CASE REPORT

Divergent Schwannoma-Like Phenotype in a Pleomorphic Adenoma

Srinivasa R. Chandra¹ · Farah Karim² · Yeshwant B. Rawal³

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Abstract The schwannoma-like pleomorphic adenoma is a rare histopathological variant of the pleomorphic adenoma. Five previous reports with seven cases exist in English language literature. These tumors present in the parotid gland most commonly. Intraparotid schwannomas of the facial nerve and schwannomas with glandular differentiation have also been reported. A 60-year-old male presented with an asymptomatic swelling over the left angle of the mandible. The swelling had been present for about 12 years with a recent increase in size. CT imaging showed a hyperdense circumscribed mass of the superficial lobe of the parotid. The working diagnosis was that of a benign tumor of salivary gland or soft tissue origin. The mass was excised with careful preservation of the facial nerve. The 3.5 cm mass was submitted for histopathological examination. The well-circumscribed, encapsulated mass showed a predominant sheet-like proliferation of Antoni type A-like tissue, Foci of glandular differentiation with duct-like structures were also seen. Cytological atypia

or mitotic activity were not seen. Nuclei of lesional cells diffusely and strongly expressed reactivity to p63. The final diagnosis was a schwannoma-like pleomorphic adenoma. No recurrence has been reported in the 15 months since the removal. Facial nerve function is unimpaired with a House Brackmann facial nerve function score of one. The potential for misdiagnosis in fine needle aspirate and incisional biopsies is real in cases of schwannoma-like pleomorphic adenoma. The diagnostic pitfalls include the schwannoma and leiomyoma. Schwannomas with glandular differentiation have also been reported and therefore a misdiagnosis may potentially occur in excised specimens. Careful application of immunohistochemistry may help in the differentiation of these lesions.

Keywords Pleomorphic adenoma · Schwannoma · Parotid · P63

Introduction

Pleomorphic adenomas (PA) account from 40 to 70% of epithelial tumors of salivary glands. Approximately 80% of PA affect the parotid glands wherein the most common location is the superficial lobe and the tail of the gland [1]. Triantafyllou et al. correlated the histology, function and secretions of normal glands to the altered microstructure in a PA. In a tabulation of histological components of PA, they have alluded to the schwannomatous arrangement of the spindled epithelial cell component [2]. A Pubmed/MEDLINE electronic database search including phrases such as “schwannoma-like pleomorphic adenoma”, “schwannoma-like mixed tumor”, “pleomorphic adenoma palisading” retrieved five papers with a total of seven cases of this rare variant of the PA (Table 1). Intraparotid schwannomas of

✉ Yeshwant B. Rawal
ybrawal@uw.edu

Srinivasa R. Chandra
chandra4@uw.edu

Farah Karim
farahk2@uw.edu

¹ Oral Maxillofacial – Head & Neck Oncologic & Reconstructive Microvascular Surgery, Harborview Medical Center, Seattle, WA, USA

² School of Dentistry, University of Washington, Seattle, WA, USA

³ Department of Oral & Maxillofacial Surgery, School of Dentistry, University of Washington, B-204 Magnuson Health Sciences Center, 1959 NE Pacific Street, Box 357133, Seattle, WA 98195, USA

Table 1 Demographics and clinical features of cases of pleomorphic adenoma with schwannoma-like phenotype

Authors	Age	Gender	Site	Duration	Size	Symptoms
Merino and LiVolsi [4]	74	F	Deep lobe, parotid	5 years	2 cm x 3 cm	Asymptomatic
	39	F	Parotid (lobe NA)	1 year	1.5 cm round	Asymptomatic
Takeda and Shimono [5]	62	M	Parotid (lobe NA)	10 months	NA	Asymptomatic
	48	F	Hard palate	3 months	NA	Asymptomatic
Kajor et al. [6]	75	F	Parotid (lobe NA)	NA	3 cm	NA
Tille et al. [7]	47	F	Deep lobe, parotid with parapharyngeal extension	Symptoms: 2 months	3.2 cm	Pain
Lombardi et al. [8]	44	F	Parotid (lobe NA)	3 months	1.5 cm	NA
Present case	60	M	Superficial lobe, Parotid	12 years	3.5 cm	Asymptomatic

NA information is not available. Age range 39–75 years (mean 56.12 years, median 54 years). M:F ratio 1:3

Fig. 1 A mass overlying the left angle of the mandible

the facial nerve have been frequently reported. A Pubmed/MEDLINE database search using the phrase “intraparotid schwannoma” produced 26 papers in a period from 2010 to 2016, including one case in a horse. To further complicate the diagnostic process, schwannomas with glandular and pseudoglandular features have also been described [3]. We present a well-documented case of a schwannoma-like pleomorphic adenoma of the parotid gland and describe the clinical features, imaging studies, intraoperative findings, histopathology and the immunohistochemical findings. A brief comparison is made with its potential diagnostic pitfall, the intraparotid schwannoma. The role of immunohistochemical markers in their differentiation is also discussed.

Case Report

A 60-year-old male presented with a mass over the left angle of the mandible (Fig. 1). The mass was slow growing and asymptomatic. It had been present for approximately 12 years. The patient was motivated to seek a consult due to a recent increase in size of the mass. The patient was

Fig. 2 CTs (*Left* coronal, *Right* axial) show a heterogenous, hyperdense mass with hypodense foci involving the superficial lobe of the parotid

a nonsmoker and his medical history showed no significant illnesses. The skin over the mass was loose and not attached to the underlying mass. The mass was freely movable in all planes. The mass felt circumscribed and firm to palpation. It was non-tender. Regional lymph nodes were not palpable. Muscles of facial expression were intact. Intraoral examination did not reveal overt mucosal, dental or periodontal disease. A computed tomography scan revealed a predominantly hyper dense soft tissue mass with focal internal hypo densities, involving the superficial lobe of the parotid (Fig. 2). The clinical and radiographic differential diagnosis included benign tumors of salivary gland and soft tissue origin and lymph node pathology of intra parotid nodes origin. The patient elected to have the mass excised.

A superficial parotidectomy was performed. The facial nerve was monitored intraoperatively using a nerve integrity monitoring system. The mass was found limited to the superficial lobe of the parotid gland (Fig. 3). The mass did not appear to be in continuity with the nerve bundles. It was

Fig. 3 The mass arose from the superficial lobe of the parotid gland

Fig. 4 Post-resection view showing intact facial nerve and its branches (arrow)

removed with a cuff of normal parotid tissue. The facial nerve and its branches were intact (Fig. 4). The excised tumor measured 3.5 cm in greatest diameter. The lesion was placed in 10% neutral buffered formalin and submitted for histopathological examination.

Cross sections of the gross specimen showed a circumscribed dense mass with areas of hemorrhage and cystic cavitation (Fig. 5). Hematoxylin and eosin stained sections confirmed a well-circumscribed mass with a collagenous capsule. Areas of intratumoral hemorrhage and cystic cavitation were seen (Fig. 6). The tumor showed a proliferation of sheets of spindle cells with palisaded nuclei and eosinophilic Verocay body-like areas. The overall impression was of Antoni type A tissue as in a schwannoma (Figs. 7, 8, 11). Limited amount of Antoni type B-like tissue mixed with fibrofatty connective tissue was also seen (Fig. 9). Focal areas of the tumor showed glandular differentiation with dilated duct-like structures bound by one to two layers of cuboidal to low columnar cells. The ductal lumen were filled with an amorphous

Fig. 5 Gross specimen sections showing a well-circumscribed dense mass with areas of cystic degeneration and hemorrhage (arrow)

Fig. 6 A well-circumscribed mass bound by a collagenous capsule containing prominent foci of hemorrhage and cystic degeneration. H & E 4X

Fig. 7 Mass showing prominent areas of nuclear palisading reminiscent of Antoni A tissue. H & E 10X

Fig. 8 Areas of the tumor showing Antoni A-like tissue with prominent Verocay body-like and hyaline areas. H & E 10X

Fig. 11 Confluence of Antoni A-like and Antoni B-like areas and glandular differentiation in the tumor. H & E 10X

Fig. 9 The tumor also showed Antoni B-like areas intermixed with fatty tissue. H & E 4X

Fig. 12 The spindle cells showing diffuse, strong nuclear reactivity to p63. 10X

Fig. 10 Areas of the lesion showing hemorrhage, hyaline-like collagen and glandular differentiation. H & E 4X

eosinophilic material and few inflammatory cells (Figs. 10, 11, 13a). Based on the histopathological findings, the differential diagnosis was a schwannoma with glandular differentiation and areas of ancient change and a schwannoma-like pleomorphic adenoma.

An S100 stain was of no differentiating use as S100 stains schwann cells and myoepithelial cells. The nuclei of the spindle cells were diffusely and strongly reactive to p63 (Fig. 12). The nuclei of myoepithelial cells around the ductal and tubular structures also expressed strong p63 reactivity. The ductal cells remained negative (Fig. 13b). Based on the immunohistochemical reactivity pattern, a diagnosis of a schwannoma-like pleomorphic adenoma was given. The circumscribed tumor appeared excised with clear margins (Fig. 6).

Post-operative follow-up was uneventful. Facial nerve function was normal with a House-Brackmann facial nerve function score of one. The most recent follow-up

Fig. 13 **a** Photomicrograph showing duct-like glandular areas within tumor (arrow). H & E 10X, **b** p63 highlights the myoepithelial cell nuclei. The ductal cells remain negative (arrow). 10X

was 15 months post-operatively with no evidence of recurrent disease.

Discussion

Pleomorphic adenomas are recognized for extreme variation in their microscopic architecture to a point that almost no two cases are histopathologically alike. This is due to the myriad variations in the epithelial and mesenchymal-like tissue in these tumors. Efforts to list the various histopathological components and architectural patterns in the PA have been made in the past [9, 10]. It is likely that some of the rare, extreme variations of the PA were misdiagnosed solely on the basis of pattern recognition. Evolution in immunohistochemical techniques has resulted in reclassification of many such tumors. Triantafyllou et al. in 2015 compiled the most comprehensive listing of histopathological components in a PA. In this list, they refer to a spindle cell type of an epithelial component with a schwannomatous arrangement [2]. Only five previous reports accounting for seven cases of a PA with a schwannomatous phenotype

have been described. Table 1 lists the demographic and clinical features of these previously reported cases. Table 1 is inclusive of our case.

PAs with schwannomatous features were diagnosed across an age range from 39 to 75 years with a mean of 56.12 years and a median of 54 years. The male to female ratio was 1:3. Seven out of the eight cases affected the parotid gland and one case affected the hard palate. Two of the seven parotid gland cases involved the deep lobe. Our case involved the superficial lobe. This information was not available in four cases. Tumors ranged in size from 1.5 to 3.5 cm. Tumor size was not available in two cases [5]. Lesional duration ranged from 3 months to 12 years. The patient with the deep lobe tumor with extension into the parapharyngeal space had pain of 2 months duration. It is likely that that this 3.2 cm tumor was present for a significantly longer period of time [7]. Five other cases were asymptomatic. This information was available in two cases [6, 8]. Imaging studies were available in three cases including our case. The tumors were well-defined. The tumor in our case was hyperdense with focal internal fluid-like hypodensities likely representing areas of cystic degeneration (Fig. 2). All the tumors were excised with facial nerve preservation. Specific information on management was limited. The tumor of the deep lobe (case 1) was removed with a subtotal parotidectomy and case 2 was treated with a partial parotidectomy [4]. The tumor of the deep lobe with parapharyngeal extension was treated with a total parotidectomy [7]. The tumor in our case was removed with a superficial parotidectomy.

Histopathologically (Table 2), four of the tumors were encapsulated. This information was not available in four cases. Schwannomatous areas with nuclear palisading were predominant in five cases [4, 7, 8 and present case]. The tumor in our case also showed cystic degeneration and hemorrhage; findings that potentially may be interpreted as characterizing “ancient” change in a schwannoma. The ductal and tubular areas in our case were focal and were also seen at the periphery of the tumor as in the case reported by Tille et al. [7]. In one case, ductal areas were found following a “prolonged search” [4, case 2]. Two cases showed predominant conventional PA features including tubules, fibromyxoid and chondromyxoid areas. Schwannomatous areas were focal [5]. Immunohistochemistry information (Table 2) was available only in three cases [7, 8 and present case]. p63 was consistent in differentiating the PA from a schwannoma in these cases. The nuclei of the fusiform and spindle cells in the schwannoma-like areas were consistently and strongly positive to p63 in our case (Fig. 12) and p63 highlighted only the myoepithelial cells surrounding the ductal/tubular structures (Fig. 13b). While myoepithelial cells stain with p63 [11, 12], p63 is negative in schwannomas [13]. S100, a marker that is most useful in

Table 2 Histopathological and Immunohistochemical features of cases of pleomorphic adenoma with schwannoma-like features

Authors	Age	Gender	Capsule	Schwannoma-like areas	Conventional PA (non-schwannoma) like areas	Immunohistochemistry
Merino and LiVolsi [4]	74	F	Encapsulated	Sheets of spindle cells. Some areas of palisading	Small areas of myxoid tissue with tubuloinciner structures and islands of epithelium. E.M: Myoepithelial cells. Ductal cells with luminal microvilli	NA
	39	F	(NA)	Fusiform spindle cells arranged parallel	Ductal areas found only after prolonged search	NA
Takeda and Shimono [5]	62	M	(NA)	Foci of palisading	Tubules, myxoid and “fibrous” tissue predominate. Chondromyxoid areas present	NA
	48	F	(NA)	Foci of palisading	Myxoid areas predominate	NA
Kajor et al. [6]	75	F	FNA cytology	NA	NA	NA
Tille et al. [7]	47	F	Encapsulated	Predominant areas of spindle cells with nuclear palisading and verocay-like bodies	Myxoid areas and tubular structures only at the periphery	p63, CD10 and cytokeratin positive in both components
Lombardi et al. [8]	44	F	Encapsulated	Predominant (~95%) spindle cells with Antoni type A areas	Foci (~5%) of tubular areas	Pankeratin and S100 strong diffuse positivity. p63, CD10 and SMA focal positivity
Present case	60	M	Encapsulated	Predominant Antoni type A areas. Many Antoni type B-like areas, cystic degeneration and hemorrhage (Ancient schwannoma-like changes)	Focal ductal and tubular structures	Strong, diffuse p63 positivity and focal CD10 positivity. P63 was positive in the spindle shaped myoepithelial cells and myoepithelial cells around ductal / tubular structures. Ductal cells were negative

the diagnosis of a schwannoma finds no application in its differentiation from a schwannoma-like PA because S100 also stains myoepithelial cells [11, 14]. Unlike previous two studies [7, 8], AE1/AE3 pankeratin was not used in this case. A study by Fanburg-Smith et al. showed that although 22 peripheral schwannomas examined were negative for AE1/AE3 pankeratin, 72/104 (69%) cases of retroperitoneal schwannomas were positive for AE1/AE3 [15]. CD10 reactivity is focal in a PA with schwannoma-like features and lends no useful information in its differential diagnosis. 5 of 11 cases (45%) of schwannoma were found to express CD10 [16] and therefore the use of CD10 in differentiating a PA with schwannoma-like features from a schwannoma is of little practical use. Similarly, SOX10 (Transcription factor SRY-related HMG-box) that has found application in salivary gland tumor diagnosis including the PA, is also expressed by schwann cells [17]. Pleomorphic adenoma gene 1 (PLAG1) nuclear expression is observed in PAs, recurrent PAs and carcinoma-ex-pleomorphic adenoma [18, 19]. PLAG1 is also expressed in a subset of lipoblastomas, gastrointestinal stromal tumors, leiomyomas, angiofibrosarcomas, synovial sarcomas and myxofibrosarcomas. However, all neural tumors including six schwannomas tested negative [20]; potentially creating a role for PLAG1 in addition to p63, in differentiating a PA with schwannoma-like features from a schwannoma.

Schwannomas of the facial nerve are more common in the intratemporal location but may also arise in the parotid gland [21–27]. While intratemporal and internal auditory canal facial nerve schwannomas may present with neurosensory hearing loss, tinnitus, progressive facial weakness or paralysis, the intraparotid facial nerve schwannoma may be entirely asymptomatic with no facial nerve dysfunction. Also, there are no imaging study findings unique to a intraparotid facial nerve schwannoma. In these ways, a proportion of intraparotid facial nerve schwannomas are impossible to distinguish from the PA that is a more common lesion at this location [21–23, 27].

Fine needle aspiration (FNA) biopsies reportedly represent the initial diagnostic modality in a parotid mass [1]. However, several reports have indicated that FNA has been either inconclusive or have resulted in a misdiagnosis of a PA in cases of intraparotid facial nerve schwannomas [27–30]. This ambiguity understandably presents intraoperative and post-operative challenges such as inability to locate and separate the facial nerve with resulting facial paralysis [27].

Further, this ambiguity is extended histopathologically when PAs show a divergent schwannoma-like phenotype as demonstrated in our case and previous reports [4–8]. Examples of epithelioid schwannomas of the parotid gland diagnosed as PAs have also been reported [31]. Schwannomas with glandular/pseudoglandular differentiation are

well recognized and pose an additional challenge to the histopathologist [32–35]. Myxoid change, cystic areas and intratumoral hemorrhage are not selective and may be variably encountered in many benign tumors. In the face of such complexity, it is necessary to rely on immunohistochemical markers for an accurate diagnosis.

Immunohistochemical markers S100, SOX10 and CD10 are unable to differentiate between a PA with divergent schwannoma-like histology and a schwannoma. p63 appears to consistently differentiate myoepithelial cells in a PA from a schwannoma. Negative staining of schwannomas with PLAG1 was studied in only six cases [20]. PLAG1 may potentially find a role in this application similar to p63.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest associated with this report.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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