Primary Extranodal Nodular Lymphocyte Predominant Hodgkin Lymphoma Involving the Thyroid

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Abstract

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is an uncommon lymphoma that accounts for 3–8% of all Hodgkin lymphomas. NLPHL typically presents as early stage disease with localized peripheral lymphadenopathy. Involvement of extranodal sites at the time of presentation occurs in 6% of cases and most commonly involves the spleen, liver, bone marrow, and Waldeyer ring. Primary extranodal NLPHL is exceedingly rare. We describe the first reported case involving the thyroid and review the six other previously described cases of primary extranodal NLPHL.

Keywords Nodular lymphocyte-predominant Hodgkin's lymphoma · Thyroid · Hodgkin · Lymphoma · Extranodal

Case

A 49-year-old woman presented with right-sided neck pain and right arm weakness. Magnetic resonance imaging (MRI) of the cervical spine identified an incidental 1.9 cm nodule of the left thyroid lobe without associated lymphadenopathy. The patient had no previous history or concurrent evidence of thyroiditis or thyroid dysfunction, and thyroid-stimulating hormone (TSH) was within normal limits (1.11 mIU/L, normal range 0.50–5.07 mIU/L). A fine needle aspiration (FNA) of the nodule was non-diagnostic.

Grossly, a circumscribed, homogeneous, tan-white, multi-lobulated nodule measuring 1.9 cm was identified within the resulting hemithyroidectomy specimen. Histologic examination of the nodule revealed a lymphoid infiltrate arranged in serpiginous nodules that mostly lacked germinal centers or well-defined mantle zones (Fig. 1). Intermingled large atypical cells with cytologic characteristics of lymphocyte predominant (LP) cells were present within and around the nodules. Reactive-appearing secondary follicles were observed at the periphery of the infiltrate. No diffuse areas containing large cells were identified. Features of lymphocytic thyroiditis were noted throughout the thyroid. A prelaryngeal lymph

node showed reactive follicular hyperplasia without LP cells, progressively transformed germinal centers, or other evidence of involvement.

By immunohistochemistry, the LP cells showed strong, homogeneous reactivity for CD45, CD20, PAX-5, and BCL-6 and were negative for CD15, CD30, and EMA (Fig. 1). CD3 and PD-1 showed rosettes of small T-cells around LP cells, and CD21 highlighted follicular dendritic cell meshworks underlying the nodules (Fig. 1). Plasma cells were polyclonal for kappa and lambda light chain expression by in situ hybridization. EBV-encoded mRNA in situ hybridization was negative, and the germinal centers were negative for BCL-2. Flow cytometry demonstrated a predominance of polytypic B cells and T cells with unremarkable antigen expression (CD4:CD8 ratio = 3:1).

The morphologic and immunophenotypic findings were diagnostic of NLPHL. Staging PET/CT imaging showed no lymphadenopathy or other evidence of disease outside of the thyroid, thus confirming primary thyroid disease. The patient subsequently received adjuvant radiation therapy to the postoperative field and remains free of disease at 18 months of follow-up.

Discussion

A search of the English literature in Pubmed (www.pubmed.org) was performed to identify all case reports and case series of extranodal NLPHL. We identified twelve case

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Fig. 1 Top left $\times 10$: shows a nodule composed of a lymphoid infiltrate arranged in serpiginous nodules with secondary follicles present at the periphery. Top right $\times 40$: LP cells are intermingled within and around the nodules. Middle left $\times 1$: the lymphoid infiltrate is composed of a mixture of small CD20+lymphocytes (pictured) and

CD3+lymphocytes (not pictured). Middle right $\times 1$: CD21 highlights follicular dendritic cell meshworks underlying the nodules. Bottom left $\times 40$: the large atypical cells are strongly positive for CD20. Bottom right $\times 40$: PD1 highlights rosettes of small T-cells around LP cells

reports and five case series relevant to our review. Only six cases of primary extranodal NLPHL were previously reported (Table 1). Six of seven patients, to include the current case, with primary extranodal NLPHL remain disease-free following initial therapy. Interestingly, anatomic locations with increased mucosal-associated lymphoid tissue (MALT) appear to be over-represented. Although too few

cases have been reported to draw firm conclusions, this finding raises the possibility that MALT may be associated with development of primary extranodal NLPHL.

Patients with primary thyroid lymphoma show a strong female predominance (2–8:1), typically present in the sixth or seventh decade of life, and commonly have a background of lymphocytic thyroiditis [8, 16]. Demographic

Table 1 Case reports of primary extranodal nodular lymphocyte-predominant Hodgkin lymphoma

Site	Age	Sex	Presentation	Diagnostic procedures	Stage	Ref
Ileum	54	M	Screening colonoscopy	Endoscopic biopsy (NLPHL)	IEA	[12]
Palate	68	F	Hard palate mass	Surgical resection of palatal tumor (NLPHL) Cervical LN excision (PTGC)	NR	[13]
Appendix	62	M	Appendicitis	Appendectomy (NLPHL)	NR	[14]
Parotid	41	M	Parotid gland mass	1. FNA (probable WT) 2. Parotidectomy (NLPHL)	IE	[7]
Cervix	43	F	Massive vaginal bleeding	Vaginal hysterectomy (NLPHL)	IE	[15]
Pancreas	75	M	Nausea and intractable vomiting	1. FNA (ND) 2. FNA (ND) 3. Core biopsy (NLPHL)	IE	[8]
Thyroid	49	F	Dysphagia, hoarseness, right sided neck pain & arm weakness	1. FNA (reactive) 2. Thyroidectomy (NLPHL)	IA	This case

All reported cases of primary extranodal NLPHL (with diagnoses rendered in the diagnostic workup)

M male, *F* female, *NLPHL* nodular lymphocyte-predominant Hodgkin lymphoma, *PTGC* progressive transformation of germinal centers, *WT* Warthin's tumor, *FNA* fine needle aspiration, *LN* lymph node, *NR* not reported, *DF* disease-free, *ref* references

characteristics that are more similar to those of primary thyroid lymphoma than NLPHL are noted in both this case and the one other report of thyroidal NLPHL.

We identified five case series that evaluated for the presence of extranodal involvement in patients with NLPHL. Of 604 total cases of NLPHL, 54 cases with extranodal involvement were identified. These series do not specify whether extranodal disease was primary or secondary; however, the latter is far more common. Nogova et al. report that 6% of NLPHL cases have extranodal involvement. The most commonly involved sites are spleen ($n=35$), liver ($n=15$), bone marrow ($n=8$), and Waldeyer ring ($n=6$). Other sites described include salivary gland ($n=3$), soft tissue ($n=3$), gastrointestinal tract ($n=2$), lung ($n=1$), bone ($n=1$), and skin ($n=1$) [1–5].

Extranodal presentations of NLPHL, whether primary or secondary, present unique diagnostic challenges due to the rarity of this neoplasm, paucity of diagnostic LP cells, and necessity to evaluate the immunoarchitecture. As seen in the current case, FNA and core biopsies often do not yield LP cells and fail to demonstrate the background required for diagnosis. Several reports and series retrospectively reviewed FNA or core biopsy material following the diagnosis of NLPHL on excisional biopsy or surgical resection. All were non-diagnostic, likely due to the factors previously mentioned [6–10].

Ultimately, identification of extranodal NLPHL requires ruling out mimics by morphologic and immunophenotypic assessment of large atypical cells and the background cellular milieu. NLPHL may be morphologically indistinguishable from T cell histiocyte rich large B-cell lymphoma (THRLBCL), lymphocyte-rich classic

Hodgkin lymphoma, and low-grade lymphomas such as follicular lymphoma and marginal zone lymphoma. LP cells have an intact B-cell program and express CD45, CD20, and B-cell transcription factors (OCT-2, BOB-1, PAX-5). These markers help to differentiate NLPHL from classic Hodgkin lymphoma. The background inflammatory infiltrate shows a mixture of non-neoplastic, polyclonal, CD20-positive B cells that present in nodular, nodular and diffuse, or diffuse patterns [11]. The background of small polyclonal B-cells, presence of residual follicles, and T-cell rosettes around the LP cells distinguish NLPHL from THRLBCL. Follicular lymphoma and marginal zone lymphoma may have scattered Hodgkin-like cells or large transformed cells. These diagnostic possibilities can be confirmed by the demonstration of a monoclonal B-cell population by flow cytometry.

Conclusion

We report the first case of primary extranodal NLPHL involving the thyroid and the seventh documented case of primary extranodal NLPHL overall. Although rare, primary extranodal NLPHL should be considered in the differential diagnosis of extranodal lymphoid neoplasms, particularly in sites containing mucosa-associated lymphoid tissue.

Compliance with Ethical Standards

Conflict of interest The authors have no conflict of interest to disclose.

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