CASE REPORT

ALK negative anaplastic large cell lymphoma of the oral cavity showing spontaneous regression

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Abstract
Anaplastic large cell lymphoma is a subset of T-cell lymphoma which is rarely seen in the oral cavity. This entity may be either primary cutaneous or systemic and the prognosis varies significantly by subtype. In addition, several similar entities have been reported which may mimic this lesion both clinically and histologically. We present a case of anaplastic large cell lymphoma, ALK negative, on the mucosal aspect of the upper lip of an 88 year-old female with a history of cutaneous T-cell lymphoma which demonstrated spontaneous regression after biopsy. A brief review of the literature along with an overview of clinical behavior, histologic presentation, immunohistochemical analysis, genetics, and differential diagnosis of this subtype of anaplastic large cell lymphoma are presented.

Key words
Anaplastic large cell lymphoma, Oral cavity, CD30+

Introduction
Anaplastic large cell lymphoma (ALCL) is a rare subtype of T-cell lymphoma that can involve mucocutaneous sites primarily or secondarily as part of systemic disease. ALCL is usually comprised of large atypical lymphoid cells with abundant cytoplasm and pleomorphic, often kidney shaped nuclei (Hallmark cells). In all cases, these cells are CD30 (Also known as Ki-1) positive and most cases they express cytotoxic granule-associated protein (Perforin, TIA-1 and granzyme B). A significant percentage of ALCL harbors the t (2; 5) (p23; q35) translocation. Based on the expression of the resulting gene product: Anaplastic lymphoma kinase (ALK), ALCL can be further subdivided into ALK (+), more common in the first three decades of life, and ALK (-) categories. The ALK (-) ALCL is more heterogeneous subgroup with more variations in morphology and immunophenotype, and worse clinical outcome. Systemic ALCL must be differentiated from primary cutaneous type of ALCL and from other subtypes of CD30 (+) lymphomas with anaplastic features [2]. Significant differences in behavior and prognosis exist between the different subtypes [1]. ALCLs comprise only 2.4% of head and neck lymphomas [3].
Oral manifestations of T-cell lymphomas are very rare; 92% of lymphomas in the oral cavity are of B cell lineage, most frequently diffuse large B-cell lymphomas (DLBCL) [3]. The majority of cases of cutaneous T-cell lymphoma involving the oral cavity represented cases of mycosis fungoides [4]. We present a patient with a history of primary T-cell lymphoma of the skin who developed oral lesions consistent with ALCL. Several previously reported cases of ALCL involving the oral cavity are presented along with a discussion of the spectrum of this disorder and other similarly-presenting ulcerating oral lymphoproliferative disorders.

Case report

An 88 year-old female presented to an oral surgeon (E.F.) with a non-healing, rapidly enlarging, ulcerated lesion measuring 2.5 by 1.0cm on the labial mucosa of the right upper lip (Figure 1). The lesion had previously been treated with antibiotics without improvement. Her medical history included cutaneous T-cell lymphoma diagnosed 4 years previously with lesions on the right flank of the abdomen confirmed by biopsy and T-cell gene rearrangement study. After the initial excisions, no further cutaneous lymphoma lesions had developed in the intervening period. Her medical history also included a previous CVA and bladder cancer. She reported no history of tobacco or alcohol use. At the time of her clinical presentation, she denied fever, night sweats, or difficulty swallowing. No lymphadenopathy was noted at her clinical examination. Results of laboratory testing at this time revealed hemoglobin, hematocrit, white blood cell and platelet counts all within a normal range.

An incisional biopsy of the labial mucosa lesion was submitted for pathologic examination. Examination of histologic sections from this lesion revealed an atypical lymphocytic infiltrate consisting of large, lymphoid cells with large pleomorphic nuclei, numerous atypical mitoses, large zones of necrosis with surface ulceration and an infiltrative pattern. A mixed inflammatory background was noted with a large number of eosinophils along with granulocytes, histiocytes, small lymphocytes and some plasma cells (Figure 2 A-C). Occasional large atypical mononuclear Reed-Sternberg-like cells were also seen. Immunohistochemical studies (Table 1) performed with appropriate positive and negative controls (Figure 2D-I) revealed that the neoplastic cells were strongly CD30 (+), with membranous and Golgi pattern of expression, CD3 (-), strongly CD8 (+), CD7 (-), ALK1 (-), CD56 (-) and performing (-) with variable immunoreactivity for CD4 and CD45 and focal weak immunoreactivity for CD5. They were also negative for B-cell markers (CD20, CD79a, OCT2, and PAX5). CD15 and EMA were negative as well. In situ hybridization study for EBV encoded RNA (EBER) was negative. Immunohistochemistry for Ki-67 showed frequent labeling of nuclei (Approximately 50% of the lesional cells). Few reactive T cells were noted in the background. A diagnosis of ALK- anaplastic large cell lymphoma was made.
Figure 2. Composite photomicrograph showing the morphologic features of this case of ALK (-) anaplastic large cell lymphoma and the immunohistochemical profile. Low power view showing a very dense and deep lymphocytic infiltrate (A) with necrosis and surface ulceration (B) (Hematoxylin and eosin stain, magnification original X 20). Higher power view (C) shows an abnormal infiltrate of large atypical lymphocytes with pleomorphic nuclei, including Hallmark cells with horseshoe- or kidney-shaped nuclei (arrows). There is a brisk mitotic activity (Hematoxylin and eosin stain, magnification original X 500. Immunohistochemical studies (D-I, original magnification X 200) show that the neoplastic cells are strongly CD30 positive (D) with membranous and Golgi-type staining, CD3 negative (E), variably CD4 positive (F), which also highlights some histiocytes in the background, strongly CD8 positive (G), CD7 negative (E), note the presence of few reactive CD7 (+) small T cells in the background, and Perforin negative (I)
Two weeks post biopsy, the patient returned to her oral surgeon with the lesion significantly reduced in size (Figure 3). She then had PET scan for staging and to rule out the presence of systemic disease, but the results were unavailable. No skin lesions or systemic signs and symptoms were reported by the patient. A plan was made for local radiation therapy to the mucosal lesion. She was lost to follow-up at this point.

Figure 3. A. Presentation of the patient two weeks after biopsy showing significant resolution in facial swelling. B. Significant spontaneous resolution of the ulcerated lesion of the mucosal aspect of the upper lip two weeks after the biopsy.

Discussion
ALCL include primary cutaneous and systemic forms [2]. Primary cutaneous ALCL (C-ALCL) shows a more indolent disease process with a good prognosis and potential for spontaneous regression [5]. It comprises approximately 25% of cutaneous T-cell lymphomas, second only to mycosis fungoides [6]. Patients with C-ALCL are generally older, in their fifth to sixth decades of life on average, and there is a male predominance [7]. Skin lesions are most frequent on the trunk, face, extremities and buttocks and patients usually present with solitary or multiple nodules or papules which are often localized [2]. Extracutaneous involvement may be seen in 5%-10% of patients at presentation [5]. The histology shows anaplastic, non-epidermotropic infiltrate of neoplastic large lymphoid cells and often a reactive lymphocytic component at the periphery, especially in ulcerated lesions where eosinophils, neutrophils, and histiocytes may be prominent [2]. The anaplastic cells have large irregular and pleomorphic nuclei and abundant pale cytoplasm [7]. Reed-Sternberg-like cells and multinucleated giant cells may be seen [5, 7]. The immunohistochemical profile of C-ALCL shows strong CD30 immunoreactivity in at least 75% of cells with expression of a T-cell phenotype (CD45RO, CD43) and variable loss of T cell antigens (CD2, CD3, CD5 or CD7) [7]. Cytotoxic granules-associated proteins (TIA1, granzyme B, perforin) may also be expressed [2]. Unlike systemic ALCL, these lesions are ALK (-) and epithelial membrane antigen (EMA) negative but usually express the cutaneous lymphocyte antigen (CLA) [2-5]. Spontaneous regression has been reported in up to 42% of patients in some studies [6, 7].

Primary systemic ALCL is mainly nodal in origin and is further subdivided into cases that show expression ALK protein, and those that are ALK-negative [2, 5]. ALK (+) and ALK (-) ALCL- compose 6.5% and 5.5% of T-cell lymphomas respectively [5]. Significant differences exist between these two categories. The average age of patients with ALK (+)
ALCL is significantly younger (3rd decade) than those with ALK (-) ALCL (5th-6th decades) \(^9\)\(^-\)\(^11\). ALK (+) ALCL often harbor chromosomal translocations, the most common of which is t (2; 5) (p23; q35) translocation \(^2\)\(^-\)\(^5\). ALK (-) ALCL lack any definitive cytogenetic abnormalities and have a much poorer prognosis than ALK (+) counterpart \(^2\). Both systemic subtypes have a worse 5-year survival rate than primary C-ALCL [A nearly 80% 5-year survival rate for ALK (+), 48% for ALK (-) versus 90% for cutaneous ALCL] \(^2\)\(^,\)\(^6\)\(^,\)\(^8\).

The morphologic features of systemic ALCL are similar to C-ALCL, both containing large anaplastic lymphoid cells growing in a sinusoidal or sheet-like, cohesive pattern \(^1\). “Hallmark cells” or large cells with eccentric, horseshoe- or kidney-shaped nuclei are frequently present \(^5\). By definition, CD30 is strongly expressed in all cases of ALCL (Both the cutaneous and systemic forms). Systemic ALCL can be have a T-cell type, expressing a range of T-cell markers with possible loss of one or more pan T-cell antigens, or of a null cell type, expressing no T-cell markers \(^2\). Regardless of expression of T-cell associated antigens, approximately 90% of cases show clonal T-cell receptor rearrangement. Cytotoxic granulocytes-associated proteins may be expressed in both systemic and cutaneous ALCL and EBV markers are generally negative \(^2\). Systemic ALCL with expression of CD56 have been shown to have an inferior outcome \(^10\).

The most common chromosomal abnormality associated with ALK (+) ALCL (In 84% of cases) is the t (2; 5) (p23; q35) reciprocal translocation between the gene encoding for ALK and the gene encoding for NPM, a nucleolar-associated phosphorprotein, on chromosome 2 \(^5\). The ALK gene encodes a tyrosine kinase receptor which acts as an insulin growth factor receptor \(^12\). Other variant translocations also occur involving the ALK gene and genes on chromosomes \(^1\)\(^-\)\(^3\), \(^17\), \(^19\), \(^22\), and the X chromosome \(^2\). These different translocations result in distinct nuclear and/or cytoplasmic patterns of immunoreactivity with ALK1 antibodies. The ALK protein expression and translocation have also been identified in varying entities other than ALCL including inflammatory myofibroblastic tumors, DLBCL, non-small cell lung cancer, esophageal squamous cell carcinoma, colon carcinoma, breast carcinoma, and neuroblastoma \(^12\)\(^-\)\(^16\). Primary cutaneous ALCL and systemic ALK (-) ALCL do not have any recurrent cytogenetic abnormalities \(^2\).

The differential diagnosis of ALCL includes Hodgkin lymphoma (HL), other forms of CD30 (+) T-or B-cell lymphoma with anaplastic morphology, and undifferentiated carcinoma or other malignancies. HL is of particular concern since it shares CD30 immunoreactivity and large atypical cell appearance. HL can be differentiated based on the expression of a variable combination of B-cell antigen (CD20, PAX-5) and CD15 and lack of expression of CD45-the leukocyte common antigen (LCA) \(^17\). Other variants of peripheral T-cell lymphoma can be ruled out based on the limited CD30 expression and lack the hallmark cells \(^17\). Anaplastic forms of DLBCL are rare but should also be considered in the differential diagnosis, and can be ruled out based on the pattern of expression of B-cell associated antigens, and have a distinct pattern of ALK immunoreactivity \(^2\). Undifferentiated carcinoma and melanoma can be identified using cytokeratin and melanoma markers \(^17\).

A search of the literature in the English language in PUBMED identified 11 prior cases of CD30 (+) ALCL involving the oral cavity \(^18\)\(^-\)\(^27\). In addition, several early cases were also reported as oral CD30+ ALCL but can be now reclassified into different categories of T- or B-cell lymphomas according to the most recent WHO classification of lymphoma \(^28\)\(^-\)\(^30\). Of the 11 reported cases, all were of the T-cell type except for one case with null cell type \(^27\). Including the current case, the average age of the patients was 59.5 years, although a large range was noted (12-88 years). Females comprised 55% of the patients and males 45%. The lesions appeared in various locations throughout the mouth including both in the soft tissue and in bone. Ulceration was a common presenting feature along with swelling. The clinical presentation of the cases varied widely with some reporting systemic or cutaneous involvement and others with the oral lesions alone. One case was reported as ALK (+), one as ALK (-), and the status of ALK expression was not reported in the remaining cases \(^24\)\(^,\)\(^27\). One other case reported spontaneous regression with relapses \(^24\).

Several other entities appear to fall into the spectrum of indolent atypical CD30 (+) oral lymphoproliferative disorders with a potential for spontaneous regression. Some cases of traumatic eosinophilic granuloma-like lesions in the oral cavity
which have been classified as oral manifestations of CD30 (+) T-cell lymphoproliferative disorder have also been reported [31-33]. These cases presented with recurring intraoral lesions that often healed spontaneously after biopsy and were composed of large atypical CD30 (+) cells of a T-cell phenotype with a mixed, eosinophil-rich reactive inflammatory cell infiltrate. None of these patients reported a previous history of cutaneous T-cell lymphoma, although one case developed a cutaneous lesion one year after the first oral ulcer [31-33], and none of these patients developed any systemic manifestations of the oral disease. A similar case was reported that showed EBV positivity in a traumatic eosinophilic granuloma-like lesion with CD30 and CD3 expression [34]. This patient also showed no cutaneous or systemic manifestations.

Current published criteria suggest that lesions resembling C-ALCL in the setting of MF should be classified as transformed MF [2]. However, this definition addresses neither differences in ALK status nor the clonal relationship between the lesions. In the present case, we cannot completely exclude the possibility that this patient’s previous cutaneous T-cell lymphoma acquired other genetic aberrations that led to its transformation into ALCL-like process. However, in this case an ALCL-like lesion arose in an anatomically different site from the previous locations of the cutaneous T-cell lymphoma, after a relatively long period of clinical remission. Tissue from the previous biopsy was unavailable to demonstrate the presence or lack of identical clonality. Overall, we favor two distinct processes.

In conclusion, oral manifestations of ALCL represent a spectrum of disease behavior and progression and pose challenges relating to the diagnosis and prognosis. Care should be taken to differentiate between this entity and other similar indolent oral lymphoproliferative disorders which may present with a similar clinical ulcerative appearance and have potential for spontaneous regression, and thus affecting therapeutic decision making.

Conflict of interest
The authors declare that there is no conflict of interest statement.

References


