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) lymphoma 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 methodsto 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 vorticules, 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
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 forHodgkin'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 (Hashimotos’ 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, CD2 and BCL2 + andkappa 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 forHodgkin'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.

*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).
Figure 3. RapidArc IMRT field arrangements in (A) first and (B) second patient.

Figure 4. Computed tomography of second patient showing (A) axial and (B) sagittal views of subglottis diffuse mass.

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 submusosal 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, et al., [10]   | 60/M        | Hoarseness of voice, Stridor        | Subglottis | DLBCL               | IE    | Tracheostomy and RT             | 4 months  | Alive  |
| Diebold J, et al., [11]  | 46/M        | NA                                  | Supraglottis | MALT               | IE    | RT                              | NA        | NA     |
| Hisashi K, et al., [12]  | 66/M        | Hoarseness of voice                 | Glottis   | MALT + SCC         | IE    | RT + total Laryngectomy         | 46 months | Alive  |
| Kato S, et al., [13]     | 3 cases M   | Hoarseness of voice                 | Supraglottis(2) Glottis(1) | MALT (2)TCL (1) | IE (2) | CT (3) RT (2 cases) Laryngectomy (1) | NA        | NA     |
| Ansell SM, et al., [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, et al., [15]| 88/M        | Hoarseness of voice                 | Supraglottis | TCL               | IE    | RT + CT (chlorambucil) Steroids | 10 months | Dead   |
| Fung FK, et al., [16]    | 78/M        | Hoarseness of voice, Dyspnea, Dysphagia | Supraglottis | MALT               | IE    | RT                              | 44 Gy in 22 fractions | Alive   |
| Zhao JD, et al., [17]    | 5 cases M   | Hoarseness of voice and dysphagia   | Supraglottis | DLBCL              | IE (3) | RT + CT                         | 24 months | NA     |
| Hadjileontis CG, et al., [18]| 53/M        | Hoarseness of voice                 | Glottis   | TCL + SCC          | NA    | NA                              | NA        | NA     |
| Palenzuela G, et al., [19]| 15/M        | Hoarseness of voice                 | Trans glottis | DLBCL              | NA    | RT + CT                         | 2 months  | Dead   |
| Kania RE, et al., [20]   | 70/M        | Hoarseness of voice                 | Glottis   | MALT               | IE    | Surgical Excision               | 24 months | Alive  |
| Roca B, et al., [21]     | 82/F        | Hoarseness of voice                 | Supraglottis | DLBCL              | IE    | RT                              | 12 months | Alive  |
| Andratschke M, et al., [22]| 58/M        | Severe dyspnea                      | Subglottis | MALT               | IE    | RT + CT                         | 12 months | Alive  |
| Word R, et al., [23]     | 76/M        | Hoarseness of voice                 | Supraglottis | DLBCL              | IE    | CT (CHOP)                       | 36 months | Alive  |
| Steffen A, et al., [24]  | 62/M        | Dry cough, stridor and exertional dyspnea | Supraglottis | MALT               | IE    | CT (CHOP)                       | 15 months | Alive  |
| Tardio JC, et al., [25]  | 52/M        | Hoarseness of voice, Dyspnea        | Supraglottis | NK/T-cell lymphoma | IIE   | CT                              | 6 months  | Dead   |
| Monobe H, et al., [26]   | 73/M        | Dyspnea                            | Supraglottis | NK/T-cell lymphoma | IE    | CT                              | 12 months | Dead   |
| Markou K, et al., [4]    | 3 cases M   | Hoarseness of voice                 | Glottis (2) Subglottis (1) | TCL (1) MALT (1) ALBL + SCC (1) | IE (2) | CT (2) CT + RT (1) 40 Gy in 20 fractions | 26-80 months | Alive |
| Elmarzghi A, et al., [27] | 24/M        | Hoarseness of voice                 | Supraglottis | DLBCL              | IIE   | CT (CHOP) + RT 40 Gy in 20 fractions | 6 months  | Alive  |
| Uri N, et al., [28]      | 45/M        | Hoarseness of voice                 | Supraglottis | NK/T-cell lymphoma | IE    | RT 40 Gy in 20 fractions        | 24 months | Alive  |
| Naciri S, et al., [29]   | 70/M        | Severe dyspnea                      | Subglottis | Mantle Cell lymphoma | IIIIE | Tracheostomy + CT (RCHOP)       | 2 months  | Dead   |
| Cikojevic D, et al., [7] | 77/M        | Dyspnea, Cough, Foreign body sensation | Supraglottis | NK/T-cell lymphoma | IIE   | CT (CHOP) + RT 40 Gy in 20 fractions | 12 months | Alive  |
| Smith MS, et al., [30]   | NA          | Hoarseness of voice                 | Supraglottis | TCL               | IE    | RT                              | 12 months | Dead   |
| Simo R, et al., [31]     | NA          | Hoarseness of voice                 | Glottis   | DLBCL              | IE    | RT                              | 8 months  | Dead   |
| de Bree R, et al., [32]  | 36/F        | Hoarseness of voice                 | Supraglottis | MALT               | IE    | RT                              | 24 months | Alive  |
| Cheng CJ, et al., [33]   | NA          | Hoarseness of voice                 | Supraglottis | DLBCL              | IE    | RT                              | 12 months | Alive  |
| Ohta N, et al., [34]     | 76/M        | Dyspnea                            | Supraglottis | DLBCL              | IE    | Laryngectomy + RT               | 36 months | Alive  |
| Cavalot AL, et al., [35] | NA          | Hoarseness of voice                 | Glottis   | DLBCL              | IE    | CT (CHOP)                       | 16 months | Alive  |
| Mok JS, et al., [36]     | 3 cases     | Hoarseness of voice                 | Supraglottis (2) Subglottis (1) | NK/T-cell (2) TCL (1) | IE (1) | CT (3) RT (1)                  | NA        | 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) should be encouraged for such patients and laryngectomy or tracheostomy should only be performed in patients withstrider 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.

Publication history
Editor: Julie Teruya-Feldstein, Memorial Hospital for Cancer and Allied Diseases, USA.
Received: 09-May-2013 Revised: 29-May-2013 Accepted: 24-Jun-2013 Published: 26-Jun-2013

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Citation:
Bayoumi Y, Maklad A M, Tunio M A, Fatani H, Mohamed R A, AlSaeed E F and Asiri M A: Clinicopathological features and treatment outcomes of primary laryngeal lymphomas in saudi population. Hematol Leuk 2013, 1:5. http://dx.doi.org/10.7243/2052-434X-1-5