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ORIGINAL RESEARCH

Hodgkin Lymphoma involving Thyroid: Case Report and Comprehensive Review

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ABSTRACT

Aim: To report a case of Hodgkin lymphoma involving thyroid gland and to review the literature for the same.

Background: Thyroid lymphomas occur most commonly in the form of non-Hodgkin lymphomas. In contrast, Hodgkin lymphoma involving the thyroid gland is a relatively rare scenario and which, by virtue of its rarity, is mistaken for usual thyroid lesions both on clinical and cytological examination.

Case report: A 34-year-old female was presented with anterior neck mass and breathlessness. The fine needle aspiration cytology of the mass was suspicious for Hodgkin lymphoma and the diagnosis was further confirmed on a thyroid biopsy. Suspicion of Hodgkin lymphoma on cytology in this patient ensued proper medical management, thus averting a surgical treatment. Patient defaulted chemotherapy and died 6 month after initial diagnosis.

Conclusion: A careful cytological examination assisted with ancillary techniques ensures a proper treatment strategy and avoids unnecessary surgical intervention.

Clinical significance: With thorough literature review, this study highlights the way immunocytochemistry and thyroid biopsy dictates the treatment decision when dealing with uncommon tumours at this site.

Keywords: Biopsy, Fine needle aspiration cytology, Hodgkin lymphoma, Surgery, Thyroid

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BACKGROUND

Thyroid lymphoma is a rare entity comprising of <5% of thyroid neoplasms.[1] Non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), is the most common lymphoma involving thyroid gland, followed by extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) and follicular lymphoma.[2] Hodgkin lymphoma (HL) involving thyroid is one of the rarer lymphomas described at this site. The data on HL involving thyroid gland is largely limited to case reports and rare case series.[3] Given its rarity, cases of HL involving thyroid have been misdiagnosed as follicular epithelial malignancy[4,5] and lymphocytic thyroiditis[6] on fine needle aspiration cytology (FNAC), subjecting these patients to surgical treatment. Consequently, recognizing HL involving thyroid on FNAC/biopsy, although difficult, becomes essential to avoid the radical surgical management in these patients. Herein, we report a case of Hodgkin lymphoma that was suspected on FNAC and the diagnosis of which was further confirmed on core biopsy thus sparing the patient of a radical surgical procedure.

CASE DESCRIPTION

A 34-year-old lady presented to the outpatient department with complaints of breathlessness which was aggravated on exertion and stridor since morning. On examination, the patient had anterior neck swelling (left>right) with retrosternal extension. In addition, the movement of deglutition was also diminished. There were no palpable neck nodes. Ultrasonography of neck revealed enlarged left lobe of thyroid with irregular surface and large nodule measuring 5.5x3.7x3.2 cm entrapping the left carotid artery. Both the left lobe and nodule were hypervascular in nature. Computed tomography (CT) scans showed a large thyroid swelling extending to mediastinum with adenopathy and compression of trachea (Figs 1A to D). The patient underwent emergency tracheostomy in view of her clinical condition. FNAC sample obtained from the left thyroid lobe showed a cellular aspirate comprising of singly scattered large atypical cells along with many tumor giant cells (Figs 2A to D). These large cells had pleomorphic nuclei and prominent nucleoli. The background had few clusters of benign follicular cells, lymphocytes and macrophages. Differentials considered were anaplastic carcinoma and hematolymphoid malignancy. In the view of same immunocytochemistry (ICC) for leucocyte common antigen (LCA) and PAX8 was performed, which revealed positivity for LCA (Fig. 2E)

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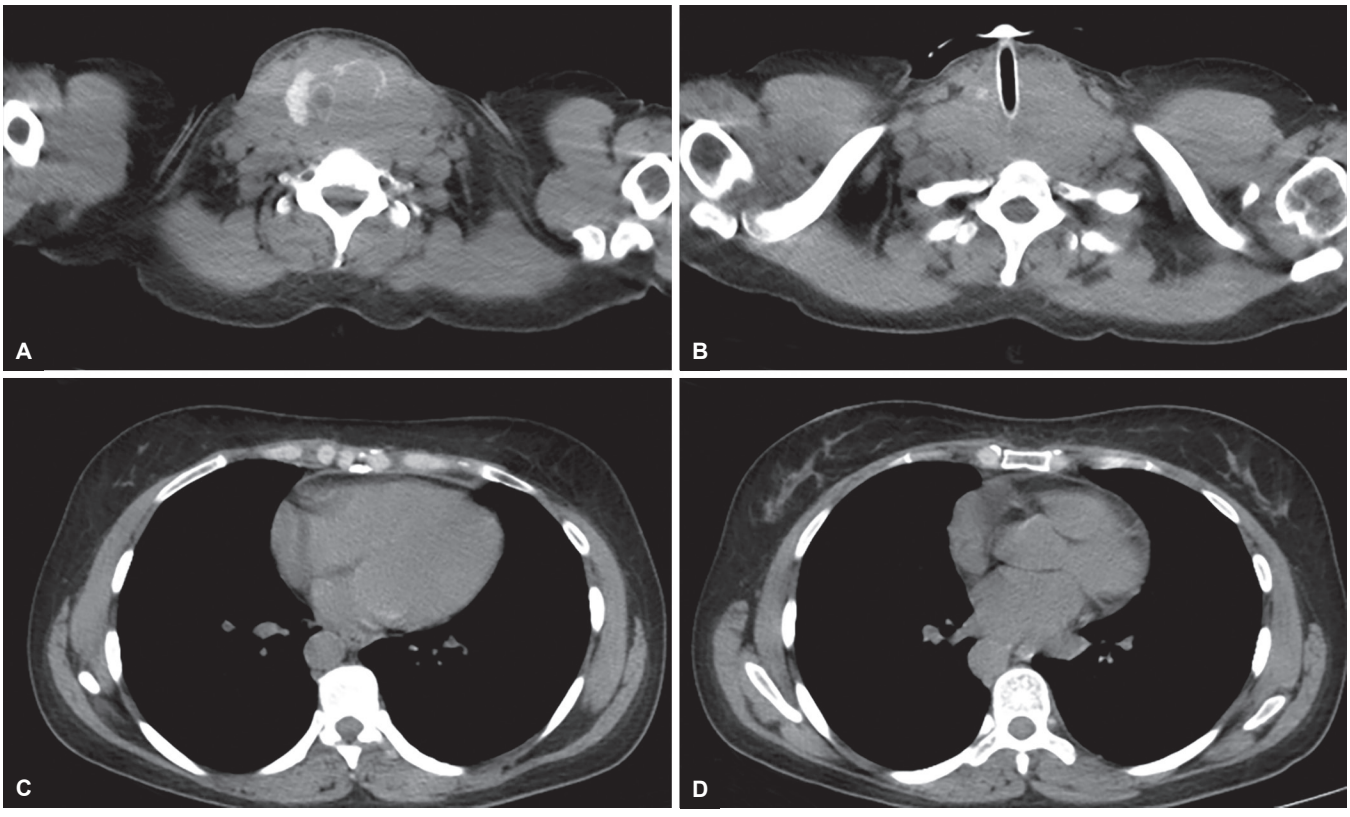
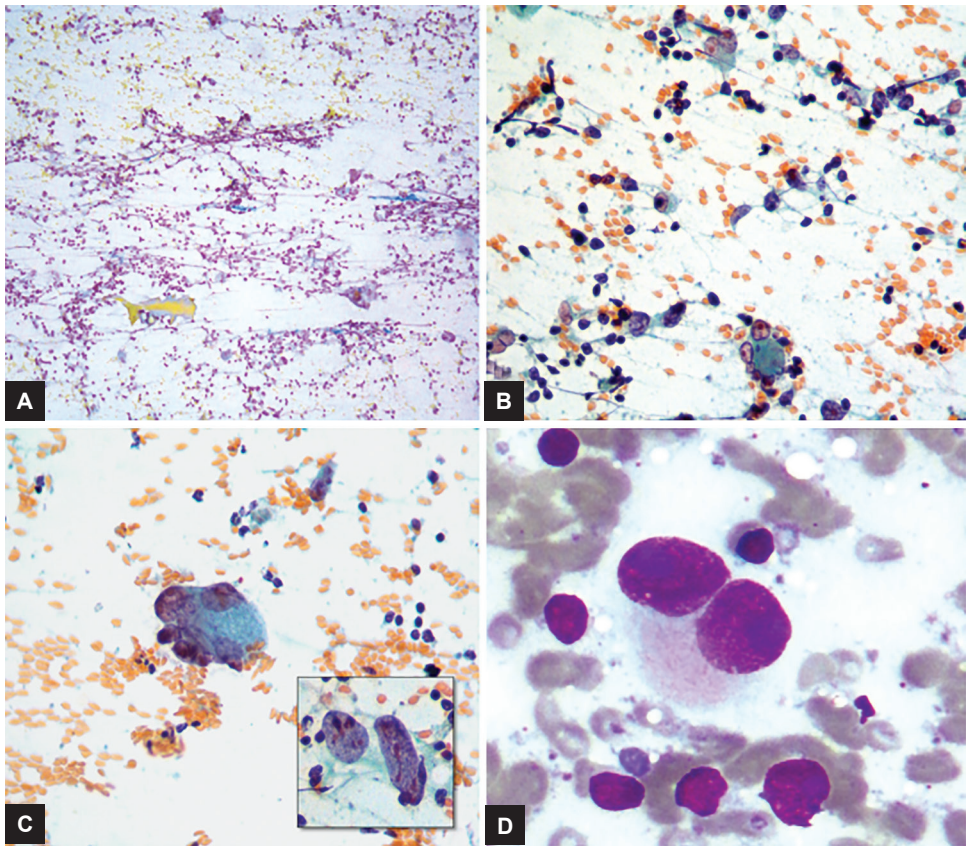
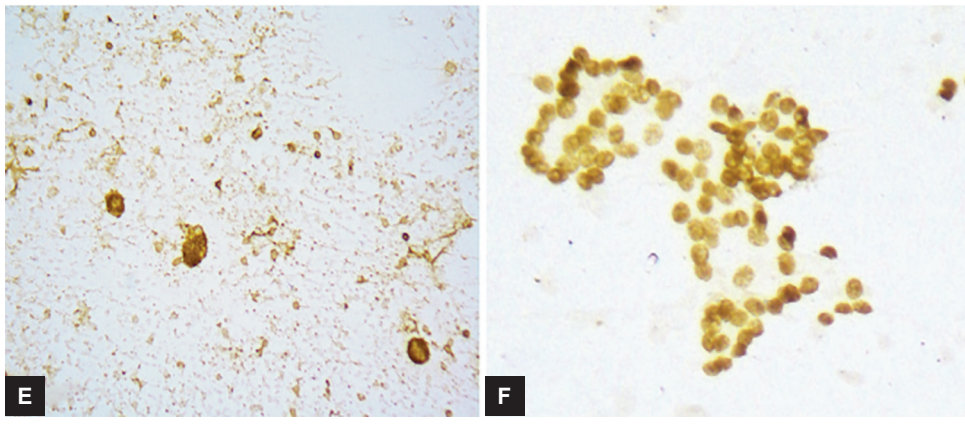


Figs. 1A to D: Computed tomography images showing (A) large neck swelling; (B) causing compression of airway; (C) extension to mediastinum; (D) along with mediastinal adenopathy



Figs 2A to D



Figs 2A to F: Cytological findings in thyroid FNAC depicts (A) papanicolaou staining showing cellular smear comprising of clusters of benign follicular cells, histiocytes and lymphocytes with giant cells; (B) Few classical binucleated RS like cells; (C) Few classical binucleated RS like cells were seen scattered amongst many multinucleated tumor giant cells; (D) Giemsa staining showing classical RS cells with owl eye appearance; [Original magnification x100 (A), x400 (B,C,D)]
Immunocytochemistry staining showing; (E) LCA positivity in large cells; (F) PAX-8 positivity in benign follicular cells [Original magnification x200 (E,F)].

and negativity for PAX8 (Fig. 2F). In the light of above findings, a diagnosis of hematolymphoid malignancy was favored over anaplastic carcinoma and a formal biopsy was advised. Meanwhile, considering the deteriorating clinical condition of the patient, prephase treatment for lymphoma was started. The core biopsy revealed thyroid follicles infiltrated by polymorphous population of lymphoid cells with scattered large atypical cells having vesicular nuclei and prominent nucleoli (Figs 3A and B). The background was rich in lymphocytes, plasma cells, histiocytes and eosinophils. Occasional Reeds-Stenberg (RS) like cells were noted. On immunohistochemistry (IHC), large cells were weakly positive for CD20 (Fig. 3C) and LCA, while being negative for CD3 (Fig. 3D). Further these cells were positive for CD30 (Fig. 3E), focally positive for CD15 (Fig. 3F), and negative for EBV-LMP1 (Fig. 3G) and ALK1 (Fig. 3H). Various antibodies used for the immunohistochemical and ICC study, their commercial sources, clones and working dilutions are summarized in Table 1. Diagnosis of classical HL, mixed cellularity type was offered. The staging bone marrow biopsy did not show involvement by lymphoma and the patient was staged IIEX by virtue of thyroid involvement and bulky mediastinal disease. Prephase treatment was withheld and the patient was started on ABVD (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) and planned for involved-field radiotherapy after completion of six cycles. However, the patient defaulted, and did not turn up for chemotherapy after the first cycle, and died of unknown cause at home, 6 months after initial diagnosis.

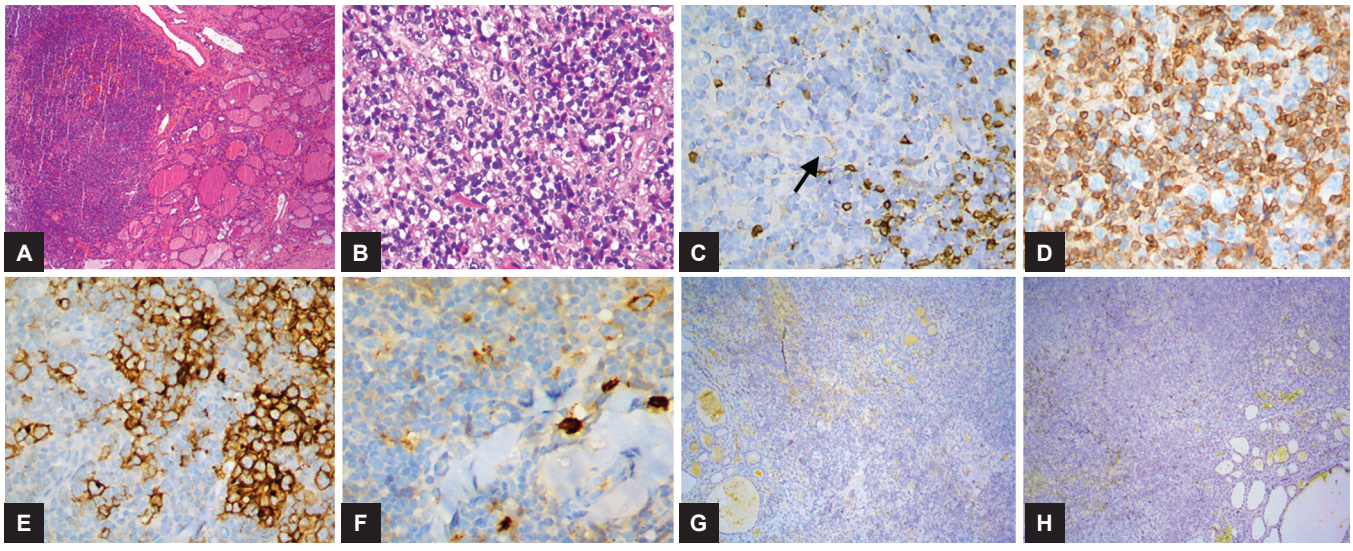
DISCUSSION

Follicular epithelial neoplasms are the most common tumors arising from the thyroid;[7] whereas thyroid lymphoma which accounts for <2% of the extranodal lymphomas is relatively rare.[8] Thyroid lymphomas, majority of which are non-Hodgkin lymphomas are seen more frequently in females (male: female 1:3-4).[1] DLBCL accounts for the majority of thyroid lymphoma (>50%) cases, followed by MALT lymphoma. Primary Hodgkin lymphoma of thyroid is extremely rare and most of the cases reported in literature correspond to secondary involvement of thyroid gland.[9]

We reviewed the English literature for Hodgkin lymphoma involving the thyroid (Table 2) and found 29 previously reported cases, with the oldest archived study on this topic in the form of a case report by Rupp et al.[10] As highlighted in Table 2, HL of thyroid was unequivocally female predominant with only three male patients amongst 30 cases (including our case). Age ranged from 18 years to 76 years (median age 39.5 years). Most of the patients were presented with enlarging thyroid gland or thyroid mass. Compressive symptoms like dysphagia,

Table 1: List of antibodies used for immunohistochemistry and ICC with their technical details

IHC Marker	*Dilution*	*Clone*	*Vendor*
AE1/AE3	1:200	AE1/AE3	Biocare
LCA	1:300	2B11+PD7/26	Dako
PAX8	1:300	MRQ 50	CellMarq
ALK1	1:50	ALK1	CellMarq
CD3	1:400	Poly	Dako
CD15	1:200	Carb3	Dako
CD20	1:400	L 26	Dako
CD30	1:100	Ber-H 2	Dako
EBV-LMP	1:800	CS. 1-4	Dako



Figs 3A to H: Histopathological findings in thyroid biopsy. (A and B) Hematoxylin-eosin staining showing infiltration of thyroid follicles by polymorphous population of lymphoid cells with scattered large atypical cells. The background was rich in lymphocytes, plasma cells, histiocytes and eosinophils, while the scattered large cells had vesicular nuclei with prominent nucleoli. Immunohistochemistry staining showing large cells having (C) weak positivity for CD20 (arrow) (D) while being negative for CD3. Further these cells were positive for CD30, (F) focally positive for CD15 and, negative for EBV-LMP1 and (H) ALK1. Original magnification x40 (A), x100 (G,H), x400 (B–F)

dyspnoea, and stridor were reported in 16/30 cases (53%), while painful enlarging mass indicating infiltration of adjacent organs was seen in two cases.

Diagnostic FNAC was performed in 19 out of 30 cases; and the diagnosis rendered is summarized in Table 3. Hematolymphoid malignancy/HL was suspected on FNAC in eight cases (40%) while it was mistaken for non-hematolymphoid tumor in four cases (20%) and erroneously called lymphocytic thyroiditis in three cases (15%). High rates (35% cases) of misinterpretation of FNAC in this scenario can be attributed to the reactive inflammatory cell rich background, rarity of RS cells in the diagnostic material, and tumor associated sclerosis leading to limited aspiration of cells of interest.[3] ICC is a valuable tool to circumvent this issue and guide upon further diagnostic workup. Among the viewed cases, ICC supported the diagnosis of hematolymphoid neoplasm in two cases (including our case).

Out of these 19 cases, eight patients (42%) were managed surgically [followed by radiotherapy (RT)/chemoradiotherapy], plausibly for alarming symptoms; while four (21%) were managed similarly for no such symptoms. On the other hand, seven patients (37%) were treated with RT/chemoradiotherapy alone without any surgical intervention. Both the above groups (treated with and without surgical intervention), however, had comparable outcomes (Table 2). In general, HL has been effectively treated with combination therapy comprising multiagent chemotherapy, usually ABVD and field RT and does not require surgery.[11,12] As can be seen from Table 4, amongst cases where FNAC diagnosis offered was hematolymphoid neoplasm/HL, half were treated with upfront RT/chemoradiotherapy; while the other half were managed with primary surgical treatment. In contrast, when FNAC diagnosis offered was other than hematolymphoid malignancy, only a minority (23%) was subjected to upfront RT/chemoradiotherapy. As seen in Table 2, pretreatment biopsy diagnosis was obtained in 13 cases (45%) while 16 patients were subjected to resection without biopsy. The surgical resection was in the form of total thyroidectomy (six cases), partial thyroidectomy/lobectomy (six cases), subtotal thyroidectomy (two cases), and subtotal resection of neck mass (two cases). For these reasons, a meticulous FNAC smear examination aided by ICC if required, is necessary, not only to induce clinicians to seek a biopsy diagnosis, but also to obviate the standard surgical treatment in a prototypal thyroid lesion setup.

Histologically, 29/30 patients were diagnosed with classical HL while one patient was offered diagnosis of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). Nodular sclerosis (22 cases) followed by mixed cellularity type (4 cases) were the most common subtype of classical HL documented. The propensity of nodular sclerosis to involve thyroid gland seems to be in keeping with its tendency to involve mediastinum and other head and neck regions.[13] Bercovici et al. have demonstrated the role of IL-6 and IL-13 produced by tumor cell in inducing local fibrosis.[14] The association between chronic lymphocytic thyroiditis and non-Hodgkin lymphoma of thyroid is well documented.[15,16] However, it is difficult to derive similar association with Hodgkin lymphoma, given the rarity of this entity. Nonetheless, in at least eight cases (26%) the adjacent thyroid tissue showed presence

Table 2: Clinicopathological features of cases of Hodgkin lymphoma involving thyroid gland described in literature

Sr No.	Authors (year)	Age/sex	Symptoms	FNAC	Lymphoma diagnosed on	HL subtype	Uninvolved thyroid	Stage	Treatment received	Outcome
1	Rupp et al[10] (1962)	64/M	Neck pain, dysphagia and B-symptoms	Not done	Resection	Not described	Lymphocytic thyroiditis	IIE	Thyroidectomy	Not described
2	Roberts et al[18] (1963)	61/M	Painful enlarging neck mass	Not done	Resection	NS	Hashimoto's thyroiditis	IIE	Subtotal neck mass resection	Not described
3	Gibson et al[19] (1968)	59/F	Painless progressive neck enlargement	Not done	Resection	NS	Lymphocytic thyroiditis	IIE	Thyroidectomy F/B RT	NED at 6 months
4	De Baets et al[5] (1981)	57/F	Goiter, with rapid painful enlargement of thyroid	Suspicious of malignancy	Resection	NS	Not described	IE	Subtotal thyroidectomy	NED at 6 years
5	Feigin et al[20] (1982)	64/F	Thyroid nodule and hypothyroidism; hoarseness and weight loss	Not done	Resection	NS	Lymphocytic thyroiditis	IIE	Thyroid lobectomy, followed by RT	NED at 3 years
6	Kugler et al[21] (1982)	27/F	Slow thyroid enlargement over 1 year. Stridor, hoarseness and dysphagia over 3 week	Not done	Resection	NS	Not described	IIIE	Subtotal resection F/B CT	NO F/U
7	Mate et al[22] (1984)	60/F	HypothroidismF/B dysphagia and hoarseness	Not done	Lymph node biopsy	MC	Not described	IIE	RT, Lung recurrence after 6 month treated with CT	Not described
8	Mate et al[22] (1984)	25/F	Enlarging goitre and dysphagia	Not done	Lymph node biopsy	NS	Not described	IIE	RT, abdominal recurrence after 2 years treated with CT	NED at 7 years
9	Smith et al[3] (1986)	19/F	H/O goitre F/B dysphagia, dyspnea and rapidly increasing thyroid	Not available	Not available	NS	Not described	IIE	Not available	Not available
10	Granados et al[23] (1991)	36/F	H/O goitre, on thyroxin, now increase in size and firmness	Suggestive of HL	Neck mass biopsy	NS	Not described	IIE	RT	NED at 1 year
11	Vailati et al[24] (1991)	29/F	H/O thyroid enlargement, stridor, low grade fever, fatigue and pruritis	HL	Resection	NS	Not described	IE	Subtotal thyroidectomy and RT	NED at 2 years
12	Jayaram et al[25] (1993)	53/F	Neck swelling F/B cervical lymphadenopathy and hepatosplenomegaly	HL	Lymph node biopsy	Not described	Not described	IV	Thyroid lobectomy	Lost to F/U
13	Hardoff et al[6] (1995)	20/F	1year H/O solitary thyroid nodule F/B cervical lymphadenopathy	Lymphocytic thyroiditis	Lymph node biopsy	NS	Not described	IIE	CT, RT	NED at 1 year
14	Hardoff et al[6] (1995)	18/F	Painless throat fullness, dysphagia, fever	Consistent with HL	Lymph node biopsy	NS	Not described	IIE	CT, RT	NED at 1.5 years
15	Luboshitzky et al[26] (1995)	19/F	Single nodule in left thyroid lobe	Possibility of HL	Lymph node biopsy	NS	Not described	IIE	CT	NED at 2 years

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Sr No.	Authors (year)	Age/sex	Symptoms	FNAC	Lymphoma diagnosed on	HL subtype	Uninvolved thyroid	Stage	Treatment received	Outcome
16	Nakamura et al[27] (1997)	18/M	Progressively enlarging neck mass with dyspnea	Not done	Thyroid biopsy	NS	Not described	IIE	RT	NED at 4 years
17	Bercovici et al[14] (2002)	44yr	Compressive goitre and hypothyroidism	Not done	Lymph node biopsy	NS	Not described	IIE	CT, RT	NED at 3 years
18	Wang et al[3] (2005)	42/F	Hoarseness and stridor	Suspicious of HL	Resection	NS	Lymphocytic thyroiditis	IIE	Partial thyroidectomy F/B CT	NED at 7 years
19	Wang et al[3] (2005)	50/F	Rapidly growing neck mass	Chronic lymphocytic thyroiditis	Resection	NS	Not described	IIE	Partial thyroidectomy F/B CT	NED at 3.5 years
20	Wang et al[3] (2005)	59/F	Dysphagia	Chronic lymphocytic thyroiditis	Resection	NS	Hashimoto's thyroiditis	IIE	Complete thyroidectomy F/B CT	CR at last F/U
21	Wang et al[3] (2005)	29/F	Dysphagia	DD: HL and NHL (based on ICC)	Lymph node biopsy	NS	Not described	IIE	CT	CR at last F/U
22	Wang et al[3] (2005)	46/F	H/O HL 14yrs ago. Painless thyroid nodule	Possibility of recurrent HL	Resection	NS	Not described	IE	Complete thyroidectomy. Recurred year later in cervical LN, treated with CT	NED at 15 months
23	Zolotar et al[28] (2011)	23/F	Nodular hard mass in the region of thyroid gland	acute suppurativ-e/ purulentinflammati-on c/w pyogenic abscess	Incisional biopsy	Not described	Not described	IIE	CT	Not described
24	Oriot et al[29] (2012)	37/F	Rapidly growing goitre with dyspnea and stridor	Acellular Material	Resection	NS	Riedle's thyroiditis	IV	CT	Not described
25	Thomas et al[30] (2012)	60/F	H/O hypothyroidism, increasing anterior neck swelling with dysphagia	Not done	Biopsy	MC	Hashimoto's thyroiditis	IIE	CT	NED at 1 year
26	Szczepanek-Parulska et al[31] (2013)	29/F	Pregnant with enlarged cervical lymph nodes	Suspicious of MTC (based on calcitonin positivity)	Resection	MC	Not described	IVB	Complete thyroidectomy with lymphadenectomy F/B CT	NED at 10 years
27	Szczepanek-Parulska et al[31] (2013)	23/F	Painless B/L enlarged neck nodes and hoarseness	Suspected cell of undetermined origin	Resection	NS	Not described	IIE	Complete thyroidectomy with lymphadenectomy F/B CT, RT	NED at 4 years

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Sr No.	*Authors (year)*	*Age/sex*	*Symptoms*	*FNAC*	*Lymphoma diagnosed on*	*HL subtype*	*Uninvolved thyroid*	*Stage*	*Treatment received*	*Outcome*
28	Sánchez-Vela et al[32] (2015)	53/F	Rapidly growing neck mass	Suspicious of HL	Resection	NS	Hashimoto's thyroiditis	IE	Left thyroid lobectomy with lymphadenectomy F/B CT	Not described
29	Bello et al[4] (2016)	76/F	Thyroid nodule with hypothyroidism	Suspicious of PTC	Resection	NLPHL	Not described	IIE	Total thyroidectomy with cervical lymphadenectomy F/B CT	NED at 5 years
30	Present case	34/F	Left thyroid swelling with withdyspnea on exertion and stridor	Hematolymphoid malignancy favoured over anaplastic carcinoma (Based on ICC)	Thyroid biopsy	MC	Not described	IIE	CT,RT	Dead, 6 months

Source: Modified from Wang et al.[3]

B/L, bilateral; CT, chemotherapy; C/W, consistent with; F/B, followed by; FNAC, fine needle aspiration cytology; F/U, follow-up; HL, hodgkin lymphoma; H/O, history of; ICC, immunocytochemistry; LN, lymph nodes; MC, mixed cellularity; MTC, medullary thyroid carcinoma; NED, no evidence of disease; NLPHL, nodular lymphocyte predominant hodgkin lymphoma; NS, nodular sclerosis; PTC, papillary thyroid carcinoma; RT, radiotherapy.

Table 3: Diagnoses offered on thyroid FNAC in literature

Diagnosis offered	*No. of cases*
Suspected hematolymphoid malignancy/HL	10
Suspicious for malignancy	1: Papillary thyroid carcinoma
	1: Medullary thyroid carcinoma
	2: Unknown cell of origin
Lymphocytic thyroiditis	3
Pyogenic abscess	1
Acellular (nondiagnostic)	1
Total	**19**

Table 4: Treatment received in patients where FNAC diagnoses were offered

	Surgical Treatment			*Non-surgical treatment*
FNAC Diagnosis	*Patient treated with surgery for alarming symptoms**	*Patients treated with surgery for non-alarming symptoms*	*Total*	*Patient treated with RT/ Chemoradiotherapy*
Hematolymphoid neoplasm/HL (n=10)	3 (30%)	2 (20%)	5 (50%)	5 (50%)
Other (n=9)	5 (54%)	2 (23%)	7 (77%)	2 (23%)
Total (n=19)	**8 (42%)**	**4 (21%)**	**12 (63%)**	**7 (37%)**

*Compression of airway (dyspnea, stridors), oesophagus (dysphagia) and pain due to involvement of adjacent vital structures (painful enlargement); FNAC, fine needle aspiration cytology; HL, hodgkin lymphoma; RT, radiotherapy

of chronic lymphocytic (Hashimoto) thyroiditis, which supports the notion that at least a subset of these tumors are associated with chronic lymphocytic thyroiditis.[3]

Clinicoradiologically, most of the patients (22/30, 73%) were staged IIE, wherein the thyroid gland was involved along with the regional cervical or mediastinal lymph nodes. This makes it difficult to arrive at a conclusive opinion that whether the involvement of thyroid is primary or secondary. It has been said that the primary thyroid Hodgkin lymphoma is extremely rare and most of the documented cases are due to secondary involvement.[9] In this review however, four cases (13%) were staged IE and probably represent bona fide primary thyroid Hodgkin lymphoma. Further, all four patients underwent thyroid resection. There has been a decreasing trend toward surgical approach for treating thyroid lymphomas due to better availability of chemoradiotherapy and minimal impact of surgical management on patient's survival; thus limiting this modality in treating only stage IE disease.[2,8,17] Nevertheless even diseases higher than stage IE have been treated with surgical management to palliate alarming symptoms like compression of airway and oesophagus and pain due to involvement of adjacent vital structures.[3] The patient in our case too presented with stridor and dyspnoea, however in view of FNAC diagnosis of hematolymphoid neoplasm, the surgical management was withheld and patient was instead subjected to tracheostomy to palliate her symptoms. The final biopsy confirmation refuted the need for surgical intervention; thus the patient was spared from losing a vital organ and the morbidities associated with it. Unfortunately, the patient defaulted and did not complete chemotherapy.

CONCLUSION

To sum up, this report thoroughly reviews the literature on Hodgkin lymphoma involving thyroid. It highlights the importance of careful examination of FNAC smears especially when the microscopic findings are unusual and unlikely for an epithelial malignancy. It underscores the importance of ICC in offering a quick rational diagnosis that can change the treatment plan and salvage the patient from morbid surgical procedures.

CLINICAL SIGNIFICANCE

Thyroid lymphomas are rare entities that possess a real diagnostic challenge. However, at least a diagnostic suspicion, if not a precise diagnosis, can help avoid patient undergo thyroidectomy. ICC can really be handy in confirming such cases if the diagnostic material is less likely to be an epithelial malignancy.

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