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CASE REPORT

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Mantle cell lymphoma involving the thyroid gland

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Abstract

Mantle cell lymphoma (MCL) rarely involves thyroid gland. Positron emission tomography–computed tomography (PET-CT) may be critical in identifying thyroid involvement by MCL and pursuing further work up of the suspicious thyroid lesions, irrespective of the thyroid function tests.

KEYWORDS

mantle cell lymphoma, PET, thyroid lymphoma

1 | INTRODUCTION

Mantle cell lymphoma (MCL) comprises 3%-8% of non-Hodgkin lymphomas and is considered an incurable malignancy.[1] MCL has two clinical presentations: the classical MCL, which involves lymph nodes and extranodal sites, and the non-nodal leukemic MCL, which presents with involvement of peripheral blood, bone marrow, and spleen.

The major sites of extranodal manifestations are blood, bone marrow, gastrointestinal tract, and lungs.[2] Notably, thyroid gland involvement is uncommonly reported, with only four case reports in the literature.[3-6] Herein, we present two MCL patients with thyroid gland involvement on presentation.

2 | CASE REPORTS

A 69-year-old woman was found to have elevated white blood cells 16.3 × 10^3/μL, absolute lymphocytes 9.5 × 10^3/μl, hemoglobin 12 g/dL, and platelet 253 × 10^3/μL. A peripheral blood smear showed numerous lymphocytes ranging from small to large, some with irregular nuclear contours and some with blastic nuclear chromatin. Peripheral flow cytometry demonstrated a kappa light chain restricted monoclonal B-cell population, representing 78% of the lymphoid cells, positive for CD5, CD19, and CD20 and negative for CD10 and CD23 and FISH analysis revealed 17p deletion and IgH-CCND1 fusion in 43% of cells. Bone marrow biopsy showed neoplastic B-cell infiltrates occupying less than 10% of marrow space, which were positive for PAX5, CD20, CD19, CD22, HLA-DR, CD5, cyclin D1, CD23, SOX11, and FMC7 and negative for CD10 and CD38 by immunohistochemistry and flow cytometry. Positron emission tomography–computed tomography (PET-CT) showed enlarged FDG avid cervical lymph nodes, mildly FDG avid low-density nodule in the right thyroid lobe, FDG avid lymph nodes in the mediastinum, retroperitoneum, and splenomegaly with diffuse FDG uptake. TSH was 1.40 mcIU/

mL (normal range 0.270-4.200). Ultrasound of the thyroid gland showed a 4.9 × 3.2 cm heterogeneous mass in the right lobe, a 2.6 × 1.6 cm solid isoechoic mass with accompanying vascularity in the left lobe and a 0.9 × 0.7 cm nodular lesion inferior to the isthmus. Fine needle aspiration of the thyroid nodules demonstrated Cyclin D1 positive lymphoma cells (Figure 1A-C). The patient was diagnosed with Stage IV MCL with leukemic phase with intermediate risk MIPI score 5.9, and since she was asymptomatic and she was followed with active surveillance.

At 16 months after diagnosis, she developed worsening anemia concerning for disease progression. She was subsequently started on bendamustine and rituximab and completed six cycles. PET-CT after the completion of chemotherapy showed resolution of splenomegaly and most of the lymphadenopathy and re-demonstrated mildly FDG avid mediastinal lymph nodes and a multinodular goiter with focal uptake in the left thyroid lobe. Ultrasound of the thyroid gland showed a new 1.6 × 1.3 cm nodule and mild increase of pre-existing nodules in the left lobe. Restaging bone marrow biopsy was negative for lymphoma involvement. She was deemed to have a partial response. She was started on Ibrutinib 560 mg, and repeated PET-CT 2 months later demonstrated a stable disease. Currently, she remains with stable disease for 22 months since the initiation of Ibrutinib.

A 61-year-old man presented with cough, drenching night sweats, flank pain, and a growing abdominal mass. Labs showed white blood cell count 18.5 × 10^3/μl, hemoglobin 8.9 g/dL, platelet 76 × 10^3/μl, absolute lymphocytes 15.4 × 10^3/μl, and lactate dehydrogenase (LDH) 468 IU/L (normal range 121-224). PET-CT showed generalized increased FDG activity in both thyroid lobes with enlargement of the right lobe with maximum SUV of 6.3, mildly FDG avid adenopathy of the mediastinum and retroperitoneum, enlarged FDG avid kidneys and splenomegaly 23 × 22 cm. Bone marrow biopsy showed infiltration with B-cells positive for CD20 and cyclin D1, accounting for 30% to 40% of marrow cellularity, and flow cytometry showed a monotypic population of B-cells positive for CD5, CD19, CD20, CD38, FMC7, HLA-DR, and CD45 and negative for CD10, CD23, or CD103. FISH was positive for deletion of 6q, 11q, monosomy 13, and CCND1-IGH fusion with translocation t(11;14). Left renal biopsy showed MCL with Ki67 staining in 70% of malignant cells. He was diagnosed with stage IV MCL with MIPI 9.6. TSH was elevated 21.520 mcIU/mL (normal range 0.270-4.200), free T4 was decreased 0.87 ng/dL (normal range 0.93-1.7) and, therefore, he was diagnosed with hypothyroidism, that was attributed to lymphoma infiltration, and was started on levothyroxine.

The MCL was treated with R-MACLO-IVAM (rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, ifosphamide, cytarabine, and etoposide). After four cycles, restaging with CT, PET-CT, and bone marrow biopsy demonstrated absence of lymphoma, confirming a complete

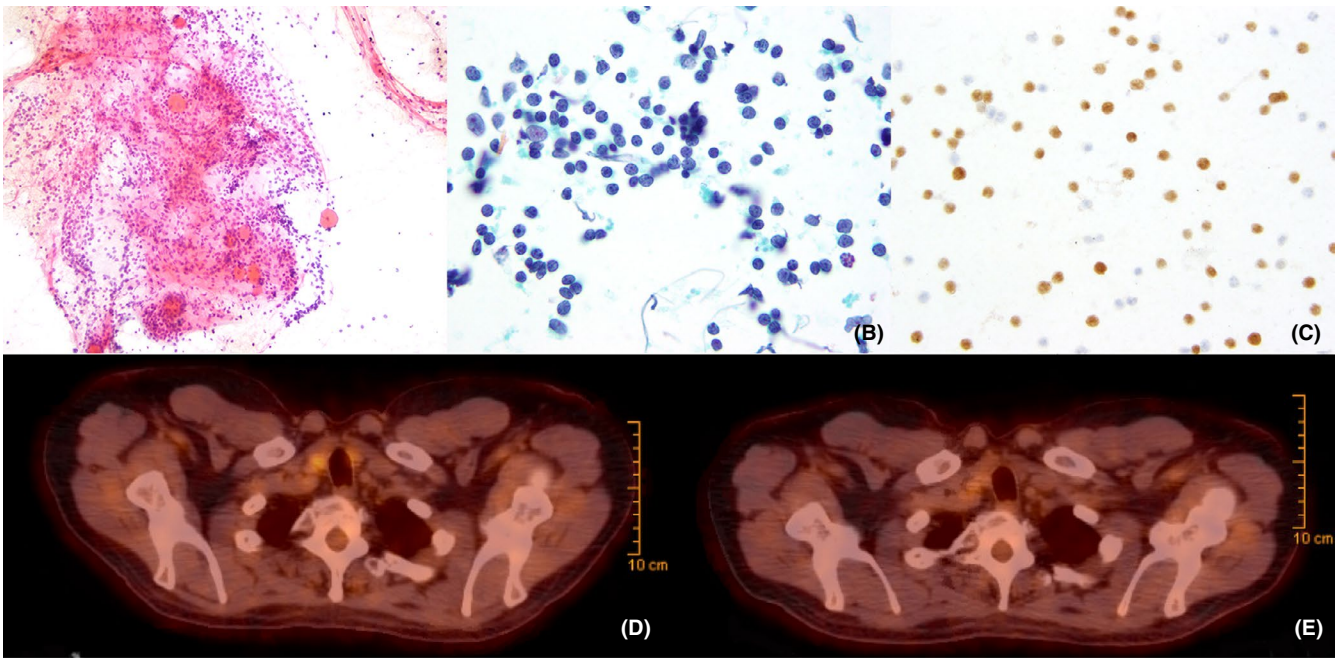

FIGURE 1 Pathological and radiological findings in thyroid MCL. A, Papanicolaou-stained fine needle aspiration of thyroid shows thyroid follicular cells and colloid with an associated lymphoid infiltrate. B, Lymphoid cells are small to intermediate in size with condensed chromatin and mild nuclear membrane irregularities. C, Immunocytochemistry for cyclin D1 is diffusely positive among the cytologically atypical lymphoid cells, confirming involvement by the patient's previously diagnosed mantle cell lymphoma. D, PET CT before the initiation of Ibrutinib demonstrating an asymmetric FDG uptake, SUV 3.7, at the lower pole of the right thyroid lobe corresponding to a subtle 8-mm hypodense nodule. E, PET CT 2 mo after the initiation of Ibrutinib demonstrating interval decrease in metabolism of the right thyroid nodule, SUV 1.4 similar to background level

response (CR). The thyroid functions were balanced, and he was started on rituximab maintenance every 6 months. Repeated PET-CT 21 months after the completion of the R-MACLO-IVAM showed interval development of isolated asymmetric FDG uptake, SUV 3.7, at the lower pole of the right thyroid lobe corresponding to a subtle 8-mm hypodense nodule. Ultrasound-guided fine needle aspiration of the right thyroid nodule showed atypical lymphocytic infiltrate with expression of cyclin D1 suggesting MCL relapse. The patient was started on Ibrutinib 560 mg daily, and repeat PET-CT 2 months later demonstrated a CR (Figure 1D-E). He remains in CR for the last 20 months.

3 | DISCUSSION

MCL's thyroid gland involvement can be due to de novo primary thyroid lymphoma (PTL) or part of a disseminated presentation. PTL accounts for 1% to 5% of the thyroid malignancies and 2.5% to 7% of the extranodal lymphomas.[7] While the majority of PTL present with a stage I disease, 10% have disseminated or multifocal involvement.[8] The most frequent histologic PTL is diffuse large B-cell lymphoma (DLBCL) (61.2%), followed by marginal zone lymphoma (MZL) (18.7%) and follicular lymphoma (FL) (8.1%), whereas the MCL is rare with an estimated frequency less than 2%.[8] Notably, only two cases of primary thyroid MCL have been described in the literature, both of which had underlying Hashimoto thyroiditis (HT) (Table 1).[3,5] Interestingly, the most common risk factor associated with PTL is HT, which can increase the risk of developing PTL by 40-80 times.[9] In a recent meta-analysis assessing the prevalence of HT in PTL, 79% of patients with PTL had evidence of HT and interestingly, the prevalence of HT was higher for MZL than in DLBCL.[10] These results imply different evolutionary mechanisms of lymphoma in the context of HT. It is possible that unrecognized antigens of the thyroid gland can stimulate B-lymphocytes at different stages of their development with a subsequent survival advantage, which in combination with acquired mutations leads to various lymphoma subtypes.

The incidence of secondary thyroid lymphoma is largely unknown. An old retrospective study reported that lymphomas could metastasize to the thyroid gland in 4%-19% of the cases.[11] It is plausible though that a portion of advanced stage PTL may be due to secondary thyroid involvement, and hence the frequency of secondary thyroid lymphomas may be higher. A clinicopathologic study from China showed that the most frequent histologic subtype of secondary thyroid lymphoma is DLBCL followed by Burkitt lymphoma, whereas MCL was not reported to affect the thyroid gland.[12] Similarly, autopsy studies of MCL did not report thyroid involvement.[2] Hence, it is tempting to speculate that MCL dissemination to the thyroid is rare or underdiagnosed. Notably,

TABLE 1 Cases of MCL of the thyroid gland reported in the literature

	Age	Primary/ Secondary	Hashimoto thyroiditis	Hypothyroidism	Stage	MIPI	Treatment	Survival outcome until publication
Patient 1	69	Secondary	No	–	IV	5.9	Bendamustine +rituximab, ibrutinib	PR with 1st line Rx, Stable disease for 16 mo with 2nd line Rx
Patient 2	61	Secondary	No	Yes	IV	9.6	R-MACLO-IVAM, ibrutinib	TTP 21 mo with 1st line Rx, Relapse free for 14 mo with 2nd line Rx
Guastafierro et al[5]	59	Primary	Yes	–	IEA	5.2	Enhanced R-CEOP	Relapse free: 4 y
Hojila et al[4]	59	Secondary	No	Yes	IV	–	Observational surveillance	PFS 2 y
Siddiqui et al[3]	63	Primary	Yes	–	IIE	3	Observational surveillance	PFS 2 y
Mengoli et al[6]	48	Secondary	No	–	IV	–	–	–

Abbreviations: PFS, progression free survival; PR, partial response; R-CEOP, rituximab, cyclophosphamide, etoposide, vincristine, and prednisone; R-MACLO-IVAM, rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, ifosphamide, cytarabine and etoposide; Rx, therapy; TTP, time to progression.

only four case reports of secondary thyroid MCL have been reported in literature, including our cases, and remarkably, only half of the cases had either prior history of hypothyroidism or developed hypothyroidism due to MCL, underscoring the clinical significance of obtaining thyroid tests in patients with MCL (Table 1).

In our cases, the clinical suspicion of the thyroid gland involvement by the MCL was based on the FDG uptake of thyroid gland. A systemic review of the role of ^{18}F-FDG PET or PET/CT in patients with MCL has shown a low sensitivity 39% (11%-60%) in detecting GI involvement and 36% (12%-100%) in detecting BM disease.[13] Interestingly, the accuracy of ^{18}F-FDG PET or PET/CT in detecting thyroid involvement in patients with MCL is unknown. While ^{18}F-FDG accumulation in the normal thyroid tissue is usually low to absent, an incidental FDG uptake of the thyroid in not uncommon and is usually divided into focal or diffuse uptake, with the latter associated with HT.[14] In a retrospective study, incidental FDG thyroid uptake was reported in 2.8% of patients with lymphoma (N = 52 out of 1868) with 58% presenting with focal and 42% with diffuse uptake.[15] Notably, the chance of malignancy in focal thyroid lesions was 30%, either due to intercurrent thyroid cancer (5/9 patients) or secondary lymphomatous involvement (4/9 patients), whereas the diffuse thyroid uptake was not associated with cancer.[15]

In summary, the two cases presented herein indicate that thyroid gland can be involved by MCL. No patient had a prior history of HT, suggesting that an autoimmune component may be a risk factor for the development of MCL only in PTL. The short-lasting effect of the chemotherapy and the primary refractoriness implies that microenvironmental factors of the thyroid gland may contribute to acquisition of resistance, which could be amenable to BTK inhibition. They also underscore the importance of ^{18}F-FDG PET in identifying extranodal non-GI or BM involvement by MCL and pursuing further diagnostic work up in the suspicious FDG avid thyroid lesions. Further studies are needed to investigate the ^{18}F-FDG activity of the thyroid gland in patients with MCL, since an underlying activity may be related to lymphoma.

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CONFLICT OF INTEREST

GNP has received honoraria from Curio Science and OncLive and has served on advisory board from Atara Biotherapeutics. JPA has received honoraria from OncLive and Oncinfo, and immediate family member has served on advisory boards from Puma Biotechnology, Inovio Pharmaceuticals, Agios Pharmaceuticals, Forma Therapeutics and Foundation Medicine. JRC does not have any conflict of interest to report. ISL has served on advisory boards from Seattle Genetics, Janssen Scientific and Verastem.

AUTHOR CONTRIBUTIONS

GNP reviewed the literature and wrote the manuscript; JPA wrote the manuscript; JRC wrote the manuscript; ISL conceptualized the idea and was involved in the treatment of these patients and wrote the manuscript; all authors read and approved the final version of the manuscript.

ETHICAL STATEMENT

Written informed consent was obtained from the patients.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during current study.

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