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Oral Atypical Cellular Blue Nevus: An Infiltrative Melanocytic Proliferation

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Abstract

The atypical cellular blue nevus is an extremely rare nevomelanocytic lesion which lacks precise histologic characterization in the current literature. Given the potential for significant architectural and cytologic overlap with melanoma, further study, including molecular analysis, is needed. This is the first description of an atypical cellular blue nevus of the oral cavity.

Keywords
Atypical, Blue, Cellular, Nevus, Oral

Introduction
The cellular blue nevus (CBN) is a well-characterized benign, acquired dermal melanocytic tumor[1, 2]. While clinically indistinguishable from the common blue nevus[3], it is microscopically distinguished by a biphasic proliferation of hypercellular, nodular aggregates of tumor cells which often lie deep to a typical blue nevus. The border shows well-demarcated tumor nodules with rare infiltration and a notably absent host inflammatory response. The cellular portion contains ovoid to spindle-shaped melanocytes with small nucleoli and variable pigmentation[2, 3]. Mitotic activity can be seen (≤2 mitoses/mm^2) while necrosis as well as junctional activity or epidermal invasion are typically absent[2, 4]. Following conservative excision, long-term follow-up data indicate a very small risk for recurrence and no metastasis[2]. In the oral cavity, common blue nevi are occasionally seen [5], while cellular blue nevi are exceedingly rare, with only 2 reported cases[6, 7].

In some instances, a blue nevus (most often CBN) is associated with a malignant melanoma and is referred to as malignant blue nevus (MBN), blue nevus-like melanoma or malignant melanoma arising in a blue nevus[4, 8–14]. When unquestionably malignant features such as widespread necrosis, mitotic activity, atypical mitoses and marked cytologic atypia are juxtaposed next to an otherwise bland CBN, the diagnosis is straightforward. However, multiple reports in recent decades of tumors with features intermediate between CBN and MBN prompted the controversial[15] designation of “atypical blue nevus” or “atypical cellular blue nevus” (ACBN)[16, 17]. While similar clinically and apparently biologically to CBN[17], discrete histologic criteria for ACBN are currently under debate even among expert dermatopathologists[18–22]. The most often cited histologic criteria include asymmetry, a deeply infiltrative and irregular border, mild cytologic atypia, and mitotic activity >2 mm^2 [17, 18, 23]. Herein we describe, to our knowledge, the first oral case of a CBN exhibiting atypical architectural features along with complementary molecular data.

Case Report
A 46-year-old white male presented with a mass of undetermined duration on his right buccal mucosa. The patient’s past medical history was non-contributory. Extraoral examination was within normal limits. Intraorally, an exophytic, red-blue, firm, sessile nodule measuring approximately 17 × 15 × 12 mm was noted on the right buccal mucosa adjacent to the grossly decayed crown of the maxillary third molar. A working diagnosis of a fibroma or a pyogenic granuloma was given. The lesion was surgically excised and submitted for histopathological examination.

Microscopic examination of tissue sections showed an attenuated surface epithelium overlying a neoplasm of nevomelanocytic differentiation. The lesion was poorly circumscribed and asymmetrical with variable intense melanin production. The lesional growth pattern included diffuse sheets of cells, small nests and islands, and strands of cells, all set within a moderately dense collagenous stroma (Fig. 1). Superficially, the organoid and theque-forming lesional cells showed intimate association with the basal layer, including some junctional activity, but with no evidence of intraepithelial spread (Fig. 2). The superficial lesional cells had a characteristic nevocytic as well as spindled morphology and

scattered nevus giant cells were seen (Fig. 3). More deeply, the biphasic architecture characteristic of CBN was noted (Fig. 4). Within the cellular nodules, the cells were fusiform to oval with indistinct cytoplasmic membranes enclosing moderate amounts of amphophilic cytoplasm. Lesional cell nuclei were round to oval with vesiculated chromatin and a single prominent eosinophilic nucleolus (Fig. 5a) or intranuclear vacuoles (Fig. 5b). The tumor cells were diffusely infiltrative within the deeper skeletal muscle bundles (Fig. 6) and extended as variably sized-nests into underlying fat (Fig. 7). Tumor was transected at the lateral and deep margins. Mitotic figures and pleomorphism were not seen, and there was no evidence of necrosis or a significant host inflammatory response to the tumor. On the basis of the features described, a histopathologic diagnosis of “CBN with architectural atypia” was made. After over 4 years without evidence of local recurrence, our patient was lost to follow-up.

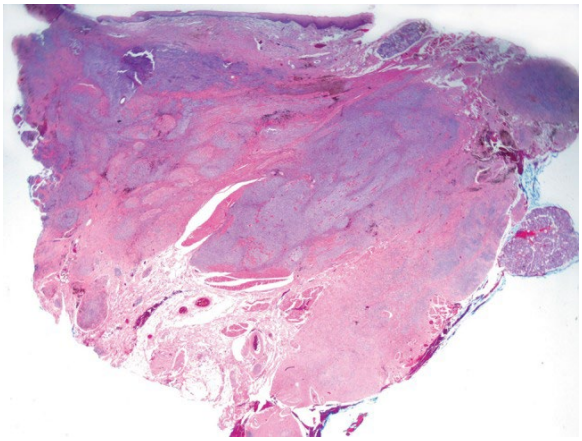

Fig. 1 The tumor is unencapsulated with an infiltrative growth pattern. Lesional cells exhibit sheet-like, nested and strand-like growth pattern. Melanin deposition is highly variable

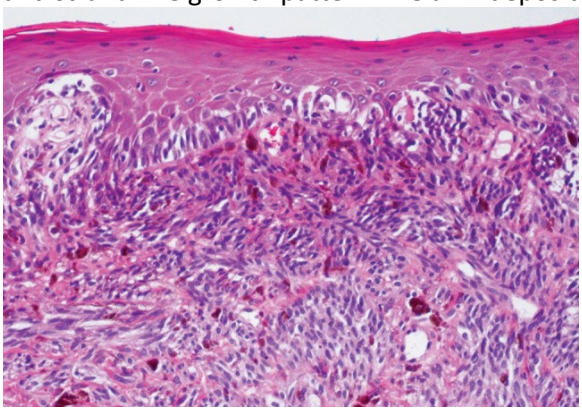

Fig. 2 Organoid and theque forming cells are intimately associated with the epithelium. There is no intraepithelial involvement

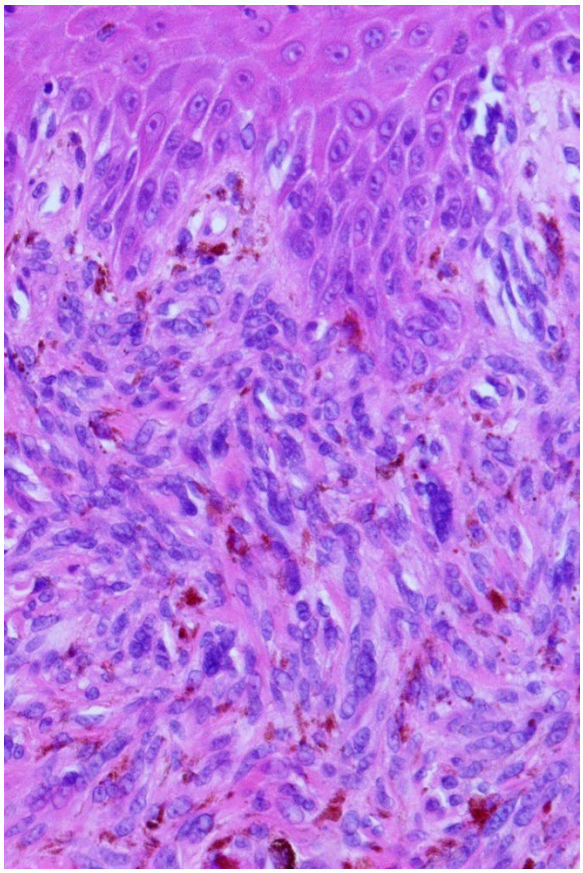

Fig. 3 Subepithelial lesional cells show nevocytic and epithelioid morphology. Scattered nevus giant cells are also seen

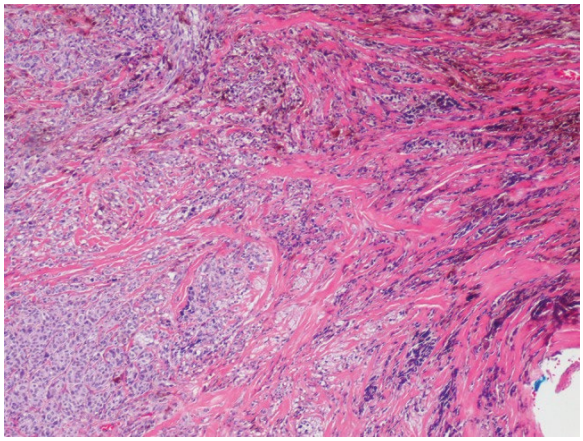

Fig. 4 Biphasic appearance: dense fibrous connective tissue containing dendritic melanocytes and melanophages typical of common blue nevus on the right and cellular nodules of cellular blue nevus on the left

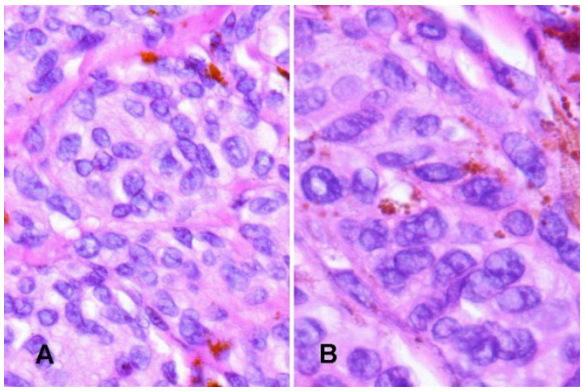

Fig. 5 Tumor cells have indistinct cytoplasmic membranes enclosing amphophilic cytoplasm and contain vesiculated nuclei with a single prominent eosinophilic nucleolus (a). Many nuclei show intranuclear inclusion-like vacuolation (b)

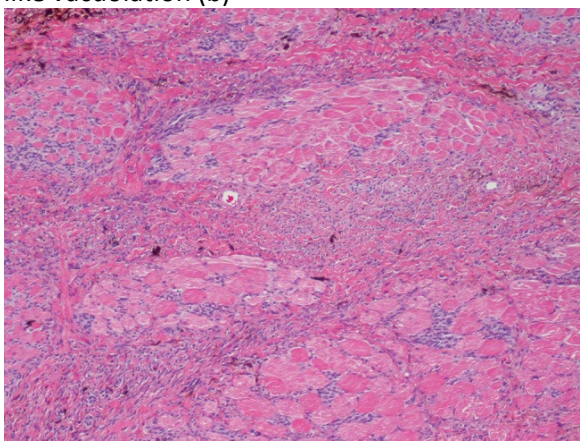
Fig. 6 Diffuse insinuation of lesional tissue between skeletal muscle fiber bundles

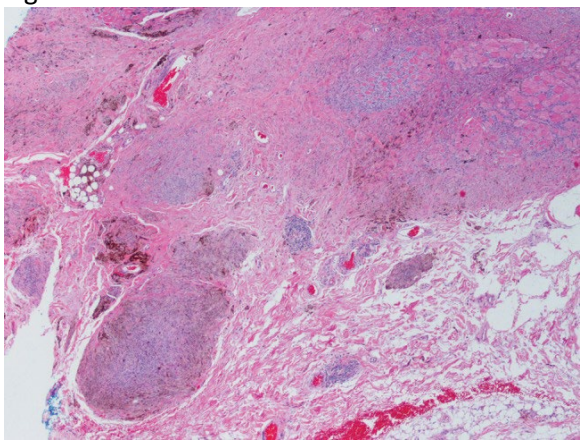
Fig. 7 Extension of small and large tumor nests into underlying fat

Immunohistochemistry was performed using antibodies to soluble adenylyl cyclase (sAC) according to a previously published procedure[24]. In brief, the R21 is a mouse monoclonal antibody directed against amino acids 203–216 of human sAC_{fl} protein. This antibody was provided to us by the laboratory of Lonny Levin and Jochen Buck. The primary antibody (3 mg/mL) was applied for 25 min in a buffered Primary Antibody Diluent (AR9352) from Leica Microsystems. The optimal dilution was determined to be 1:1200. Following this step, the sections were treated by a post primary AP step for 20 min for signal amplification as part of the procedure detailed in the Leica Microsystems Bond Polymer AP Red Detection kit (part number DS9305). The amplification polymer was then added for 30 min followed by two washes in wash buffer and one wash in deionized water. Finally, the mixed red substrate was applied for 10 min, followed by an additional 10 min with new substrate, three washes

in deionized water only, and, finally, mounting with a coverslip. The sAC pattern exhibited a variable pattern comprising perinuclear golgi, incomplete granular nuclear and pan nuclear staining (Fig. 8). The cells exhibiting a pan nuclear staining pattern showed the greatest extent of atypia and this feature was most apparent in areas of cellular fascicular growth.

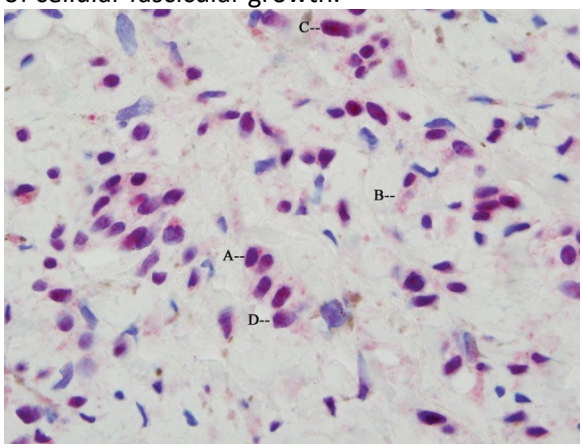

Fig. 8 Immunohistochemistry for sAC antibody (see letters): **a** The dominant pattern is characterized by perinuclear broad golgi and or **b** weak diffuse cytoplasmic staining. Some cells exhibit either a **c** pan nuclear and or **d** incomplete granular nuclear staining pattern typical for borderline tumors; the extent of pan nuclear staining is not as great as that seen in classic melanoma

Fluorescence in situ hybridization targeting 6p25 (RREB1), 6q23 (MYB), and 11q13 (cyclin D1), and Cep6 was performed based on a previously published study[25] which provided validation that this particular set of probes was useful in the distinction of melanoma from a benign nevus. Fluorescent in situ hybridization (FISH) was performed using the Abbott melanoma FISH test (Abbott Park, Illinois). Positive results were defined as 1) a gain in 6p25 (RREB1) relative to CEP6 greater than 55 %, a 2) gain in 6p25 (RREB1) greater than 29 % a 3) loss in 6q23 (MYB) relative to CEP6 greater than 40 % or a 4) gain in 11q13 (CCND1) greater than 38 %. Our analysis revealed that the CCND1 and RREB1 probes showed no amplification. There was no loss of MYB.

Discussion

The group of lesions characterized as “atypical cellular blue nevus” falls into a category that some have referred as “melanocytic tumor of uncertain malignant potential (MELTUMP)[20, 21, 23].” This designation derives from the diagnostic difficulty in classifying these lesions as benign or malignant. Some believe that this group represents low-grade tumors with potential for lymph node metastasis but rare distant metastasis[20]. The topic of ACBN has drawn considerable attention in the last several years given the struggle among experts to agree upon strict clinical and histologic criteria[18–21]. For instance, when 14 dermatopathologists used a defined set of criteria to discriminate CBN from ACBN and MBN only 18.2 % of the ACBN lesions were correctly identified by the majority of the pathologist [18]. The authors concluded that histologic overlap makes it difficult to define the “limits of atypicality” for a diagnosis of ACBN over CBN as well as to establish the minimal criteria to warrant a malignant diagnosis. These challenges are reiterated in the most recent literature[19–21]. Some contend that this intermediate designation should be eliminated in favor of just CBN or melanoma in association with a blue nevus[15]. They suggest that if the expected biologic behavior is in question, a consultative second opinion should be procured or that complete excision is advised. Similarly, other authors suggest that ACBN is likely

not a distinct entity, but rather a group of lesions that are either CBN with atypical histologic features (will behave in an indolent fashion) or CBN-like low grade melanoma[19]. While the quest for a simple dichotomous classification is desirable, it is likely that atypical lesions fall within a biologic continuum between benign and malignant[26]. Certainly, further study leading to more precise diagnostic criteria is necessary, with hope that molecular methods may help to stratify these histologic uncertainties into benign (nevus) or malignant (melanoma)[19–21]. Herein, we compare our case to the previously reported clinical and histologic criteria for ACBN as it relates to CBN and MBN. For a specific discussion on the histologic differential diagnosis with other lesions sharing some features of ACBN (e.g. epithelioid blue nevus, deep penetrating nevus) the reader is referred to several recent reviews[3, 19, 20, 22].

While comparisons of the clinical presentations of CBN, ACBN and MBN have not yielded clearly distinctive features, some trends have been noted. A summary by Tran et al.[17] indicates that CBN tend to occur at a younger average age (32.6 years) versus ACBN (37 years) and MBN (48.8 years). Evaluation of their ACBN case series (N = 9) alone yielded an average age of 47.4 years; similar to our case. The CBN occur on the buttocks/lumbosacral region followed by the scalp, face and hand[2, 23]. ACBN cases similarly affect the buttocks, scalp and the extremities[16, 17, 27] while MBN have somewhat greater propensity to affect the scalp[11]. Women are affected more often than men for CBN and ACBN whereas MBN affects men more frequently[1, 17] but these differences are modest. Hence, neither location nor gender are particularly distinctive in our case.

While many authors report that increasing size is more often associated with atypical or malignant lesions, there is disagreement over precise values. Cutoffs for distinguishing ACBN from CBN varies from >1–2 cm[17, 18] to >2–3 cm[22] to >5 cm[3]. As the size increases from >3 cm[23] to >6 cm[3], melanoma is reported to be more likely. Lesions falling within the 1–2 cm range (our case was 1.7 cm) have been reported for CBN[2, 4] as well as for MBN[9] such that size is not discriminatory in our case.

As previously mentioned, defining histologic criteria for ACBN is difficult. While CBN are typically symmetrical with well-circumscribed nodules[2, 23], ACBN are often characterized by asymmetry[17, 18], deep extension into subcutaneous tissue[3], and an infiltrating border[3, 17]. Our case exhibited an asymmetric (Fig. 1) and infiltrating border (Fig. 7), and deep extension through muscle and fat. While CBN are dermal-based tumors lacking an epidermal or junctional component, our case exhibited tumor cells that often intermingled with the surface epithelium and showed focal junctional activity (Fig. 2). No intraepithelial spread suggestive of melanoma was identified. Only once has epidermal involvement been reported in an ACBN, wherein an overlying junctional nevus was identified[17].

Cytologic characteristics cited in early reports of ACBN were thought to be distinctive for this entity. Specifically, cellular pleomorphism, numerous bizarre and heavily pigmented multinucleated cells and giant cells[16, 27] as well as atypical and mostly nonpigmented cells with hyperchromatic nuclei were reported[27]. Only a “few mitoses” were reported in 1 of the 5 cases from these 2 studies. Of the 9 cases reported by Tran et. al.[17], seven showed abnormal cytologic features: nuclear pleomorphism, hyperchromatism, bizarre cells, high nuclear/cytoplasmic ratio and mitotic activity (1–2 mm^2 in 5 cases), particularly at the deeper aspect. The authors did not consider these features as malignant, reserving “marked cytologic atypia”, atypical mitoses, necrosis, and marked histologic heterogeneity as characteristic of MBN[17]. While rare to absent in CBN 2, mitotic activity is nearly always seen in MBN[10, 11], though at a variable rate. While mitotic rates often overlap in ACBN and MBN[8, 18, 19, 22], the presence

of mitotic activity in atypical blue nevi is associated with unfavorable biologic behavior[21] and multiple groups have reported that atypical mitoses are a feature of malignancy[4, 9, 11, 13, 28]. Our case lacked atypical cytologic features as may occur in ACBN. Atypical mitotic activity was also absent, suggesting a more indolent biologic potential. As such, the diagnosis of ACBN rendered in this case rests on the atypical architectural features, which is within the spectrum previously described in these lesions.

Other important features include necrosis and host inflammation. While necrosis may be seen in MBN, it is not observed in the majority of cases[9, 11, 14], though other groups report that it is invariably found[29]. Necrosis has been reported in some cases of ACBN[17] and in a small percent of CBN[4]. Therefore, while necrosis suggests a more aggressive process, it is not entirely specific for malignancy. Lastly, inflammation is frequently noted at the periphery of melanomas but is typically absent in CBN[2]. Inflammation in MBN is highly variable[9, 11] and in the 14 well-documented cases of ACBN it was seen in 10 (71 %), with 6 showing only a "mild" reaction[16, 17, 27]. Our case lacked necrosis or a significant inflammatory response, both indicating a less aggressive process.

Given the challenge of defining ACBN histologically, hopes have been raised that molecular techniques may help provide distinction[19–21]. Building on initial data using comparative genomic hybridization, a 4-probe fluorescent in situ hybridization (FISH) assay (Abbott melanoma FISH test, Abbott Park, Illinois) was developed to assist in separating benign and malignant melanocytic lesions, with particular emphasis on histologically ambiguous cases[25, 30, 31]. Most recently, this technique was specifically used to try to distinguish CBN from CBN with atypical features[32]. A positive result was found in 5 blue nevus-like melanomas and was negative in 17 cases of CBN. Assessment of certain cytogenetic abnormalities encountered in melanoma is another important diagnostic adjunct that was applied in this case. We did not observe any of the cytogenetic abnormalities potentially encountered in melanoma; in particular we were unable to detect abnormalities in RREB1, MYB, and CCND1.

The antibody to sAC has emerged as another important diagnostic adjunct in the assessment of melanocytic lesions[24]. A discriminatory staining pattern is observed that separates benign melanocytic proliferations from melanoma. In borderline tumors, an intermediate pattern between the perinuclear dot-like golgi pattern of a benign nevus to one of frank pan nuclear staining is observed. Indeed in our case the sAC profile was variable and included foci of enhanced nuclear staining in areas of severe atypia. However, in the majority of lesional cells the staining pattern was not pan nuclear but was dominated by an incomplete granular nuclear and perinuclear staining pattern. While this approach has not been applied to a large number of ACBN cases, it may prove to be a promising adjunctive technique in the evaluation of atypical melanocytic lesions[33].

Perhaps the most useful criterion for the accurate classification of these lesions is assessment of biologic behavior. Cases of CBN rarely recur and do not metastasize[2] while MBN often recur, metastasize and frequently lead to death[9–11]. The intermediate designation of ACBN has drawn some criticism[15] due to the fact that, of the well-characterized cases, only one has recurred and none have metastasized[16, 17, 27]. The follow-up period varied tremendously in these cases from 12 to 228 months with an average of nearly 59 months. While most MBN metastasize within 1–2 years[1, 8, 11, 13], there are 5 reports of delayed metastasis from 5 to 19 years after initial surgery[11, 34–36], suggesting that malignancy cannot be ruled out in a small percent of cases without extensive follow-up. In our case, tumor was transected at the deep and lateral surgical margins, potentially predisposing to regrowth[23,

[37]. Yet the patient refused reexcision, and after 4 years without recurrence, he was lost to follow-up. No report of lymphadenopathy was given by the surgeon in our case. Compared to reported studies, this significant follow-up period would suggest a favorable course.

Despite the ongoing debate, most investigators currently consider ACBN as a low-grade malignant melanocytic tumor with the potential for spread to regional lymph nodes and rare distant metastasis[18, 20, 21]. Most authors currently recommend complete surgical excision[10, 11, 19, 21, 37] with assured clear histologic margins[20]. While some advocate reasonably extending the surgical margins up to 1 cm[21], there is no consensus at this point if this is appropriate until further study of these unusual tumors occurs[20].

In this report, we document the first complete description of an atypical CBN of the oral cavity. While cytologically bland, the atypical architectural features are sufficient to warrant this diagnosis. Based on 4 years of follow-up without regrowth of the incompletely excised lesion, along with molecular data, a good prognosis is likely.

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