Schwannoma-Like Pleomorphic Adenoma: Two Cases and a Review of the Literature

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Received: 20 February 2019 / Accepted: 3 April 2019 / Published online: 9 April 2019
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Abstract

Schwannoma-like pleomorphic adenoma is a rare variant of the common benign salivary neoplasm, pleomorphic adenoma. This entity's cytomorphology closely mimics a schwannoma, potentially making a diagnosis of cytologic preparations or of surgical specimens a challenge. To the best of our knowledge, there are only six previous reports of schwannoma-like pleomorphic adenoma with eight total cases in the English language literature prior to the addition of the two cases detailed in this report. Our report includes what we believe to be the first documented case of this entity occurring in the submandibular gland. One of our cases occurred in the submandibular gland of a 90-year-old woman and the other occurred in the left parotid gland of a 40-year-old woman. We also examine the diagnostic considerations used to differentiate these two entities.

Keywords Pleomorphic adenoma · Schwannoma · Benign · Spindle cell lesion · Fine-needle aspirate · Cytopathology · Parotid gland · Submandibular gland · Schwannoma-like pleomorphic adenoma

Introduction

Salivary gland tumors represent approximately 3% of all head and neck neoplasms [1]. Of these, pleomorphic adenoma (PA) is the most common, representing between 45 and 74% of all salivary gland tumors and 66% of all benign tumors from all salivary glands. Only about 9% of PAs occur in the submandibular gland. PAs occur over a wide age range, but the average age is approximately 43 years old. There is a female predominance [2]. Histologically,

PAs are an admixture of epithelial and mesenchymal-like components with a stromal component that could appear myxoid, cartilaginous, osseous, or hyalinized [3]. PAs are morphologically myxoid (stroma-rich), cellular (myoepithelial-predominant), or a combination of the two. Malignant transformation occurs in 2–7% of PAs [4].

Schwannoma, a benign peripheral nerve sheath tumor, is relatively common in the head and neck with 25% of schwannomas occurring in this region [5]. However, most of these lesions occur centrally, and only 9% of schwannomas affecting the facial nerve occur extratemporally [6]. Glandular and pseudoglandular variants of schwannoma have been reported but these variants are rare [7]. The majority of glandular tumors with schwannian differentiation are malignant peripheral nerve sheath tumors (MPNSTs), representing 1.7% of these uncommon malignancies [8]. Almost all of the reported cases of benign glandular schwannomas have been localized to the dermis, subcutaneous tissue or chest wall [7]. There has been a case of glandular schwannoma reported in the submandibular gland, however, the histology displayed variably dilated ducts and p63-positive myoepithelial cells that were present exclusively surrounding the epithelial ductal elements. The spindled element of this lesion was neither positive for cytokeratin nor myoepithelial markers [9]. Whether the glandular structures observed in these neoplasms are entrapped ducts of native glands or

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de novo glandular differentiation is controversial [10]. It is also worth noting that there has been a reported case of concurrent monomorphic adenoma and schwannoma of the superficial parotid gland, however, these tumors were encapsulated and separated from one another and their coexistence is likely coincidental [5].

A rare subset of PAs display areas of spindled cells arranged in a fascicular pattern that mimics the Antoni A areas observed in schwannomas. This subset of tumors has been designated as schwannoma-like pleomorphic adenoma [11, 12]. We report two cases of schwannoma-like pleomorphic adenoma (one in the parotid gland, the other in the submandibular gland). Schwannoma-like pleomorphic adenomas can be differentiated from intrasalivary gland schwannomas and schwannomas with glandular differentiation with the understanding of the morphologic and immunohistochemical differences between these lesions.

Case Report

Case 1

A 90-year-old woman presented to a head and neck surgeon with a history of a longstanding, unilateral, asymptomatic mass of the left submandibular gland. The patient was uncertain as to how long the mass had been present but reported that there had been recent enlargement, which prompted her consultation.

A fine-needle aspiration biopsy (FNA) was performed. The cytopathology exhibited sheets of spindle cells with round to oval nuclei in the background of hemorrhage. A cell block was not available for further evaluation. The FNA specimen was signed out as “positive for spindle-cell neoplasm”.

The patient underwent an excision of the contents of the submandibular triangle. The left submandibular gland, surrounding fat, and lymph nodes were removed and sent for histologic examination. The lingual and hypoglossal nerves were both preserved. On gross examination, there was a tan-yellow, homogenous soft tissue mass measuring $3.2 \times 3.0 \times 2.2$ cm within the $4.7 \times 3.2 \times 2.2$ cm of removed tissue.

The histologic examination revealed an encapsulated neoplasm predominated by a spindle cell component that featured a schwannoma-like morphology juxtaposed against a small focus of classic PA morphology (Fig. 1a). The spindle cells were arranged in palisaded fascicles with areas similar to the Verocay bodies found in the Antoni A areas of a schwannoma (Fig. 1b). A focus of classic pleomorphic adenoma morphology that was composed of a biphasic population of epithelial and myoepithelial cells and formed well-defined ducts within a markedly myxoid stroma was

identified within the same lesion (Fig. 1c). Four lymph nodes were included in the resection, all of which were negative for tumor.

Immunohistochemistry was performed on the surgical specimen to further classify the lesion. In both the schwannoma-like and classic PA areas of the lesion, there was strong, diffuse positivity for CK7, p63, and S-100, patchy positivity for smooth muscle myosin heavy chain (SMMHC) and focal positivity for calponin. CK7 was most intense in the areas of classic PA morphology. Pancytokeratin AE1/AE3 was strong and diffusely positive in the area of classic morphology but negative in the schwannoma-like area (Fig. 2).

The patient was discharged the day after the excision and has not reported recurrence in the 25 months subsequent to surgical treatment.

Case 2

A 40-year-old woman presented to her primary care physician with a slowly enlarging mass of the left parotid gland that had been present for over 1.5 years. She was referred to an ENT surgeon. An ultrasound exam demonstrated a well circumscribed hypoechoic mass without significant internal vascularity. An MRI exam (Fig. 3) showed a well circumscribed, enhancing mass measuring 1.4 cm in the tail of the left parotid gland.

A fine-needle aspiration biopsy was performed under ultrasound guidance, and 4 ETOH slides, 2 air-dried slides, and 1 Surepath slide were prepared. The cytology specimen was cellular and revealed groups of bland to slightly atypical spindled cells with very elongated nuclei associated with homogeneous extracellular material (Fig. 4a). There were very rare mitoses and minimal cellular atypia, but no evidence of necrosis and no overt malignant features. There were frequent areas of nuclear palisading with a clear demarcation between the cells and the matrix material, suspicious for an Antoni A area observed in a schwannoma (Fig. 4b). Using the Milan system for reporting salivary gland pathology, this lesion was diagnosed as Neoplasm: Uncertain malignant potential [13]. Cytologic material for ancillary testing was not available. The differential diagnosis included schwannoma, cellular pleomorphic adenoma, and myoepithelioma. The possibility of a low grade myoepithelial carcinoma was also considered.

The patient underwent a left subtotal parotidectomy with facial nerve monitoring. An approximately 2.0×2.0 cm superficial mass was surgically excised with a cuff of uninvolved parotid tissue from the left parotid tail. Histologic examination revealed an unusual cellular neoplasm with a schwannoma-like growth pattern juxtaposed to areas with more myxoid stroma and ductal organization (Fig. 5a–c). Cells in the schwannoma-like portion were very elongated

Fig. 1 The histologic features of the schwannoma-like pleomorphic adenoma in case 1. **a** A low-power image of the histology in case 1 ($\times 40$). Within the field, an area of schwannoma-like spindle cells was identified near an area of more traditional pleomorphic adenoma morphology consisting of clusters of myoepithelial cells, ductal structures, and a myxoid stroma. **b** The spindle cells, which predominated

the lesion, appeared palisaded, forming Verocay body-like structures that mimic an Antoni A area observed in schwannomas ($\times 200$). **c** There were focal areas of the lesion in case 1 that display a classical PA morphology: ductal elements comprised of epithelial and myoepithelial components in a background of myxoid stroma ($\times 200$)

Fig. 2 Immunohistochemical profile of the schwannoma-like pleomorphic adenoma in case 1. The areas of schwannoma-like spindle cells stained positively for CK7 (**a**), S-100 (**b**), and p63 (**c**). The areas

of classic pleomorphic adenoma also stained positively for CK7 (**d**), S-100 (**e**), and p63 (**f**) which highlighted the subepithelial myoepithelial cells of the ductal elements

Fig. 3 MRI scan of the patient in case 2. Magnetic resonance imaging revealed a 1.4 cm, circumscribed, enhancing mass of the tail of the left parotid gland

(Fig. 6a). Nuclei were stratified, and had even granular chromatin with indistinct nucleoli. Occasional mitoses were present, and there was no evidence of invasion or necrosis. Immunohistochemical stains showed that the spindled cells

were positive for pancytokeratin AE1/AE3, S-100, and p63 (Fig. 6b). Ki-67 was slightly elevated at 10%. The tumor was diagnosed as a cellular myoepithelial-predominant pleomorphic adenoma with diffuse schwannoma-like growth pattern. The patient has been alive without evidence of disease recurrence for 2 years.

Discussion

Schwannoma-like PAs have been reported across a wide age range from 39 to 90 years old (the first case in this report), with a mean age of 57.9 years old and a median age of 54 years old. 8 of 10 cases were diagnosed in the parotid gland, 1 of 10 cases was diagnosed in the hard palate, and our first case represents the first described submandibular gland manifestation of this entity. As expected, there is a female predominance with a 1:5 male to female ratio. The majority of cases were asymptomatic (6 of the 7 cases that reported on symptoms). Table 1 lists the demographic and clinical features of the previously reported cases. Histopathologically, the reported cases all displayed areas of spindled cells with palisaded or parallel arrangement. Many of the cases exhibited histology that was similar to our cases, wherein the spindle cell component predominated the lesion. p63 was consistently positive when immunohistochemistry was reported, effectively ruling out schwannoma in these cases [1, 14, 15].

The myoepithelial component of a PA can present in many forms. These myoepithelial cells, sometimes referred to as modified myoepithelial cells (MMCs), can display

Fig. 4 The cytologic features of the schwannoma-like pleomorphic adenoma in case 2. **a** A photomicrograph of the fine-needle aspirate showing groups of spindle cells with elongated nuclei devoid of atypia within an extracellular matrix. **b** Many fields within the aspi-

rate displayed the elongated nuclei in a palisaded architecture with distinct zones of palisaded nuclei and extracellular matrix. This pattern is suggestive of an Antoni A area in a schwannoma

Fig. 5 The overall histology of the schwannoma-like pleomorphic adenoma and higher power images of the more classic pleomorphic adenoma components in case 2. **a** Histologic examination of the surgical specimen revealed a lesion predominated by spindled cells juxtaposed to an area of myxoid stroma and ductal elements at lower

power magnification ($\times 100$). **b** On higher magnification, the focal area that contained the myxoid matrix commonly observed in pleomorphic adenomas can be appreciated ($\times 400$). **c** Ductal structures were also observed within the area of more classic PA morphology ($\times 400$)

Fig. 6 The histology and immunohistochemistry of the schwannoma-like areas of case 2. **a** A higher magnification view of the schwannoma-like area revealed elongated nuclei arranged in a stratified pat-

tern that resembles the Antoni A area of a schwannoma ($\times 400$). **b** The spindled cells stained positively for p63 ($\times 400$)

ter, polygonal, spindled, or plasmacytoid appearances in sheets, clumps, or strands, often admixed with a myxoid component. A diagnostic challenge can occur for both the cytopathologist and the surgical pathologist when this myoepithelial component is spindled and forms interlacing fascicles reminiscent of neurogenic or myogenic tumors [12]. Approximately 1% of PAs exhibit these spindled cells, often in a palisaded fascicular arrangement [11]. Caution is advised when examining specimens with a spindle cell component in a minor or major salivary gland tumor, and the origin of these cells should be determined if possible. Ancillary

studies are required to differentiate spindled myoepithelial cells from the spindle cells of other entities, especially when they form palisaded fascicles that mimic the Antoni A pattern of a schwannoma.

Ultrastructurally, MMCs contain desmosomes, confirming their origin as myoepithelial cells [16]. Immunohistochemistry is also helpful to delineate the origin of these spindled cells as schwannoma-like cellular PAs consistently express p63 and cytokeratins [12]. p63 is an especially helpful marker as it will stain diffusely positive in the nuclei of the spindle cells in schwannoma-like areas but is negative in

Table 1 Demographic and clinical features of previously reported cases of schwannoma-like pleomorphic adenoma

Authors	Age	Gender	Site	Duration	Size	Symptoms	Immunohistochemistry
Merino and Livolsi [16]	74	F	Parotid gland: deep lobe	5 years	2.0 cm × 3.0 cm	Asymptomatic	NA
	39	F	Parotid gland	1 year	1.5 cm	Asymptomatic	NA
Takeda and Shimono [12]	62	M	Parotid gland	10 months	NA	Asymptomatic	NA
	48	F	Hard palate	3 months	NA	Asymptomatic	NA
Kajor et al. [17]	75	F	Parotid gland	NA	3.0 cm	NA	NA
Tille et al. [1]	47	F	Parotid gland: deep lobe with parapharyngeal extension	2 months	3.2 cm	Pain	p63, CD10, and cytokeratin positive in PA and schwannoma-like areas
Lombardi et al. [18]	44	F	Parotid gland	3 months	1.5 cm	NA	Pancytokeratin (AE1/AE3) and S-100 strong, diffuse positive in both components (stronger in glandular component). p63, CD10, and SMA focally positive
Chandra et al. [14]	60	M	Parotid gland: superficial lobe	12 years	3.5 cm	Asymptomatic	Strong, diffuse p63 positivity in both components (ductal myoepithelium positive, ductal epithelium negative). Focally CD10 positive
Case 1	90	F	Submandibular gland	NA	3.2 × 3.0 cm	Asymptomatic	Strong, diffuse positivity for p63, S-100, and CK7 in both areas (CK7 stronger in areas of classic PA). Patchy SMMHC and focal calponin positivity. AE1/AE3 strong and diffusely positive in classic PA areas, negative in schwannoma-like areas
Case 2	40	F	Parotid gland	1.5 years	2.0 × 2.0 cm	NA	Positive for AE1/AE3, S-100, and p63

NA Information not available or unknown

the spindle cells of schwannomas [14, 19]. Both of our cases stained diffusely positive for p63 in the schwannoma-like areas, excluding the diagnosis of a benign glandular schwannoma or intrasalivary gland schwannoma and confirming our diagnoses of schwannoma-like pleomorphic adenoma. S-100 proves to be an ineffective marker for differentiating these entities as both schwannian and myoepithelial cells will stain positively. PLAG1 can provide diagnostic aid as one study found that all neural tumors, including six schwannomas, did not express PLAG1 protein [15].

Treatment for both schwannoma and pleomorphic adenoma is often surgical excision. However, some authors suggest that in cases of either small schwannomas or patients who are over the age of 70, monitoring the tumor's growth with serial MR scans is an acceptable alternative to ensure preservation of facial nerve function, as facial nerve damage is a possible complication of surgical excision of lesions in this anatomic location. The recurrence potential

of schwannomas is very low, at approximately 5% [20]. The recurrence rate following sufficient excision of a pleomorphic adenoma that includes complete removal of the lesion with a rim of uninvolved native glandular tissue is approximately 3–5%, however, with insufficient excision recurrence rates approach 45% [21, 22]. PA recurrence following insufficient surgical excision often presents with multiple small tumor nodules, creating a more difficult surgical scenario and a higher possibility of even further recurrence with incomplete excision [23]. In addition, malignant transformation can occur in 2–10% of pleomorphic adenomas [4]. These distinctive characteristics necessitate differentiating these entities.

Careful diagnosis and appropriate ancillary studies are recommended in all spindle-cell lesions appearing schwannian in nature within salivary gland tissue to differentiate between a schwannoma and a schwannoma-like pleomorphic adenoma.

Acknowledgements The authors would like to acknowledge Dr. Kas-turi Das, MD for her assistance with the cytopathologic interpretation of these cases.

Compliance with ethical standards

Conflict of interest The authors have nothing to disclose.

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