CASE SERIES

Primary thyroid lymphoma: Case series of patients from a developing country

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Abstract

Primary Thyroid Lymphoma (PTL) is a rare disease, mostly affecting middle-to-old aged females. It has a strong association with pre-existing thyroiditis, which increases the risk of its development. The disease has been studied in detail in the Western populations. However, there is lack of data for south Asians, especially in Pakistani population. This study was carried out to learn more about the disease characteristics in our area. This was a retrospective study where we reviewed four diagnosed and/or treated cases of primary thyroid Lymphoma at tertiary care hospital of Pakistan (Aga Khan University Hospital), Karachi, Pakistan. Each patient's medical record was reviewed and studied. The participants' average age was 62.8±10.12 years,, with two males and two females. The histology of all of the patients was compatible with the Diffuse B cell Lymphoma subtype. One patient died as a result of complications, one patient was lost to follow up, and the remaining two patients are doing well with no active complaints and are being followed up on a regular basis.

Keywords: Primary Thyroid lymphoma, Pakistani population, Diffuse large B cell subtype.

DOI: https://doi.org/10.47391/JPMA.4281

Introduction

Primary thyroid lymphoma is a rare cancer that accounts for 1% to 5% of all thyroid cancers, as well as 2% of all extranodal tumours.[1] However, this figure was obtained from studies conducted in the western countries. A study conducted in ten non-western countries, revealed the incidence of PTL that was 0.54%.[2] Most patients were females of middle-to-old age and had pre-existing autoimmune thyroiditis. It has been reported that individuals with lymphocytic thyroiditis have 40 to 80 times greater risk of developing Primary Thyroid lymphoma in comparison to the general population.[3] Primary thyroid lymphoma peaks between 60-70 years of age.[4] Most patients present with a rapidly enlarging painless neck mass while others present with compressive symptoms like dysphagia and shortness of breath.[5] Common subtypes include Diffuse large B-cell lymphoma (DLBCL) (50-70%), followed by Mucosa associated lymphoid tissue (10-50%). Other less common subtypes include Follicular Lymphoma, small lymphocytic lymphoma, Burkitts lymphoma, mantle cell lymphoma,T-cell lymphoma and Hodgkins Lymphoma.[6] Diagnostic modalities commonly used include Ultrasound, CT scan and FNAC. Small retrospective studies done to evaluate the accuracy of FNAC for diagnosis of primary thyroid lymphoma, exhibit that it has a greater sensitivity and specificity when combined with other techniques like flow cytometry, immuno-histochemical studies or use of molecular techniques like PCR.[7] Ultrasonography is the modality of choice when investigating enlarged thyroid gland or nodules. Fine needle aspiration should be performed to classify the patient as having a benign or malignant disease, without the need to perform any thyroid surgery.[8] Most cases of Primary thyroid lymphoma are treated using a combination of chemotherapy and radiotherapy. Case series on patients of primary DLBCL recommend a combination of chemotherapy and radiotherapy for better results. Relapse rates were 7.7 % for combined chemo and radio therapy, 37.1 % for only radiation therapy and 43 % for just chemotherapy, according to Doria et al.[9]

Despite being extensively studied in the western world, only a handful of studies have been done in south Asian population, particularly in Pakistan. The main purpose of this retrospective review was to explore the common clinicopathological features of the diseases, commonly expressed genes on immunohistochemistry, investigations, treatment modalities, outcomes and prognosis of the disease specific to the Pakistani population. Subsequently, we aimed to compare these findings with already known facts about primary Thyroid Lymphoma and note any differences amongst our population and the world population at large.

In this retrospective case series we reviewed the medical records of all four primary thyroid lymphoma cases and relevant data was recorded for analysis. To maintain patient confidentiality, we gave a unique serial number to each patient, and removed any personal information or identities (Table-1). The study was reviewed and approved by the Ethics Review Committee of our institution (ERC # 2021-6196-18230).

Case Series

Case 1: A 69-year old male, known case of type 2 Diabetes Mellitus presented to our hospital in April 2010 with rapidly increasing right sided neck swelling, dysphagia for solids,

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dyspnoea, weight loss of four kgs and hoarseness of voice for the past four weeks. On presentation, the patient was vitally stable. Respiratory examination revealed mild shortness of breath while local neck examination showed diffuse right sided neck swelling, which was immobile, non-tender and fixed to the underlying tissue. Thyroid function tests were done which had results of TSH of 4.18 mIU/ml (0.5-8.9) and Free T4 of 0.96 ng/dl (0.89-1.76). CT scan of the neck showed a right sided neck mass extending up to the superior mediastinum and compressing the respiratory tract. Additionally, fiberoptic bronchoscopy was done which showed diffuse bulge in the posterior pharyngeal wall. Histopathology was consistent with Diffuse large B-cell lymphoma (DLBCL) showing linear cores of tissue with diffuse sheets of atypical lymphoid cells. Brisk mitotic activity and apoptosis were present with following immunohistochemistry (IHC) findings- CD 20^{+}, $CD3^{-}$, $CD10^{-}$, Bcl-2^{+} and Ki-67^{+}. Other investigations including CSF cytology and Bone Marrow trephine, both had no significant findings.

He received combination chemotherapy R-CHOP (rituximab-cyclophosphamide, doxorubicin, oncovin, prednisolone) protocol along with Triple Intrathecal therapy. The patient remained stable during the first two cycles of the R-CHOP therapy after which his condition deteriorated with progressive increase of neck swelling.

Subsequently, patient received External beam radiation for palliative purposes, of which he received four doses. Prior to the fifth dose, patient developed severe respiratory distress for which emergency tracheostomy was performed. The patient went into cardiac arrest, cardiopulmonary resuscitation was performed to revive the patient. However, it was unsuccessful and the patient expired.

Case 2: A 47-year old female, known case of Type 2 Diabetes Mellitus, Hypothyroidism, Asthma, Right breast Intra ductal carcinoma type III, presented to the Aga Khan hospital in August 2016 with complaints of left sided neck swelling, dysphagia and feeling of globus in her throat for the past one month. The patient was hypertensive on presentation, otherwise vitally stable. On local neck examination there was a diffusely nodular swelling on the left side of anterolateral aspect of the neck, which was mobile, moving with deglutition and non-tender. Ultrasound of the neck showed a nodule measuring 3.7x1.9 cm without any calcification, while, CT scan neck showed diffusely enlarged thyroid gland with multiple cervical and mediastinal lymph nodes. TFTs showed TSH of 2.28 mIU/ml (0.4-4.2) and TT4 of 14 µg/dl (5.5-11). FNAC of Thyroid gland was done twice but no conclusive results were obtained. Total thyroidectomy was planned and subsequently done. Intraoperatively, thyroid mass was seen to be adherent to the underlying structures. Post resection, the patient developed stridor and emergency tracheostomy was done to relieve it.

Histopathology was consistent with Diffuse large B-cell lymphoma with immunohistochemistry showing - CD 20^{+}, $CD3^{-}$, Ki 80-85%.

The patient was started on R-CHOP protocol and was given six cycles of the chemotherapy along with G-CSF for five days. Post treatment, she had an episode of pulmonary embolism for which she was started on anticoagulant therapy. Currently the patient is well and under surveillance, with regular follow ups.

Case 3: A 70 year old male, ex-smoker, s/p angioplasty done two weeks back, came to the Aga Khan hospital in March 2012 with complaints of progressive left sided neck swelling, dysphagia, dyspnoea with stridor, hoarseness of voice, weight loss of five kgs since the past four months. Respiratory examination revealed stridor while local thyroid examination showed neck swelling, which was hard in consistency. Lymph nodes were also palpable on the left side of the neck. CT scan showed diffuse enlargement of thyroid gland with hypodense areas representing oedema with relative sparing of part of right lobe associated with diffuse thickening of posterior pharyngeal wall and cervical oesophagus, while, thyroid scan showed poorly outlined left lobe with cold nodule. TSH was 0.03 uIU/ml (0.5-8.9) and TT4 was 9.41 µg/dl (5.5-11). With disease progression, patient's respiratory distress exacerbated for which an elective tracheostomy was performed. Thyroid tissue was obtained during the tracheostomy procedure and sent for biopsy. Biopsy was consistent with Diffuse B cell Lymphoma (DLBCL) with following immunohistochemistry findings- LCA +ve, CD20 +ve, CD3 +ve and Mib-1 +ve. Considering his workup findings, he was advised R-CHOP chemotherapy along with and Intrathecal therapy. However, the patient only received one cycle of R-CHOP chemotherapy and then was lost to follow-up.

Case 4: A 58-year old female, no known co-morbids, came to the Aga Khan hospital in May 2012 with complaints of right sided progressive neck swelling and difficulty in swallowing for the past six months. Local neck examination revealed a right sided neck mass, measuring 4x4cm, moving with deglutition. Ultrasound neck done showed right sided thyroid nodule with multiple hypoechoic lesions and the largest one measuring 1.4 x 0.8 cm, which showed peripheral vascularity. CT scan of the neck showed an irregular, ill-defined, hypodense, non-enhancing lesion in the right lobe of the thyroid gland measuring 2.3x3.2x2.9 cm. No calcifications were noted. Further workup was done

Table-1: Summary of the Case Reports.

	Demographic details	Presenting signs and symptoms	Duration of symptoms	Histopathology	FNAC	Treatment
Case 1	69-year male	Rapidly progressive right sided neck swelling, Dysphagia, Dyspnoea, Weight loss and hoarseness of voice	1 month	Consistent with DLBCL	Not done	2 cycles of R-CHOP therapy+Triple intrathecal therapy + 4 cycles of external beam radiation. Emergency tracheostomy was done
Case 2	47-year female	Left sided neck swelling, dysphagia	1 month	Consistent with DLBCL	Done twice but inconclusive	6 cycles of R-CHOP therapy+G-CSF. Total thyroidectomy followed by tracheostomy was done
Case 3	70-year male	Progressive left sided neck swelling, dysphagia, dyspnoea with stridor, hoarseness of voice and feeling of globus in the throat	4 months	Consistent with DLBCL	Not done	1 cycle of R-CHOP therapy+tracheostomy
Case 4	58-year female	Progressive right sided neck swelling and difficulty swallowing	6 months	Consistent with DLBCL	Inconclusive	4 cycles of R-CHOP therapy and 1 dose of external beam radiation + Total thyroidectomy

including flexible laryngoscopy and Bone Trephine, both of which were normal. FNAC of the thyroid gland was done which was inconclusive. Additionally, Thyroid function tests were done prior to the treatment, TSH was 38.76 mIU/ml (0.5-8.9) and FT4 was 0.49 ng/dl (0.89-1.76). Total thyroidectomy was done, there were no intraoperative complications. However, post-operatively, patient developed hypocalcaemia and was treated for that accordingly. Histopathology was consistent with Diffuse large B-cell, non-Hodgkin's lymphoma arising in the background of Hashimotos thyroiditis with following immunohistochemistry findings - CD20 +ve, CD3 -ve, Ki-67 80% and Cytokeratin AE1/AE3 -ve.

Subsequently, she was started on a combination of R-CHOP chemotherapy along with External beam radiation therapy, she received four doses of R-CHOP along with external beam radiation. Currently, the patient is well and under surveillance with regular follow-up visits.

Discussion

This is a retrospective case series, where we reviewed four cases of Primary Thyroid Lymphoma, including their demographic details, course of disease, treatment outcomes and current status of the patients. Women are more likely than males to develop primary thyroid lymphoma[10] and the average age of onset is in the sixth or seventh decade.[11] There were an equal number of males and females in our study. Furthermore, previous studies reveal that the average presenting age of males is younger than that of females[11] but men, on the other hand, presented at a substantially older age than women in our study.

All our patients had symptoms of a rapidly progressing neck mass and dysphagia which is a common presentation of this disease.[12] Patients can also present with B symptoms such as fever, night sweat, and weight loss which is seen in 10–20% of cases,[13] weight loss was noted in two of the patients in our case series. According to various researches, the average length of symptoms is one to three months[13] and the mean time it took for our cases to be presented was also three months. One of the risk factors for the development of the disease is the presence of Hashimoto's thyroiditis (HT).[5] Only one out of the four patients had Hashimoto's thyroiditis in our study.

Table-2: Immunohistochemistry findings.

	CD 20	BCL 2	Ki 67	LCA	Pan B	CD 3	Mib-1
Case 1	+	+	+	-	-	-	-
Case 2	+	-	+	-	-	-	-
Case 3	+	-	-	+	-	+	+
Case 4	+	-	+	-	-	-	-

Two out of the four patients had FNAC procedure done, however, results of both the patients were inconclusive. Histopathology was performed in all four patients and was consistent with diagnosis of Diffuse Large B-cell lymphoma. The immunohistochemistry findings of all the patients are summarized in the table 2.

Diffuse B cell lymphoma subtype is an aggressive subtype and requires multimodal treatment.[12] With regards to the treatment of the disease, all four patients received the R-CHOP therapy (Rituximab, Cyclophosphamide, Doxorubicin Hydrochloride, Vincristine, Prednisolone). Additionally, two out of the four patients received external beam radiation therapy as well. Thyroidectomy was done in two out of the four patients.

Conclusion

The clinicopathological characteristics, treatment modalities and outcome of the patients with primary thyroid lymphoma were consistent with earlier researches. This suggests that we can investigate and treat this disease using a similar strategy because the disease acts similarly in Pakistani and Western populations. However, it would be advantageous to the medical community as a whole if a Pakistan-specific database was built and the cases recorded so that they may be used in future research.

Disclaimer: None.

Conflict of interest: None.

Funding disclosure: None.

Consent: Consent of all patients was obtained for publishing their cases.

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