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ORIGINAL PAPER

Systemic Non-Hodgkin T Cell Lymphomas Presenting in the Head and Neck Region: An Institutional Experience of a Rare Entity

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Abstract
T cell lymphoma (TCL) is a group of rare and aggressive diseases. TCL primary to head and neck organs often present as extranodal NK/T cell lymphoma, nasal type. Systemic TCL with initial head and neck presentation is extremely rare. Here we report our institutional experience. Clinicopathologic data was collected from patients diagnosed with TCL and treated at the University of Alabama at Birmingham between 2002 and 2012. Eleven cases of systemic TCL initially presented at head and neck region were identified. The median age was 54 years and male:female ratio was 1.8. The most common sites involved were sinonasal tissue, tonsil, tongue and larynx. Most patients presented with a mass lesion without systemic symptoms. The presentation of TCL primary to the head and neck region is often non-specific. A misdiagnosis of undifferentiated tumor or chronic inflammation due to ambiguous morphology is not uncommon. TCL should be considered in differential diagnosis and a thorough evaluation is warranted for accurate diagnosis.

Keywords Non-Hodgkin · T Cell · Lymphoma · Head and neck

Introduction

Head and neck is the second most common site for extranodal lymphomas after gastrointestinal tract with diffuse large B cell lymphoma being the most common type [1, 2]. T cell lymphomas are rare in this region and often present as extranodal NK/T cell lymphoma, nasal type [2, 3] followed by peripheral T Cell lymphomas, not otherwise specified (PTCL, NOS), angioimmunoblastic lymphomas (AITL), anaplastic large cell lymphoma (ALCL), and adult T cell leukemia/lymphoma (ATLL) [4, 5]. Extranodal peripheral T cell lymphomas, not otherwise specified, most commonly involve the gastrointestinal tract. Less frequent, involvement of lung, salivary gland, and central nervous system is reported. These patients often present with advanced disease, and B symptoms [4, 6]. Angioimmunoblastic lymphomas almost always present with generalized lymphadenopathy with frequent involvement of spleen, liver, skin and bone marrow. Most commonly, these patients will present with skin rash and pruritus. Often, patients have pleural effusions, arthritis, and ascites [4, 7]. Adult T cell leukemia/lymphoma most often presents with widespread lymph node involvement and peripheral blood. Extra nodal sites include skin (> 50% of occurrences), lung, liver, gastrointestinal tract, and central nervous system [4, 7]. Anaplastic large cell lymphoma is subdivided into Anaplastic lymphoma kinase (ALK) positive (+) and negative (−) entities. ALK (+) occurs in both nodal and extranodal sites frequently. The common extranodal site involved is skin, bone, soft tissues, lung, and liver. Gastrointestinal and central nervous system involvement is rare. Approximately 70% of patients will present with advanced stage III–IV disease with lymphadenopathy. And, about 75% of patients will present with B symptoms, specifically with high fevers. Additionally, the ALK (−) group often involves both lymph nodes and extranodal tissues [notably, extranodal is less common in ALK (−) compared to ALK (+)]. Extranodal commonly involves bone, soft tissue, and skin. As with ALK (+), patients present in advanced stage III–IV disease with lymphadenopathy and B symptoms [4, 7]. The above-mentioned systemic T cell lymphomas with primary presentation in head and neck region are extremely rare. Given low suspicion for disease and heterogeneity in morphology and phenotypic findings, they might potentially be underdiagnosed as reactive

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inflammation or misdiagnosed as non-hematologic tumors. Here we report our institutional experience of these rare lymphomas.

Materials and Methods

Study Group

Eleven patients, diagnosed with systemic T cell lymphoma according to WHO criteria (4) involving the head and neck region at the University of Alabama at Birmingham (UAB) between January 1, 2002, and December 31, 2012, were retrospectively identified. Extranodal NK-T cell lymphoma, nasal type, cutaneous T cell lymphomas and cases with secondary involvement of the head and neck region were not included in this study. Electronic medical records were reviewed and relevant clinic data was documented, including age, sex, race, prior history of medical disease, social history, location of tumor, stage at time of diagnosis, overall survival. Follow up data was available for each patient.

Histology and Immunohistochemistry

Hematoxylin-eosin-stained slides and immunohistochemistry (IHC) slides of formalin-fixed, paraffin-embedded tissue sections prepared at initial diagnosis were reviewed to confirm the diagnosis of T cell lymphoma according to the WHO criteria (4). Immunohistochemical stains performed for diagnosis are summarized in Table 1. Autolink uses 4 µm sections obtained from formalin-fixed, paraffin-embedded block preparations. The immunostaining was accomplished with a semi-automated immunostainer (Dako Autostainer Link 48, Capinteria, CA) and an Envision FLEX HRP system. For Ventana, 5 µm sections were obtained from formalin-fixed, paraffin-embedded block preparations and the immunostaining was accomplished with a semi-automated immunostainer (Ventana Inc. Tucson, AZ) and an Ultraview HPR Multimer approach. Appropriate positive and negative control slides were prepared. No additional immunohistochemistry, beyond what was required for diagnosis at the time of diagnosis, was performed. Flow cytometry was not ordered in any of the cases at the time of biopsy.

Clonality assessment for T cell receptor (TCR)-beta and TCR-gamma chain genes using polymerase chain reaction (PCR) method was performed for four cases at the time of diagnosis and was additionally performed for case 1 (Table 2).

Table 1 Antibody list used for diagnosis

Antibody	Clone	Machine tested	Company
ALK	ALK1	Autolink	Dako
CD2	AB75	Autolink	Dako
CD3	POLY RABBIT	Autolink	Dako
CD4	4B12	Autolink	Dako
CD5	4C7	Benchmark ultra	Roche-Ventana
CD7	CBC.37	Autolink	Dako
CD8	1A5	Benchmark ultra	Roche-Ventana
CD30	BER-H2	Autolink	Dako
CD45	2B11&PD7/26	Benchmark ultra	Roche-Ventana
EBER	RNA PROBE	Benchmark ultra	Roche-Ventana

Results

The clinicopathologic features of the 11 patients identified are summarized in Table 2. The median age was 54 years (range 22–86 years) and male:female ratio was 1.8 (7:4). Nine patients (82%) were white; two (18%) were African–American. The location of primary tumor and site of biopsy included sinonasal tissue in five patients (45%), tonsil in three patients (27%), tongue in two patients (18%), and larynx in one patient (10%). At time of diagnoses, six patients (54%) had prior medical conditions. PTCL, NOS (n = 6, 54%), and ALCL [(n = 3, 27%); ALK (−): 2 and ALK (+): 1] were the most common types. One patient was diagnosed with ATLL with Human T lymphotropic virus and one patient was diagnosed with AITL. Staging showed one patient with multi-regional lymph node involvement and one patient with intracranial disease. Two patients had bone marrow involvement by TCL. The most common presentation was a mass in the area often without systemic symptoms. The median overall survival was 36 months (ranging 4–125 months). At time of review, all 11 patients had deceased.

The typical morphologic features and immunohistochemical properties of these lymphomas are shown in Table 2. Case 6 was initially classified as undifferentiated neoplasm with little specific morphology to identify the cellular origin (Fig. 1a, b) in addition to negative staining with CD45, which is the most commonly used lymphoid marker for lymphoid origin. Two of the cases (cases 2 and 3) were significant for an infiltration of small to intermediate-sized lymphocytes without prominent morphologic atypia, mimicking a reactive chronic inflammatory infiltrate (Fig. 1c, d). A diagnostic difficulty was experienced in Case 10 due to limited viable tumor cells that appeared undifferentiated and did not express CD45, CD3 or CD20. These four cases were eventually given the correct diagnosis upon consulting with the hematopathologist(s) and performing additional lymphoid markers. Case 7 was significant for a dense chronic inflammatory infiltrate with admixed scattered clusters of large atypical lymphoid cells including many with features of "Hallmark" cells. A broad diagnostic work-up using IHC

Table 2 Clinicopathologic findings of systemic T cell lymphoma cases primary to head and neck region

Case no.	Age (years)/sex (race)	Diagnosis	Prior disease	Location	Stage	Overall survival (months)	Morphology	Positive	Negative	Clonality by PCR
1	86/M (W)	PTCL	DLBCL	Nasal cavity	–	4	Intermediate to large-sized atypical lymphoid cells	CD2, CD3, CD30 (p), CD45, EBER	ALK, CD4, CD8	n/a
2	44/M (W)	PTCL	None	Larynx	IIE	8	Small to intermediate-sized atypical lymphoid cells	CD2, CD3	CD45, CD4, CD5, CD7, CD8, CD30, EBER	Positive TCR-β and TCR-γ
3	57/F (W)	PTCL	MZL psoriasis	Tongue	IVB	10	Small to intermediate-sized atypical lymphoid cells	CD45, CD2, CD4, CD5, CD7, CD30 (p)	CD3, CD8	n/a
4	62/M (AA)	ATLL−/HTLV+	Gout	Maxillary Sinus	IVA	8	Intermediate to large-sized atypical lymphoid cells	CD2, CD3, CD4, CD5, CD8	ALK, CD7, CD30, EBER	n/a
5	22/M (W)	PTCL	None	Ethmoid	IB	78	Intermediate-sized lymphoid cells with no distinct atypia	CD3, CD4, CD30 (p)	ALK, CD8	Positive TCR-β
6	64/M (W)	ALCL/ALK−	Plasmacytoma, CLL Hypogammaglobulinemia	Neck Lymph Node, Tonsil	IVB	72	Large atypical mononuclear cells with significant morphologic atypia	CD2, CD43, CD4, CD30	CD45, CD3, CD8, ALK	Positive TCR-β
7	43/M (W)	ALCL/ALK−	None	Maxillary Sinus	IE	75	Scattered large atypical lymphocytes in the background of heavy acute and chronic inflammation	CD3, CD30	ALK, CD4, CD8	n/a
8	52/F (W)	AITL	UC	Tonsil	IVB	26	Intermediate sized lymphocytes with scattered large forms in the background of eosinophils and plasma cells	CD2, CD3, CD4, CD5, CD7	CD8, CD30, ALK, EBER	Positive TCR-β

Table 2 (continued)

Case no.	Age (years)/sex (race)	Diagnosis	Prior disease	Location	Stage	Overall survival (months)	Morphology	Positive	Negative	Clonality by PCR
9	54/M (AA)	ALCL/ALK+	None	Tonsil	IIB	18	Large atypical lymphocytes with numerous "hallmark" cells	CD2, CD30, ALK	CD3, CD4, CD8	n/a
10	56/F (W)	PTCL	Hypothyroid	Nasal cavity	–	125	Large pleomorphic mononuclear cells and extensive necrosis	CD2, CD4, CD43, CD8	CD45, CD3, CD30, CD56	n/a
11	51/F (W)	PTCL	None	Tongue	IE	8	Large atypical lymphocytes	CD45, CD3, CD4, CD5	CD8, CD30, EBER	n/a

M male, *F* female, *W* White, *AA* African–American, *PTCL* peripheral T cell lymphoma, *ATLL* adult T cell leukemia/lymphoma, *HTLV* human T lymphotropic virus, *ALCL* anaplastic large cell lymphoma, *ALK* anaplastic lymphoma kinase, *AITL* angioimmunoblastic T cell lymphoma, *DLBCL* diffuse large B cell lymphoma, *MZL* marginal zone lymphoma, *CLL* chronic lymphocytic leukemia, *LN* lymph node, *p* partial, *n/a* not available

was performed to rule out carcinoma, melanoma as well as Hodgkin lymphoma. The clusters of neoplastic large lymphocytes were diffusely positive for CD3 and CD30. Of note, a prior biopsy from the same lesion was interpreted as inflammatory polyp due to lack of large atypical cells in the sample. Case 8 posed a significant diagnostic challenge with the intermediate sized lymphoma cells lacking morphologic atypia and heavy inflammatory background of eosinophils and plasma cells. The case was sent to UAB Pathology for consultation and the hematopathologist rendered a diagnosis of AITL based on the morphologic and phenotypic features as well as positive T cell re-arrangement by PCR. All the tumors were negative for a keratin stain excluding carcinoma, and some cases were also stained with melanoma markers revealing negative results. Neoplastic cells showed positivity with one or more lymphoid and T cell markers including CD2. CD3 negativity in some of the tumors also posed a challenge in determining the B or T cell origin (Fig. 2a, c). Other cell surface markers were helpful to render a diagnosis of TCL (Fig. 2b, d). Notably, the common T cell markers that aberrantly lack in the lymphoma cells in most cases were CD7 and CD3. Cases with diffuse CD30 with or without ALK staining were sub classified as ALCL. In case 1, with lymphoma of nasal cavity, the phenotype was rather ambiguous with expression of CD2, CD3, and partial CD30 by IHC and some of the neoplastic lymphocytes were positive for EBER. There was no CD56 expression. In this particular case, a diagnosis of PTCL was favored over Extranodal NK/T cell lymphoma, nasal type based on lack of CD56 expression and the presence of EBV in only a fraction of lymphoma cells. Further testing for T cell clonality was also performed in this case using PCR and positivity for TCR-beta gene was demonstrated ruling out the latter diagnosis.

Discussion

TCL are malignant proliferations of mature T cells and often associated with an aggressive behavior [8]. TCL primarily presenting in the head and neck region are rare and the incidence ranges from 1 to 17% in various countries with limited information in the Western World [9–11]. Extranodal TCL in head and neck region can develop as a primary lymphoma, i.e. NK-T cell lymphoma, nasal type, or involve secondarily. Extranodal systemic TCL with primary presentation in the head and neck region is extremely rare and the biology of the disease is poorly understood due to very limited data. The clinical presentation of systemic TCL primary to the head and neck region is often non-specific and not commonly considered in the differential diagnosis, since many patients present with mass in the area without systemic "B-type" symptoms of fever, night sweats, and weight loss [11]. One

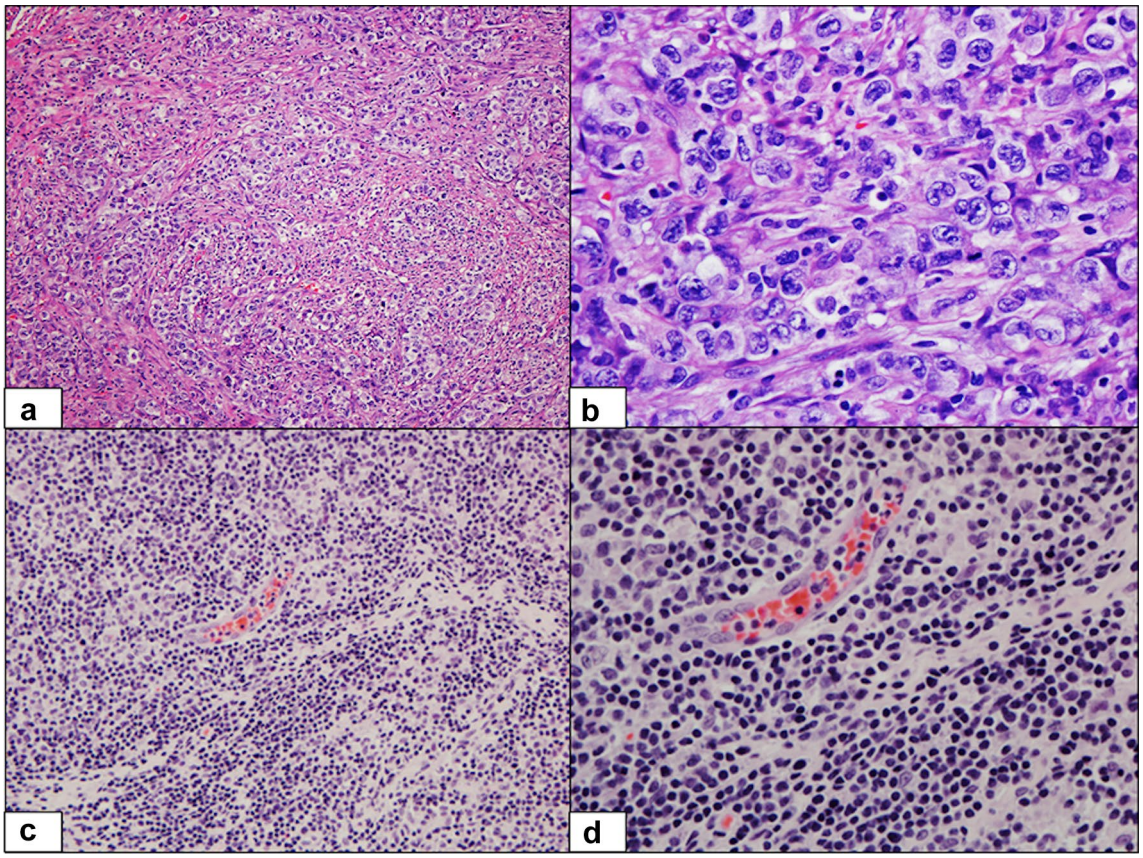

Fig. 1 H&E stains demonstrating anaplastic and undifferentiated morphology in anaplastic T cell lymphoma (case 9). The majority of the tumor mass consists of bizarre shaped nuclei with irregular chromatin clumping and many mitotic figures (**a, b**). Case 5 with peripheral T cell lymphoma composed of small to intermediate-sized cells without prominent atypia, mimicking reactive lymphoid infiltrate in ethmoid sinus (**c, d**)

study described 62 cases of non-Hodgkin lymphoma of the head and neck region; the majority of which were B cell lymphomas (52 out of 62) with only 7 patients with diagnosis of TCL, including cutaneous forms [11]. Another study focusing on nasopharyngeal lymphoma in 1,119 cases, reported NK/T cell lymphoma comprising only 6% (n = 67) of the cases [12]. However no further sub classification of the TCL, i.e. systemic TCL vs. nasal type NK/T cell lymphoma, was provided. Additionally, this fairly large SEER data showed a significantly short overall survival (OS) in NK/T cell lymphoma (13.6 months) (12). The median OS in our study was 36 months, ranging from 4 to 125 months.

To our knowledge, the current study provides the largest series of systemic T cell lymphoma primary to head and neck region excluding NK-T cell lymphoma, nasal type and cutaneous lymphomas. NK-T cell lymphoma, nasal type is often in the differential diagnosis and can easily be diagnosed based on morphologic exam and distinct immunophenotype—CD2+, CD7+, CD56+, and EBER+ as well as cytoplasmic CD3-epsilon+ (4) which may not be easily detected by flow cytometry when using surface CD3 antigen only. However, this panel may not be sufficient to rule in or out a systemic T cell lymphoma as many of them lack CD7 and also, not uncommonly, CD3. CD56 expression is not common in the majority of systemic TCL, nor EBER. Cutaneous lymphomas often present with a rather specific clinical picture including local/generalized rash with or without lymphadenopathy.

T cell lymphoma is a group of aggressive diseases requiring chemotherapy with or without radiation. A thorough clinical, morphologic and immunophenotypic evaluation is warranted to establish an accurate diagnosis to provide the best care to these patients. In a case of strong suspicion for lymphoma and no expression of CD45, additional IHC staining is warranted including CD43 and CD2 as well as a pan-B cell marker, i.e. CD79a or CD20. In addition, molecular testing for T cell gene re-arrangement using PCR might support a diagnosis of TCL in the right clinical, morphologic and phenotypic setting. It is important to remember that T cell receptor and Immunoglobulin genes are in germline configuration in most cases of extranodal NK/T cell lymphoma, nasal type. These tumors not uncommonly display an undifferentiated morphology

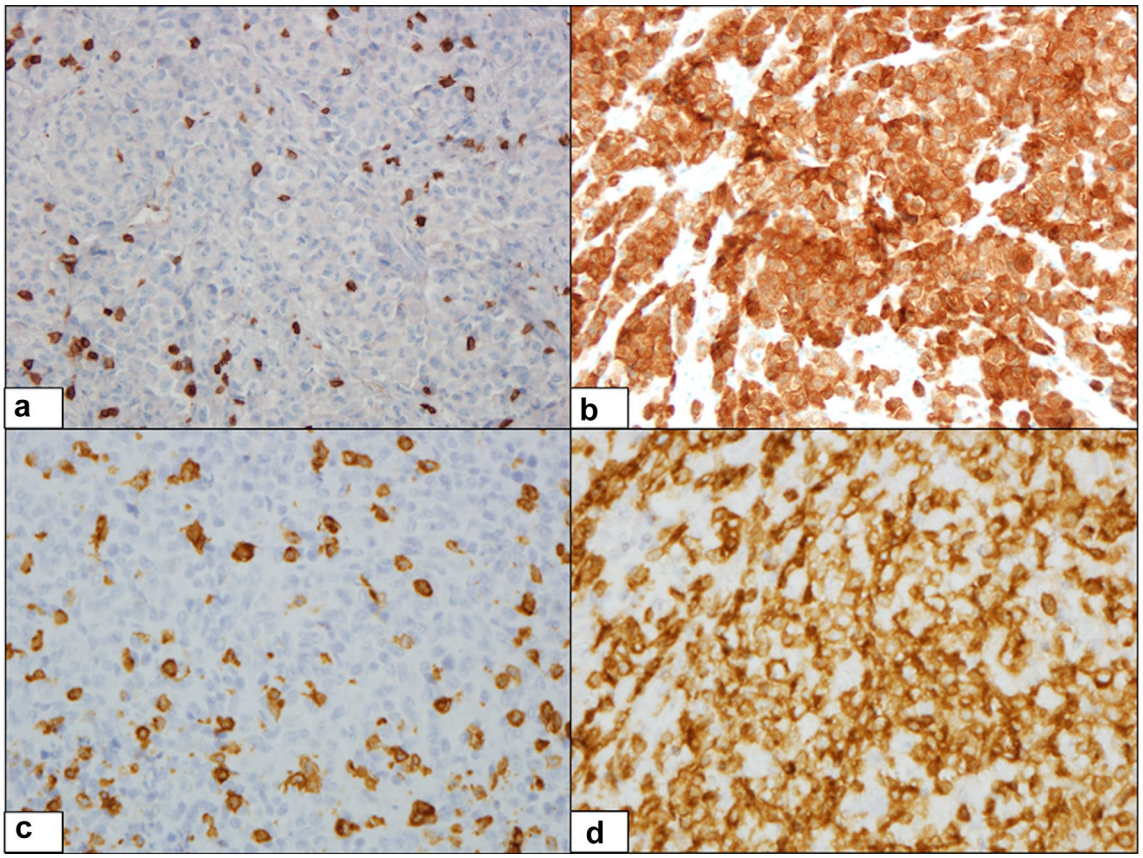

Fig. 2 Case 9 with anaplastic large T cell lymphoma staining negative for T cell marker CD3 (**a**) and positive for ALK (**b**). Similarly, Case 10 with peripheral T cell lymphoma stains negative for CD3 (**c**) and positive for CD2 (**d**)

prompting the pathologist to consider other differentials, i.e. sarcoma of unknown origin. This incorrect diagnosis may result in unnecessary treatment with chemo-toxic pharmaceuticals or radiation therapy that will provide little to no benefit to the patient.

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Compliance with Ethical Standards

Conflict of interest Authors Peker and Broadwater do not have any conflict of interest to disclose.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by UAB Institutional Review Board (Protocol Approval # X160701001).

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