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Mantle cell lymphoma of the oral cavity. Case Series and Comprehensive Review of the Literature

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Abstract

Objective—Mantle cell lymphoma (MCL) is a rare B cell neoplasm that has only recently been defined as a distinct entity. Because of its rarity and histological similarities with other small cell lymphomas, the microscopic diagnosis of MCL may be challenging. This is particularly true within the oral cavity where other lymphomas are more frequent. To date, few cases of MCL presenting within the oral cavity have been reported.

Study Design—We present 2 new cases of MCL presenting within the oral cavity and systematically reviewed 7 other cases of MCL reported in the English language literature. Historical cases were reviewed and available data regarding morphology, special stains, demographics, clinical presentation, radiographic findings, management and outcome were extracted. Data from our current series was then compared with the earlier published literature.

Results—To the best of our knowledge, this is the largest reviewed series of MCL within the oral cavity totaling 9 cases. The features of our cases, including histology, clinical presentation and outcome, are consistent with the 7 previously reported cases. The majority of oral MCLs occur in an older male population and a high proportion occur on the palate.

Conclusion—We conclude that MCL of the oral cavity is an uncommon diagnosis. Most oral MCLs occur in an elderly male population and have a possible predilection for the palate. The microscopic diagnosis can be challenging given its similar appearance to other small cell lymphomas requiring a comprehensive immunohistochemical panel for the accurate diagnosis. Like MCL occurring in other sites in the body, the prognosis and outcome of oral MCL appears to be poor.

Keywords

mantle cell lymphoma; oral cavity; tumor; pathology; neoplasia

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Introduction

Mantle cell lymphoma (MCL) is a lymphoid malignancy of B-cells of the mantle zone or primary lymphoid follicle. Although the term mantle cell lymphoma was initially coined in 1992¹, the term was not officially recognized by the World Health Organization (WHO) until its 2001 lymphoma classification scheme.² MCL typically occurs in middle-aged to older adults with a marked male predilection.²⁻⁴ It is an uncommon B-cell malignancy and in most series makes up only a relatively small percentage of all lymphoma types.²

Recognition of MCL and its differentiation from other non-Hodgkin's lymphoma (NHL) subtypes is important because of both the variable prognosis and changing therapeutic regimens. MCL is a small-to-medium-sized lymphoma whose usual differential diagnosis includes small lymphocytic lymphoma (SLL), marginal zone lymphoma (MZL) and occasionally follicular lymphoma (FL). Definitive diagnosis of MCL is predicated on appropriate immunohistochemical staining with or without ancillary molecular and flow cytometric studies. Characteristic of MCL is the overexpression of cyclin D1 protein, a feature not seen in other similar appearing lymphomas.

Few cases of MCL arising within the oral cavity have been reported. To date, there have been only 7 reported cases. Our review was prompted by the unusual discovery of two cases of oral cavity MCL in short sequence. The aim of this paper is to review the salient clinical and pathological features of MCL presenting in the oral cavity.

Material and methods

Case series

The databases of the UCSF Oral Pathology Biopsy Service and UCSF Department of Pathology were systematically searched for all mantle cell lymphomas occurring within the oral cavity for the period 2001-2007. All slides and case reports were retrieved and reviewed. For cases reported prior to 2001, when the term mantle cell lymphoma was not commonly used, the databases were searched for all lymphomas occurring in the oral cavity and then the original sections and case reports were retrieved for review. Those cases showing histological features suggestive of mantle cell lymphoma were then re-examined using CyclinD1 (CCND1) immunoperoxidase staining.

Immunohistochemistry

Immunohistochemistry was performed on unstained sections using selected antibodies (see Table 1). Five-micron thick sections were cut and mounted on adherent glass slides, dewaxed in xylene and rehydrated in graded ethanols. Endogenous peroxidase activity was blocked by immersion in 0.3% aqueous peroxide for 15 minutes followed by two washes in 1X phosphate-buffered saline (PBS) for five minutes each. Slides were treated with a 0.6M sodium citrate buffer and heated in a microwave at 100°C. Incubating in a 2% solution of bovine serum albumen in PBS for 20 minutes blocked endogenous proteins. The sections were then incubated for one hour at room temperature with the primary antibody diluted in PBS. This was followed by two washes in PBS and then incubation with a hapten/peroxidase secondary antibody complex (Envision Plus, Dako Corp., Carpinteria CA) for 30 minutes. The bound complexes were visualized by the application of either aminoethylcarbazole (AEC) or diaminobenzidine (DAB) (Sigma Corp. St. Louis, MO.) containing 0.3% hydrogen peroxide as a substrate. Following incubation the sections were washed and then lightly counterstained with hematoxylin and coverslipped. Negative controls consisted of omission of the primary antibody in selected cases.

Literature review

We conducted a comprehensive computer search of the English language literature (<http://www.ncbi.nlm.nih.gov/sites/entrez>) using combinations of the components terms of lymphoma, mantle cell, head and neck, and oral cavity published between 1980 and 2007. Following careful review of each published case, tumors were selected for inclusion if they were both diagnosed as MCL and primarily presented within the oral cavity defined anatomically as posterior to lips and anterior to palatine tonsils. Each case was evaluated for diagnostic rationale for MCL including review of immunohistochemical findings. Data regarding demographics, clinical presentation, radiographic findings, management and outcomes was extracted. Published cases or case series that did not report sufficient clinical or pathologic data were excluded from the analysis.

Results

We identified 2 oral cavity MCL cases from within our files (see table 2; cases 1 & 2) and an additional 7 published cases. All cases diagnosed as small cell lymphomas of the oral cavity prior to 2001 were reviewed (n=70). Of these 70 cases, 12 were subsequently stained with CCND1. All of these failed to demonstrate CCND1 staining. The clinical findings of all 9 patients are summarized in table 2. The mean patient age of our 2 patients at presentation was 77 years, similar to the overall mean age of 71 years in the prior published cases. The majority (5/9; 56%) of oral MCL cases occurred in men. The intra-oral sites of presentation were: palate (4), floor of mouth (1), tongue (2) and base of tongue (2). While the majority of patients presented with a mass (6/7), a single patient presented with dysphagia. Case number 7 had no presenting history listed.⁵ None of the patients had a contributory medical history and there was no recorded history of B-type symptoms. Reported treatments included: combination chemotherapy alone (4), combination chemotherapy and radiotherapy (2), no treatment/treatment declined (2) and unknown treatment status (1). Five of 9 patients (56%) succumbed to their disease with a mean survival of 21 months. Three patients were alive with disease with an average of 11.5 months follow-up, while a single patient, who received combination chemotherapy, was alive and well without evidence of disease at 53 months post diagnosis.

Table 3 summarizes the macro- and microscopic findings of the cases. Seven of nine cases of MCL were composed of classic variant MCL with diffuse or nodular infiltrates while two cases showed blastoid variant morphology (BV-MCL). The diffuse variants were composed of monomorphic sheets of cells that obscured the native architecture. Cells were small-to-medium-sized with moderately irregular nuclear contours. All cases with recorded immunohistochemistry confirmed a CD20-positive B-cell infiltrate which co-expressed CD5 and CCND1. Additional antibodies used to confirm the diagnosis of MCL are listed in table 1. Our two cases were positive for CD20, CD5, CD43 and CCND1 but negative for CD10, bcl-6, CD21 and CD23. An appropriate immunohistochemical panel for MCL is well-described in the WHO 'blue-book'.² Given our existing panel, neither stains for bcl-2 nor those for FMC7 were performed as these were felt to be redundant. None of the cases had supplementary testing with flow cytometry but two cases (nos. 5 & 9) showed cytogenetic analysis confirming the translocation, t(11; 14)(q13; q32). Neither FISH nor PCR studies were performed on our cases of MCL as it is well documented that the final common endpoint of this cytogenetic translocation is CCND1 protein overexpression. We chose to employ immunoperoxidase staining for the CCND1 protein given its high sensitivity and specificity.²

Discussion

Although as a group NHL is the second most common malignancy presenting within the head and neck region, involvement of the head and neck by MCL is unusual and the primary presentation of MCL within the oral cavity is rare.^{3,4,6-16} To our knowledge, this is the largest

reviewed series of MCL arising within the oral cavity that has been reported in the English literature. The pathologic and demographic findings of our 2 patients are generally consistent with those of the 7 previously reported cases.

MCL is an uncommonly encountered B-cell neoplasm characterized by small to medium-sized lymphoid cells.¹⁻³ Antiquated diagnostic terminologies of this entity include intermediate lymphocytic lymphoma, centrocytic lymphoma and mantle zone lymphoma.^{2,17,18} In 1992, Banks *et al.* introduced the term mantle cell lymphoma that was subsequently adopted by the WHO in 2001 and is currently the favored nomenclature.^{1,2} Despite recent data showing an increase in the incidence of MCL to 0.55/100,000/yr persons, it remains one of the least common B-cell malignancies. Depending on the study, MCLs accounts for between 6 and 10% of all B-cell lymphomas.^{3,19} Although the majority of MCLs occur in lymph nodes, many patients have extranodal involvement with the spleen, gastrointestinal tract and Waldeyer's ring being the most commonly affected sites.^{3,19}

The typical microscopic appearance of extra-nodal MCL is that of a monomorphic lymphocytic infiltrate that destroys the native architecture, and organizes itself in solid sheets or in vague nodules. Small, hyalinized vessels frequently support this malignant infiltrate. Cells are small to medium-sized and nuclei are oval to round with typically inconspicuous nuclei. In this setting, the typical immunophenotype for MCL is a B-cell lymphoma expressing CD20 antigen, co-expressing CD5 and CD43 and negative CD23 antigen expression.² The chromosomal translocation t(11; 14) (q13; q32), which results in the juxtaposition of the cyclin D1 (*bcl-1*) gene locus to the Ig heavy chain promoter, is a characteristic, but not universal, molecular feature of this lymphoma subtype.²⁰ This translocation results in the characteristic overexpression of CCND1 protein, a driver of G1/S progression.

The primary entities in the differential diagnosis include marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), and follicular lymphoma (FL). MZL is relatively more common in the oral cavity particularly in the setting of autoimmune exocrinopathy sharing some microscopic similarities with MCL.²¹ However, MZL is characterized by small to medium-sized neoplastic cells that are CD20+ but negative for CCND1 and CD5. SLL is a neoplastic proliferation of non-activated, mature-appearing small lymphocytes. Like MCL, it is typically CD5 positive; however, it lacks CCND1 expression. The finally FL, composed of follicular center B lymphocytes, shows positive staining for CD10 but fails to express CD5, CD43 or CCND1.²

Both the blastoid-variant MCL (BV-MCL) and the pleomorphic variant MCL (PV-MCL) are aggressive MCL subtypes. Although some believe these entities represent variants along the same spectrum, the WHO has recognized these two as distinct subtypes.² BV-MCL is characterized by cells that resemble lymphoblasts with unusually high mitotic rates ($\geq 20\text{-}30/10\text{hpf}$). Unlike conventional MCL, extra copies of the CCND1 gene characterize BV-MCL and the proliferation rate, as can be assessed by the expression of Ki67 antigen, is in excess of 50%.^{22,23} This variant more commonly affects older patients and has a shorter response duration after first-line therapy.²³ PV-MCL, similar to BV-MCL, is histologically unique with large, pleomorphic cells that have round to oval nuclear contours, pale cytoplasm and with, at least some cells having, prominent nucleoli.²

Similar to previously published cases, our series of oral cavity MCL occurred more commonly in older men.^{5, 24-26} The finding of a mass, which may or may not be ulcerated, is the most common oral manifestation of NHLs.^{9,27} Eight of the 9 patients in this series presented with a mass. Treatment provided to these patients varied from combination chemotherapy to chemotherapy and radiotherapy to observation. Typically, MCL has a relentless clinically aggressive course that is resistant to therapy and a mean survival of only 3 years.^{2,28,29} In

keeping with the previously published poor prognosis for MCL, 4 of 9 patients were dead of disease at a mean of 21 months.

We conclude that although NHL is the second most common malignancy to affect the head and neck, MCL of the oral cavity is a very uncommon diagnosis. In keeping with other NHLs, most oral MCLs occur in an elderly male population and have a possible predilection for the palate. The microscopic diagnosis can be challenging given its similar appearance to other small cell lymphomas requiring a comprehensive immunohistochemical panel for the accurate diagnosis. Like MCL occurring in other sites in the body, the prognosis and outcome of oral MCL appears to be poor.

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Figure 1.
Low power image of mantle cell lymphoma, classic variant (Case 2) showing a monomorphic population of small lymphoid cells in submucosa, (H&E 10x)

Figure 2.

a: High power image of mantle cell lymphoma (Case 2) with small to medium-sized lymphoid cells (H&E 40x)

b: Higher power image of mantle cell lymphoma (Case 2) showing detailed cytomorphology of moderately irregular nuclear contours, (H&E 100x oil)

Figure 3.

- a: High power image of mantle cell lymphoma, blastoid variant (Case 1) with larger, more atypical lymphoid cells (H&E 40x)
- b: High power image of mantle cell lymphoma, blastoid variant (Case 1) showing the prominent nucleoli found in this unusual variant (H&E 100x oil)

Figure 4.
Comparative immunohistochemistry of classic variant of MCL (Case 2) showing positive staining for all of: CD20(A), CD5(B), CD43(C) and CCND1(D)

Table 1
Antibodies used for immunophenotyping of current cases

Antibody	Source	Clone	Dilution	Specificity
CD3	Dako	F7.2.38	1:400	T-cells
CD20	Dako	L26	1:100	B-cells
CD43	Dako	DF-T1	1:400	CLL, mantle cell lymphoma, T-cells, myeloid cells
CD5	Novocastra	4C7	1:800	T-cells, mantle cell lymphoma, CLL
CCND1	Lab Vision Corp.	SP4	1:80	Mantle cells
CD10	Novocastra	S96-16556	1:160	Lymphoblastic leukemia (CALLA)
bcl-6	Cell Marque	IG191E/A6	1:2	B-cells
CD21	Novocastra	2G9	1:240	Follicular dendritic cells, CLL, T-ALL
CD23	Novocastra	1B12	1:160	B-cells, CLL, mantle zone lymphoma

Table 2
Summary of clinical features and outcome of oral mantle cell lymphomas

Case	Sex	Age	Site	Stage	Clinical features	Medical history	Treatment	Outcome	Follow-up
1*	M	67	Palate	N/A	Mass for 6 months	N/A	declined	AWD	2 years
2*	M	87	Palate	N/A	Mass	Metastatic prostate carcinoma	chemotherapy	DOD	8 months
3	F	62	Palate	N/A	Mass for 1 week	Hypertension, arthritis	chemotherapy	AWD	N/A
4	F	72	Floor of mouth	4A	Mass for 2 months	Hypertension, DVT, arthritis	N/A	AWD	N/A
5	F	62	Tongue	N/A	Mass for 2 months	N/A	chemotherapy	AWD	5.5 years
6	M	68	Base of tongue	N/A	Mass for 6 months	N/A	chemotherapy radiotherapy	DOD	1.5 years
7	M	84	Palate	4	N/A	N/A	chemotherapy	DOD	1.5 years
8	M	74	Base of tongue	N/A	Mass	N/A	N/A	DOD	1 month
9	F	63	Tongue	1A	Dysphagia	N/A	radiotherapy chemotherapy	DOD	4 years

* UCSF cases; N/A = data not available; AWD: Alive without disease; DOD = died of disease; DVT = deep vein thrombosis

Table 3
Summary of pathological and immunophenotyping of oral mantle cell lymphomas

Case	Size (mm)	Architectural pattern & cytologic features	CD20	CD5	CD43	CCND1	Cytogenetics
1*	3×3×8	Diffuse, blastoid variant	+	+	+	+	N/A
2*	3×3×4	Vaguely nodular, classic	+	+	+	+	N/A
3	2×3×5	Diffuse, classic	+	+	+	+	N/A
4	15	Diffuse, classic	+	+	+	+	N/A
5	N/A	Diffuse, classic	+	+	N/A	+	t(11;14)(q13;q32)
6	40	N/A, classic	N/A	N/A	N/A	N/A	N/A
7	N/A	N/A, classic	N/A	N/A	N/A	N/A	N/A
8	N/A	Diffuse, blastoid variant	+	N/A	+	+	N/A
9	N/A	Vaguely nodular, classic	+	N/A	+	+	t(11;14)(q13;q32)

* UCSF cases; N/A = data not available or not done