Primary Thyroid Lymphoma: An Interesting Case Emphasising Early Diagnosis

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ABSTRACT

Introduction

Primary thyroid lymphoma is defined as a lymphoma involving only the thyroid gland, or thyroid gland with regional lymph nodes without contiguity or metastasis to other areas at the time of diagnosis. Hashimoto's thyroiditis is a known risk factor for the disease. It responds well to chemotherapy but since it is not so common clinical entity, the diagnosis is often missed, thereby subjecting the patient to extensive surgery.

Case Report

A 69 years old male presented with rapidly progressive swelling in front of neck for 10 days associated with dysphagia, odynophagia and dyspnoea. He had right lobe thyromegaly with multiple cervical lymphadenopathy with ultrasonographic risk stratification of 5 in Thyroid Imaging Reporting and Data System. Diagnosis was clinched by core biopsy report on immunohistochemistry as Diffuse Large B-Cell Non-Hodgkin's Lymphoma. Positron emission tomography computerized scan revealed 18-fluorodeoxyglucose avid grossly enlarged thyroid lobes and isthmus with multiple bilateral cervical lymph nodes. Documenting the stage of disease as III E, he was managed with Chemo-immunotherapy consisting of RCVP regime with complete remission.

Conclusion

Primary thyroid lymphoma with extra-thyroid involvement can be rapidly progressing and life threatening. However, timely investigation leads to correct diagnosis, appropriate curative medical management and can avoid unwarranted surgery.

Keywords

Primary thyroid lymphoma; Diffuse Large B-Cell Lymphoma; Anaplastic carcinoma; lymph nodes; Immunohistochemistry; Chemo-immunotherapy

Thyroid gland is devoid of lymphoid tissue, however, lymphocytes may appear due to chronic antigenic stimulation leading to development of lymphoma. Primary thyroid lymphoma (PTL) is defined as a lymphoma involving only the thyroid gland, or thyroid gland with regional lymph nodes without contiguity or metastasis to other areas at the time of diagnosis.[1] Hashimoto's thyroiditis, an autoimmune chronic lymphocytic thyroiditis, is a known risk factor contributing to 90% of theincidence of PTL.[2]

PTL responds well to chemotherapy but since it is a rare clinical entity, the diagnosis is often missed, thereby subjecting the patient to extensive surgery. A case of PTL is being reported to lay emphasis on early correct histological diagnosis of a thyroid swelling so that surgery can be avoided.

Case Report

A 69 years old male patient, with multiple medical co-morbidities of Diabetes, Coronary Artery Disease (Post-CABG, on pacemaker) and Primary Hypertension,

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presented with complaints of rapidly progressive swelling in front of neck for 10 days associated with dysphagia, odynophagia and dyspnoea. Clinical examination of neck revealed a swelling of size 4x3 cm involving right thyroid lobe and isthmus which was firm in consistency, moved upwards on deglutition but not on protrusion of tongue. Multiple cervical lymph nodes were also palpable in level II, III and IV right side, largest node measuring 2x2 cm which was firm and immobile (Fig. 1). There was no abnormality detected in any other site of head and neck region. Vocal cords were mobile with adequate glottic chink on laryngoscopic examination.

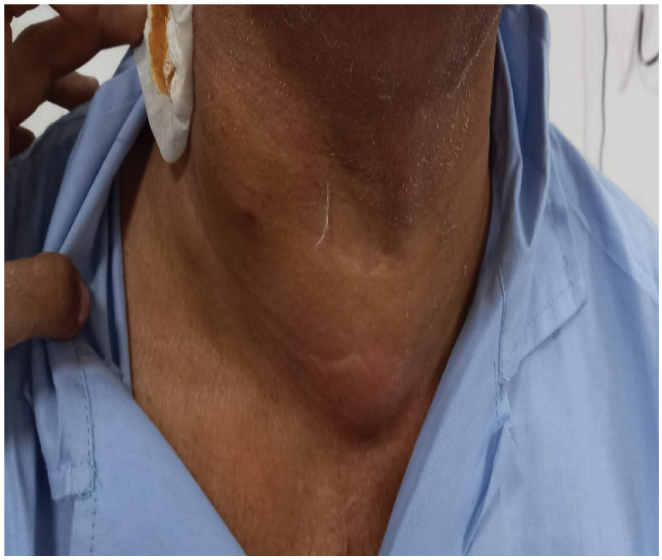

Fig. 1. Clinical photograph of the patient showing enlarged right thyroid lobe and isthmus with multiple cervical lymph nodes at level II, III and IV

Ultrasonography (USG) of neck revealed an enlarged thyroid gland, right lobe measuring 3.2 cm, left lobe measuring 3 cm and isthmus 0.9 mm. Multiple conglomerate lymph nodes with lost fatty hila were noted on both sides at level Ib, II, III and IV. The largest lymph node measuring 2.8x3 cm was noted with significant peripheral vascularity. Risk stratification by Thyroid imaging reporting and data system was labelled as TIRADS 5.

Since the fine needle aspirate cytology (FNAC) from right lobe of thyroid was suggestive of lymphoproliferative disorder, a core biopsy was performed which on immunohistochemistry was reported as Non-Hodgkin's Lymphoma (NHL) of B-Cell type (Diffuse Large B-Cell Lymphoma) positive for CD 20 and B-Cell Lymphoma-2 (BCL2) protein, and focally positive for CD79a (Fig.2).

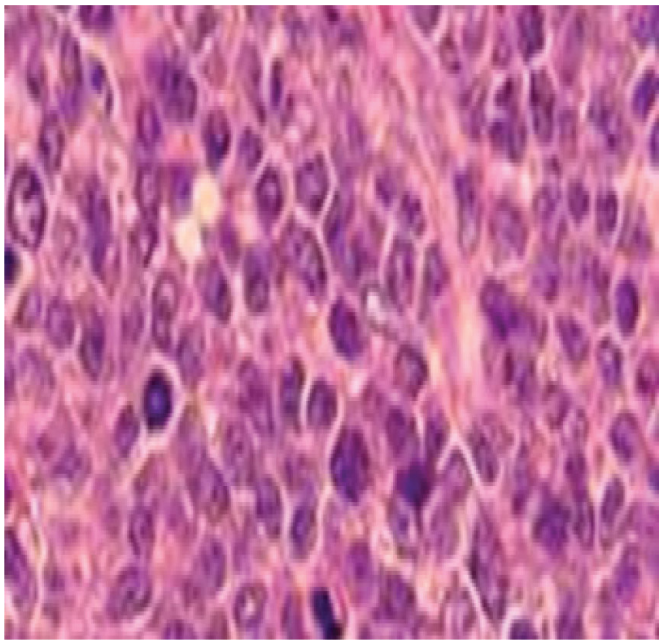

Fig. 2. Photomicrograph, HE stain, 40x magnification showing monomorphic population of cells with highnucleus-to-cytoplasmic ratio, round to oval nuclei, inconspicuous nucleoli and scant cytoplasm

Positron emission tomography computerized scan (PET-CT scan) (Fig.3) revealed 18-fluorodeoxyglucose (FDG) avid grossly enlarged thyroid lobes and isthmus with maximum standardized uptake value (SUV max) 27.19. Multiple conglomerate and discrete cervical lymph nodes were noted involving level II, III and IV on both sides of neck. SUV max was measured as 25.67 in right level II and III nodes. Mediastinal lymph nodes were also found in prevascular, para-aortic and upper paratracheal region with SUV max 22.37 in right upper paratracheal station. Right external iliac lymph node had SUV max of 16.80.

The case was diagnosed as PTL, type - Diffuse Large B-Cell Lymphoma (DLBCL), stage III E and was managed with Chemo-immunotherapy consisting of RCVP regime. Six cycles of Inj. Rituximab 500mg IV,

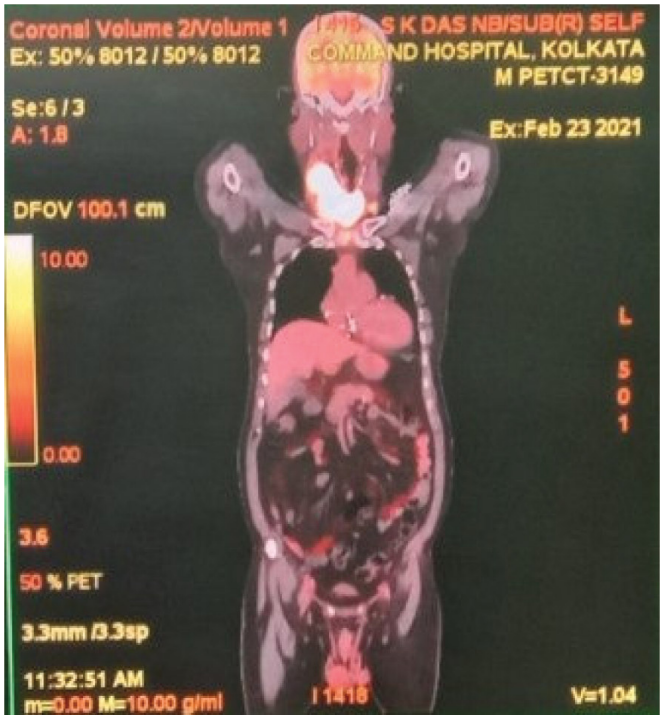

Fig. 3. PET CT scan showing FDG avid grossly enlarged thyroid lobes (right > left) and isthmus, multiple bilateral cervical lymph nodes at level II, III and IV, mediastinal lymph nodes and right external iliac lymph node

Inj. Vincristine 2mg IV, Inj. Cyclophosphamide 1000mg IV and tablet Prednisolone 100mg from day 1 to day 5 were given at 3 weeks interval. Patient showed complete remission on follow up over last one year.

Discussion

A large thyroid mass involving regional lymph nodes invariably raises the suspicion of a tumour arising from cells within thyroid gland. It indeed turns out to be so in more than 90% of cases. Sometimes, a lymphoma does secondarily metastasize into thyroid gland as a part of widespread disease with increased mortality. It is rare for a lymphoma to arise primarily in the thyroid. PTL accounts for only 5% of thyroid malignancy and only up to 2% of all extra-nodal lymphomas.[3] It occurs more often in female than in male, ratio being 4:1, majority presenting in 7th decade of life, with a rapidly enlarging neck mass.[4]

DLBCL constitutes 70% and Extra-nodal Marginal Zone B-cell Lymphoma of mucosa-associated lymphoid tissue (MALT) constitutes 15–30% of all primary non-Hodgkin PTLs.[5]

Follicular lymphoma, Hodgkin's disease, small lymphocytic lymphoma, Burkitt's lymphoma and T cell PTLs make up for the other rare subtypes. Approximately 30% of patients have compressive symptoms at the time of diagnosis.[6] Only 10% patients may be found to be hypothyroid and additional 10-20% of patients may suffer from B symptoms like fever, night sweats or weight loss.[7]

Ann Arbor staging system (Table I), originally developed for Hodgkin's lymphoma, is presently applied to non-Hodgkin's lymphoma as well, for staging the disease. The suffix A and B are used for presence or absence of constitutional symptoms respectively whereas the suffix E and S are used for extra-nodal and splenic involvement.[8]

Table I. : Ann Arbor Classification for PTL

STAGE	LOCALIZATION OF DISEASE
IE	**Involvement of thyroid gland only**
IIE	**Involvement of thyroid gland and regional lymph nodes on the same side of diaphragm**
IIIE	**Involvement of thyroid gland and regional lymph nodes on both sides of diaphragm**
IVE	**Disseminated disease**
MODIFIERS	**CONSTITUTIONAL SYMPTOMS**
A	**Absent**
B	**Present (Fever >38, weight loss > 10% in 6 months, night sweats)**

Study of cellular characteristics is of utmost importance, as DLBCL has to be carefully differentiated from Anaplastic carcinoma because DLBCL responds well to chemotherapy whereas surgery is the primary modality of treatment in Anaplastic carcinoma. There should be

no hesitation in conducting an USG guided aspirate or a core biopsy and asking for flow cytometry, immunohistochemical studies or polymerase chain reaction (PCR) to enhance the sensitivity and specificity of the tests. In presence of common features of cellular dysplasia, increased mitosis, nuclear molding and prominent nucleoli, diagnosis of DLBCL can be clinched by noting the presence of lymphoglandular bodies.[9] Immunohistochemistry shows neoplastic cells being diffusely immunoreactive to CD20 with kappa light chain reaction. USG is usually the first imaging modality performed in any case of goitre. Though three categories of findings, namely nodular, diffuse and mixed have been described; the real task is to differentiate DLBCL from Anaplastic carcinoma by lack of calcification, necrosis, and cystic degeneration.[10] Since the lesion avidly uptakes FDG within the thyroid and regional lymph nodes, FDG-PET has been well used in staging the disease and in assessing response to treatment.

DLBCL is often curable. If uncurable, the treatment can reduce symptoms, control cancer and extend life. The gold standard first line of treatment is Chemo-immunotherapy consisting of RCHOP instituted in 21 days cycle followed by a week of rest.[11] The addition of Rituximab, a chimeric monoclonal antibody that acts against CD20, to combination chemotherapy has been shown to improve quality of life and increase recurrence-free survival. Response is assessed after 2 to 4 cycles of immunochemotherapy by clinical examination and PET CT scan. In cases of complete or partial response, treatment is completed with 6 cycles. Involved site radiation treatment (ISRT) is also given to prevent recurrence. In cases of no response or progression of disease, a second line treatment is recommended to be adopted. This depends on whether a blood stem cell transplant is planned or not. Autologous stem cell transplant is preferred. If it is not an option, the other options can be either chemotherapy alone, or chemoimmunotherapy or antiCD19 Chimeric Antigen Receptor (CAR) T-cell therapyand supportive care.[11] CAR T-cell therapy is reserved for patients where cancer remains refractory or recurs even after two or more cycles of chemo-immunotherapy in the past. Two drugs, namely Axicabtagene ciloleucal and Tisagenlecleucel are given which specifically target CD19 on the surface of malignant B-cells, thus killing them.

Conclusion

Primary thyroid lymphoma seldom comes into a clinician's mind when he comes across a rapidly increasing goitre with regional lymphadenopathy in an elderly male. The doubt of anaplastic thyroid malignancy precedes other differential diagnosis which may misguide the clinician to prepare the patient for an early surgery. However, timely investigation leads to correct diagnosis, appropriate curative medical management and thus avoidance of any unwarranted surgery.

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