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ORIGINAL PAPER

Melanoma of the Oral Cavity: an Analysis of 46 New Cases with Emphasis on Clinical and Histopathologic Characteristics

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Abstract Melanoma of the oral cavity is a rare malignancy that carries a poor prognosis. We identified 46 new cases of both primary and metastatic melanoma to the oral cavity. Following IRB approval, these cases were obtained from the Oral Pathology Biopsy Service archives of the UF College of Dentistry (1994–2014), the UK College of Dentistry (1997–2015), and the UM Medical Center (1988–2015). All slides were reviewed. The location, age, race, gender, clinical impression, duration of lesion, histopathologic diagnosis, and histopathologic features were recorded. Cases from the facial skin and those with an ambiguous diagnosis were excluded. Forty-six cases fulfilled the inclusion criteria with 32 primary cases, 11 known metastases, and 3 cases where metastasis could not be excluded. The primary cases included a total of 20 females and 12 males with an average age of 66.7 (range 27–95), and the majority (80 %) of the patients were Caucasian when race was known. Twenty-two of the 32 primary cases (68.8 %) were located in the maxillary mucosa, 5 in the mandibular mucosa or bone, and 5 in other locations. The clinicians' impressions varied from benign fibrous growths to high grade malignancies. The histopathology varied widely among the cases, however two cell types predominated (often in combination): epithelioid cells (50.0 %) and spindle cells (50.0 %). Only 53.1 % demonstrated melanin pigmentation. Oral melanoma remains one of the most diverse clinical and histopathologic diagnoses. Better understanding of this neoplasm may promote earlier diagnosis and may lead to improved outcomes.

Keywords Melanoma · Oral cavity · Mucosal · Histology · Clinical · Review

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Introduction

Primary melanoma of the oral cavity is a rare, aggressive entity that originates from malignant transformation of oral mucosal melanocytes. Primary oral melanoma represents 0.2–8 % of all melanomas [1–3] and 0.5 % of all oral cavity malignancies [1, 4–6]. The age range varies between 7 and 95 years [7] and typically is diagnosed in the 5th through 7th decades of life [1, 3]. The peak age for diagnosis of oral melanoma tends to be one to two decades later than cutaneous melanomas [8]. By and large, no sex predilection exists, although some authors cite a slight male predominance [1–3, 9, 10].

Acral lentiginous melanoma (also referred to as mucosal lentiginous melanoma) is the most common type of oral melanoma. Classically, melanoma of the oral cavity presents as an asymptomatic dark brown to black macule, typically in the maxillary gingiva/alveolar mucosa and/or palatal mucosa. These lesions often have asymmetric and irregular borders and may demonstrate ulceration or hemorrhage. As the lesions progress, they may appear more nodular and exhibit erosion of the bone or surrounding structures. Satellite lesions (lesions that surround the initial

tumor) also have been reported in many primary oral melanoma lesions [1, 4, 11].

Criteria for diagnosis of primary oral melanoma were originally put forth by Greene et al. [12] in 1953. These criteria include: (1) Intraepidermal (junctional) activity, (2) Evidence of malignant melanoma in the oral mucosa, and (3) Failure to demonstrate any other primary site. When these criteria are not met, the lesion generally is considered metastatic, which is even more uncommon [3, 7, 13]. When metastatic melanoma to the oral cavity is known, frequent sites of metastasis include the tongue, gingiva, palate and tonsils [3, 7, 13]. One rare case of a primary intraosseous melanoma was reported in a 31-year-old patient by Lombardi et al. Although a thorough medical examination (including radiography, an abdominal ultrasonography, and a thorough skin evaluation) was performed, and the patient is living disease-free 7 years later, the authors do make the point that the possibility of a metastasis from a previously regressed primary melanoma can never be excluded because the features of a regressed melanoma are rather nonspecific [14].

Because most oral melanomas are asymptomatic until later stages and carry such a poor prognosis, early recognition is of utmost importance. However, melanoma frequently mimics several entities, both clinically and histopathologically, making it difficult for the clinician and pathologist to quickly render a definitive diagnosis. The purpose of this article is not only to report new cases of oral melanoma, but also to characterize the diversity of clinical and histopathologic appearance in this rare entity.

Materials and Methods

A database was created consisting of malignant melanoma cases from the oral pathology biopsy services of the University of Kentucky (1997–2015), the University of Mississippi Medical Center (1988–2015), and the University of Florida (1994–2014). Both primary and metastatic lesions were included in the database. Any cases from the skin or those with an ambiguous diagnosis were excluded. An IRB-approved retrospective study, characterizing the age, sex, race, location of lesion, clinical impression, duration of lesion at biopsy, histopathologic diagnosis, and histopathologic features was performed. The original slides (hematoxylin and eosin-H&E and any special stains), accession sheets, and biopsy reports of all cases but one were reviewed by board certified oral pathologists in the respective centers. The original slide for one case was unavailable, however, a new H&E slide was made from the original tissue block, and the original accession form and biopsy report were reviewed for this case.

Results

Of the 46 total cases of oral malignant melanoma collected in our database, there were 32 primary melanomas (Table 1), 11 known metastases, and 3 cases in which a metastasis was suggested based on histopathologic or clinical appearance, however no follow-up information about known metastases was available (Table 2). These 3 cases have been excluded from the group of primary melanomas in the following statistics (but are listed in Table 2 under "Suggested Met"). Of the primary melanomas in our retrospective review, there were 20 females (62.5 %) and 12 males (37.5 %). The mean age was 66.7 years (median = 71.5), ranging between 27 and 95 years. The race was known in 25 of the 32 cases, with 80.0 % (20/25) being Caucasian, 12.0 % (3/25) being African American, and 8.0 % (2/25) being Hispanic. Twenty-two of the 32 cases (68.8 %) were located in the maxillary mucosa (9 alveolar mucosa, 5 palatal mucosa, 1 vestibular mucosa, and 7 combination of maxillary locations), 5 in the mandibular region (1 unspecified mandibular extraction site, 1 retromolar pad, 1 unspecified alveolar mucosa, 1 unspecified anterior mandible, and 1 combination of floor of mouth/retromolar pad, tongue, mandible), and 5 in other locations (2 labial mucosa, 1 unspecified gingiva, 1 tongue, and 1 buccal mucosa). Due to the retrospective nature of the study, clarification of exact location sites when not originally given was not possible.

The clinician provided the color of the lesion in 18 of the 32 cases. Ten of these 18 (55.6 %) were described as the classic pigmentation for melanoma (black, brown, tan, blue, or purple); however, 8 of the 18 (44.4 %) were described as red or pink (Fig. 1). Twenty-six of the 32 cases had a clinical impression listed by the provider. Of these, 15 (57.7 %) listed a benign diagnosis as their first impression. Nine (34.6 %) listed only malignant diagnoses in their differential (7 of which specifically list melanoma). The remaining cases listed both benign and malignant impressions.

The histopathologic presentations varied significantly among the different cases and within each specific case. The following prevalence of cell morphology and any distinct histopathologic features was observed among the cases of primary melanomas: 17/32 (53.1 %) pigmented, 16/32 (50 %) epithelioid cells, 16/32 (50 %) spindle cells, 12/32 (37.5 %) oval cells, 9/32 (28.1 %) round blue cells, 9/32 (28.1 %) organoid pattern, 4/32 (12.5 %) clear cells, 3/32 (9.4 %) significantly pleomorphic cells, one case of pseudoalveolar pattern (3.1 %), and one case of melanoma in situ (3.1 %). Because the majority of our biopsies were incisional and sample size may have been limited, tumor

Table 1 Primary cases of oral melanoma

Case	Age	Sex	Race	Location	Clinical description	IHC	Microscopic description
1	79	F	C	Maxillary vestibule	Black, painful mass; Impr: clot	HMB45+	Epithelioid, RBCM, clear cells, organoid, pigment
2	30	F	N/a	Maxillary gingiva	Pink, red, exophytic	HMB45+, S100+	Spindle, clear cells
3	64	F	N/a	Anterior mandible	Impr: inflamed lesion	HMB45+, S100−	RBCM, spindle, pigment
4	84	M	C	Gingiva	Soft, black/red; Impr: dysplasia versus pigmentation	HMB45+, S100+	Oval, epithelioid, pleomorphic, pigment
5	89	F	C	Posterior palate, wrapping around gingiva #2	Blue/black; Impr: amalgam tattoo	HMB45+, S100+	RBCM, pigment
6	87	F	H	Hard palate, gingiva	Spongy, exophytic; Impr: hemangioma versus melanoma	HMB45−, S100+, MelanA+	Spindle, clear cells, pigment
7	27	F	C	Upper labial mucosa, extending slightly past vermillion onto lip	Black; Impr: melanotic macule, r/o cancer	HMB45+	Oval, pleomorphic, pigment
8	63	F	C	Retromolar pad	Red; Impr: inflammatory tissue, r/o melanoma	HMB45+, S100+	Epithelioid, RBCM, pigment
9	93	M	C	Anterior and posterior palate	Blue; Impr: amalgam tattoo, r/o melanoma or heavy metal deposition	HMB45+, S100−, MelanA+	Spindle, RBCM pigment
10	87	F	C	Lower labial mucosa	Slow-growing, firm, red mass; Impr: epulis, r/o malignancy	HMB45+, S100+, MelanA+	Oval, epithelioid, organoid, clear cells, pseudoalveolar, pigment
11	81	M	C	Junction of soft and hard palate	Purple/black; Impr: R/o malignancy	HMB45+, S100+, MelanA+	Oval, epithelioid, organoid, pigment
12	73	F	C	Posterior palate, over tuberosity	Red; Impr: TUGSE versus carcinoma	HMB45+, S100+	Oval, RBCM, pleomorphic
13	39	M	N/a	Palate	N/a	HMB45+, S100+	Oval, spindle, organoid, pigment
14	88	M	C	Mandibular alveolar edentulous ridge	Purple mass; Impr: Vascular lesion	MelanA+, pT4aBRAF V600E/K mutations not present	RBCM, organoid
15	92	F	N/a	Anterior maxillary mucosa	Impr: melanoma versus SCCa	S100+, MelanA+	Oval, spindle
16	45	M	C	Anterior maxillary mucosa	Ulcerated mass; Impr: SCCa	S100+, MelanA+	Oval, epithelioid
17	54	F	C	Mandible, #20 ext site	Prink/red, non-healing ext site; Impr: epulis granulomatosa	HMB45+, MelanA+	Epithelioid, organoid
18	42	F	C	Anterior maxillary mucosa, Facial #9	Red raised mass; Impr: Pyogenic granuloma	HMB45+, S100+, MelanA+	Epithelioid, spindle, organoid
19	32	F	C	Palate/gingival mucosa, around #12–16	Impr: R/o melanoma	None	Melanoma in situ, junctional theques
20	81	F	C	Soft palate	Brown/tan; Impr: melanoma	HMB45+	Epithelioid, spindle
21	61	F	N/a	Maxilla, around #9	N/a	HMB45+	Oval, RBCM, pigment
22	63	M	AA	Maxillary tuberosity	Red lesion; Impr: Granuloma	None	Epithelioid, spindle, pigment
23	88	M	N/a	Anterior maxillary edentulous ridge	Hemorrhagic bubbly growth; Impr: epulis	HMB45+, S100+, MelanA+	Epithelioid, spindle, pigment
24	95	F	C	Anterior maxillary alveolar ridge/ vestibule	Exophytic vascular mass; Impr: carcinoma	HMB45+, S100+, MelanA+	Epithelioid, organoid
25	91	F	C	Posterior maxillary edentulous ridge	Pink/gray growth; Impr: pyogenic granuloma	S100+, MelanA+	Oval, spindle

Table 1 continued

Case	Age	Sex	Race	Location	Clinical description	IHC	Microscopic description
26	70	M	H	Anterior maxillary ridge/vestibule	Black mass; Impr: melanoma	None	Oval, spindle, pigment
27	74	F	C	Buccal mucosa	Grey/brown lesion; Impr: focal fibrous hyperplasia	None	Epithelioid, spindle, pigment
28	29	F	C	Palate	Palatal boggy swelling	HMB45+	Epithelioid, spindle, organoid
29	40	M	C	Dorsal tongue	Chronic ulceration	HMB45+, S100+	Epithelioid
30	44	M	N/a	Maxillary alveolar mucosa, around #3	Ulcerated, fungating mass, enveloping #3, loss of alveolar bone, opacification of sinus; Impr: SCCa, lymphoma, neural/salivary gland tumor	S100+, MelanA+	Oval, spindle
31	90	M	AA	Maxillary hard palate/alveolar ridge	Large, dark, ulcerated, fungating mass	None	Epithelioid, spindle, pigment
32	60	F	AA	Floor of mouth, left ventrolateral tongue and retromolar pad, involves anterior mandible	Consistent with SCCa	HMB45+, S100+, MelanA+	RBCM

IHC immunohistochemistry, *Impr* clinical impression, *RBCM* round blue cell morphology, *R/o* rule out, *SCCa* squamous cell carcinoma, *TUGSE* traumatic ulcerative granuloma with stromal eosinophilia, *ext* extraction

thickness and the presence of perineural and/or lymphovascular infiltration were not recorded.

Seventeen of the 32 primary cases had the duration of the lesion listed on the accompanying biopsy accession form. Eleven of these (64.7 %) listed a duration of less than 6 months, while the remaining cases were present longer than 6 months.

Regarding immunohistochemistry, S-100 protein was run in 20 of the 32 primary cases, with 90 % showing positive reactivity. HMB-45 was performed on 22 of the 32 cases with 95.5 % positivity, and all cases in which Melan-A was run (14/32 cases) were positive.

Among the metastatic lesions, 8 of the 11 (72.7 %) were male. The age ranged from 27 to 89, with a mean of 55.5 years. Seven cases (63.6 %) were found in the mandibular region (2 gingiva, 2 vestibular region, 1 unspecified extraction socket, 1 unspecified intrabony lesion, 1 unspecified mandible), two cases in the maxillary mucosa (1 gingiva, 1 palatal mucosa), and two cases in the tongue.

To the best of our knowledge, no cases were misdiagnosed initially.

Discussion

Due to the rarity of oral melanoma cases, lack of information on the etiology, and unreliable clinical detection methods, we still depend greatly on clinical and histopathologic presentations of what case reports do exist in order to further our knowledge of this often deadly disease. We present 46 new cases of oral melanoma to be added to the literature, which, to our knowledge, is one of the largest single series of unreported oral melanoma examples.

In regards to demographics, our study is mostly in line with previously reported statistics for primary oral melanoma. The mean age for our group is 66.7 years with a range of 27–95 years; most studies cite an age range of 5th–7th decades [1, 3]. Although most studies have found no gender predilection [1] or a slight male predominance [2, 9], we found a slight female predominance (1.67:1) in our study. The race was known in 25 of our 32 primary melanoma cases. Of these cases, 80 % (20/25) of the patients were Caucasian, while only three patients were African American, and two patients were Hispanic. Several authors have proposed that mucosal melanomas may be more prevalent in specific geographic regions, such as Japan and Uganda [5, 8, 9, 15, 16], however, this statement may be skewed due to the lower prevalence of cutaneous melanomas in these populations [7, 15]. The intraoral location was similar to previously cited data, with 68.8 % located in the maxillary mucosa (palatal mucosa, alveolar

Table 2 Cases of metastatic melanoma, known and suggested metastases (based on microscopic and clinical presentation)

Case	Age	Sex	Race	Location	Clinical description	Microscopic description
Known Met						
1	27	M	C	Mandibular gingiva	Impr: melanoma	Oval, pleomorphic, organoid, pigment
2	29	F	N/a	Posterior, mandibular mucogingival area	Impr: R/o metastatic tumor, Ca	Oval, epithelioid, clear cells, organoid
3	69	F	C	Anterior mandibular vestibule	N/a	Oval, spindle, pleomorphic, RBCM, organoid, clear cells, pigment
4	78	M	C	Lateral tongue	Blue; Impr: SCCa, melanoma	Epithelioid, organoid, pigment
5	36	F	C	Maxillary facial gingiva	Raised, dark blue/black lesion; Impr: melanoma versus kaposi's	Epithelioid, spindle, pigment
6	58	M	C	Mandible	R/o met	RBCM
7	74	M	C	Dorsal tongue	Impr: scar, foreign body reaction, mucocele	Epithelioid
8	78	M	C	Mandibular vestibule, around 22, 23	Grey/tan lump; Impr: r/o mucoepidermoid Ca	Epithelioid, lobular growth pattern
9	60	M	C	Mandible, #32 ext socket	Exophytic vascular mass; Impr: carcinoma	Epithelioid, spindle, pigment
10	58	M	H	Palate, around #15	Red/pigmented papillary mass; Impr: SCCa versus recurrent melanoma	Oval, spindle
11	43	M	C	Mandible, periapical to #28	Inflammatory process versus melanoma (numb lip)	Oval, pigment
Suggested Met						
1	89	M	C	Lateral tongue	Impr: SCCa	Epithelioid, organoid
2	63	M	C	Maxilla, around #6	Red, exophytic; Impr: SCCa	Spindle
3	73	F	A	Palate, maxillary vestibule	Blue, exophytic ulcerated lesion; Impr: salivary gland neoplasm	Pleomorphic, giant cells, pigment

Impr clinical impression, *RBCs* round blue cells, *R/o* rule out, *Ca* carcinoma, *SCCa* squamous cell carcinoma, *ext* extraction

mucosa, vestibular mucosa, or a combination of these sites).

Upon histopathologic review of the cases, we found that not only did the cell types differ significantly among the cases, but the majority of individual cases displayed a polymorphic cell population, with 50 % demonstrating a spindle cell population, 50 % epithelioid cells, 37.5 % oval cells, 28.1 % round blue cells, and 12.5 % clear cells. Our "round blue cell" category includes previously described "neuroendocrine-like" [17] or "lymphoma-like" [18] morphology, as well as plasmacytoid cells. Because of this predominantly polymorphic, non-epithelial cell population, a malignant appearing proliferation with more than one cell type should be viewed with high suspicion for melanoma. Other features noted during histopathologic examination were that only about half of our cases (53.1 %) contained melanin pigmentation on hematoxylin and eosin stain, 28.1 % showed an organoid or nesting pattern, and 3.1 % displayed a pseudoalveolar pattern. We noted 1 of our 32 primary cases to be melanoma in situ, which is infrequent; eighty-five percent of oral melanomas are invasive or have an invasive and in situ arrangement [4]. One case of pseudoalveolar pattern, described by previous authors [18, 19], also is noted in our series. Tariq et al. [18] describe this pattern as "tumor cells lining fibrous septae along with formation of clear space due to loss of cohesiveness of tumor cells in the center" (Fig. 2f). These distinct histopathologic features, when present, are helpful in considering melanoma in a differential diagnosis; however, when absent, the pathologist still cannot exclude melanoma from the differential.

When melanin pigmentation is present, the histopathologic diagnosis is obvious. However, when the lesion is amelanotic, the histopathologic differential diagnosis varies immensely and may include the following entities: (a) Spindle cell malignancies (e.g. leiomyosarcomas, spindle cell carcinoma, malignant peripheral nerve sheath tumor (MPNST), undifferentiated pleomorphic sarcoma, angiosarcoma, synovial sarcoma), (b) Epithelioid variants of malignancies (e.g. epithelioid sarcoma, epithelioid MPNST), (c) Round blue cell tumors (e.g. lymphomas, neuroendocrine tumors, rhabdomyosarcoma, plasmacytoma, or multiple myeloma), (d) Malignancies with clear cells (clear cell variants of malignancies, mucoepidermoid carcinoma, renal cell carcinoma), and (e) A variety of metastatic lesions. Therefore, the use of immunohistochemistry is essential. Variable expression of S-100 protein, MART-1/melan-A, MITF, tyrosinase, and HMB-45 is present in oral melanoma specimens. S-100 protein and tyrosinase tend to be more sensitive markers, and HMB-45 may show more specificity [19]; however, not one single

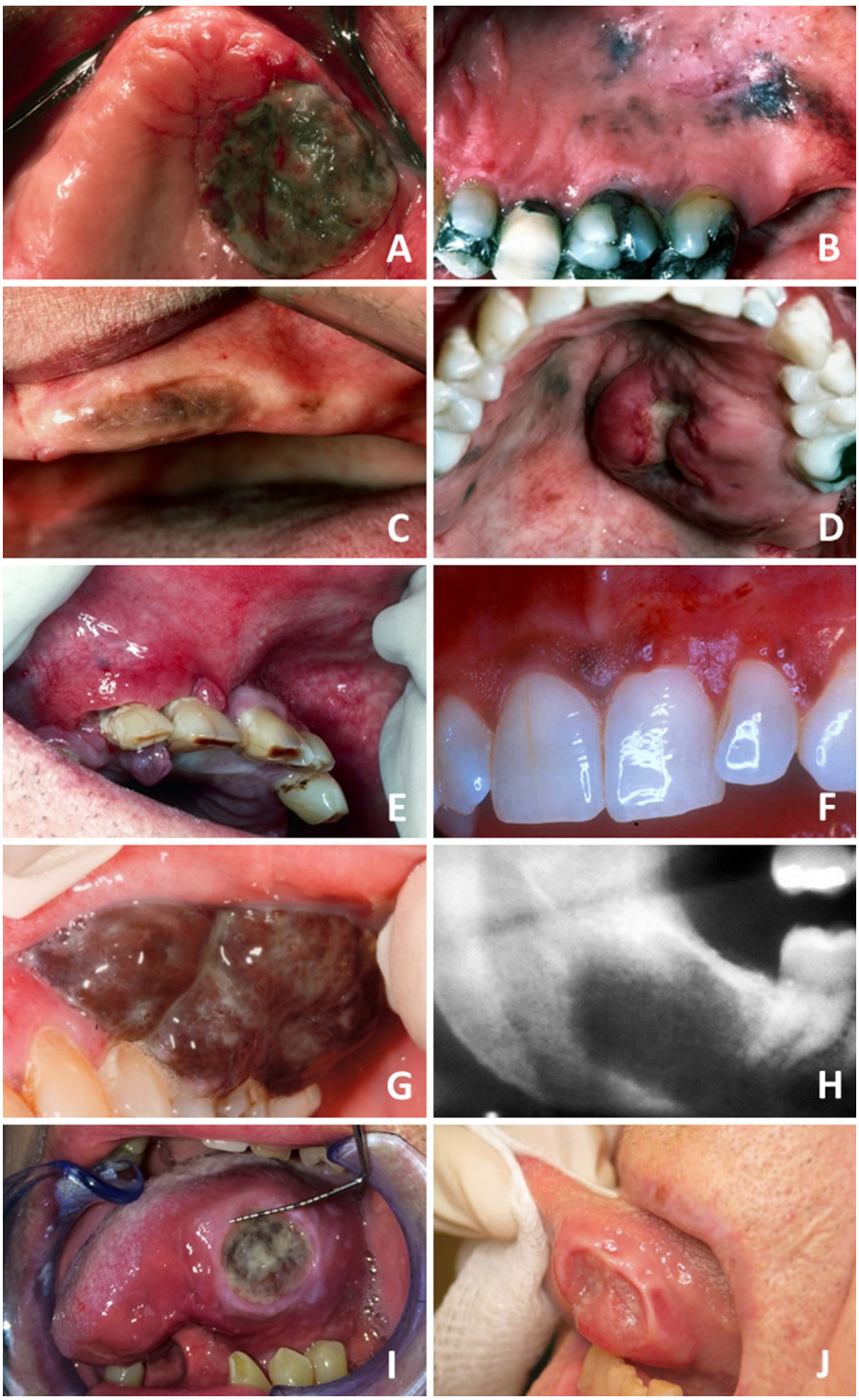

Fig. 1 Clinical appearance **a** Large, exophytic, ulcerated *black and red mass* of the alveolar ridge and palate. **b** Multifocal and diffuse bluish macules of the hard and soft palate. **c** Poorly-defined, linear *brown patch* of the maxillary edentulous ridge, demonstrating satellite lesions. **d** Ulcerated palatal swelling with mixed *blue, grey, red, and pink* coloration. **e** *Red/pink* lobular and inflamed-appearing swelling of the maxillary vestibule and alveolar mucosa. **f** *Red and brown macules* of the anterior maxillary attached mucosa. **g** Lobular, exophytic *black mass* of the maxillary vestibule and alveolar mucosa. **h** Metastatic melanoma of the posterior mandible, presenting as a poorly-defined radiolucency. **i** Metastatic melanoma of lateral tongue, demonstrated by an ulceration with *grey/brown pigmentation.* **j** Amelanotic metastatic melanoma of the lateral tongue, presenting as an exophytic mass with an ulcerated surface

marker is 100 % sensitive. We found that two of our primary cases in which S-100 was run were negative (90 % positivity). This statistic is similar to the 91 % immunoreactivity of mucosal melanomas found in a review of 115 cases by Thompson et al., reinforcing the need to run a panel of immunohistochemical stains [19, 20]. One hundred percent of our primary cases in which Melan-A was performed were positive, and 95.5 % of our cases in which HMB-45 was run were positive. Because not one marker is completely sensitive, Thompson et al. [20] suggests that a panel of S-100, tyrosinase, and HMB-45 is sufficient to adequately identify cases of melanoma.

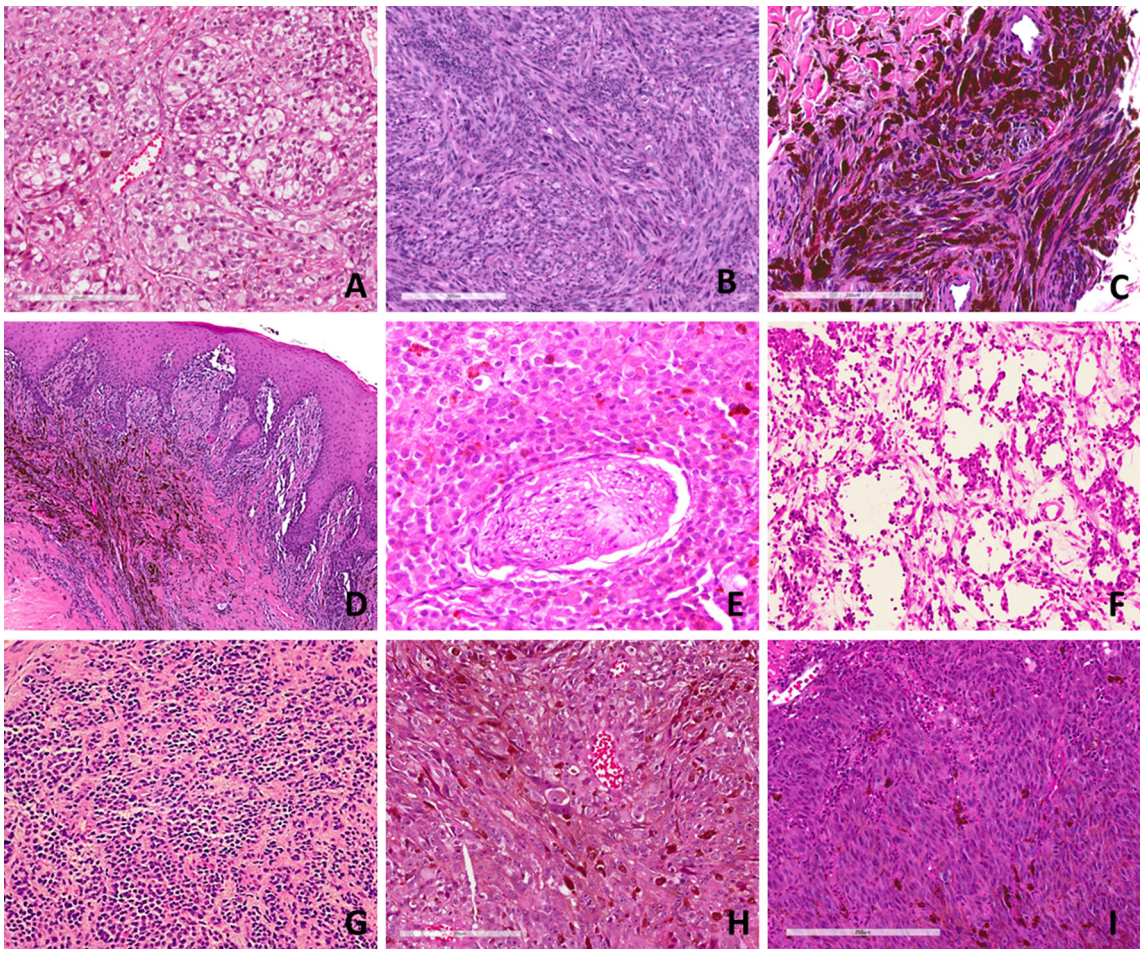

Fig. 2 Histopathologic features **a** Organoid pattern with prominent clear cells (20×). **b** Spindle cells arranged in fascicles with no pigment (10×). **c** Heavy pigment (20×). **d** Demonstration of junctional component (4×). **e** Epithelioid cells showing perineural invasion (40×). **f** Pseudoalveolar pattern (20×). **g** *Round blue cell* morphology (10×). **h** Pleomorphic cells (20×). **i** *Oval cells* (20×)

Interestingly, while 55.6 % of the 18 primary melanoma cases in which the clinical color was listed were of classic pigmentation for melanoma (blue-black, tan-brown), 44.4 % were described as pink or red lesions. Also of significance, 57.7 % (15/26) of the providers who included their clinical impression listed a benign entity as their first impression, while 34.6 % (9/26) listed a malignant impression only. The majority (73.3 %) of those clinicians who listed a benign entity as their first impression listed an inflammatory or hemorrhagic entity, such as pyogenic granuloma or clot, while only 20.0 % listed a flat, pigmented lesion (e.g. amalgam tattoo or melanotic macule), and 0.07 % listed an unspecified ulceration (Table 1). Due to the extreme variation of clinical impressions found in our series, a differential diagnosis for intraoral melanoma could include any of the following: (a) Benign pigmented lesions: amalgam tattoo, melanotic macule, melanotic nevus, melanoacanthoma, post-traumatic or racial pigmentation, pigmentation associated with systemic disease (e.g. Peutz-Jeghers syndrome, Addison disease), drug-induced pigmentation, and vascular lesions, (b) Benign inflammatory or reactive lesions such as epulis, pyogenic granuloma, irritation fibroma, peripheral giant cell granuloma, and peripheral ossifying fibroma, (c) Malignant pigmented lesions such as Kaposi sarcoma, and (d) A wide variety of primary and metastatic non-pigmented malignancies [21]. The findings of our study reinforce the principle that even the most unsuspecting of lesions, such as those appearing like fibrous hyperplasias or epulides, merit investigation with possible biopsy for definitive diagnosis.

The prognosis for oral melanoma is extremely poor. By the time the tumor is diagnosed, the malignant cells often have invaded to a deeper level and are thus at a higher stage than the average cutaneous melanoma [6, 9, 22]. The 5-year survival rate varies between 15 and 20 % [4, 6, 23], with older age, extent of the primary tumor, poor accessibility for resection, and non-pigmented lesions contributing to a poorer outcome [19, 24]. Lymph node involvement tends to have a direct negative effect on prognosis in mucosal melanomas [24]. Lymph node metastases have

been reported in 25 % of the patients diagnosed with melanoma of the oral cavity [19]. Unfortunately, prognosis and treatment information were unavailable for our retrospective review.

As stated previously, the original criteria for metastatic melanoma of the oral cavity were put forth by Greene et al. [12] in 1953, however, other authors recently have suggested that perhaps the presence of junctional activity should not be listed among the diagnostic criteria, as several metastatic melanomas also may involve the epithelial junction [9]. Lopez et al. [19] proposed looking for atypical melanocytes or junctional activity within the epithelium adjacent to the lesion (with or without pagetoid spread) to help differentiate between primary and metastatic tumors, however, the diagnostic challenge still exists when the surface is ulcerated, as was the case in several of our specimens. Therefore, a thorough medical history, physical examination, and further diagnostic tests, including examination of skin and lungs, liver function, and brain and bone scans, are imperative in ruling out a metastatic lesion [7].

Conclusion

In this study, we report 46 new cases with emphasis on the extreme variability of clinical and histopathologic presentation of melanoma of the oral cavity, which may expedite diagnosis and treatment. Due to the rarity of oral melanoma, the current lack of knowledge about etiology, and unreliable clinical detection methods, the foundation of information for this deadly disease still is based on contributions of case reports to the literature. Our findings suggest that while certain histopathologic patterns or clinical presentations may suggest melanoma as a possible diagnosis, there are overlapping features with a wide variety of lesions. Clinicians should keep in mind that even the most clinically benign appearing lesions potentially could represent oral melanoma; therefore, interpretation of biopsies with an appropriate immunohistochemistry panel should be performed for definitive diagnosis if any doubt exists.

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