thyroid carcinoma and to propose a tentative classification (Table 2).

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Amyloid Goiter: Preoperative Scintigraphic Diagnosis Using Tc-99m Pyrophosphate

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Amyloid goiter is a rare clinical entity. The diagnosis is rarely made preoperatively because clinical and laboratory findings are nonspecific. We report two cases of amyloid goiter in whom the diagnosis was made preoperatively using Tc-99m pyrophosphate scintigraphy.

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The incidental finding of amyloid deposits in the thyroid gland in patients with systemic amyloidosis is not unusual, occurring in 50-80% of patients. However, amyloid deposits large enough to cause thyroid enlargement are very rarely found, with only 70 such cases reported in the English literature. Although first described by Berkman in 1858, the specific term amyloid goiter was coined by von Eiselberg in 1904 (*1-3*). In view of the nonspecific clinical presentation and laboratory findings, amyloid goiter is rarely diagnosed preoperatively. We report two cases of amyloid goiter that show unique scintigraphic findings with Tc-99m-labeled pyrophosphate, a bone-seeking radiopharmaceutical. This simple scintigraphic procedure may be used to diagnose amyloid goiter in those patients clinically suspected of having this entity.

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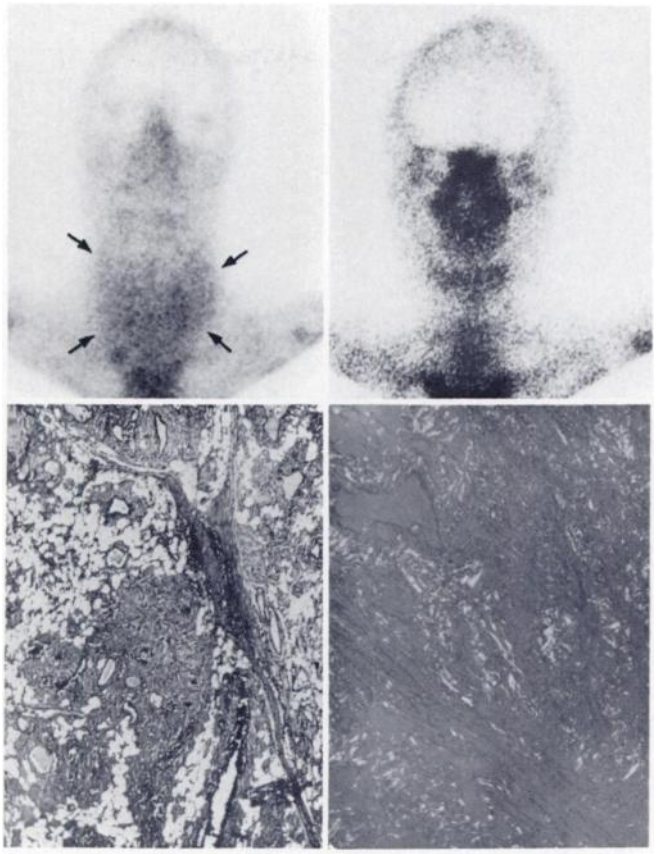

FIG. 1. Tc-99m pyrophosphate (Tc-PPi) image of head and neck (upper left) showed marked and diffuse uptake in entire thyroid gland, which was enlarged (arrows). Histological section of thyroid (25X) shows diffuse amyloid deposits with large amount of adipose tissue present (lower left). Polarized-light microscopy confirmed presence of diffuse amyloid deposits in thyroid (lower right). Follow-up Tc-PPi image was performed 6 mo after subtotal thyroidectomy (upper right). No abnormal uptake was seen in cervical soft tissue (Case 1).

CASE 1

A 31-yr-old man was referred to our laboratory for evaluation of systemic amyloidosis. Since age 3, when he had measles followed by intermittent episodes of productive cough, he had sustained a long history of repeated episodes of pulmonary infections. At age 19 he was exposed to histoplasmosis and coccidiomycosis, followed by repeated episodes of recurrent cough and fever. Serum fungal antibody titers at that time were negative for the presence of either microorganism. Bronchoscopy was negative, and a lung biopsy showed caseating granulomata. Although bacterial cultures were negative, he received a course of treatment for tuberculosis that included isoniazid, paraminosalicylic acid, and streptomycin.

In 1977, at the age of 28, a goiter was noticed. He was judged to be euthyroid clinically, and thyroid function tests were normal. Over the following 3 yr his thyroid gland continued to enlarge bilaterally despite adequate suppression with L-thyroxine. A needle biopsy of the thyroid revealed amyloid, and he was referred to our laboratory for complete evaluation of amyloidosis. He was asymptomatic at the time of admission, although his goiter was obvious.

On physical examination, his thyroid gland was markedly enlarged bilaterally, especially the left lobe. The gland was estimated to weigh more than 300 g; and on palpation it was smooth and nontender. It moved with swallowing and was not fixed to the underlying structures. No thrill or bruit was detected. There was no Pemberton's sign, lymphadenopathy of the neck, or clinical signs of hypo- or hyperthyroidism. The rest of the physical examination was unremarkable, except for a slight anisocoria. Furthermore, ophthalmological and neurological evaluation showed no evidence of Horner's syndrome or retro-orbital infiltration.

Thyroid function tests were normal: T_4 9.3 μg/dl (normal 4–11); T_3 111 ng/dl (100–190); TSH 2.0 μIU/ml (0–4). Antimicrosomal and antithyroglobulin antibodies were not detectable. A barium swallow revealed a large soft-tissue mass in the neck, causing anterior bowing of the trachea and a circumferential impression on the esophagus. A subcutaneous biopsy of the abdominal fat pad showed the presence of the amyloid deposits on staining with Congo red and polarized light microscopy (*4*).

As part of a protocol study aimed at assessing the sensitivity of radionuclide imaging in the diagnosis of systemic amyloidosis (*5,6*), total-body scintigraphy was performed using Tc-99m pyrophosphate (Tc-PPi). It showed markedly abnormal uptake over the entire enlarged thyroid gland (Fig. 1). In intensity this uptake resembled that of the clavicle. A localized area in the left lobe showed intensity greater than that of the clavicles and equal to that of the sternum. No other abnormal soft-tissue uptake was seen on the scintigram.

His thyroid gland continued to enlarge after discharge. One year later, following the onset of pressure symptoms, including dysphagia and dyspnea, a subtotal thyroidectomy was performed. Pathological sections confirmed diffuse amyloid infiltration of the thyroid gland (Fig. 1). A Tc-PPi image performed 6 mo after the thyroidectomy revealed no abnormal uptake in the cervical region (Fig. 1).

CASE 2

A 67-yr-old Venezuelan woman was referred to our laboratory for evaluation of systemic amyloidosis. The patient had a 6- to

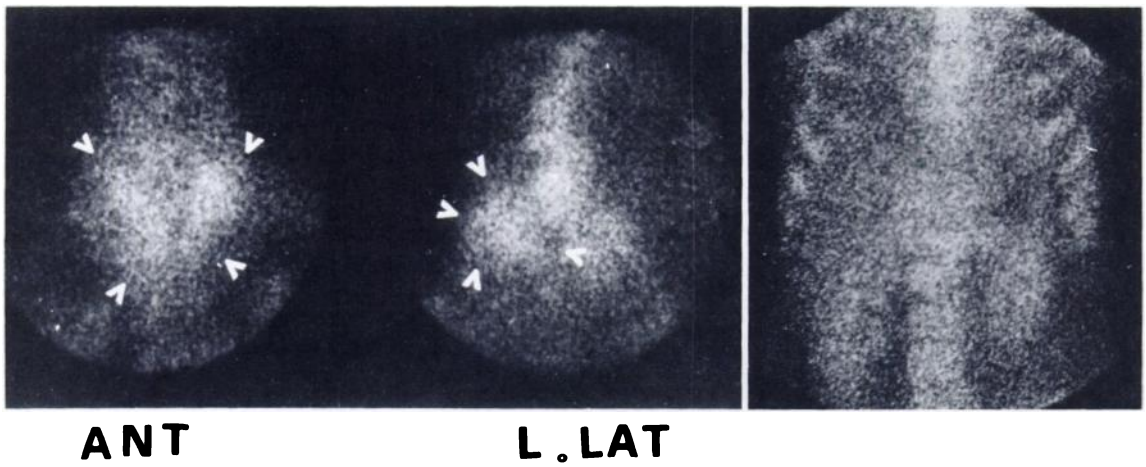

FIG. 2. Tc-PPi images of neck were performed in anterior (ANT) and left lateral (L. LAT) projections using a pinhole collimator to magnify thyroid gland (left). There was marked and diffuse uptake of Tc-PPi over entire thyroid glands (arrow heads). In left lateral projection, thyroid uptake of Tc-PPi was clearly separated from cervical spine, which normally concentrates Tc-PPi. Tc-PPi images over thorax and abdomen (right) showed diffuse uptake over liver and heart, indicating amyloidosis of these two organs (Case 2).

9-mo history of dyspnea on exertion, paroxysmal nocturnal dyspnea, a 30-lb weight loss, anorexia, postprandial nausea and vomiting, diarrhea, easy bruisability, and asymptomatic enlargement of the thyroid gland. Physical examination revealed jugular venous distension, a ventricular diastolic gallop, and hepatomegaly. The thyroid gland was diffusely enlarged, nontender, slightly firm, and irregular in contour, with an estimated weight of 50 to 55 g. Serum thyroid antibody titers were not performed. Thyroid function tests were normal: T_4 9.2 μg/dl; T_3RU 26.2%; TSH 4.5 mIU/ml). Evaluation revealed amyloid involvement of the heart, liver, and gastrointestinal tract. Technetium-99m pyrophosphate imaging revealed marked uptake in the thyroid gland, heart, and liver. Needle biopsy of the liver confirmed the diagnosis of amyloidosis. In view of the asymptomatic nature of the goiter, the unique radionuclide image, and the possibility of hemorrhage into the goiter, biopsy of the thyroid was deferred. Although thyroiditis cannot be absolutely ruled out, since serum antibody titers were not measured, this possibility was considered unlikely on clinical grounds. The positive Tc-PPi image was also against the diagnosis of thyroiditis, since review of the literature failed to reveal any report of Tc-PPi avidity of thyroiditis. Although no microscopy of the thyroid was obtained, the diagnosis of amyloid goiter was made in view of the clinical features, evidence of systemic amyloidosis (liver biopsy) and scintigraphic findings (Fig. 2).

CONTROL

We considered the possibility of radiopharmaceutical contamination by free pertechnetate as the cause of thyroidal uptake in Cases 1 & 2. This was ruled out, since total-body images had revealed no uptake over the gastric region or in the salivary glands.

Tc-PPi was the radiopharmaceutical used in our hospital for routine bone imaging before September, 1978. The records of 200 consecutive Tc-PPi bone images performed in 1978 were reviewed retrospectively to evaluate the incidence of thyroid uptake of Tc-PPi. None of these scintigraphs showed any definite uptake over the thyroid gland.

As part of the protocol study to assess the sensitivity of Tc-PPi imaging for soft-tissue amyloidosis, a control group of ten patients was also studied prospectively to determine the incidence of soft-tissue uptake of Tc-PPi. Again the findings showed no thyroid uptake (*5,6*).

DISCUSSION

Amyloidosis is a disease of uncertain cause, characterized by the extracellular deposition of a fibril protein in one or more organs of the body. The classification of amyloidosis has undergone considerable change in recent years as a result of increasing information about the chemical composition of this fibrous protein. The current classification is well summarized in the recent literature (*7*).

Since amyloidosis is usually a systemic condition that may involve any organ, the finding of amyloid deposits in the thyroid gland is not unusual. However, the thyroid seldom enlarges as a result of amyloid infiltration, and hence an amyloid goiter is a clinical rarity (*1-3*). Typically, in patients with amyloid goiter, the thyroid enlarges relatively rapidly to four to five times its normal size in a matter of months. The enlargement is usually diffuse, although it may start in one lobe and later involve the rest of the gland. Local pressure symptoms, such as a choking sensation, dyspnea, dysphagia, or hoarseness, are common. Thyroid function usually remains normal, although both hyper- and hypothyroidism have been reported (*1-7*). Surgery is usually performed because of a suspicion of neoplasm, or to relieve local pressure symptoms. A preoperative diagnosis is rarely made, although diagnosis by needle aspiration biopsy of the thyroid has been reported recently (*8*).

Generally, the thyroid is only one of many organs in the body to be involved by amyloid. In systemic disease, the kidneys, liver, and heart are commonly involved at the time of diagnosis. Indeed, there is only one case report wherein the thyroid was the only organ involved. As the result of its rare occurrence and lack of specific clinical manifestations, the diagnosis of amyloid goiter has rarely been considered preoperatively or before biopsy (*8,9*). Kranes (*9*) concluded that the rapid and diffuse enlargement of the thyroid in a young patient was characteristic enough to warrant a diagnosis of amyloid goiter.

Amyloid may be present in the thyroid in three conditions: amyloid goiter, nongoitrous amyloid of the thyroid, and medullary carcinoma of the thyroid (*1,10,11*). In most patients with systemic amyloidosis, the thyroid is usually normal anatomically and functionally. In 50% to 80% of cases, however, small amounts of amyloid can be demonstrated in small vessels within the thyroid gland. The follicles are normal and no significant adipose tissue is present. In patients with amyloid goiter, on the other hand, the thyroid enlarges rapidly. Macroscopically, the entire thyroid is

infiltrated with amyloid, and histopathologically it shows almost complete replacement by perifollicular amyloid and distortion of the thyroid follicles. The presence of a large amount of adipose tissue is considered to be an important histological characteristic of amyloid goiter. This association may not be incidental, since the amount of fat tissue maybe inversely proportional to the vascular supply to the thyroid (*1,12*). Vascular involvement with amyloid is a common feature of systemic disease (*1*).

In medullary carcinoma, amyloid deposits are closely associated with neoplastic tissue, which is focal in nature, although the tumor may be bilateral. The rest of the thyroid remains undisturbed, unlike the diffuse infiltration found in amyloid goiter. When bilateral, medullary carcinoma tends to involve the middle of the lateral parts of thyroid (*11*). Microscopically, sheets of amyloid are present among clusters of neoplastic cells. Absence of fat is also a prominent feature, and the small vessels are not involved (*1,11*). In spite of these clinical and pathological differences, the distinction can be difficult if needle biopsy of the thyroid is used as the sole diagnostic procedure. In fact, misdiagnosis and confusion between medullary carcinoma and amyloid goiter have been reported when needle biopsy was used (*1,8,10*). We had the opportunity to scintigraph, using Tc-PPi, a patient who later proved to have medullary thyroid carcinoma (MTC). She was a 63-year-old woman who complained of progressively enlarging neck mass for 1 yr. Physical examination showed nodular and bilateral enlargement of the thyroid. Serum calcitonin was elevated. An I-123 thyroid image demonstrated large and bilateral "photopenic" nodules. A Tc-PPi bone image failed to show convincingly any significant uptake in the thyroid gland, even with a pinhole collimator. Subtotal thyroidectomy 3 wk later demonstrated presence of MTC in the left lobe. Microscopy with Congo red stain showed presence of amyloid in the tumor. This negative Tc-PPi scintigram—in spite of the presence of thyroidal amyloid in the tumor—may be the result of insufficient quantity of amyloid, or possibly a difference in the amino-acid sequence of the amyloid. Further investigation is indicated.

In general, tissue obtained by surgery or needle biopsy is required to establish a definitive diagnosis of amyloidosis involving a particular organ. However, a biopsy from an amyloid-laden organ is not entirely risk-free, because of the potential danger of bleeding due to the friability of amyloid-laden tissues, or of concomitant coagulopathy. Subcutaneous abdominal fat-pad aspirate has been established as a safe and simple procedure in making the diagnosis of amyloidosis without the risk of internal bleeding (*4*). Even after a diagnosis is made by needle aspiration, however, the extent of the disease still needs to be delineated. Conceivably, total-body imaging using radionuclides with great affinity for amyloid deposits could provide this information by noninvasive means. The affinity of amyloid deposits for Tc-PPi may give scintigraphy a complementary role, along with needle biopsy, in the diagnosis of amyloid involvement of the thyroid. In our cases, diffuse and almost universal involvement of the entire thyroid gland was clearly demonstrated in amyloid goiter. On the other hand, only focal uptake of Tc-PPi would be expected in medullary carcinoma.

Various radiotracers have been reported in the past for detection of amyloidosis, and bone-seeking radiopharmaceuticals (Tc-99m-labeled phosphates) have been shown to be the most effective. Gallium-67 citrate has shown rather inconsistent findings. Our recent study suggested that Tc-99m pyrophosphate (Tc-PPi) is superior to Tc-99m methylene diphosphonate (Tc-MDP) in its affinity for amyloid deposits, even though the latter is a better bone-imaging agent (*5,6,13*). The findings on conventional thyroid images are nonspecific for amyloid goiter (*1*).

The mechanism of amyloid uptake of Tc-PPi has not been established. The high focal calcium content of amyloid tissue may be considered the cause of Tc-PPi avidity. Another theory, however, proposes that transchelation of Tc-99m atoms from Tc-PPi to the abnormal amyloid protein may be the reason for high avidity of Tc-PPi in amyloid deposits (*5,6,13*). Further investigation is needed to establish the exact mechanism.

Soft-tissue uptake of Tc-PPi is by no means unique for amyloidosis. Other conditions have been known to show high avidity to Tc-PPi, including acute myocardial infarction, soft-tissue trauma, and certain types of neoplastic lesions (e.g., breast carcinoma, osteogenic sarcoma). The thyroid gland, however, is almost never involved in these diseases (*5,6,13*). In amyloid goiter, as we have demonstrated, the thyroid involvement is massive, with diffuse and marked uptake of Tc-PPi in the enlarged gland. Therefore, in an individual with a history of rapidly enlarging goiter and the histological finding of amyloid in any organ, the diagnosis of amyloid goiter can be established preoperatively by scintigraphy. Furthermore Tc-PPi imaging enables the entire body to be surveyed at the same time, so the extent of amyloidosis can be evaluated simultaneously, and unsuspected sites of amyloid involvement (*6*)—e.g., the heart—can be detected.

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