Is ^{18}F-FDG PET/CT Useful for Distinguishing Between Primary Thyroid Lymphoma and Chronic Thyroiditis?

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Purpose: This study aims to investigate the usefulness of ^{18}F-FDG PET/CT for distinguishing between primary thyroid lymphoma (PTL) and chronic thyroiditis.
Methods: We retrospectively reviewed the data of 196 patients with diffuse ^{18}F-FDG uptake of the thyroid gland and enrolled patients who were diagnosed as having PTL or chronic thyroiditis based on the medical records, pathological findings, and laboratory data. The enrolled patients comprised 10 PTL patients (M/F = 4:6) and 51 chronic thyroiditis patients (M/F = 8:43). Images had been acquired on a PET/CT scanner at 100 minutes after intravenous injection of ^{18}F-FDG.
Results: The PTL group consisted of 7 patients with diffuse large B-cell lymphoma (DLBCL) and 3 with mucosa-associated lymphoid tissue (MALT) lymphoma. The maximum standardized uptake value (SUV_{max}) was significantly higher in the PTL group than that in the chronic thyroiditis group (25.3 ± 8.0 and 7.4 ± 3.2, $P < 0.001$). On the other hand, the CT density (Hounsfield unit: HU) was significantly lower in the PTL group than that in the chronic thyroiditis group (46.1 ± 7.0 HU and 62.1 ± 6.9 HU, $P < 0.001$). Within the PTL group, the SUV_{max} was significantly higher in the cases of DLBCL than in those of MALT lymphoma (29.0 ± 6.4 and 16.7 ± 2.3, $P = 0.017$).
Conclusions: The SUV_{max} was significantly higher and the CT density was significantly lower in PTL as compared with those in chronic thyroiditis. Thus, ^{18}F-FDG PET/CT may be useful for distinguishing between PTL and chronic thyroiditis.

Key Words: primary thyroid lymphoma, chronic thyroiditis, ^{18}F-FDG, PET/CT, diffuse thyroid uptake

(*Clin Nucl Med* 2013;38: 709–714)

Primary thyroid lymphoma (PTL) is a rare thyroid tumor, accounting for approximately 5% of all malignant tumors of the thyroid and 2%–7% of all extranodal malignant lymphomas[1–3]; it is well known to have a strong association with chronic thyroiditis.[4–6] ^{18}F-FDG PET/CT is an established imaging tool for the evaluation of patients with malignant lymphoma or inflammatory diseases.[7–9]

Chronic thyroiditis is known to be characterized by diffuse thyroid uptake on ^{18}F-FDG PET, and diffuse ^{18}F-FDG uptake of the thyroid gland has been considered to be suggestive of benign disease.[10–13] On the contrary, a few cases of evaluation of PTL by ^{18}F-FDG PET have been reported, with all exhibiting various degrees of elevation of the ^{18}F-FDG uptake by the thyroid gland[14–21]; among these cases, some patients with PTL also showed diffuse thyroid uptake,[15,20] and the differences in the findings on ^{18}F-FDG PET between PTL and chronic thyroiditis were not addressed.

In addition, PET/CT allows evaluation of not only ^{18}F-FDG uptake but also of the CT attenuation of the thyroid gland. According to previous reports, patients with chronic thyroiditis exhibit decreased CT density of the thyroid gland as compared to healthy subjects.[22,23] On the other hand, the CT density of the thyroid gland has been reported for small number of PTL patients[24] and is not well known.

The aim of this study was to investigate whether ^{18}F-FDG PET/CT might be useful to distinguish between PTL and chronic thyroiditis in the situation of diffuse thyroid uptake.

PATIENTS AND METHODS

Patients

We conducted a retrospective review of the data of 7622 patients who underwent ^{18}F-FDG PET for the evaluation of known/suspected cancer or for general health screening between January 2005 and October 2011, and then analyzed the data of 196 of these patients who showed diffuse ^{18}F-FDG uptake in the thyroid gland. For each case, we reviewed the clinical information pertaining to the thyroid gland, including the serological test results for antithyroglobulin antibody (TgAb; reference value: less than 28 IU/mL), antithyroperoxidase antibody (TPOAb; reference value: less than 16 IU/ml), antithyroid microsomal antibody (reference titer value: less than 1:100), and thyroid-stimulating hormone (TSH; reference value: 0.35–4.94 mIU/L), and the serum-free thyroxine level (fT4; reference value: 0.70–1.48 ng/dL). We also reviewed the thyroid ultrasonographic and histological findings of these patients.

Ten patients with PTL (M/F = 4:6, age range 44–88 years) who had been histopathologically confirmed as having malignant lymphoma and had never previously received chemotherapy or radiation therapy were included in the PTL group. The histologic subtype of the malignant lymphoma was also investigated.

A total of 51 patients with chronic thyroiditis (M/F = 6:45, age range 31–87 years) who had been diagnosed as having chronic thyroiditis by clinical and laboratory assessment or by histopathological examination were included in the chronic thyroiditis group. The diagnosis was based on the guideline for the diagnosis of chronic thyroiditis drafted by the Japan Thyroid Association, including (1) positive test result for TgAb (13 patients); (2) positive test result for TPOAb or antithyroid microsomal antibody (26 patients); (3) overt or subclinical hypothyroidism without any other identifiable cause, supported by elevated serum TSH and/or decreased fT4 level (24 patients); (4) hypoechoic and/or nonhomogeneous pattern on thyroid ultrasonography (30 patients); and (5) lymphocytic infiltration of the thyroid gland confirmed by cytological examination (3 patients).

Two patients with Graves disease and 133 patients without sufficient thyroid function test data were excluded.

This study was conducted with the approval of the Ethics Committee for Clinical Research of Asahi General Hospital.

Received for publication March 28, 2013; and revision accepted May 8, 2013.

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Conflicts of interest and sources of funding: none declared.

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ISSN: 0363-9762/13/3809–0709

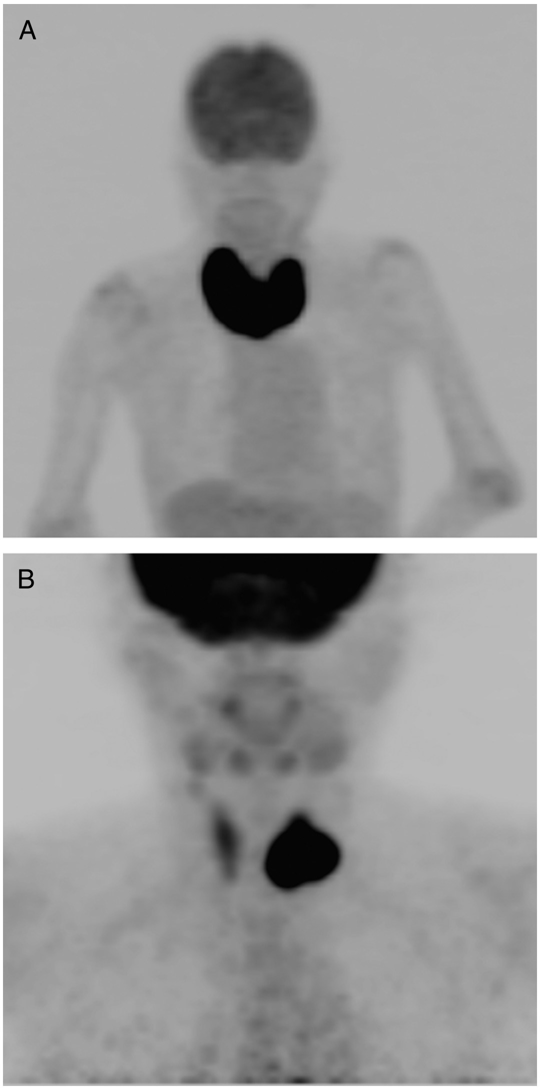

FIGURE 1. ^{18}F-FDG uptake pattern of the thyroid gland. Shown are examples of maximum-intensity-projection images with diffuse uptake (**A**) and diffuse plus focal uptake (**B**).

^{18}F-FDG PET/CT Protocol

Images were acquired on a PET/CT scanner (Siemens Biograph LSO DUO, Knoxville, TN, USA). CT studies for attenuation correction and anatomic coregistration were performed without contrast medium under free-breathing. CT studies for attenuation correction were performed with low-dose protocol (mAs = 40–45, pitch = 1.65). PET emission data were obtained in 3D mode for 2 minutes at each bed position, over a total of 14–16 minutes (7–8 bed positions) in all cases. After he/she had fasted for at least 5 hours, the subject was administered ^{18}F-FDG at 3 MBq/kg (81 μCi/kg) body by intravenous injection. Most of the subjects drank approximately 300 mL of water (room temperature) as oral hydration, and bladder evacuation was carried out before collection of the PET/CT data. Whole-body scanning was performed at 100 minutes after the ^{18}F-FDG injection.

Image Analysis

All acquired images were interpreted by the consensus of at least 2 radiologists (MN, KY, YR, IU). We manually drew a circular region of interest (ROI) measuring 1–1.5 cm in diameter in the area of the thyroid gland showing the highest ^{18}F-FDG uptake to calculate the maximum standardized uptake value (SUV_{max}) and also the mean CT density (Hounsfield unit: HU) for each patient. The thyroid uptake pattern was classified, based on the maximum intensity projection (MIP) images, as diffuse uptake or diffuse plus focal uptake (Fig. 1).

Statistical Analysis

The SUV_{max} and CT density values were compared using unpaired Student *t* test. Between the cases of DLBCL and MALT lymphoma, the nonparametric Mann-Whitney *U* test was used to determine the significance of differences. Numeric data for each group were expressed as the means ± standard deviation. *P* values <0.05 were considered to indicate statistically significant differences.

RESULTS

The clinical characteristics of the patients with PTL are shown in Table 1. The PTL group consisted of 7 DLBCL patients and 3 MALT lymphoma patients. In regard to the distribution of the pattern of elevated ^{18}F-FDG uptake, 5 patients showed diffuse uptake, while the remaining 5 showed diffuse plus partially focal uptake. Six of the 10 PTL patients had previously been diagnosed as having chronic thyroiditis and received thyroid hormone therapy, and 1 patient was diagnosed based on the serological test result for thyroid antibody after PET/CT, while no information related to the chronic thyroiditis was available for the remaining 3 cases. In the chronic thyroiditis group, 46 patients showed diffuse ^{18}F-FDG uptake, 3 patients showed diffuse uptake plus partially

TABLE 1. Clinical Characteristics of the 10 Patients With Primary Thyroid Lymphoma

Case	Age	Sex	Distribution	SUV_{max}	CT Value	Subtype	Extrathyroidal Lesion
#1	88	F	D	21.7	43	DLBCL	None
#2	58	F	D + F	30.0	44	DLBCL	Neck LNs
#3	48	M	D + F	29.5	50	DLBCL	Neck LNs
#4	70	F	D	18.2	47	MALT	None
#5	49	F	D + F	19.5	46	DLBCL	None
#6	73	M	D + F	17.9	56	MALT	None
#7	71	M	D	31.9	34	DLBCL	Neck LNs
#8	57	F	D	32.3	47	DLBCL	None
#9	69	F	D	38.0	38	DLBCL	Neck LNs
#10	63	M	D + F	14.1	56	MALT	None

CT indicates computed tomography; D, diffuse; D + F, diffuse + focal; DLBCL, diffuse large B-cell lymphoma; F, female; LNs, lymph nodes; M, male; MALT, mucosa-associated lymphoid tissue; SUV_{max}, maximum standardized uptake value.

focal high uptake, and 2 patients showed diffuse uptake plus partially focal low uptake.

The SUV_{max} in the PTL group was 25.3 ± 8.0 (range 14.1–38.0), while that in the chronic thyroiditis group was 7.4 ± 3.2 (range 3.1–16.1). The SUV_{max} was significantly higher in the PTL group than that in the chronic thyroiditis group ($P < 0.001$) (Figs. 2, 3A).

The CT density in the PTL group was 46.1 ± 7.0 HU (range 34–56 HU), while that in the chronic thyroiditis group was 62.1 ± 6.9 HU (range 47–79 HU). The CT density was significantly lower in the PTL group than that in the chronic thyroiditis group ($P < 0.001$) (Fig. 3B).

Within the PTL group, the SUV_{max} in the cases of DLBCL was 29.0 ± 6.4 (range 19.5–38.0), while that in the cases of MALT lymphoma was 16.7 ± 2.3 (range 14.1–18.2). Thus, the SUV_{max} was significantly higher in the cases of DLBCL than in those of MALT lymphoma, without any overlap ($P = 0.017$) (Fig. 3A).

DISCUSSION

Our results suggest the diagnostic usefulness of ^{18}F-FDG PET/CT for differential diagnosis between PTL and chronic thyroiditis. To the best of our knowledge, this is the first study to compare the ^{18}F-FDG PET findings of PTL and chronic thyroiditis from both the aspects of SUV_{max} and the CT density.

Receiver Operating Characteristic (ROC) Curve Analysis

We drew ROC curves for determining the optimal cutoff values of the SUV_{max} and CT density for differential diagnosis between PTL and chronic thyroiditis (Fig. 4). The suggested cutoff value of SUV_{max} to discriminate PTL from chronic thyroiditis was 14.1, which yielded a sensitivity of 100%, specificity of 94.1%, and area under the curve (AUC) of 0.994. The suggested cutoff value of CT density was 51 HU, which yielded a sensitivity of 94.1%, specificity of 80%, and AUC of 0.951. We thought it unnecessary to combine SUV_{max} and CT density to improve the diagnostic accuracy because the SUV_{max} alone had sufficient diagnostic value. Besides, Han et al[25] and Tateishi et al[26] demonstrated the existence of a negative correlation between the SUV_{max} and CT density in chronic thyroiditis patients, which indicated with both findings reflecting the ^{18}F-FDG avid cellularity of the thyroid gland, and being interdependent.

Difference in the SUV_{max} of the Thyroid Gland Between PTL and Chronic Thyroiditis

Case reports reveal a wide range of SUV_{max} in cases of PTL (7.4–39.6).[14–17] A few reports have described both the SUV_{max} and the histologic subtypes of the lymphomas. According to previous reports,

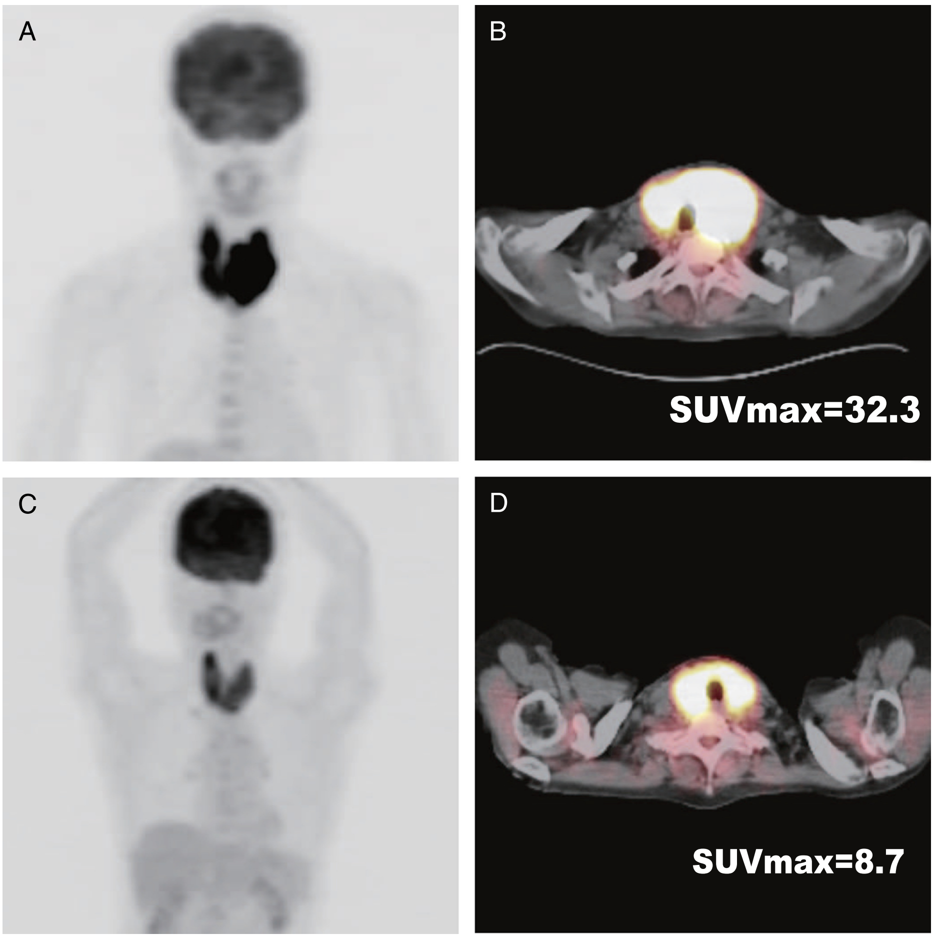

FIGURE 2. Maximum-intensity-projection image (**A**) and transaxial fused image (**B**) with diffuse ^{18}F-FDG uptake in a primary thyroid lymphoma patient (**C**, **D**) and those in a chronic thyroiditis patient. It is difficult to distinguish between the primary thyroid lymphoma and chronic thyroiditis visually. However, the maximum standardized uptake value (SUV_{max}) was significantly different between the 2 lesions.

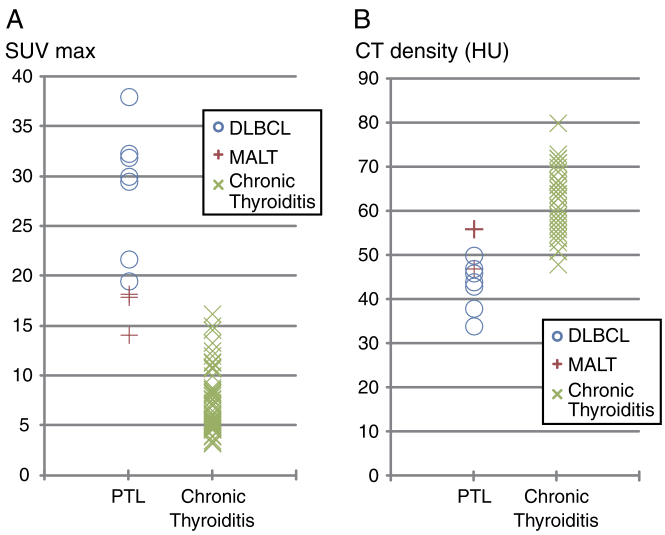

FIGURE 3. Comparison of the SUV_{max} (**A**) and CT density (**B**) between primary thyroid lymphoma and chronic thyroiditis. CT indicates computed tomography; DLBCL, diffuse large B-cell lymphoma; HU, Hounsfield unit; MALT, mucosa-associated lymphoid tissue; PTL, primary thyroid lymphoma; SUV_{max}, maximum standardized uptake value.

the SUV_{max} was 12.2 in cases of MALT lymphoma,[14] and 9 and 39.4 in cases of DLBCL.[16,17]

It is well known that the ^{18}F-FDG uptakes of malignant lymphomas differ by the histologic subtypes and that DLBCLs show higher uptake values than MALT lymphomas.[27,28] However, there are no reports comparing the ^{18}F-FDG uptake values in only cases of PTL. Our study revealed higher ^{18}F-FDG uptake values in the cases of DLBCL than in those of MALT lymphoma, consistent with the results reported previously from the nodal or extranodal malignant lymphoma study. Still, our 3 cases of MALT lymphoma showed higher ^{18}F-FDG uptake values than usual, and we think that they had tumors of a transformed type, based on the high ^{18}F-FDG uptake values[29] and the clinical characteristic of rapid growth in size of the thyroid gland.

With respect to chronic thyroiditis, a range of SUV_{max} has been reported by several ^{18}F-FDG PET studies.[10,11,25,26,30,31] The mean SUV_{max} reported for chronic thyroiditis in previous literature is in the range of 2.8–8.2 and the highest SUV_{max}, reported by Karantanis et al,[11] is 16.8. While this value is slightly higher, it is in almost the same range as that in our chronic thyroiditis group.

Considering previous reports and our results together, there is a partial overlap of the ^{18}F-FDG uptake between PTL and chronic thyroiditis. Thus, we think that it might be difficult to distinguish between PTL with low ^{18}F-FDG uptake and chronic thyroiditis with high ^{18}F-FDG uptake. However, it is clear that diffuse ^{18}F-FDG uptake of the thyroid gland does not always reflect a benign condition and diffuse very high ^{18}F-FDG uptake, especially with an SUV_{max} of 17 or more, may represent potentially malignant lesions.

Difference in CT Values Between PTL and Chronic Thyroiditis

According to previous studies, the mean noncontrast-enhanced CT density of PTL is 51 HU[24] and that of chronic thyroiditis is in the range of 61.4–86.2 HU.[22,23,25,26] Our data for these 2 groups revealed values of 46.1 and 62.1, respectively, consistent with the aforementioned reports. On CT imaging, normal thyroid gland shows high attenuation because thyroid follicles contain much iodine. The decreased attenuation in chronic thyroiditis is thought to reflect the decreased iodine density in the thyroid gland caused by diffuse infiltration of the gland by lymphocytes and lymphoid follicles with reactive germinal centers.[6,22] On the other hand, mainly tumor attenuation is seen in cases of PTL, regardless of the iodine content of the thyroid, because most PTL cases show dense proliferation of lymphoma cells and sheet-like effacement of the thyroid parenchyma, and microscopic examination reveals few normal thyroid follicles (Fig. 5).[6] The differences in the CT density among PTL and chronic thyroiditis might be accounted for by the different degrees of effacement of the thyroid follicles.

Study Limitations

In this study, many patients with diffuse thyroid uptake for whom sufficient results of thyroid examination were not available were excluded, and most of the chronic thyroiditis patients had not undergone biopsy, which could lead to the following possible limitations of this study.

First, a selection bias may have been introduced in our chronic thyroiditis group because we included only ^{18}F-FDG–avid cases. Rothman et al[32] reported that only 9.5% of hypothyroid patients showed diffuse ^{18}F-FDG uptake of the thyroid gland, which indicates that the mean SUV_{max} in chronic thyroiditis may differ depending on the selection of the patients. However, for the purpose of this study, that is, of determining whether ^{18}F-FDG PET/CT might be useful to distinguish between PTL and chronic thyroiditis under the condition of diffuse thyroid uptake, this patient selection might be reasonable.

Furthermore, in a subanalysis, statistically significant differences were observed in the SUV_{max} (7.4 ± 3.2 and 6.0 ± 2.4, respectively, $P < 0.01$) and mean CT value (62.1 ± 6.9 HU and 65.6 ± 10.4 HU, respectively, $P < 0.01$) between our diagnosed chronic thyroiditis patients and excluded patients. This difference could be explained by the higher tendency of patients with higher thyroid uptake towards having undergone adequate thyroid examinations, or by the presence of other clinical conditions characterized by low ^{18}F-FDG uptake in the excluded

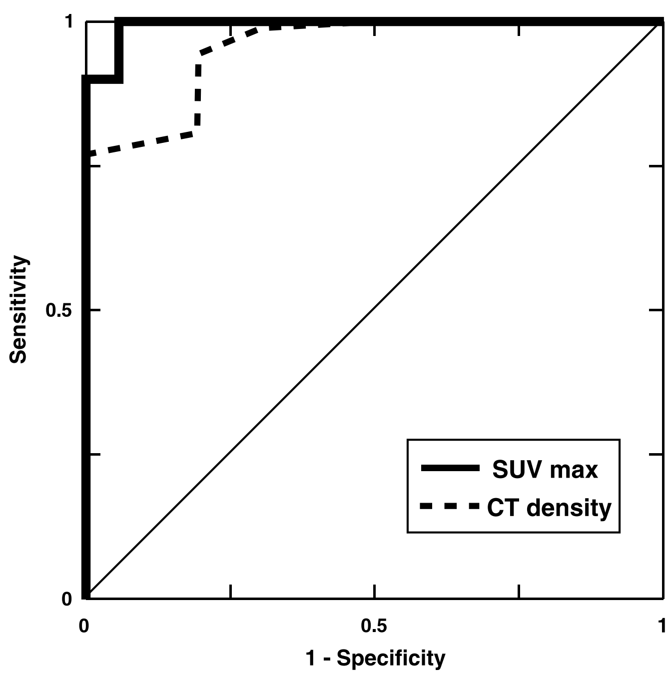

FIGURE 4. Receiver operating characteristic (ROC) curves of the maximum standardized uptake value (SUV_{max}) and CT density.

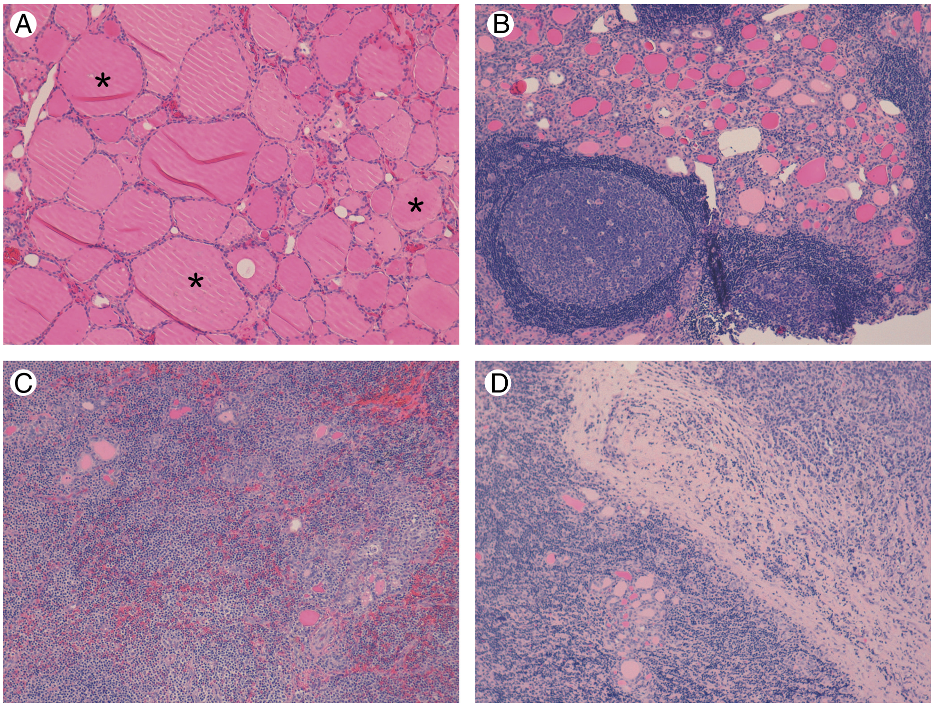

FIGURE 5. Low-power magnification (×10 objective) of hematoxylin-and-eosin–stained (**A**) normal thyroid gland, (**B**) chronic thyroiditis, (**C**) mucosa-associated lymphoid tissue lymphoma, and (**D**) diffuse large B-cell lymphoma. The number and size of the thyroid follicles with colloids (*asterisks*), which contain much iodine, are decreased in chronic thyroiditis compared to the findings in the normal thyroid gland. Mucosa-associated lymphoid tissue lymphoma and diffuse large B-cell lymphoma also show a decrease in the sizes of the thyroid follicles, and a greater degree of effacement of the thyroid follicles, caused by the massive infiltration by lymphoma cells, is seen in the case of PTL than in that of chronic thyroiditis.

cases. Thus, our chronic thyroiditis group did not represent the entire spectrum of chronic thyroiditis patients and included only those patients who showed higher uptake in the thyroid. Nevertheless, there were significant differences in the FDG uptake values between PTL and chronic thyroiditis.

Second, because of the strong association between PTL and chronic thyroiditis,[4–6] undiagnosed PTL cases may have been included in the chronic thyroiditis group. However, considering this possibility, our results could be restated as representing the differences between patients with aggressive lymphoma and chronic thyroiditis with or without indolent lymphoma. The detection of high-grade malignant lymphoma is informative for treatment because it indicates the necessity for aggressive treatment as compared to that for indolent lymphoma.[1] Besides, this is the first report of a single-center consecutive study of PTL associated with diffuse thyroid ^{18}F-FDG uptake, and these results might also be useful for daily clinical practice.

Another potential limitation of our current study was that it was a retrospective study involving only a small number of PTL patients. Further studies with large numbers of patients are needed to improve the diagnostic accuracy of ^{18}F-FDG PET/CT for PTL.

CONCLUSIONS

In conclusion, the SUV_{max} was significantly higher and the CT density was significantly lower in PTL patients as compared to those in chronic thyroiditis patients. In addition, the SUV_{max} of the thyroid gland was higher in cases of DLBCL than in those of MALT lymphoma. Diffuse ^{18}F-FDG uptake of the thyroid gland is not always reflective of a benign condition, and ^{18}F-FDG PET/CT may be useful for distinguishing between PTL and chronic thyroiditis from both the aspects of SUV_{max} and the CT density.

ACKNOWLEDGMENTS

The authors would like to thank the staff of the PET imaging center at Asahi General Hospital for their skillful technical support.

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