine, and grouped these cells in APUD (amine and precursor uptake and decarboxylation) series[20]. Consequently, it is inferred that the tumors arising from this series may reveal various clinical manifestations such as carcinoid like syndrome, Cushing like syndrome and so on according to the substances produced by the tumor cells.

As described above, medullary carcinoma is often associated with pheochromocytoma and frequently found with familial occurrence[3,13]. Sipple[1] suggested the coexistence of medullary carcinoma with pheochromocytoma in a significantly high incidence. Ljungberg et al.[3] investigated 150 members of the family and found 7 patients with medullary

thyroid carcinoma. They suggested the syndrome "medullary carcinoma and pheochromcytoma" as an inherited disorder of the chromaffin system. Other additional reports supporting the heredity of medullary carcinoma are presented[15,22]. In our case 3, it is deserved of this syndrome mentioned by Sipple and has the heredity because her sister (case 4) also had medullary carcinoma of the thyroid.

Many authors describe that medullary carcinoma resembles carcinoid histologically[7,8,13,15] and electron microscopically[14]. Diarrhea has been seen in about 25% of patients with medullary carcinoma[7]. Serotonin (5-HT)[6] or 5-hydroxyindole acetic acid (5-HIAA)[7,8] has been demonstrated in some medullary carcinomas. Williams classified the carcinoid tumors in accordance with its arising portion such as in the foregut, midgut or hindgut origin, and described the correlation between these tumors and their reaction for silver staining[23]. According to his opinion, bronchial carcinoid arising from the foregut is to disclose the argyrophilia but no argentaffinity. As the thyroid gland is also derived from the foregut, a carcinoid tumor arising from the thyroid gland might be positive for the argyrophilic reaction but negative for the argentaffin. All our cases showed the argyrophilia, but no argentaffinity was noted.

It is not reasonable to discuss the carcinoid tumor only by silver staining because the argyrophilia in medullary carcinoma may be rather due to calcitonin than serotonin-like substances. In our cases it is not adequate to regard them as carcinoid because neither 5-HT nor 5-HIAA is proved and no clinical manifestations of carcinoid syndrome are seen. However, it would be preferable to regard such a thyroid tumor as carcinoid, when 5-HT or 5-hydroxytryptophan was disclosed in the tumor tissue or in urine, and apparent carcinoid syndrome was observed clinically, and no amyloid could be identified microscopically. Medullary carcinoma should be regarded as apudoma, namely, one type of the tumor derived from APUD series and having multipotent secretive activity. The argyrophilia of the tumor cells is one of the characteristics in the diagnosis of medullary carcinoma of the thyroid gland.

SUMMARY

We experienced four biopsy cases of medullary carcinoma of the thyroid gland and brief clinical courses and detailed histological findings have been reported. Three cases were associated with amyloid. All cases were positive for the argyrophil and negative for the argentaffin staining. Demonstration of the argyrophilic granules in the tumor cells and stromal amyloid is a convincing finding to make a diagnosis of medul-

lary carcinoma of the thyroid.

ACKNOWLEDGEMENT

We thank Moji Tetsudo Hospital, Toyota Chuo Hospital and Ehime Rosai Hospital for providing the biopsy specimens.

REFERENCES

1) Sipple, J.H.: The association of pheochromocytoma with carcinoma of the thyroid gland. *Amer. J. Med.*, 31 : 163-166, 1961.
2) Williams, E.D.: A review of 17 cases of carcinoma of the thyroid and pheochromocytoma. *J. Clin. Pathol.*, 18 : 288-292, 1965.
3) Ljungberg, O., Cederquist, E. and Studnitz, W.: Medullary thyroid carcinoma and pheochromocytoma. A familial chromaffinomatosis. *Brit. Med. J.*, 1 : 279-281, 1967.
4) Marks, A.D. and Channick, B.J.: Extra-adrenal pheochromocytoma and medullary thyroid carcinoma with pheochromocytoma. *Arch. Intern. Med.*, 134 : 1106-1109, 1974.
5) Williams, E.D. and Pollock, D.J.: Multiple mucosal neuromata with endocrine tumors: A syndrome allied to von Recklinghausen's disease. *J. Pathol. Bact.*, 91 : 71-80, 1966.
6) Moertel, C.G., Beahrs, O.H., Woolner, L.B. and Tyce, G.M.: "Malignant carcinoid syndrome" associated with noncarcinoid tumors. *New Engl. J. Med.*, 273 : 244-248, 1965.
7) Williams, E.D.: Diarrhea and thyroid carcinoma. *Proc. Roy. Soc. Med.*, 59 : 602-603, 1966.
8) Ibanez, M.L., Cole, V.W., Russell, W.O. and Clark, R.L.: Solid carcinoma of the thyroid gland. Analysis of 53 cases. *Cancer*, 20 : 706-723, 1967.
9) Szijj, I., Csapó, Z., László, F.A. and Kóvacs, K.: Medullary cancer of the thyroid gland associated with hypercorticism. *Cancer*, 24 : 167-173, 1969.
10) Tateishi, R. and Takahashi, Y.: A case of medullary carcinoma of the thyroid gland - An electron microscopic and histochemical observation - *Jap. J. Cancer Clin.*, 17 : 465-468, 1971. (in Japanese)
11) Tateishi, R., Wada, A., Takahashi, Y., Noguchi, A., Noguchi, S. and Ito, J.: Medullary carcinoma of thyroid gland. Histological and histochemical studies. *Jap. J. Cancer Clin.*, 17 : 607-617, 1971. (in Japanese)
12) Hazard, J.B., Hawk, W.A. and Crile, G.: Medullary (solid) carcinoma of the thyroid - a clinicopathologic entity. *J. Clin. Endocrinol.*, 19 : 152-161, 1959.
13) Williams, E.D., Brown, C.L. and Doniach, I.: Pathological and clinical findings in a series of 67 cases of medullary carcinoma of the thyroid. *J. Clin. Pathol.*, 19 : 103-113, 1966.
14) Horvath, E., Kovacs, K. and Ross, R.C.: Medullary cancer of the thyroid gland and its possible relations to carcinoids. An ultrastructural study. *Virchows Arch. Abt. A Path. Anat.*, 356 : 281-292, 1972.
15) Gordon, P.R., Huvos, A.G. and Strong, E.W.: Medullary carcinoma of the thyroid gland. A clinicopathologic study of 40 cases. *Cancer*, 31 : 915-924, 1973.
16) Tubiana, M., Parmentier, C., Gerard-Marchant, R., Lacour, J., Milhaud, G., Bok, B. and Weiler, J.: Etude comparative des epithéliomas médullaires du corps thyroide avec et sans stroma amyloide. *Europ. J. Cancer*, 6 : 39-47, 1970.
17) Normann, T., Johannessen, J.V., Gautvik, K.M., Olsen, B.R. and Brennhovd, I.O.: Medullary carcinoma of the thyroid, diagnostic problems. *Cancer*, 38 : 366-377, 1976.
18) Williams, E.D.: Histogenesis of medullary carcinoma of the thyroid. *J. Clin. Pathol.*, 19 : 114-118, 1966.
19) Gonzalez-Licea, A., Hartmann, W.H. and Yardley, J.H.: Medullary carcinoma of the thyroid.

Ultrastructural evidence of its origin from the parafollicular cell and its possible relation to carcinoid tumors. *Amer. J. Clin. Pathol.*, 49 : 512–520, 1968.
20) Pearse, A.G.E.: Common cytochemical and ultrastructural characteristics of cells producing polypeptide hormones (the APUD series) and their relevance to thyroid and ultimobranchial C-cells and calcitonin. *Proc. Roy. Soc. London B.*, 170 : 71–80, 1968.
21) Pearse, A.G.E.: The cytochemistry of the thyroid C-cells and their relationship to calcitonin .*Proc. Roy. Soc. London B.*, 164 : 478–487, 1966.
22) Chong, G.C., Beahrs, O.H., Sizemore, G.W. and Woolner, L.H.: Medullary carcinoma of the thyroid gland. *Cancer*, 35 : 695–704, 1975.
23) Williams, E.D. and Sandler, M.: The classification of carcinoid tumors. *Lancet*, 1 : 238–239, 1963.