Original Article
Anaplastic lymphoma kinase-positive large B-cell lymphoma (ALK+ LBCL) presenting as a subglottic mass: a case report and clinical course involving haplo-identical stem cell transplant

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Abstract: Anaplastic lymphoma kinase-positive large B-cell lymphoma (ALK+ LBCL) is an extremely rare variant of lymphoma with less than 100 cases reported in the literature since the first description by Delsol et al in 1997. Malignant lymphomas represent approximately 5% of all malignant neoplasms of the head and neck and are rarely found within the larynx. Extra nodal involvement of the head and neck is extremely rare with only a few reported cases. Median survival is 12 months with standard chemotherapy including CHOP-like regimens. Here, we present a 40-year-old male presenting with expiratory stridor found to have a large subglottic mass on CT who underwent tracheostomy and biopsy sampling revealing ALK+ LBCL. PET-CT scan revealed diffuse metabolic foci throughout the axial and appendicular spine in addition to an FDG avid soft tissue subglottic mass with extension into the anterior thyroid cartilage. The patient underwent high intensity chemotherapy followed by consolidation autologous stem cell transplant, salvage radiotherapy at site of primary local recurrence, salvage chemotherapy for systemic relapse followed by haplo-identical stem cell transplant from his donor son and anti-PD1 immunotherapy post-transplant. He passed away 24 months after diagnosis from progressive lymphoma.

Keywords: ALK-positive large B-cell lymphoma, anaplastic lymphoma kinase (ALK), subglottic mass, haplo-identical, stem cell transplant, CD30, brentuximab vedotin

Introduction
Malignant lymphomas represent 5% of all malignant neoplasms of the head and neck and are rarely found within the larynx [1]. ALK+ LBCL is an extremely rare variant of lymphoma different from ALK-positive anaplastic large cell lymphoma (ALCL). It accounts for less than 1% of large B-cell lymphomas. Less than 100 cases have been reported in the English literature since the first description by Delsol and colleagues in 1997 [2]. In 2008, the WHO Classification of Tumors and Haematopoetic and Lymphoid Tissues began listing ALK+ LBCL as a distinct entity [3]. The median age at diagnosis is 37 to 44.5 years, male predominance on the order of 3:5:1 and geographic distribution including cases in Europe, North America, and Asia. It appears to be an entity of immunocompetent individuals [4]. ALK+ LBCL is an aggressive tumor with a poor response to conventional therapies including CHOP or CHOP-like regimes. The median survival is 12 months with a 5-year survival rate of 25% [5]. High intensity regimes including hyper-CVAD, dose adjusted (DA) EPOCH, COD-OX-M, and the Nordic regimen have improved outcomes for aggressive B-cell Non Hodgkin Lymphoma (NHL). Here, we describe the first case report of ALK+ LBCL presenting as a subglottic mass and the clinical course including autologous stem cell transplant (SCT) and eventual allogeneic haplo-identical stem cell transplant.

Case report
A 40-year-old previously healthy male Navy officer presented as an inpatient to inpatient transfer from an outside hospital following several...
weeks of worsening upper respiratory symptoms and globus sensation. Previous to his arrival, he was initially treated with antibiotics for a presumed pneumonia. His symptoms progressed despite the antibiotics and he presented to the emergency room with expiratory stridor but was able to maintain oxygen saturation above 90%. Computerized Tomography (CT) imaging revealed a large subglottic mass. He was admitted to the outside hospital and underwent an unsedated tracheostomy complicated by a pneumothorax as well as biopsies of the lesion. Frozen section pathology revealed a poorly differentiated malignancy. The patient was then transferred to the inpatient ward at SAMMC for further workup and treatment. He underwent repeat fiberoptic laryngoscopy which demonstrated a posterior nodular and irregular subglottic mass (50% airway obstruction) with surface hypervascularity seen in (Figure 1). The mass extended from the intraarytenoid space at the posterior commissure to approximately 2 cm below the inferior surface of the vocal cords; the patient had normal vocal cord motion. Repeat biopsy and careful debulking of the mass was performed for further tissue characterization. An enhanced CT scan of the patient’s neck demonstrated a hyperdense fungating 1.7 × 1.2 cm endotracheal mass contiguous with the subglottic left posterolateral tracheal wall (Figures 2, 3). LDH,
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uric acid, ESR, thyroid panel, CBC, and chemistry panel were all normal. PET imaging demonstrated an FDG avid soft tissue mass anterior to the trachea with likely extension to the anterior aspect of the thyroid cartilage, bilateral cervical nodal metastasis, and extensive foci of metastatic osseous disease throughout the axial and appendicular skeleton (maximum SUV 20.3) represented in (Figure 4).

Pathological analysis showed a proliferation of large lymphocytes with abundant cytoplasm and a plasmablastic/immunoblastic morphology. Immunostains showed the malignant cells to be diffusely positive for CD45, CD138, CD10, MUM-1 and EMA. In addition, ALK-1 exhibited the classic strong granular cytoplasmic staining pattern (Figure 5). In situ hybridization assay revealed a lambda light chain restriction. EBER was negative. The cells were negative for CD30, CD15, CD20, CD56, myeloperoxidase, bcl-2 and PAX-5. CD3 stained reactive background T cells only (Figure 5). Ki-67+ fraction was 80%. In addition, Lu-5 (cytokeratin) and S100 were negative.

Bone marrow biopsy revealed ALK positive immunostain of scattered cells in clot section that stained in a granular cytoplasmic pattern and had eccentric nuclei with prominent nucleoli, similar to the subglottic mass biopsy (Figure 6). Lumbar puncture was negative for lymphomatous involvement by cytology and flow cytometry.

The final diagnosis was determined to be Ann Arbor Stage IVA ALK+ LBCL. The patient was started on modified hyper-CVAD (hyperfraction-
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ated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high dose methotrexate and cytarabine). The patient was also given intrathecal prophylaxis with methotrexate and cytarabine during induction. During his first cycle of high dose methotrexate plus cytarabine he developed grade 4 transaminitis likely due to high dose methotrexate. Once the transaminitis was resolved, he was transitioned to DA-EPOCH (etoposide, prednisone, oncovin, cyclophosphamide, and hydroxydoxorubicin). He completed four cycles without complication, reaching dose level three. PET-CT showed a near complete resolution of soft tissue prominence anterior to trachea with persistent focal FDG avidity as well as persistent diffuse FDG avidity of osseous structures (maximum SUV 4.2) without anatomic correlate.

He proceeded to high dose consolidation therapy with BEAM (BCNU, etoposide, ara-c, melphalan) conditioning prior to autologous SCT. Two months post SCT, the PET-CT revealed resolved FDG avidity in osseous structures, but focal FDG avidity anterior to the thyroid cartilage (maximum SUV 12.4, previously 13.5) as well as asymmetric FDG avidity in the posterior right larynx without anatomic correlate (maximum SUV 9.9). MRI neck performed one month later revealed a 7 x 6 mm superficial

Figure 6. Bone Marrow H&E stain (A), Bone Marrow Aspirate (B) and Bone Marrow CD138 IHC stain (C).
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Fig. 7. CD30 IHC stain.

A nodule just anterior to thyroid cartilage to the right of midline, corresponding with persistent focal FDG activity seen on the thyroid cartilage. Biopsy of the subglottic lymph node confirmed residual ALK+ LBCL with an identical IHC pattern to the original subglottic mass biopsy. Also, there was noted a 4 × 8 × 6 mm subglottic nodule at the posterior inferior aspect of the right vocal cord, corresponding to the new focus of asymmetry at the posterior right larynx. The larynx and surrounding neck was treated with external beam radiotherapy to a total of 60 gray to the residual disease.

Two months after completion of radiation, he presented with palpable adenopathy and widespread relapse including a lesion on his scalp, calvarium and dura with extension to frontal cortex. Marrow evaluation was positive for ALK1+, CD138+, and new CD30 positivity (5-10% of cells) by IHC (Fig. 7). Salvage chemotherapy with GIFOX (gemcitabine, 5-fluorouracil and oxaliplatin) plus IT depocyt for 2 cycles was completed with chemo responsive disease. This was followed by Fludarabine/Cyclophosphamide/TBI conditioning and haplo-identical SCT from his donor son with post-transplant Cytoxan with MMF and tacrolimus for GVHD prophylaxis.

The initial post-transplant course was uneventful, but by day +50 he had clear relapse of his disease with rapid progression despite abrupt withdrawal of immunosuppression; PET-CT imaging revealed extensive marrow and nodal involvement. At that time it was decided to approach treatment as purely palliative with the goal of maintaining his quality of life. In an attempt to limit suppression of a graft versus lymphoma effect, he was treated with brentuximab vedotin (Adcetris) on a 21 day cycle. This resulted in a significant improvement in symptoms and adenopathy. Despite early withdrawal of immunosuppression he did not develop acute graft versus host disease. His response to Adcetris was short lived as just prior to his third cycle he developed clinical progression of his scalp lesion. Given that his other sites of disease seemed to be controlled, it was decide to proceed with therapy and arrange palliative radiation therapy for the scalp lesion. Unfortunately, shortly after his third dose of Adcetris he developed new adenopathy, but was feeling well so he continued with radiation therapy. Post radiation, he was given one cycle of Nivolumab 3 mg/kg IV but developed a grade 2 skin GVHD. Treatment was initiated with prednisone and titration of tacrolimus. He had continued progression of adenopathy and marrow involvement. Gemcitabine-oxaliplatin × 1 cycle did not slow down his disease and he enrolled on hospice care.

The patient passed away at 24 months post diagnosis from progressive lymphoma.

Discussion

The clinical characteristics for ALK+ LBCL include mainly nodal disease; however, extra-nodal involvement including a nasal tumor, CNS, gonads, small intestine, muscle and marrow involvement has been described [5, 6]. As far as we know, this is the first case report of this disease entity arising from the subglottis. ALK+ LBCL is an aggressive lymphoma with poor response to conventional therapies used for DLBCL. The largest sets of data include Laurent and colleagues who reviewed outcomes for 31 patients; median survival was 12 months for patients with advanced stage disease [5]. Another review by Beltran and colleagues of a bimodal population of 41 pediatric and adult patients, approximately split between early and advanced stage, documented 56% of patients dying primarily from progressive lymphoma with overall survival time of 24 months [6]. In the pediatric cohort, 11 patients were treated with regimens designed to treat lym-
phoblastic, Burkitt and aggressive B-cell lymphomas with moderate success in that six out of eleven (55%) achieved long term survival. No difference in survival between the pediatric versus adult patients was noted. The strongest factor for survival was clinical stage at presentation with 18 months as median survival for advanced disease; however median survival was not reached in early stage presentations.

No standard of care exists for treatment of this disease. Given the poor overall survival reported with prior cases of advanced stage ALK+ LBCL with CHOP regimens, a more aggressive chemotherapy regimen was chosen. Modified hyper-CVAD was used as a reasonable alternative in this young, otherwise healthy active duty service member. Due to grade 4 transaminitis from high dose methotrexate, induction was completed with DA-EPOCH followed by autologous SCT transplant for consolidation. Ultimately, after local and widespread relapse, haplo-identical SCT was pursued and as far as we know, this represents the first time this type of transplant has been described with ALK+ LBCL. Novel approaches are required to improve outcomes in this difficult to treat lymphoma. Our intent was to share our clinical experience and expand the approaches used to treat this lymphoma including conventional chemotherapy, transplant, targeted agent and immunotherapy.

Disclosure of conflict of interest

None.

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