Case Report

Primary thyroid lymphoma with double expression of MYC and B-cell lymphoma-2 Gene

Ramesh Mundle[1], Kunal Ajay Patankar[2], Jignesh Rajguru[3], Mohan Paliwal[4]

From [1]Professor, Department of General Medicine, [2]Junior Resident, Department of General Medicine, N.K.P. Salve Institute of Medical Sciences and Research Centre, [3]Junior Resident, Department of Oral and Faciomaxillary Surgery, VSPM Dental College and Research Centre, [4]Junior Resident, Department of General Medicine, N.K.P. Salve Institute of Medical Sciences and Research Centre, Nagpur, Maharashtra, India

ABSTRACT

Primary lymphomas of the thyroid (PTLs) are rare entities. We report a case of high-grade B-cell lymphoma double hit (DH) of the thyroid gland with dual expression of MYC and BCL-2 gene in a 55-year-old woman. Most PTLs have a good prognosis to combined modality treatment but identification of DH lymphomas or double-expressor lymphomas is important as these are resistant to chemotherapy and radiotherapy and pose a challenge for the treatment of the same.

Key words: B-cell lymphoma genes, Hashimoto thyroiditis, MYC Genes, Rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin

Freeman *et al*. in 1972 stated that primary thyroid lymphoma (PTL) is a rare malignancy that accounts for 1–5% of all thyroid malignancies and 1–7% of all extranodal lymphomas. The annual incidence of PTL is approximately two cases per million. PTL has a predilection for women with an incidence peak in the seventh decade [1]. Hashimoto's thyroiditis (HT) causes a 40–80-fold increase in the risk of PTL [2]. PTL is classified as B-cell lymphomas which include mucosa-associated lymphoid tissue (MALT) lymphomas and diffuse large B-cell lymphomas (DLBCL) [3]. Patients harboring an MYC rearrangement along with a B-cell chronic lymphoid leukemia (CLL)/lymphoma 2 (BCL2) and/or B-cell CLL/lymphoma 6 (BCL6) are now formally classified as a new diagnostic entity termed as high-grade B-cell lymphoma (HGBL). These rearrangements are commonly called double-hit lymphoma (DHL) or triple-hit lymphoma (THL), respectively [4].

Here, we review the clinical presentation in a 55-year-old woman with diffuse large B-cell lymphoma with concurrent C-MYC and BCL2 expression and its diagnostic evaluation with a practical discussion of current treatment considerations in similar cases.

CASE REPORT

A 55-year-old woman reported to the department of medicine with a chief complaint of swelling in the midline of the neck for three months. She had a history of difficulty in swallowing, hoarseness of voice, and breathlessness for a month. The patient was a known case of systemic hypertension and bronchial asthma, on medications for the same for a year.

On physical examination, her vitals were stable. The thyroid swelling was approximate of size 3 cm × 3 cm × 4 cm and moved with deglutition (Fig. 1). No visible pulsations were seen. Signs of thyrotoxicosis were absent. All findings of inspection were confirmed on palpation. The swelling was diffuse and firm to hard inconsistency. The surface of the swelling was smooth with retrosternal extension and no lymphadenopathy. Bruit was absent on auscultation. Bilateral rhonchi and basal crepitations were present on systemic evaluation.

Routine laboratory investigations such as complete blood count, liver function tests, renal function tests, international normalized ratio, blood grouping, and random blood sugar levels were done. Thyroid profile was suggestive of hypothyroidism.

An ultrasound of the thyroid revealed an ill-defined heterogeneous lesion of approximately 2.5 cm × 6.3 cm × 6.6 cm involving the entire left lobe, isthmus, and partly the right lobe. Computed tomography of the neck for local spread of the lesion was performed and showed luminal narrowing at the seventh cervical vertebra measuring 3.8 mm, as shown in Fig. 2a. Fine-needle aspiration cytology was suggestive of lymphocytic thyroiditis (Hashimoto thyroiditis).

The patient was discharged on steroids (methylprednisolone 1 mg/kg once a day), oral supplements of thyroxine (25 μg/day),

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Correspondence to: Kunal Ajay Patankar, Department of Medicine, N.K.P. Salve Institute of Medical Sciences and Research Centre, Nagpur - 440 019, Maharashtra, India. E-mail: drkunalpatankar@gmail.com

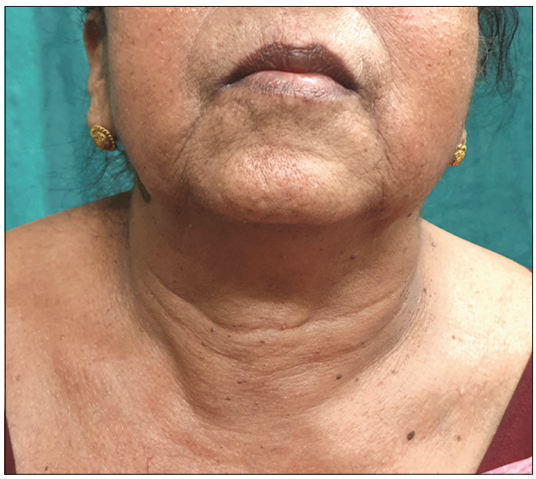

Figure 1: Patient with a midline neck swelling

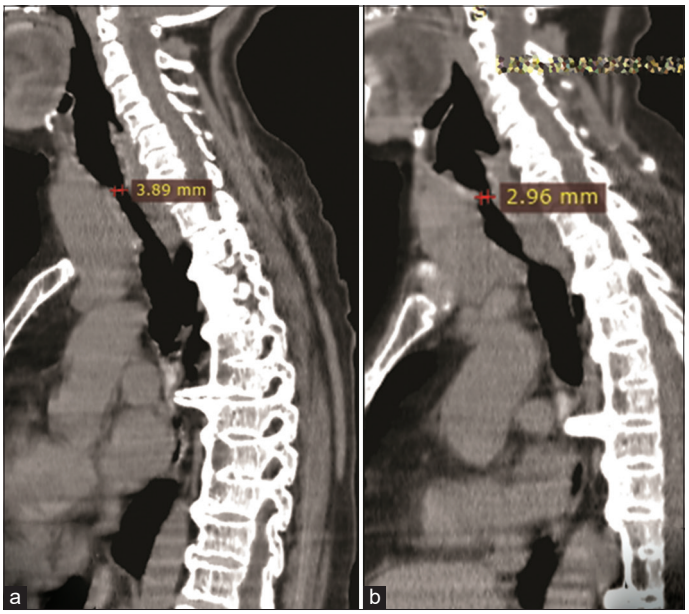

Figure 2: Computed tomography sagittal view of the mediastinal window showing tracheal luminal narrowing at the seventh cervical vertebrae from 3.8 mm (a) to 2.9 mm (b)

and bronchodilators (levosalbutamol 1.25 mg + Ipratropium 500 mcg) for 2 months and follow-up.

The patient presented after 2 months with an increase in the size of swelling, breathlessness, loss of voice, and stridor. Follow-up imaging showed luminal narrowing from 3.8 mm to 2.9 mm with an increase in retrosternal extension and the involvement of the tracheal rings, as shown in Fig. 2b. A core biopsy was conclusive of non-Hodgkin lymphoma versus undifferentiated carcinoma (Fig. 3). Immunohistochemistry revealed MYC and BCL-2 dual expression and fluorescence *in situ* hybridization (FISH) was recommended to study the rearrangement of molecular structure. Treatment with a rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) chemotherapy regime was initiated. However, the patient succumbed after two scheduled chemotherapy cycles.

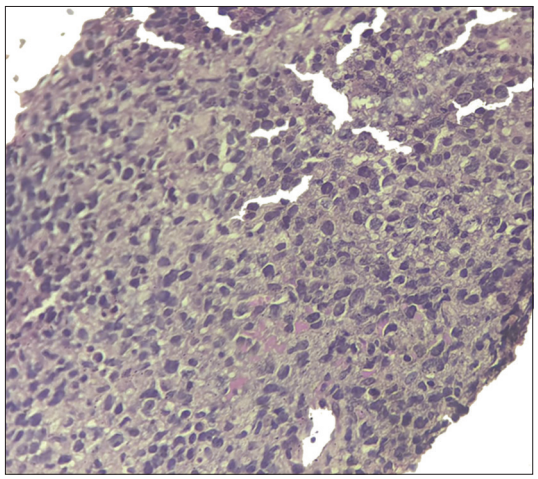

Figure 3: Photomicrograph (H and E × 400) showing irregular tissue fragment composed of sheets of monomorphic cells. The cells are round to oval and are of intermediate size with scanty cytoplasm and hyperchromatic nuclei without nucleoli. At places, scattered plasmacytoid cells are also seen

DISCUSSION

HT is the most important risk factor for PTL [2]. The most common symptom usually seen is a rapidly enlarging mass with shortness of breath, stridor, dysphagia, and hoarseness. However, a few have mediastinal involvement and small amounts have B symptoms.

In 2016, the World Health Organization documented a new classification of lymphomas within the group of large B-cell lymphomas based on several distinct entities characterized by unique clinical and pathological features and its diagnosis, namely, cell of origin (COO); germinal center B-cell (GCB); or activated B-cell/non-GCB subtypes [5].

A rearrangement of MYC along with BCL2 and/or BCL6 is called DHL or THL, respectively. Our patient had coexpression of the MYC and BCL2 gene, the new adverse prognostic indicator termed double-expressor lymphoma (DEL) [6]. Such cases are rarely documented in the literature and its lack of prospective data makes it challenging to establish the optimal induction regimens for DHL. Acar *et al*. reported a case series in 2019 in which four patients were treated for primary thyroid lymphoma; two of which were DLBCL, one was MALT and one was HGL. The HGL on further pathological evaluation tested negative for BCL-2 and BCL-6, further reinforcing the status of double expression lymphomas being the rarest of entities [7].

The MYC proto-oncogene is located on chromosome 8q24, whereas, BCL-2 is an oncogene located on chromosome 18q21. MYC gene encodes for a transcription factor with roles in protein synthesis, cellular differentiation, and metabolism while BCL-2 encodes for a pro-survival protein and plays a role of paramount significance in maintaining cellular viability through inhibition of apoptosis. About lymphoma, MYC leads to genomic instability, gene amplification, and cellular proliferation and is synergistic with BCL-2 overexpression promotes the progression of lymphoma and resistance to chemotherapy.

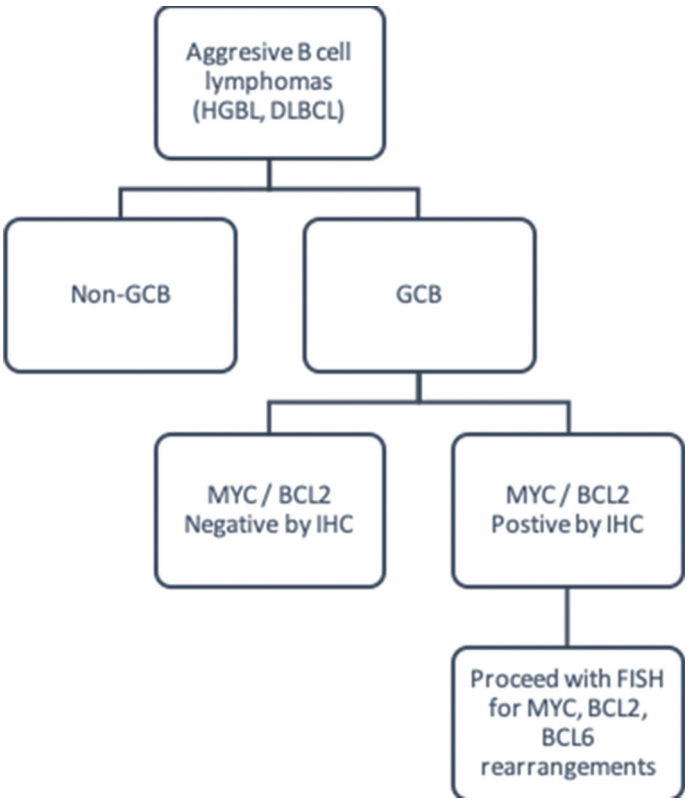

Figure 4: Suggested algorithm for the diagnosis of double-hit lymphoma in resource-poor settings

Approximately 90% of DHL are GCB subset; similarly, DEL appears to be highly correlated with non-GCB. The approach proposed to limit FISH analysis in selected cases is shown in Fig. 4 [4]. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) and R-EPOCH are currently the drug regimes. A superior progression-free survival (PFS) and overall survival (OS) were seen in patients treated with R-EPOCH in comparison with standard R-CHOP. R-EPOCH with the BCL-2 inhibitor (venetoclax) and R-EPOCH with the immunomodulatory agent (lenalidomide) is currently under evaluation as a possible treatment regime.

A relapse rate of 18% and 80% was noted in DEL treated with R-EPOCH and R-CHOP groups, respectively. Chemotherapy followed by autologous stem cell transplantation (ASCT) failed to demonstrate an improvement in the 2-year PFS or OS [8]. Chimeric antigen receptor T-cell therapy targeting the CD19 moiety has demonstrated potent clinical activity in patients with chemotherapy-refractory DLBCL and patients relapsing after ASCT, including patients with durable complete remissions (CR) lasting more than 2 years. Axicabtagene ciloleucel was Food and Drug Administration approved (October 2017) for the treatment of large B-cell lymphoma after two or more lines of systemic therapy including DLBCL, NOS, and HGBL [9].

CONCLUSION

PTL of MALT subtype achieves CR to combined modality treatment, however, DHL and DEL are resistant to chemotherapy. Identifying patients with DHL and/or DEL in practice are difficult based on clinical features. R-EPOCH for DHL is the preferred intensive treatment but DEL is more complex as they have a better outcome than patients with DHL. Chimeric antigen receptor t-cells or other investigational approaches should be considered in refractory cases.

REFERENCES

1. Travaglino A, Pace M, Varricchio S, Insabato L, Giordano C, Picardi M, *et al*. Hashimoto thyroiditis in primary thyroid non-Hodgkin lymphoma. Am J Clin Pathol 2020;153:156-64.
2. Derringer GA, Thompson LD, Frommelt RA, Bijwaard KE, Heffess CS, Abbondanzo SL. Malignant lymphoma of the thyroid gland: A clinicopathologic study of 108 cases. Am J Surg Pathol 2000;24:623-39.
3. Watanabe N, Noh JY, Narimatsu H, Takeuchi K, Yamaguchi T, Kameyama K, *et al*. Clinicopathological features of 171 cases of primary thyroid lymphoma: A long-term study involving 24553 patients with Hashimoto's disease. Br J Haematol 2011;153:236-43.
4. Riedell PA, Smith SM. Double hit and double expressors in lymphoma: Definition and treatment. Cancer 2018;124:4622-32.
5. Chen BJ, Fend F, Campo E, Quintanilla-Martinez L. Aggressive B-cell lymphomas from morphology to molecular pathogenesis. Ann Lymphoma 2019;3:1.
6. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, *et al*. The 2016 revision of the world health organization classification of lymphoid neoplasms. Blood 2016;127:2375-90.
7. Acar N, Acar T, Avcı A, Haciyanlı M. Approach to primary thyroid lymphoma: Case series. Turk J Surg 2019;35:142-5.
8. Hu S, Xu-Monette ZY, Wu L, Visco C, Tzankov A, Montes-Moreno S, *et al*. MYC/BCL2 protein co-expression defines a unique subset of aggressive lymphoma and contributes to the inferior prognosis of activated b-cell subtype of diffuse large b-cell lymphoma: A report from the international DLBCL rituximab-CHOP consortium program study. Clin Lymphoma Myeloma Leukemia 2013;13:S382-3.
9. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, *et al*. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-Cell lymphoma. N Engl J Med 2017;377:2531-44.

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