DOI: 10.33470/2379-9536.1400

CASE REPORT Volume 9 Issue 2

B-Cell Non-Hodgkin's Lymphoma: Viewing an Aggressive Neck Mass in an Older Adult from a Primary Care Perspective

Tanner Jeffrey Bakhshi, PhD[1], Emily Hendricks, MD[2], Evan McClanahan, MD[1], Scott Gibbs, MD[1], Adam Franks, MD[1], Kathleen M. O'Hanlon, MD[1], Vincent Graffeo, MD, JD[1]

ABSTRACT

Patients with neck masses typically present to primary care providers, but most are unfamiliar with the management of aggressively expanding neck masses. With so many varied structures in the cervical region, a rapidly growing neck mass can be a diagnostic dilemma. The broad initial differential includes infectious, inflammatory, vascular, and malignant causes. When the clinical course points to an aggressive malignancy, the location of the mass helps provide clues to the likely etiology. Potential sites of involvement include the musculature, bone, larynx, trachea, esophagus, lymph tissue, and thyroid tissue. Anterior neck masses at the level of the thyroid should prompt a differential of primary thyroid lymphomas. Diffuse large B-cell lymphoma is most common, followed by mucosa-associated lymphoid tissue lymphoma, follicular lymphoma, and small lymphocytic lymphoma. Anaplastic thyroid carcinoma should be considered as well. A history of Hashimoto's thyroiditis should lead the clinician toward the large B-cell lymphoma. Prompt diagnosis via fine-needle aspiration biopsy is essential because compressive symptoms and airway collapse may rapidly ensue. A correct clinical and histopathologic diagnosis is essential. Primary thyroid lymphoma can often be treated with chemoimmunotherapy and radiation and has a mean overall survival of 9.0 years. Anaplastic thyroid carcinoma is often locally aggressive with advanced metastatic disease at presentation, and treatment options are more limited. Primary care physicians need to be familiar with these relatively rare etiologies for an aggressively expanding neck mass in order to recognize and rapidly coordinate diagnostic and treatment options in a timely fashion.

Author affiliations are listed at the end of this article.

Corresponding Author:
Kathleen O'Hanlon, MD
Marshall University
Joan C. Edwards
School of Medicine
kohanlon@marshall.edu

KEYWORDS

Primary Thyroid Lymphoma, Non-Hodgkins lymphoma, Diffuse B-Cell Lymphoma, Hashimoto's Thyroiditis, neck mass

INTRODUCTION

Primary thyroid lymphoma (PTL) is a rare malignancy affecting both the thyroid gland and regional lymph nodes that accounts for 5% of thyroid malignancies and 3% of all Non-Hodgkin's lymphoma (NHL). PTL has an incidence of 0.5 per 100,000, with an annual percent chance of 4.0% before 1994 and 2.4% after.[1-3] It typically occurs in the seventh decade of life, with a median age of 67 years old.[4,5] Women are 4 times more likely to be affected than men.5 Studies have shown that chronic autoimmune Hashimoto's thyroiditis is associated with a higher risk of PTL and increased relative risk of at least 60-fold compared to patients without Hashimoto's thyroiditis (HT).[6] Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of PTL, occurring nearly 70% of the time.[4] It is more aggressive and carries a worse prognosis than the second-most common subtype, Mucosa-Associated Lymphoid Tissue Lymphoma (10%).[4,7] Other subtypes include follicular lymphoma (10%) and small lymphocytic lymphoma (3%).[5] Historically, DLBCL was associated with a poor prognosis, as 60% of patients had metastatic disease at first presentation.[1] Today, PTL is more likely to be diagnosed at Stage I disease, although it is still associated with a median survival of 9.3 years.[4] Poor prognostic factors include age >80, Stage II-IV

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disease, and histology (large B-cell, follicular, or other non-Hodgkin's).[4]

The most common presentation of PTL is a rapidly enlarging, painless neck mass.[8] Other symptoms include dyspnea, dysphagia, hoarseness, stridor, and superior vena cava obstruction.[1,8] Symptoms such as fever, night sweats, and unintentional weight loss may also occur.[9] Because these lesions tend to be aggressive, provider familiarity is important, as quick recognition of these cancers can minimize morbidity and mortality. Primary care providers are usually the first physicians to encounter a new mass in an adult patient. Clinical practice guidelines recommend considering any neck mass to be malignant until proven otherwise.[10] The following case illustrates the difficulty of evaluating a neck mass in the face of infectious symptoms.

CASE PRESENTATION

A 68-year-old male presented with a 1-week history of postnasal drip, a sore, scratchy throat, acute laryngitis, and odynophagia. He denied fever, chills, cough, night sweats, or weight loss. His family history was pertinent for breast cancer in his mother and Non-Hodgkin's Lymphoma in his father. A physical exam revealed diffuse soft tissue swelling in the anterior neck region with palpable cervical adenopathy. COVID-19 and Flu A & B swabs were negative. A contrast computerized tomography (CT) of the neck's soft tissues showed a 2.7-cm solid mass in the right lateral wall of the supraglottic larynx between the hyoid bone and right thyroid cartilage, abnormal soft tissue thickening extending into the musculature overlying the thyroid cartilage and out to the right sternocleidomastoid muscle, and enlarged cervical chain lymph nodes.

Fiberoptic laryngoscopy revealed no visible mass of the nasopharynx, but submucosal fullness in the right hypopharynx extended to the piriform sinus and the inferior base of the tongue. The right supraglottic larynx was edematous, and the right true vocal fold showed decreased mobility. Positron emission tomography (PET) showed hypermetabolic bilateral thyroid nodules and right cervical adenopathy. Thyroid malignancy, such as anaplastic thyroid carcinoma (ATC), was suspected due to the aggressive clinical presentation, as was squamous cell carcinoma of the base of the tongue. However, CT-guided thyroid and laryngeal mass core biopsies yielded lymphoid proliferation consistent with DLBCL, non-germinal center type.

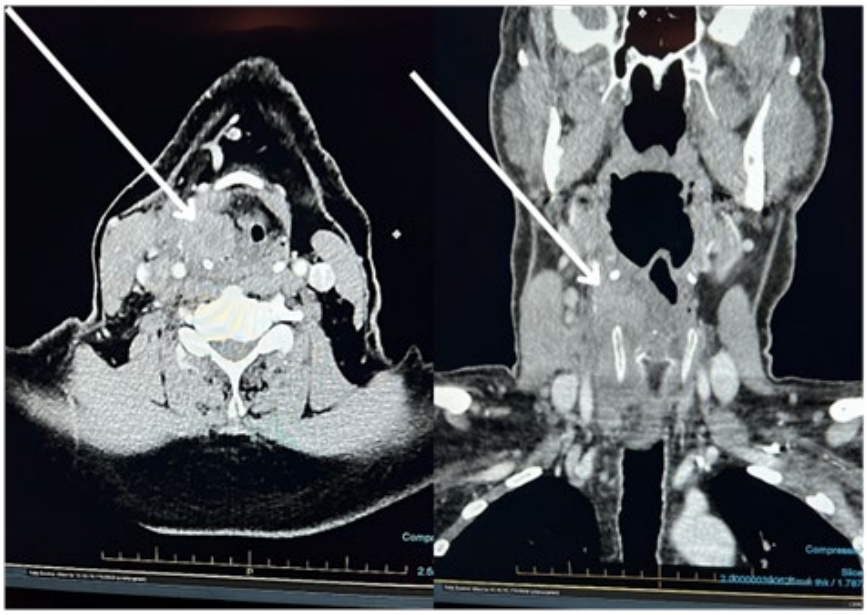

FIGURE 1. Axial and Coronal Imaging of neck mass by computed tomography

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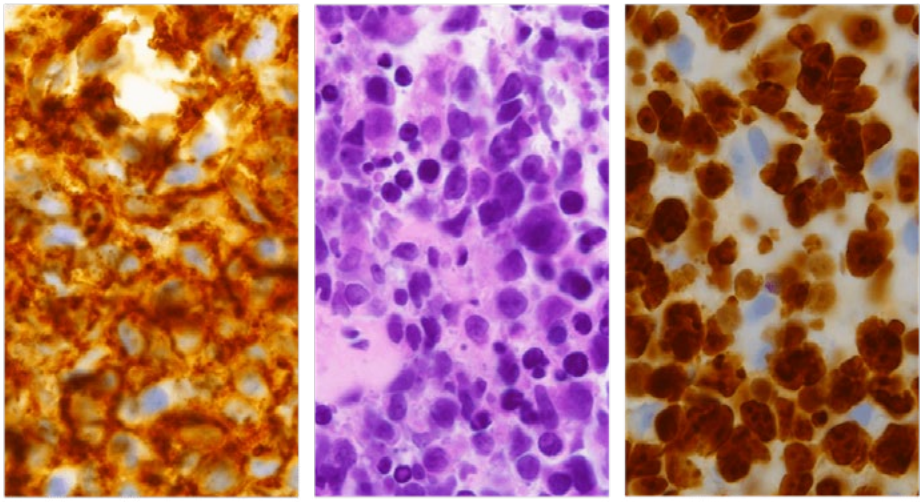

FIGURE 2. Histological sections of DLBCL, non-germinal center type stained with CD20 (left), H&E (middle), and Ki-67 (right) (1000x). (Image credit: Vincent A. Graffeo, M.D., J.D.)

The patient developed coarse dysphonia, occasional dysphagia, leftward tracheal deviation, and mild dyspnea. This impending airway compromise necessitated a tracheostomy, roughly 3 weeks after his initial presentation.

Bone marrow aspiration and biopsy showed normocellular bone marrow with trilineage hematopoiesis, negative for involvement (Stage II). Per National Comprehensive Cancer Network (NCCN) guidelines, he was treated with 3 cycles of chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone plus Rituximab (R-CHOP). Palpable lymphadenopathy resolved, and a repeat PET scan showed resolution of the hypermetabolic thyroid nodules and cervical masses. Repeat fiberoptic laryngoscopy was normal, except for weak abduction of the right true vocal cord. His tracheotomy was decannulated. He then completed consolidated radiotherapy to a total dose of 3060 cGy in 17 fractions. A third PET/CT 7 months later confirmed complete resolution.

DISCUSSION

Pathophysiology

While the pathogenesis of PTL is not fully understood, a working model has been proposed and described in the literature.[1] The strongest known risk factor is a history of HT, in which B- and T-lymphocytes diffusely infiltrate the thyroid gland, interact with thyroid antigens, and stimulate the production of autoantibodies. This is thought to trigger antibody-directed cellular cytotoxicity (ADCC), resulting in chronic thyroid damage and hypothyroidism.[11] Approximately 0.6% of all HT patients later develop PTL, and nearly 80% of patients with PTL have been diagnosed with HT.[12] It is thought that chronic antigen stimulation promotes the gradual evolution of lymphoid tissue within the thyroid into NHL.[1] The most common of NHL and PTL is DLBCL, which is an aggressive and heterogeneous cancer arising from mature B-cells as they progress through an antigen-stimulated germinal center reaction within lymphoid follicles. B-cells undergo rapid proliferation and somatic hypermutation of the genes that encode the variable regions of immunoglobulins. Although this reaction is required for adaptive immunity, increased tolerance of DNA damage increases its oncogenic potential.[13] Due to its aggressive nature, DLBCL is significantly more likely to demonstrate soft tissue and vascular invasion, abundant apoptosis, and a high mitotic rate. These features of DLBCL were associated with a significantly increased likelihood of death.[14] Therefore, DLBCL presenting to the thyroid must be rapidly diagnosed and treated.

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Diagnosis

Best clinical practices begin with avoiding antibiotics when a bacterial etiology is not suspected or the mass is not fluctuant. Masses that have existed for either ≥2 weeks or for an unknown period of time are concerning for cancer. Furthermore, physical exam findings of a firm, fixated mass >1.5 cm with overlying skin ulceration should increase the level of suspicion for malignancy.10 Laboratory analysis is useful in the diagnosis of PTL, but most patients are euthyroid upon initial presentation. Up to 80% of patients with PTL have circulating thyroid peroxidase antibodies, indicating an association between PTL and Hashimoto's Thyroiditis.

Diagnosis of PTL typically starts with imaging due to the relatively inconclusive results of laboratory analysis. Ultrasonography is the imaging modality of choice. Typically, 1 of 3 patterns will be revealed including nodular, diffuse, or mixed.[1,15] Appearance of a solitary PTL mass has a homogenous appearance without calcification, necrosis, and cystic degeneration, which can distinguish PTL from anaplastic thyroid carcinoma. Certain types of PTL may have other distinguishing features on ultrasound, such as asymmetric enlargement of the right and left glands seen in PT-NHL.[15] Other imaging studies are used in certain situations. For instance, MRI or CT scan may be used to assess for extension of a PTL mass into the surrounding structures, with MRI being more sensitive.[1] Initial pathologic assessment of PTL is done by fine needle aspiration cytology (FNAC) with ultrasound guidance. Immunohistochemical analysis done with FNAC will show PTLs are positive for leukocyte common antigen, CD20, and lambda light chain; they will be negative for cytokeratins.[1] Further analysis can be done with core biopsy which yields more tissue than FNAC and can help distinguish between Hashimoto's Thyroiditis, PTL, and anaplastic carcinoma.[1]

Diagnosis of PTL will also include determination of the subtype of tissue growth. This is done with cytologic analysis and immunohistochemical staining. The most common subtype of PTL is Diffuse Large B-Cell Lymphoma (DLBCL) which appears as a uniform population of large, abnormal lymphoid cells and may also show segmentation of nuclei or micro-nucleoli.[7] Another common subtype is MALT lymphoma which has a heterogeneous appearance with high cellularity and a prominent population of intermediate-size lymphoid cells containing large amounts of plasma cells.[7] Further diagnosis of PTL subtypes can be done with immunohistochemistry. DLBCL will typically show Bcl-6 and Bcl-2 positivity. MALT lymphomas will show the presence of Ig light chains, Bcl-2, and IgM heavy chains.[7]

Treatment

Because PTL is uncommon, much of what is known about its response to different treatment modalities has been derived from small retrospective studies. While the ideal treatment regimen is still debated, the growing consensus is that it should include both chemotherapy and radiation therapy.[1] This is consistent with the 2016 NCCN guidelines, which recommend first-line treatment with R-CHOP +/- radiation for limited-stage DLBCL (Stage I-II).[16] Specifically, non-bulky (<7.5 cm) limited-stage DLBCL can be treated with either 3 or 6 cycles of R-CHOP + radiation. Bulky (≥7.5 cm) limited-stage DLBCL requires 6 cycles. There is still debate as to whether limited-stage DLBCL should receive radiation, as a 2018 randomized clinical trial comparing R-CHOP with and without radiation in non-bulky, limited-stage DLBCL found no statistically significant difference in 5-year overall survival between the two groups. Extra-nodal site presence did not affect survival in this cohort, as 39% had extra-nodal sites, including 1.8% in the thyroid. The authors concluded that patients who achieve complete remission after 4-6 cycles of R-CHOP should be spared radiation to avoid toxicity.[17]

Prognosis

Several retrospective studies have been conducted in order to develop prognostic models of PTL.[3,18-20] The largest study to date includes data from 3,466 PTL patients in the National Cancer Database between 2004 and 2015.[19] A mean overall survival of 9.0 years was calculated for all PTL patients. Patients with DLBCL, the most common subtype (61.2%), had the lowest mean survival (8.5 years). Stage I (54.8%), Stage II (30.8%), Stage III (4.7%), and Stage IV (9.7%) disease were associated with decreasing mean survival of 9.3, 9.0, 8.1, and 7.5 years, respectively. Patients undergoing lobectomy (18.1%), or total/subtotal thyroidectomy (28.6%) had significantly improved mean survival of 9.9 and 9.7

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years, respectively, compared to no surgery (46.3%, 8.0 years). Beam radiation (41.1%) significantly increased mean survival to 9.8 years compared to not receiving radiation therapy (58.4%, 8.3 years). Multi-agent chemotherapy (64.5%) significantly increased mean survival beyond not receiving chemotherapy (31.7%,8.2 years). Only 16.1% of patients were marked as having received immunotherapy.[19]

CONCLUSION

The case presented in this study highlights the difficulties of recognizing, diagnosing, and treating a patient with PTL who initially presents in a primary care setting. Although the initial presentation was with non-specific upper respiratory symptoms, a neck mass in an adult should always be considered malignant until proven otherwise. Additionally, PTL is not common (~5% of thyroid malignancies and ~3% of extranodal lymphomas)[1], especially in males and those without a preexisting history of HT. Furthermore, PTL is difficult to distinguish from ATC,[21-22] as either can present as a rapidly growing neck mass accompanied by compressive symptoms (e.g., dysphonia, dysphagia, and dyspnea) in older patients. However, HT helps one distinguish PTL from ATC,[23] as does the presence or absence of calcifications on CT imaging.[22] Making the correct diagnosis is essential because ATC carries a poor prognosis and is very rarely able to be surgically resected. In contrast, PTL can be treated with chemoimmunotherapy and radiation therapy and has a mean OS of 9.0 years.[19] Lastly, this case demonstrates the importance of multidisciplinary care and knowing when to consult specialists (e.g., ENT, IR, oncology, pathology), especially for patients with complex medical problems that may require a higher level of care.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Paris Johnson, MPH and Michelle Peters, MAT for their assistance in researching and formatting this manuscript.

AUTHOR AFFILIATIONS

1. Marshall University Joan C. Edwards School of Medicine, Huntington, West Virginia
2. West Virgina University School of Medicine, Morgantown, West Virginia

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