Physical and Radiological Findings Specific for Medullary Carcinoma of the Thyroid Gland

YOSHIHIDE FUJIMOTO, ATSUSHI OKA, MASAYUKI FUKUMITSU, TAKAO OBARA, MASAYOSHI AKISADA AND KAZUYOSHI YAMAGUCHI

The Second Department of Surgery, Faculty of Medicine, University of Tokyo, Tokyo 113
Department of Radiology, Mitsui Memorial Hospital, Tokyo 101, and Department of Pathology, Institute of Medical Science, University of Tokyo, Tokyo 108.

Synopsis

Preoperative physical and radiological findings, if specific to a certain extent, are important for detecting patients with sporadic form of medullary thyroid carcinoma and especially for the first patient in the family having a hereditary form of medullary thyroid carcinoma and pheochromocytoma syndrome. To delineate clinical features of medullary thyroid carcinoma, a total of 9 patients with this tumor were reviewed retrospectively. In most patients, the thyroid lesions were located in the upper two thirds of the lobe, which was determined by careful palpation or 131I scintiscanning of the thyroid. The primary lesion in the thyroid could be felt more or less as a round, sharply demarcated nodule with fairly good mobility. These findings suggested rather a benign thyroid nodule when there was no lymph node involvement. However, it could be considered a sign suggesting medullary thyroid carcinoma when accompanied by marked lymph node metastasis. In our recent 2 cases, the diagnosis of medullary thyroid carcinoma was strongly suspected on these clinical bases, one of the cases being presented in detail. In 4 patients, lymph node metastasis in the central neck extended to either submandibular or upper mediastinal regions or both. In about one third of the patients, calcified deposits were shown in the cervical roentgenograms. With the use of soft tissue roentgenography, grossly punctate calcific deposits associated with psammoma-like shadows were recognized and the pattern was a criterion for definitive diagnosis of medullary thyroid carcinoma.

Preoperative diagnosis of the medullary thyroid carcinoma is important, because firstly in cases of Sipple's syndrome, thyroidectomy should be performed after the removal of the associated pheochromocytoma (Sjoerdsma et al., 1966; Cervi-Skinner and Castleman, 1973). Secondly, a total thyroidectomy accompanied by a modified neck dissection is recommended, because both the thyroid lobes are frequently involved by the neoplasms and extensive lymph node metastasis usually occurs in the early stage (Melvin et al., 1971). Recently the definitive diagnosis of medullary thyroid carcinoma has become possible by determining the elevated plasma calcitonin levels by the use of radioimmunoassay technique (Tashjian et al., 1970; Melvin et al., 1972; Hill et al., 1973; Jackson et al., 1973). Although the calcitonin assay is very useful for the detection of patients with a familial form of the disease (Melvin et al., 1971), its routine use for all the patients with thyroid nodules appears to be impractical because of the rarity of sporadic form of medullary thyroid carcinoma and of the limited availability of the calcitonin radioimmunoassay.

The diagnosis in sporadic cases has most often been made from the pathological examination of surgically resected specimen.
We have, however, experienced 2 cases in which a diagnosis of medullary thyroid carcinoma was strongly suspected preoperatively only from physical findings of the neck. In one of them, soft tissue roentgenogram of the neck provided further confirmative findings, and then the association of pheochromocytoma could be detected through the urinary chemical analysis. This illustrative case will be presented in this communication and also a review of physical and radiological findings observed in 9 patients with medullary thyroid carcinoma thus far we have experienced is presented here.

Case Report

A 24-year-old woman was admitted to hospital on January 23, 1974. Her chief complaints were the swelling of the left submandibular lymph nodes of one year duration and a thyroid nodule recently noticed. The patient was a well developed woman with a blood pressure of 112/70 and a pulse rate of 76 per minute. She had no diarrhea. There was a firm, oval nodule, 2 by 3 cm in size, in the upper part of the left thyroid lobe which was not tender. The nodule had a smooth surface and was readily movable. There was marked lymph node enlargement in the submandibular area, along the left internal jugular chain, and around the cervical trachea just above the sternal notch.

The soft tissue roentgenogram of the neck (Fig. 1) showed grossly punctate calcified deposits, associated with psammomatous calcification, at the sites of the thyroid lesion and the cervical lymph nodes involved. The chest x-ray was normal except for a localized round tumor shadow at the right upper mediastinum. The $^{131}$I thyroid scintiscanning revealed a cold area in the upper part of the left lobe. Thyroid function tests were normal. Results of laboratory examinations were all within the normal ranges, including values for serum calcium of 9.5 mg, phosphorus of 2.9 mg per 100 ml and alkaline phosphatase of 8.2 King Armstrong units. The EKG was normal.

Since the physical and roentgenologic findings stated above strongly suggested the presence of medullary thyroid carcinoma, urinary chemical analysis was performed for 3 successive days in order to examine the possible association of pheochromocytoma. In 24-hour urine samples, the norepinephrine was less than 40.8 mg (normal 0–100) and epinephrine showed an increase, ranging from 81.7 to 172.8 mg (normal 0–10). The pneumoretroperitoneum revealed tumorous shadows in the regions of both adrenals. Selective venous samplings for catecholamines showed an elevated epinephrine content in both renal veins and the inferior vena cava at the level of the diaphragm. Thus a diagnosis of Sipple's syndrome was established before the operation.

On February 25, 1974, bilateral total adrenalectomy was carried out, when three minute metastatic lesions were found on the surface of the liver. Pathologic examination revealed metastatic lesion from the medullary thyroid carcinoma. One month later, thyroidectomy was carried out along with the removal of the cervical and upper mediastinal lymph nodes. A solid, well circumscribed nodule, 2 by 3 cm in size was found in the upper half of the left thyroid lobe and another nodule, less than 1 cm in diameter, was detected in the right lobe at the junction of the upper and the middle third (Fig. 2). A parathyroid adenoma was removed from the posterior surface of the right thyroid lobe at the level of the middle third. Biopsy of the left superior parathyroid revealed it as normal and two other parathyroids could not be found.

Fig. 1. Lateral view of the neck taken by soft tissue roentgenographic technique, showing coarse punctate calcified deposits associated with psammomatous shadows at sites of the primary lesion in the thyroid and the cervical lymph nodes involved.
Fig. 2. Cut surfaces of the right (R) and left (L) lobes of the thyroid and the paratracheal lymph nodes involved by metastatic lesions. Both lobes of the thyroid contained tumors in the upper half. Note the sharply circumscribed tumor mass in the left thyroid lobe, which was felt as a round, movable nodule from outside preoperatively.

Soft tissue roentgenogram of surgically removed specimens showed the psammomatous calcification in association with coarse, punctate calcified deposits in the thyroid lesions and lymph nodes involved (Fig. 3).

The postoperative course was uneventful and the patient has been well, taking desiccated thyroid and hydrocortisone daily.

The surgically removed thyroid tissue and the plasmas before the operation were kept frozen until the assay of parathyroid hormone (PTH) or calcitonin. PTH and calcitonin were determined by the radioimmunoassay techniques (PTH assay, Tanaka et al., 1974; and calcitonin assay, Adachi et al., 1974). Plasma PTH level was 1.25 ng/ml (normal value, less than 0.5 ng/ml) and calcitonin was 22.4 ng/ml (normal value, less than 0.05 ng/ml). The calcitonin content of the resected medullary carcinoma determined by bioassay was 700 MRC units/g wet tissue.

Review of Physical and Radiological Findings

During the 15-year period from July, 1959 to June, 1974, we have experienced 9 patients who underwent thyroid operations for medullary thyroid carcinoma at the Second Department of Surgery, University of Tokyo Hospital. The case report of one of these was given in the previous section of this
Paper. The clinical and pathological records of all the cases were reviewed and paraffin sections were reexamined. Standard roentgenography had been performed on the neck of selected patients and, since January, 1970, soft tissue roentgenography was adopted as a routine examination for patients with thyroid nodules. Thus, standard roentgenograms of 6 patients and soft tissue roentgenograms of 2 patients were available for the review. Roentgenograms of surgically re-moved specimens were obtained in all the cases by a soft tissue roentgenographic technique. The radiologic methods used were described in detail elsewhere (Akisada and Fujimoto, 1973). A long term follow-up study was summarized in April, 1974.

Physical Findings

Physical findings on the neck are summarized in Table 1. The size of the primary tumors in the thyroid varied from $1 \times 1.5$ cm to $10 \times 12$ cm. In all but one patient, the thyroid tumor was relatively sharply demarcated, having a smooth surface, round or oval shape and little or no limitation of mobility.

The location of the thyroid lesions was estimated by palpation in relation to the thyroid cartilage, cricoid cartilage and the trachea. A thyroid scan showed a cold area which coincided with the palpation finding. In 2 patients the nodule occupied almost the entire lobe and was too large to localize the primary site of lesion. The tumor occupied the upper one third of the lobe in one patient, the upper two thirds in three and the middle third in three.

The patients were divided into three groups on the basis of their degree of lymphadenopathy; 2 patients had no lymph node metastasis, 2 had no palpable nodes preoperatively, but involved nodes were found and removed at operation, and 5 showed bulky lymph node enlargement due to metastases in the neck. In the 5 patients in the latter group, the lymph node swelling was noticed by the patients themselves or by the physicians before or at the time the thyroid lesion was found, and in all but one the nodal swelling in the submandibular region was noted first. Lymphadenopathy was unilateral in 3 patients and bilateral in 2.

Radiological Findings

In 2 of the 6 cases in which standard X-ray films were available for review, coarse,
dense calcified deposits were recognized in positions corresponding to the thyroid lesions. In one of the two cases in which soft tissue roentgenograms were taken, no calcified deposits were seen, while in the other (the case presented in this report) grossly punctate calcified deposits were seen associated with psammomatous shadows in the regions of both the thyroid lesion and the cervical lymph nodes involved.

Soft tissue roentgenograms of surgically removed specimens showed much more clearly the psammomatous calcification in association with coarse deposits in all but one case (Table 1). The amount of calcification varied. Much calcification was observed in 3 patients with marked lymph node involvement, in whom both the thyroid lesions and the metastatic lesions in the lymph nodes had calcified deposits.

Comparison of roentgenographic and histologic findings showed that the calcifications of both coarse and psammomatous patterns were present mainly in the amyloid stroma. Histologically the calcified deposits in amyloid stroma were amorphous and varied in size from small psammoma-like deposits to fairly large gross ones (Fig. 4). Coarse calcification was also seen in the fibrotic tissue formed within and at the capsule of the neoplastic tissue.

One patient (Case 6 in Table 1), having marked cervical lymph node metastases and clinically persistent diarrhea, showed multiple dense calcifications within metastatic deposits of medullary thyroid carcinoma in the liver. When two roentgenograms taken in 1968 and in 1974 were compared, only a slight increase was noted in the size and number of dense calcifications.

**Long Term Follow-up Study**

Two patients died after prolonged hypertension, caused in one case by arteriosclerosis and in the other by chronic nephritis. Two other patients died of aggressive spread of the medullary thyroid carcinoma. It seems noteworthy that, of five patients with marked lymph node metastases, the three in whom the lesions had little or no calcification died of carcinoma 4 months and 1 year, respectively, after the operation.

**Discussion**

Medullary thyroid carcinoma can be diagnosed in several ways before the operation. The family history may be helpful, if there is any indication of familial incidence. The diagnosis can only be made from an elevated plasma level of calcitonin, determined either by bioassay (Takai et al., 1974) or by the more sensitive radioimmunoassay.
technique (Melvin et al., 1972; Hill et al., 1973, Jackson et al., 1973). This is especially valuable for early detection of the disease, before clinical evidences become apparent. The case of Sipple’s syndrome presented here was found to have a younger brother with the medullary thyroid carcinoma, which will be reported in a succeeding paper.

The sporadic form of medullary carcinoma is found in less than 2 per cent of all cases of thyroid carcinoma in Japan (Takai et al., 1974), while it is reported in English literatures to constitute around 7 per cent (Fletcher, 1970). During the 4-year-period from January, 1970 through December, 1974, a total of 534 patients visited our clinic with some form of thyroid nodule. Of the 281 patients who underwent thyroid operations, 124 were found to have thyroid cancer, and among them there was only one case that had medullary carcinoma. Thus cases of medullary carcinoma are so rare that it seems impractical to perform a calcitonin assay routinely on all patients with thyroid nodules.

Patients with medullary thyroid carcinoma may present symptoms suggestive of the disease, such as persistent diarrhea, and a carcinoid syndrome with bouts of flushing, abdominal pain and diarrhea. Unfortunately these symptoms are rare and are usually seen in cases with the advanced disease. Patients may also have associated disorders, such as multiple mucosal neuromas, neurofibromatosis, marfanoid habitus, hyperparathyroidism, pheochromocytoma or Cushing’s syndrome. Therefore, when a patient with a thyroid nodule has some of these signs or symptoms, the possibility of medullary thyroid carcinoma should be considered. The case presented here actually had hyperparathyroidism and pheochromocytoma, but they were not apparent clinically and only laboratory examinations revealed that she had these disorders.

Physical findings in cases of medullary thyroid carcinoma have not been well documented thus far. Hill and his associates (1973) stated in their review on a large number of cases that medullary thyroid carcinoma could not be distinguished clinically from other histological types of thyroid carcinoma. Baylin (1974) also gave the similar statement and noted that the diagnosis in the sporadic cases was usually a postoperative one based on the interpretation of the surgical histology. In our experience, however, findings on palpation in the neck in some of the patients with medullary thyroid carcinoma were characteristic. Firstly, in most cases the primary tumor was located in the upper two thirds of the thyroid lobe. Second, most primary lesions in the thyroid were round, sharply defined, fairly mobile nodules. Therefore, by palpating the primary lesion only, it may be misdiagnosed as a benign nodule or a noninvasive thyroid cancer which is usually not accompanied by lymph node metastasis. On the other hand, medullary thyroid carcinoma often has a marked tendency to involve regional lymph nodes. The metastasis frequently extends to the submandibular and upper mediastinal lymph nodes and the individual nodal mass occasionally becomes larger than the primary lesion.

Therefore, when a patient has a nodule in the upper two thirds of the thyroid lobe, with physical findings suggestive of rather a benign tumor which is accompanied by a bulky lymph node enlargement apparently due to metastasis, the most likely diagnosis is medullary carcinoma. In our 2 recent cases, a diagnosis of medullary carcinoma was strongly suspected based on these physical findings prior to the operation.

The fact that calcification frequently occurs in the primary lesion as well as the metastatic lesions in lymph nodes and the liver in cases of medullary thyroid carcinoma has been reported by our group (Fujimoto and Akisada, 1970), Wallace et al. (1970), Pearson et al. (1973), and Takai et
al. (1974). The presence of calcification itself is rather a common finding in thyroid cancers in general. In 138 histologically proven thyroid cancers that we have experienced for the past 5 years, coarse calcification only was seen in 66 cases, psammomatous calcification only in 22 and combined coarse and psammomatous calcification in 15 cases. The pattern of calcification seen on the neck roentgenogram is important in making a preoperative diagnosis of thyroid cancers. The reports except the authors described only coarse, irregular calcification in cases of medullary thyroid carcinoma. However, as the comparative study of the surgical specimen roentgenogram and the histologic evidence shows, most of the calcific deposits in the medullary carcinoma occur in the amyloid stroma which is unique product of this kind of neoplasm and the size of calcium deposits varies from a psammomatous small one to a fairly large one. Therefore, the pattern of calcification seen in the preoperative neck roentgenogram is, in typical cases, characterized by multiple grossly punctate deposits associated with faint psammomatous shadows. We demonstrated them by using soft tissue roentgenography. If this pattern of calcification is obtained, it is of definite value in making a diagnosis of medullary thyroid carcinoma. However, the typical calcific deposits are not always seen in medullary thyroid carcinomas. In general, the amount of calcification is in parallel with that of amyloid deposition.

The possibility of medullary thyroid carcinoma must be kept in mind with a patient having any of the physical and radiological findings mentioned above, which are unique to this variety of thyroid carcinoma. About such a patient a careful survey should be made on the association of pheochromocytoma and the laboratory studies should include determination of urinary catecholamine excretion even in the absence of symptoms, because pheochromocytoma occurring with medullary thyroid carcinoma is generally less symptomatic than when it occurs alone. In addition, the survey about the family should be done. In the case presented in this report, a clinically silent pheochromocytoma was detected by urinary catecholamine measurements and pneumo-retroperitoneum, which was successfully removed before surgically approaching the thyroid tumor. If thyroidectomy is carried out on a patient with Sipple's syndrome, without knowing the presence of pheochromocytoma, a dangerous complication may be followed by surgical stress, which may result in the fatal consequence.

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