Pleomorphic Adenoma Misinterpreted as Mucosal Melanoma: A Case Report and Literature Review

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Abstract

Pleomorphic adenoma is the most common benign salivary gland neoplasm, yet it can histologically mimic mucosal melanoma, an aggressive and rare cancer associated with poor prognosis. Misinterpretation of pleomorphic adenoma as mucosal melanoma can result in unnecessary medical treatment and can lead to undue stress for the patient. Here we present a case of a 54 year-old woman with a history of chronic rhinosinusitis who was incidentally found to have a left palatal mass. The initial incisional biopsy and subsequent resection demonstrated histologic features consistent with mucosal melanoma, including positive S100 and Sox10 stains and focally positive areas of MelanA. However, upon second review and additional work-up a biphasic pattern and strong cytokeratin staining were identified, resulting in a final diagnosis of pleomorphic adenoma.

Keywords: Pleomorphic adenoma; Mucosal melanoma; S100; Sox10; histology

Introduction

Pleomorphic adenomas are the most common benign salivary gland neoplasms [1]. Histologically, pleomorphic adenomas are commonly composed of a biphasic mixture of epithelial and stromal elements with variable proportions of each component leading to a spectrum of morphologic appearances [2]. This morphologic variability often leads to diagnostic challenges and requisite need to definitively exclude histologic mimics.

Mucosal melanoma of the head and neck is a rare but aggressive disease associated with poor prognosis. Approximately 1% of melanomas are mucosal melanomas and 55% of all mucosal melanomas arise from the head and neck region. The incidence of oral mucosal melanoma is reported to be 1.2 cases per 10 million population per year and account for only 0.5% of all oral malignancies [3]. Mucosal melanoma of the head and neck commonly presents as a painless pigmented and edematous area in the nasopharynx, palate, or maxillary ridge [4, 5]. Mucosal melanoma can also have a variety of histological appearances including epithelioid, plasmacytoid, or spindled, and notoriously mimics numerous neoplasms including pleomorphic adenoma [6]. Immunohistochemical staining is frequently required for definitive diagnosis or exclusion of melanoma.

Distinguishing pleomorphic adenoma and mucosal melanoma is important for planning proper treatment and avoiding undue stress for the patient. Current immunohistochemical markers used in...
the diagnosis of mucosal melanoma include S100, human melanoma black-45 (HMB-45), Melan-A, microphthalmia transcription factor (MITF), Tyrosinase and PNL-2 [7, 8]. S100 protein has been the gold standard for the diagnosis of melanocytic lesions due to its high sensitivity [9]. Sox10 is a novel melanocytic marker that was recently shown to be a reliable marker of neural crest differentiation and is consistently expressed in melanocytic tumors [10]. In addition, multiple studies concluded that Sox10 serves as a more sensitive and specific marker for the diagnosis of melanocytic tumors than S100 protein [9,10].

Adding to this diagnostic complexity, multiple studies have demonstrated consistent positive expression of S-100 in pleomorphic adenomas [11-13]. Expression of SOX10 has also been identified in normal salivary glands [9, 14,15] and recent studies have demonstrated a connection between Sox10 and salivary gland tumors [16]. Here we report a case of pleomorphic adenoma that was diffusely positive for S100 and Sox10 and focally positive for MelanA to illustrate the potential for misinterpretation of pleomorphic adenoma as mucosal melanoma.

**Case Presentation**

A 54 year-old female with a history of chronic rhinosinusitis (CRS) was found to have an incidental left palatal mass during a follow up visit for her CRS exacerbation. During history taking, she reported symptoms of subjective fevers and left more than right ear fullness for months, raspy voice changes, and dysphagia to solids for weeks. She denied any history or family history of head and neck cancers including melanomas. She reported a 0.3 pack year smoking history and quit 34 years ago and denied alcohol use. On physical exam, a 2x3 cm firm ovoid submucosal mass extending from the left junction of the hard and soft palate posteriorly onto the soft palate just reaching midline was observed. The mass was nontender to palpation and hypomobile without any sensory changes to the overlying mucosa. The overlying mucosa did not show any irregularity, ulceration or bleeding, and fiberoptic exam revealed no involvement of the nasal cavity or nasopharyngeal mucosa.

Incisional biopsy was performed and showed sheets of malignant cells (Figure 1A, 1B) that by immunohistochemistry were strongly positive for S100 (Figure 1C), Sox10 (Figure 1D) and focally positive for melanA and p16. CK5/6 showed equivocal positivity, with stains for p63, HMB-45, and calponin negative. A PAS with diastase stain did not show the presence of increased mucin. Overall, the morphologic and immunophenotypic features most favored a diagnosis of mucosal melanoma.

Figures 1A-1H demonstrate histological sections of the pleomorphic adenoma described in this report. Figures A-D are the initial biopsy. Figures A and B are H&E stains which show sheets of cells suggestive of malignancy. Figures C and D are S100 and Sox10 stains, respectively, both of which are strongly positive. Figures E through H are the resected specimen. Figure E is an H&E stain which demonstrates a biphasic pattern with both a myxoid stroma and a cellular epithelioid proliferation of uniform small cells with uniform small nuclei, suggestive of benign disease. Figures F and G show S100 and Sox10 stains, respectively, which are again strongly positive. Figure H is a mixed cytokeratin stain, which is also strongly positive. All of the images are 100x magnification.

Ten days after the biopsy, an MRI of the head and neck demonstrated a well-circumscribed enhancing soft palate lesion, without associated lymphadenopathy. PET-CT was significant for a discrete focus of hypermetabolism in the left aspect of the soft palate. There were no pathologically enlarged or hypermetabolic cervical or supraclavicular lymph nodes. There were no signs of local or distant metastasis. The mass did not involve the greater palatine

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**Figure 1:** Specimen Histology: Light microscopy at 100x magnification of the pleomorphic adenoma described in this report. A and B are the initial biopsy with H&E stains which show sheets of cells suggestive of malignancy. C and D are S100 and Sox10 stains, respectively, both of which are strongly positive. E through H are the resected specimen. E is an H&E stain which demonstrates a biphasic pattern with both a myxoid stroma and a cellular epithelioid proliferation of uniform small cells with uniform small nuclei, suggestive of benign disease. F and G show S100 and Sox10 stains, respectively, which are again strongly positive. H is a mixed cytokeratin stain, which is also strongly positive.
foramen. The case was discussed at a multidisciplinary Head and Neck Meeting and the patient underwent wide local excision of the tumor at the junction of the hard palate and soft palate and reconstruction of the defect with an inferior turbinate flap and a local palate advancement flap. She was discharged post-op day two without complications.

The surgical specimen revealed a tan-white, firm mass measuring 1.5 x 0.9 x 0.7cm. Initial histologic evaluation of the resection was consistent with the findings found in the prior biopsy, and the diagnosis of mucosal melanoma was confirmed. The final margins were negative for tumor. The patient subsequently met with the radiation oncologist and medical oncologist and was scheduled for postoperative radiation therapy for a total dose of 60Gy over a period of 6 weeks. The surgeon requested that the case be re-evaluated by the pathologist given the relatively low clinical concern for mucosal melanoma in the context of a 54 year old with a firm mass deep to normal appearing mucosa [17]. The excision was uneventful without the vascularity/friability that is often seen with mucosal melanoma. Furthermore, following excision, the mass was sectioned to show a tan-white parenchyma without gross involvement of the mucosa.

On re-examination, the neoplasm demonstrated a biphasic pattern with both a myxoid stroma and a cellular epithelioid proliferation of uniform small cells with uniform small nuclei (Figure 1E). A panel of immunohistochemical stains were repeated. The tissue was strongly positive for S100 (Figure 1F) and Sox10 (Figure 1G). In addition, there was strong cytokeratin staining with mixed cytokeratins (AE1 and CAM5.2; Figure 1H). Given the biphasic pattern together with the strong cytokeratin staining, the diagnosis was altered from mucosal melanoma to pleomorphic adenoma. The diagnosis was confirmed by external review from the pathology department from the University of California San Francisco (UCSF). The patient was informed of the change in result and the scheduled radiation therapy was canceled. Following initial resection, the patient developed an oral-nasal fistula, which was repaired with a subsequent operation.

The initial misdiagnosis of mucosal melanoma took a very heavy emotional toll on the patient. She was understandably devastated by the initial misdiagnosis and started antidepressant medication for clinical depression. However, over time the patient has improved and has been able to resume work as a teacher. The patient has been followed for 4 years with no evidence of recurrence of her palatal minor salivary gland pleomorphic adenoma.

**Discussion**

Pleomorphic adenomas are the most common benign salivary gland neoplasms, accounting for up to 50% of all salivary gland tumors. They are most frequently found in the parotid gland (85%) but can also arise from the submandibular (8%), sublingual (<1%), as well as the minor salivary glands (7%) [1, 2]. Seventy percent of the tumors of the minor salivary glands are found to be pleomorphic adenomas, and the most common intraoral site is reported to be the palate [18]. Pleomorphic adenoma commonly presents in women during the fourth to sixth decades of life as a slow-growing, painless and mobile mass. For palatal pleomorphic adenomas, they are generally non-mobile and lack a well-defined capsule [2]. Histologically, pleomorphic adenoma is composed of a mixture of epithelial and myxoid, chondroid, or hyaline stromal elements [2]. However, pleomorphic adenomas can be highly variable in morphologic appearance. The histologic complexity of these neoplasms is thought to be due to the ability of the neoplastic ductular myoepithelial cell to transform into cells such as squamous epithelial cells and mesenchymal-appearing cells (stellate, spindle-shaped and chondroid), to modulate intermediate filament composition, and to produce large amounts of matrix substances [12]. The treatment for pleomorphic adenomas is wide local excision with negative surgical margins. Postoperative radiotherapy is recommended for a small subset of patients with positive margins and/or multifocal recurrences [19].

Mucosal melanoma is most frequently found in the nasopharynx although it can occur in the oral cavity [17]. The mean age of diagnosis ranges between 60 and 69 [17]. The preferred treatment for localized mucosal melanoma of the oral cavity is surgery. Postoperative radiotherapy is shown to improve local-regional control but no studies have shown an improvement in overall survival. For mucosal melanomas of the head and neck, elective neck dissection or adjuvant radiation therapy may be indicated given the higher neck metastatic potential (25%) for mucosal melanoma that originate from the oral cavity [8, 19, 20].

Given the variable yet similar histologic appearances of both pleomorphic adenomas and mucosal melanomas, it is challenging to distinguish between these entities by their histologic appearance alone. Immunohistochemical stains are frequently required to help further classify these tumors. S100, Sox10, and MelanA are useful markers used in identifying melanocytes as well as in diagnosing mucosal melanoma. S100 protein has been the gold standard for the diagnosis of melanocytic lesions due to its high sensitivity [9]. Sox10, a member of the SOX (SRY-related HMG-box) family of transcription factors, has been identified as a reliable marker for neural crest differentiation and a more sensitive and specific maker for the diagnosis of melanocytic tumors than S100 [9, 10]. Karamchandani et al reported 668 cases of mesenchymal neoplasms of nonschwannian, nonmelanocytic soft tissue, and found that Sox10 had a 99% specificity as compared to 91% for S100 [10]. In another study, Sox10 nuclear expression was found in 76 of 78 melanomas (97%) whereas S100 protein was expressed in 71 melanomas (91%) [9]. Sox 10 has also demonstrated utility as a marker in diagnosing mucosal melanoma. In one study of 28 mucosal melanoma cases, Sox10 nuclear expression was found in 100% of cases compared to 82.1% for S100. The sensitivity and intensity of Sox10 immunohistochemistry were both found to be higher than S100 in diagnosing mucosal melanoma [21].

Melanocytes have been identified in both normal major and minor salivary gland tissue [22, 23]. In a study of labial minor salivary glands obtained from autopsies and biopsies, melanocytes were found in eight of 445 subjects...
thus reporting an overall incidence of 1.8% [22]. Notably, melanocytes have also been identified in minor salivary gland pleomorphic adenoma of the soft palate [24]. The presence of melanocytes in pleomorphic adenoma might explain why this case in the minor salivary gland demonstrated strong positive staining for S100, Sox10, and MelanA. Benign neoplasms with admixed melanocytes present a diagnostic challenge, which was evident in this case. Fortunately, since a similar surgical approach would be used for a mucosal melanoma or pleomorphic adenoma, and the diagnostic interpretation was altered before the patient’s radiation therapy, there was no adverse outcome for the patient.

Conclusion

The importance of this case report is recognition of the potential for pleomorphic adenoma to stain positively for melanocytic markers and to mimic mucosal melanoma by immunohistochemistry.

References