Clinicopathological features and treatment outcomes of primary laryngeal lymphomas in saudi population

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Abstract

Background: Primary laryngeal lymphomas (PLLs) are rare and account for 1% -3% of all laryngeal neoplasms. Our aim was to describe the symptomology, diagnosis, histological variants and treatment outcomes of PLL in Saudi population.

Materials and methods: Retrospective review of medical records of patients with laryngeal neoplasms, who were treated in our center in the period from July 2005 to December 2012, was performed. Demographic, radiologic and histopathological features and treatment outcomes were collected.

Results: Among 57 records of patients with laryngeal carcinoma, two (3.51%) patients were diagnosed with PLLs. The frequent clinical presentation was hoarseness of voice. One (50%) patient had marginal zone B-cell mucosa-associated lymphoid tissue (MALT) lymphomas and other (50%) patient had T- Cell lymphoma (TCL). Both patients were treated with involved field radiotherapy 30-36 Gy in 15-18 fractions using RapidArc intensity modulated radiation therapy (IMRT). Median follow up was 12 months (6-14) with overall survival and disease free survival rates of 100% and 100%.

Conclusion: PLLs are uncommon but with better outcomes than other sites lymphomas. Efforts are required for incorporation of immunohistochemical methods to reach proper diagnosis and multimodality approach to improve the diagnosis and treatment outcomes.

Keywords: Primary laryngeal lymphomas, rare malignancy, clinicopathological features, treatment outcome, saudi population

Introduction

Primary laryngeal lymphomas (PLLs) represent 1-3% of all laryngeal cancers and less than 1% of all extranodal lymphomas [1]. Apart from supra-glottic region which contains follicular lymphoid tissue in lamina propria and ventricles, the remaining larynx is devoid of lymphoid tissue and PLLs are thought to develop from lymphocytes, that are acquired during the course of a chronic inflammatory process and for this reason, supra-glottis is commonly affected region in larynx [2]. PLLs are mainly non-Hodgkin lymphoma (NHL) and most PLLs are the diffuse large B-cell lymphoma (DLBCL) and the mucosa-associated lymphoid tissue (MALT) lymphomas [3].

The most common sites for extra-nodal NHL in the head and neck are Waldeyer's ring, salivary glands and thyroid. The PLLs are rare and most are at stage IE or IIE at the time of diagnosis. Median age for occurrence of PLLs is the 7th decade but can present in any groups [4,5]. The presenting symptoms

are similar to squamous cell laryngeal cancers as; hoarseness of voice, foreign body sensation, dysphagia, stridor, dyspnea and cervical lymphadenopathy [6]. Immunohistochemistry is only confirmatory for diagnosing PLLs as radiological features are often similar to primary squamous cell laryngeal cancers [7]. PLLs are considered to respond better to multi-modality treatments as compared to other sites lymphomas [8].

The present study aimed to evaluate the clinical, pathological, radiological and treatment outcomes of patients with PLLs in Saudi population.

Materials and methods

After formal approval from institutional ethical committee, medical charts of 57 patients with confirmed pathologic diagnosis of laryngeal cancers were reviewed, who were treated in our hospital during period of July 2005 and December 2012 using computer data based system. Patients with PLLs were

Table 1. Patient's characteristics.

No:	Age at presentation [years]	Gender	Presentation	Type	location	Stage	Treatment	Status at last visit
1	71	M	Hoarseness of voice Foreign body sensation	MALT lymphoma	Transglottis	IE	Radiation 30 Gy in 15 fractions	CR Alive
2	27	M	Hoarseness of voice	TCL	Subglottis	IE	Radiation therapy 36 Gy in 18 fractions	CR Alive

Abbreviations: M= male, MALT= Mucosa associated lymphoid tissue, TCL= T cell lymphoma, Gy= Gray, CR= complete response.

Figure 1. Case1 (a) Computed tomography showing transglottic mass with (b) SUV uptake 4.2 on CT-PET imaging and (c) virtual laryngoscopy showing right true vocal cord swelling with extension in supraglottis.

Figure 2. Immunohistochemical examination on biopsy showing positivity for (a) CD20 and (b) Bcl-2 (first case).

retrieved in following manner;

- Demographic data (age at diagnosis, gender and symptomatology).
- Histopathological characteristics: For laryngeal MALT lymphoma immunohistochemical positivity for CD20, CD45, CD15, and CD30 and negativity for BCL6, CD5, Cyclin D1, CD43 and kappa or lambda expression from core biopsy and surgery and the presence of small lymphoid cells, for T cell lymphoma/leukemia (TCL/T-ALL), appearance of diffusely infiltrating lymphocytes with immunopositivity T-cell markers (CD3 and CD45) and for Hodgkin's lymphomas, presence of Reed Sternberg cells with immunopositivity for CD15 and CD30 was evaluated. Additional heavy chain Immunoglobulin (IgH) and T cell receptor (TCR) gene

rearrangements, cytogenetic karyotyping and Fluorescent in Situ hybridization (FISH) were also performed for diagnosis confirmation.

- Clinical stage according to Musshoff's modification of Ann Arbor staging system [9] by findings from physical examination, hematological tests and electrolytes, computed tomography (CT) and magnetic resonance imaging (MRI) and positron emission tomography (PET) scans and bone marrow examination findings.
- Treatment modalities (surgery, chemotherapy and radiation therapy) and outcomes.
- Disease-free survival (DFS) was defined as the duration between the completion of treatment and the date of documented disease recurrence, death resulting from the cancer, and/or last follow-up visit (censored). Overall survival (OS) was defined as the duration between the completion of treatment and the date of patient death or last follow-up visit (censored).

Results

Among 57 diagnosed thyroid carcinoma patients, two (3.51%) patients with PLLs were found. The patients' characteristics are listed in (Table 1).

Case 1

First case was 70 year-old male known hypertensive and hypothyroidism (Hashimoto's thyroiditis) with no previous history of smoking who presented to us with 12 months history of hoarseness of voice and foreign body sensation. Indirect laryngoscopy (IDL) showed mobile true vocal cords (TVC) with a huge mass in both TVC (transglottic) consistent with CT scan neck (Figure 1). The biopsy of transglottic lesion showed immunopositivity for CD20, CD3 and BCL2 + and kappa or lambda expression and immunonegativity for CD10, BCL6, CD5, Cyclin D1, and CD43. The Ki67 index was found less than 10% (Figure 2) (showing IHC positivity for CD20 and BCL2). Baseline hematological, biochemical, hepatic, renal and lactate dehydrogenase (LDH) were found within normal limits. CT chest, abdomen, pelvis and bone marrow biopsy were found negative. Patient was staged as IE. Patient refused chemotherapy which was advised prior to radiotherapy. Patient was treated with involved field radiotherapy (IFRT) using RapidArc intensity modulated radiotherapy (IMRT) with total dose of 30 Gy in 15 fractions (Figure 3a). The course of treatment was tolerated well and at one year of follow up he was found alive and disease free.

Case 2

Second case was a 27-year old male non- smoker with no significant medical history presented to us with 6 months history of hoarseness of voice. IDL showed a submusocal thickening below level of TVCs in subglottic region consistent with CT neck findings (**Figure 4**). Biopsy confirmed the T cell lymphoma/T cell acute lymphoblastic leukemia. There was immunopositivity for CD99 (**Figure 5**), CD3, CD4, CD7, CD8 and Tdt and immunonegativity for CD5, CD10, CD20, CD34 and BCL6. Karyotyping, IgH and PCR (to detect notch mutations) were not performed for this patient. Myeloid markers were

done to exclude a myeloid neoplasm with any aberrant T cell expression. Baseline LDH, hematological, biochemical, hepatic and renal functions were found normal. Remaining staging work up was negative and he was staged as IE. Patient refused chemotherapy and he was treated with IFRT using RapidArc IMRT with total dose 36 Gy in 18 fractions (**Figure 3b**). The treatment was tolerated well with grade 1 dysphagia. At 12 months, he was alive with complete recovery of normal and disease free.

Discussion

PLLs are rare with diverse clinicopathological features and treatment outcomes as reported in previous published data (**Table 2**). In our series, PLLs were seen 3.51% of all laryngeal malignancies which is much higher frequency as reported by other studies. PLLs were seen in 3rd and 7th decade and predominantly in males. Predominant histopathological type DLBCL was not seen in our both patients and both patients had non-supraglottic involvement of larynx with stage IE. Causative factors for PLLs are not well known, however, PLLs cases have seen in patients with Wiskott Aldrich syndrome, acquired immunodeficiency syndrome (AIDS), rheumatoid arthritis and Sjogrens syndrome [19,30,41,42]. Our first patient had Hashimoto's thyroiditis.

Diagnosis is challenging as radiological features are similar to other squamous cell laryngeal cancers as in our patient CT/PET imaging was non diagnostic. Incorporation of immunohistochemistry (IHC) is only a confirmatory tool. We treated both patients with radiotherapy with excellent response rates. Due to rarity of PLLs there is no consensus

Table 2. Case reports and series of primary laryngeal lymphoma published between 1986 to 2013.

Authors	Age/ Gender	Symptoms	Location	Histologic type	Stage	Treatment	Follow up	Status
Ghosh KC, <i>et al.</i> , [10]	60/M	Hoarseness of voice Stridor	Subglottis	DLBCL	IE	Tracheostomy and RT 19 Gy in 8 fractions	4 months	Alive
Diebold J, <i>et al.</i> , [11]	46/M	NA	Supraglottis	MALT	IE	RT	NA	NA
Hisashi K, <i>et al.</i> , [12]	66/M	Hoarseness of voice	Glottis	MALT + SCC	IE	RT + total Laryngectomy	46 months	Alive
Kato S, <i>et al.</i> , [13]	3 cases M	Hoarseness of voice	Supraglottis (2) Glottis (1)	MALT (2)TCL (1)	IE (2) IV (1)	CT (3) RT (2 cases) Laryngectomy (1)	NA	NA
Ansell SM, <i>et al.</i> , [14]	6 cases M	Hoarseness of voice	Supraglottis(2) Glottis (3) Subglottis(1)	MALT (3)MALT (3)	IE	CT (2) RT (4)	40-228 months	Dead (5) Alive (1)
Marianowski R, <i>et al.</i> , [15]	88/M	Hoarseness of voice	Supraglottis	TCL	IE	RT +CT (chlorambucil) Steroids	10 months	Dead
Fung EK, <i>et al.</i> , [16]	78/M	Hoarseness of voice Dyspnea Dysphagia	Supraglottis	MALT	IE	RT 44 Gy in 22 fractions	30 months	Alive
Zhao JD, <i>et al.</i> , [17]	5 cases M	Hoarseness of voice and dysphagia	Supraglottis	DLBCL	IE (3) IV (2)	RT + CT	24 months	NA
Hadjileontis CG, <i>et al.</i> , [18]	53/M	Hoarseness of voice	Glottis	TCL + SCC	NA	NA	NA	NA
Palenzuela G, <i>et al.</i> , [19]	15/M	Hoarseness of voice Dyspnea	Trans glottis	DLBCL	NA	RT +CT	2 months	Dead
Kania RE, <i>et al.</i> , [20]	70/M	Hoarseness of voice	Glottis	MALT	IE	Surgical Excision	24 months	Alive
Roca B, <i>et al.</i> , [21]	82/F	Hoarseness of voice Dysphagia	Supraglottis	DLBCL	IE	RT	12 months	Alive
Andratschke M, <i>et al.</i> , [22]	58/M	Severe dyspnea	Subglottis	MALT	IE	RT +CT	12 months	Alive
Word R, <i>et al.</i> , [23]	76/M	Hoarseness of voice	Supraglottis	DLBCL	IE	CT(RCHOP)	36 months	Alive
Steffen A, <i>et al.</i> , [24]	62/M	Dry cough, stridor and exertional dyspnea	Subglottis	MALT	IE	CT (CHOP)	15 months	Alive
Tardío JC, <i>et al.</i> , [25]	52/M	Hoarseness of voice- Dyspnea	Supraglottis	NK/T-cell lym- phoma	IIE	CT	6 months	Dead
Monobe H, <i>et al.</i> , [26]	73/M	Dyspnea	Supraglottis	NK/T-cell lym- phoma	IE	CT	12 months	Dead
Markou K, <i>et al.</i> , [4]	3 cases 67/M 53/M 32/M	Hoarseness of voice Dyspnea Stridor	Glottis (2) Subglottis (1)	TCL (1) MALT (1) ALBL +SCC (1)	IE (2) IIE (1)	CT (2) CT +RT (1) 40 Gy in 20 fractions	26-80 months	Alive
Elmazghi A, <i>et al.</i> , [27]	24/M	Hoarseness of voice Dyspnea	Supraglottis	DLBCL	IIE	CT (CHOP) + RT 40 Gy in 20 fractions	6 months	Alive
Uri N, <i>et al.</i> , [28]	45/M	Hoarseness of voice Dyspnea	Supraglottis	NK/T-cell lym- phoma	IE	RT 40 Gy in 20 frac- tions	24 months	Alive
Naciri S, <i>et al.</i> , [29]	70/M	Severe dyspnea	Subglottis	Mantle Cell lym- phoma	IIIE	Tracheostomy + CT (RCHOP)	2 months	Dead
Cikojevic D, <i>et al.</i> , [7]	77/M	Dysphagia Cough Foreign body sensation	Supraglottis	NK/T-cell lym- phoma	IIE	CT (CHOP) +RT 40 Gy in 20 fractions	12 months	Alive
Smith MS, <i>et al.</i> , [30]	NA	Hoarseness of voice Dyspnea	Supraglottis	TCL	IE	RT 40 Gy in 20 fractions	12 months	Dead
Simo R, <i>et al.</i> , [31]	NA	Hoarseness of voice	Glottis	DLBCL	IE	RT 40 Gy in 20 fractions	8 months	Dead
de Bree R, <i>et al.</i> , [32]	36/F	Hoarseness of voice Dyspnea	Supraglottis	MALT	IE	RT 28 Gy in 14 fractions	24 months	Alive
Cheng CJ, <i>et al.</i> , [33]	NA	Hoarseness of voice Dyspnea	Supraglottis	DLBCL	IE	RT	12 months	Alive
Ohta N, <i>et al.</i> , [34]	76/M	Dysphagia	Supraglottis	DLBCL	IE	Laryngectomy + RT	36 months	Alive
Cavalot AL, <i>et al.</i> , [35]	NA	Hoarseness of voice	Glottis	DLBCL	IE	CT (CHOP)	16 months	Alive
Mok JS, <i>et al.</i> , [36]	3 cases	Hoarseness of voice Dyspnea	Supraglottis (2) Subglottis (1)	NK/T-cell (2) TCL (1)	IE (1) IIE (2)	CT (3) RT (1)	NA	Dead

Continuation of Table 2.

Authors	Age/ Gender	Symptoms	Location	Histologic type	Stage	Treatment	Follow up	Status
Nayak JV, et al., [37]	NA	Hoarseness of voice Dyspnea	Supraglottis	DLBCL	NA	CT	13 months	Alive
Caletti G, et al., [38]	NA	Hoarseness of voice	Glottis	MALT	IE	Anti-Helicobacter pylori therapy	46 months	Alive
King AD, et al., [39]	3 cases	Hoarseness of voice	Trans glottis	NK/T-cell (3)	IE	CT (3) RT (1)	11-36 months	Dead (1) Alive (2)
Agada FO, et al., [40]	NA	Hoarseness of voice Dyspnea	Supraglottis	DLBCL	IE	CT	6 months	Alive
Patlar S, et al., [41]	NA	Hoarseness of voice Dyspnea	Supraglottis	DLBCL	IE	CT	NA	Alive
Korst RJ, et al., [42]	NA	Hoarseness of voice Stridor	Subglottis	MALT	IIE	Laryngectomy	4 months	Alive
Monobe H, et al., [43]	73/M	Hoarseness of voice Dyspnea	Supraglottis	NK/T-cell	IIE	CT	1.5 months	Dead

for radiation therapy doses and fractionation and radiation doses between 19 Gy to 44 Gy have been given in past reports [4,10,16,27,28,30,32]. RCHOP (cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab) chemotherapy alone also have shown complete regression of PLLs in many patients [23-26,35,37,40,41,43]. However we believe that multimodality approach (chemotherapy regimen and radiation therapy) shall be encouraged for such patients and laryngectomy or tracheostomy should only be performed in patients with stridor or coexistent squamous cell laryngeal cancers, as PLLs respond well with chemotherapy and radiotherapy. Excellent outcomes in our in both patients without prior induction chemotherapy were possibly due to early stage PLLs and use of novel radiation therapy techniques (Rapid IMRT).

In conclusion, PLLs are rare with considerable heterogeneous behavior and clinicopathologic features in our Saudi population. With improvements in IHC frequency of PLLs is rising and multimodality approach shall be considered for treating such patients.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YB: concept of study, MAA, EFA: manuscript writing and related research data collection, HF: pathological data writing and collection, YB, MAT: statistical analysis, manuscript writing, AMM, KR: data collection, manuscript editing.

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