ORIGINAL PAPER

Sclerosing Polycystic "Adenosis" of Salivary Glands: A Neoplasm Characterized by PI3K Pathway Alterations More Correctly Named Sclerosing Polycystic Adenoma

Justin A. Bishop[1] · Jeffrey Gagan[1] · Daniel Baumhoer[2] · Anne L. McLean-Holden[1] · Bahram R. Oliai[3] · Marta Couce[4] · Lester D. R. Thompson[5]

Abstract

Sclerosing polycystic adenosis (SPA) is a rare benign salivary gland lesion that usually arises from the parotid gland. SPA was originally interpreted to be a non-neoplastic alteration analogous to fibrocystic changes of the breast, but now there is uncertainty about whether it may represent a neoplasm. SPA often contains intraductal proliferations with an appearance similar to ductal neoplasia of the breast, and one study reported X-chromosome inactivation using polymorphisms of the human androgen receptor (Skalova et al., in AJSP 30:939–944, 2006). We investigated the genetics of SPA through targeted next generation sequencing (NGS). Four cases of SPA were retrieved from the authors' consultation files. A custom, targeted NGS panel including 1425 cancer-related genes was performed on all cases, followed by immunohistochemistry for PTEN. All four cases developed in females, ranging from 40 to 69 years (mean 52.5 years), affecting the parotid (n = 3) and submandibular glands (n = 1). All cases exhibited characteristic histologic features of SPA: well-circumscribed lesions with fibrosis and an admixture of ducts, myoepithelial cells and acinar cells, the latter containing brightly eosinophilic intracytoplasmic granules. Two cases had intraductal apocrine epithelial proliferations. By targeted NGS, loss-of-function mutations in *PTEN* were revealed in all 4 cases. In addition, 2 of 4 cases harbored *PIK3CA* mutations and 2 of 4 possessed *PIK3R1* alterations; one case lacked both *PIK3CA* and *PIK3R1* mutations. PTEN expression by immunohistochemistry was lost in the ductal and acinar elements but not the myoepithelial cells in all cases. SPA is characterized by genetic alterations in the PI3K pathway, with *PTEN* mutations seen most frequently. This molecular profile is similar to salivary duct carcinoma and the apocrine variant of intraductal carcinoma (i.e., salivary duct carcinoma-in situ). PI3K pathway alterations were found in cases both with and without intraductal apocrine proliferations, and PTEN immunohistochemistry suggested that the ductal and acinar cells, but not myoepithelial cells, were affected. Taken together, these findings strongly support that SPA is a neoplasm, more correctly named "sclerosing polycystic adenoma." The salivary duct carcinoma-like genetic alterations, coupled with the fact that the surrounding myoepithelial cells appear to be non-neoplastic, suggest a close relationship between SPA and apocrine intraductal carcinoma.

Keywords Sclerosing polycystic adenosis · Sclerosing polycystic adenoma · Salivary gland neoplasms · Intraductal carcinoma · Parotid gland · Phosphatidylinositol 3-Kinases (PI3K) · PTEN · Oncogenes · Salivary ducts

Introduction

Sclerosing polycystic adenosis (SPA) is a rare salivary gland disorder that was first described in 1996 [1, 2]. It usually affects the parotid gland (around 70% of cases), with occasional examples in the submandibular glands and oral cavity [1–8]. SPA occurs over a wide age range (7 to 84 years), with a mean presentation in the 5th decade and a female predominance [1–10]. SPA is benign, with a small subset (about 10%) recurring locally and a single case reportedly transforming into invasive carcinoma following multiple recurrences over decades [10].

In their initial description of SPA, Smith, et al. theorized, based on overlapping histologic features, that SPA represented a non-neoplastic, reactive lesion analogous to

✉ Justin A. Bishop
  justin.bishop@utsouthwestern.edu

Extended author information available on the last page of the article

fibrocystic changes of the breast [1]. Over time, however, it has been increasingly suspected that SPA may actually be a neoplasm. Most cases of SPA harbor foci of apocrine intraductal proliferation that closely resemble ductal neoplasia (i.e., atypical ductal hyperplasia or ductal carcinoma in situ) of the breast. Further, a single study utilizing polymorphisms of the human androgen receptor (HUMARA) on 6 cases of SPA reported X-chromosome inactivation in all cases, a result that suggested SPA is a clonal, neoplastic process [3]. It was unclear from that study, however, whether the underlying SPA or the apocrine ductal proliferations, or both, were assessed by the HUMARA assay, and there have been no additional genetic studies dealing with SPA. We sought to further understand the genetic underpinnings of SPA by performing next generation sequencing on a series of cases.

Methods

Case Selection

Cases of SPA were selected from the authors' consultation files. Recent cases were given preference as they more likely to have well-preserved genetic material required for sequencing. All cases were reviewed by two or more of the study authors and were confirmed to meet diagnostic criteria for SPA as detailed in the 2017 World Health Organization Classification of Head and Neck Tumours [2].

Next-Generation Sequencing

DNA and RNA are isolated from formalin-fixed, paraffin-embedded tissues blocks using Qiagen Allprep kits. Sequencing libraries are generated using Kapa Biosystems and Illumina chemistry. A custom panel of DNA probes is used to produce an enriched library containing all exons from over 1425 cancer-related genes, which are sequenced on Illumina NextSeq 550 instrument. DNA and RNA sequence analyses are done using custom germline, somatic and mRNA bioinformatics pipelines run on the UTSW Bio-High Performance Computer cluster and optimized for detection of single nucleotide variants, indels and known gene fusions. Median target exon coverage for the assay is 900X with 94% of exons at $> \times 100$. The minor allele

frequency limit of detection is 5% for single nucleotide variants and 10% for indels and known gene fusions. Variants are not reported in exons covered $< \times 100$.

Somatic variants were identified on the basis of their variant allele frequencies (VAF), as well as their presence in databases of germline variants including dbSNP and gnomAD. All variants were reviewed in the Integrated Genomics Viewer (IGV) software prior to reporting.

Immunohistochemistry

Based on the targeted NGS results (see "Results" section), immunohistochemistry for PTEN was performed on each case. Briefly, formalin-fixed paraffin-embedded tissues were sectioned at 4 μm and mounted on adhesive slides, along with multi-tumor control tissues. The slides were deparaffinized in xylene and rehydrated in graded alcohols to tap water. Endogenous peroxidase activity was quenched for 10 min at room temperature, using 0.3% H_2O_2 with 0.1% Sodium Azide.

Epitope retrieval for the PTEN stain was achieved by placing the slide in 1 mM EDTA, pH 8.5 for 48 min. After rinsing the slides in phosphate buffered saline (PBS) buffer, primary antibody incubation (Rabbit monoclonal anti-PTEN, clone D4.3, diluted 1:200, Cell Signaling, Danvers, MA) was performed for 50 min at room temperature, using gentle orbital rotation at 40 rpm.

Incubation with anti-rabbit horseradish peroxidase-conjugated polymer (PowerVision Poly-HRP anti- Rabbit IgG, Leica-Buffalo Grove, IL) was performed for 45 min at 25 °C. The slides were then immersed in 25 °C diaminobenzidine (Invitrogen, Carlsbad, CA) to develop brown staining. The slides were placed in 0.5% copper sulfate for 1 min at RT. Finally, the slides were rinsed in water, counterstained in Thiazin (Wescor, Logan, UT) followed by Hematoxylin (Leica), dehydrated in graded alcohols and xylene, and coverslipped.

Results

Four cases of SPA were retrieved, and they are summarized in Table 1. They occurred in four women ranging from 40 to 69 years (mean 52.5 years). Three lesions developed in the parotid gland and 1 case in the submandibular gland.

Table 1 Clinical characteristics of the sclerosing polycystic adenosis cases

Case	Age	Sex	Location	Size	Presentation	Follow-up (months)
1	44	F	Parotid gland	2.2	Slowly-growing mass	NED [6]
2	57	F	Parotid gland	3	Slowly-growing mass	NED [5]
3	69	F	Submandibular gland	2.4	Unknown	None
4	40	F	Parotid gland	1.9	Slowly-growing mass	NED [13]

The tumors ranged from 1.9 to 3 cm in greatest dimension (mean 2.4 cm). Clinical information was limited in these consult cases. Clinical presentation of a slowly-growing, painless mass was reported in 3 patients. Available follow-up for 3 patients documented no recurrences. No patients had Cowden syndrome.

Histologically, all cases demonstrated the classic diagnostic findings of SPA. The lesions were well-circumscribed, lobular proliferations of haphazardly arranged ducts, myoepithelial cells, and acini separated by frequent bands of hyalinized fibrosis (Fig. 1a). The ducts ranged from small ductules to cystically dilated spaces which frequently contained secretory material or foamy macrophages (Fig. 1b). All cases demonstrated variable numbers of serous acinar cells with altered zymogen granules in the form of brightly hyper-eosinophilic intracytoplasmic granules (Fig. 1c). Two cases harbored apocrine metaplasia with intraluminal proliferations resembling atypical ductal hyperplasia of the breast (Fig. 1d); the remaining two cases lacked any apocrine features.

Targeted NGS results are summarized in Table 2. All 4 cases harbored loss-of-function mutations in *PTEN*. In 3 of 4 cases, there were two *PTEN* mutations, suggesting biallelic loss of protein function. In addition, 2 of 4 cases harbored well-described activating mutations of *PIK3CA* and 2 of 4 cases had *PIK3R1* alterations (one single nucleotide variant and one in-frame deletion), with one of these cases showing *PTEN*, *PIK3CA* and *PIK3R1* alterations. one case lacked both *PIK3CA* and *PIK3R1* mutations. One case harbored a mutation in *CDK2A* which is involved in cell cycle regulation, while another single case had a *MYB* mutation. There were additional mutations and copy number changes of unknown significance, listed in Table 2. Fusions were not found by RNA sequencing in any of the 3 cases for which RNA was successfully isolated. Copy number analysis was done as part of the targeted NGS and did not give any indication of *ERBB2* amplification. To summarize, all 4 cases of SPA had sequencing results consistent with a neoplastic process, and most affected genes (*PTEN*, *PIK3CA*, *PIK3R1*) were part of the PI3K pathway involved in regulating the cell cycle.
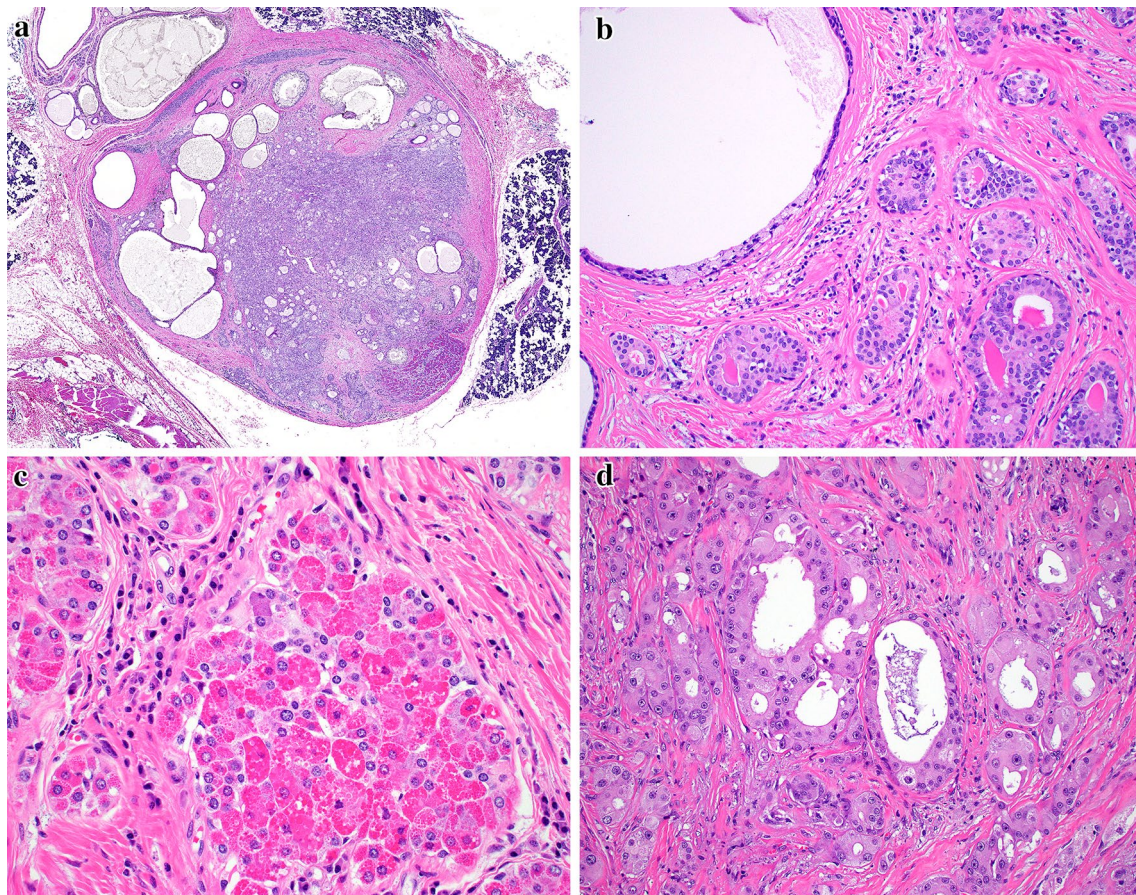

Fig. 1 The sclerosing polycystic adenosis cases were very well-circumscribed lesions (**a**). The tumors were made up of variably cystic ducts, surrounded by myoepithelial cells (**b**) and serous acini, many of which contained enlarged, eosinophilic granules (**c**). Two cases demonstrated foci of proliferative, atypical apocrine changes in the ducts (**d**)

Table 2 Next-generation sequencing results for the sclerosing polycystic adenosis cases

Case #	PTEN (variant allele frequency)	PIK3CA (variant allele frequency)	PIK3R1 (variant allele frequency)	Other
1	c.1003C > T (p.Arg335Ter); 57.4%		c.1138_1140delTTA (p.Leu380del); 27.4%	
2	• c.697C > T (p.Arg233Ter); 25.2% • c.445C > T (p.Gln149Ter); 21.2%			Copy number changes of undetermined significance: 14q, 16p, 1p
3	• c.170_172delTGG (p.Leu57_Asp58delinsTyr); 20.5% • c.141delG (p.Asn48 fs); 29.1%	c.1633G > A (p.Glu545Lys); 25.3%		MYB p.Ser356Cys (33.1%) Copy number changes of undetermined significance: 1p, 5q
4	• c.497_498insC (p.Thr167 fs); 19.3% • c.892C > T (p.Gln298Ter); 23.5%	c.3140A > G (p.His1047Arg); 38.2%	c.1694G > T (p.Ser565lle); 5.1%	CHEK2 p.Lys373Glu (12.5%) CDKN2A p.Arg128 (5.4%) POLD1 p.Phe1099Leu (30.7%) MYH11 p.Arg1011 (5.9%) RNF43 p.Lys189Arg (46.6%)

As a result of all cases having *PTEN* mutations, PTEN protein expression was analyzed. Nuclear expression of PTEN was lost in all of the ductal and acinar cell components of SPA, but expression in the myoepithelial cells surrounding the ducts was retained (Fig. 2) in all cases.
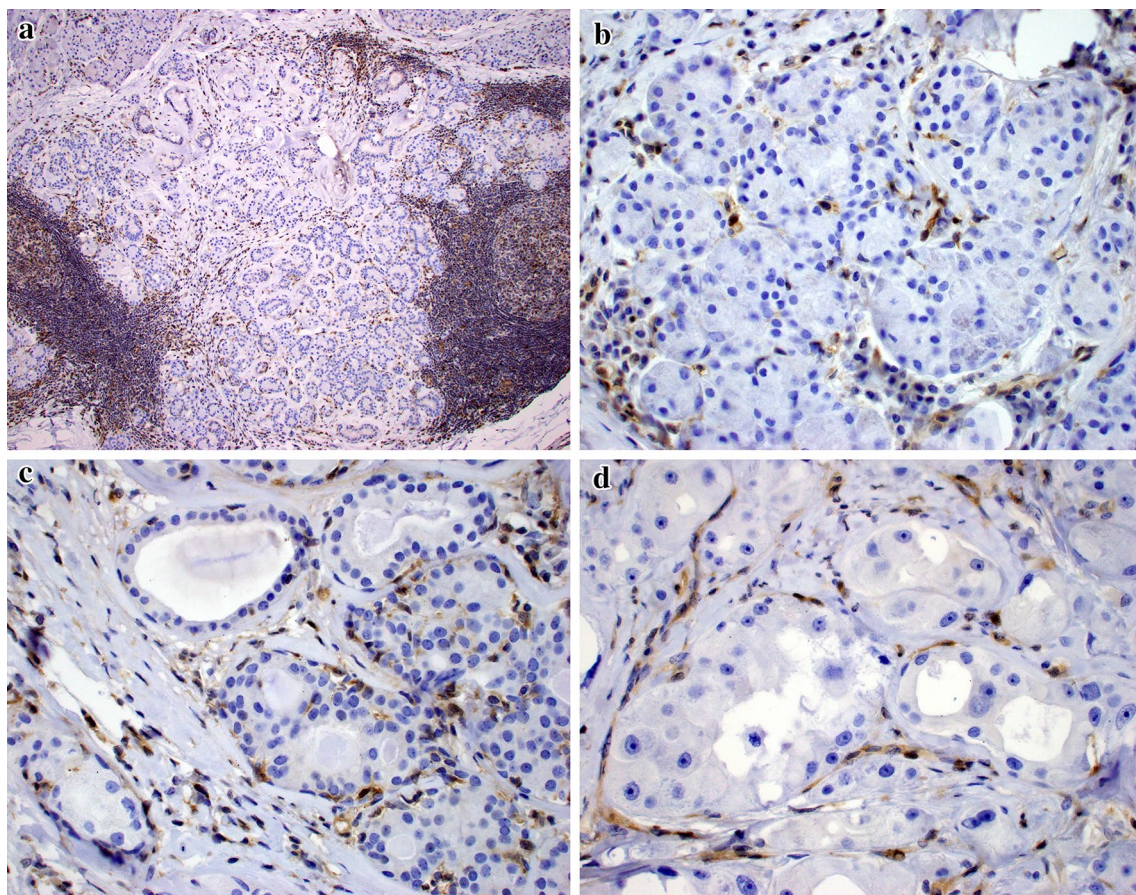

Fig. 2 PTEN immunostaining demonstrated loss of expression in the sclerosing polycystic adenosis cases, with retention in the inflammatory and stromal cells (**a**). PTEN loss was seen in the acinar (**b**), ductal (**c**), and atypical apocrine (**d**) epithelial elements, but throughout the lesion, the surrounding myoepithelial cells exhibited retained nuclear expression

Discussion

Salivary gland tumor classification is one of the most challenging areas in head and neck pathology. Over the past decade, however, numerous molecular findings have shed light on the nature of these tumors and refined their classification significantly. Many salivary gland neoplasms are now known to be characterized by specific fusions (e.g., *EWSR1* in clear cell carcinoma, *MAML2* in mucoepidermoid carcinoma, and *ETV6* in secretory carcinoma) [11–14] or mutations (e.g., *HRAS* in epithelial-myoepithelial carcinoma and *CTNNB1* in basal cell adenoma) [15–17]. Despite the established usefulness of genetic analysis in refining salivary gland tumor classification, there are still many rare salivary gland lesions that have not been well studied at the molecular level.

SPA has been an enigmatic entity since its initial description [1]. Although it does bear some resemblance to fibrocystic changes of the breast, its bizarre admixture of ducts, myoepithelial cells, and acini (including those with altered zymogen granules) is truly unlike any other well-described lesion, salivary gland or otherwise. The combination of unusual features in SPA results in an extensive differential diagnosis that includes non-neoplastic lesions (e.g., obstructive sialadenitis), benign neoplasms (e.g., pleomorphic adenoma), and malignancies of various grades (e.g., acinic cell carcinoma and salivary duct carcinoma). Due to its superficial resemblance to fibrocystic changes and an appearance dissimilar to any known neoplasm, SPA was originally believed to be a reactive, non-neoplastic process [1]. In fact, it was still classified as such in the 2017 World Health Organization Classification of Head and Neck Tumours [2]. Nevertheless, SPA has many characteristics that suggest that it is a neoplasm. First, it is well-circumscribed and often encapsulated, while reported to have a low but significant risk of local recurrence (around 10%). Further, most cases contain a proliferation of apocrine ductal cells with a rigid cribriform appearance and nuclear atypia that resembles apocrine intraductal neoplasia of the breast. Finally, a study in 2006 by Skalova et al. utilizing HUMARA found that 6 of 6 cases were clonal [3]. However, no additional molecular studies of SPA had been published, and its genetic underpinnings have remained unclear.

Utilizing targeted NGS, we found that 4 of 4 SPAs tested harbored mutations in genes that are well established to be drivers in human neoplasms. These mutations were in genes that included *PTEN* (4 of 4), *PIKCA* (2 of 4) and *PIK3R1* (2 of 2), all of which are members of the PI3K pathway of cell cycle regulation. The PI3K pathway is recurrently mutated in a variety of tumor types, and its inhibition is the subject of many ongoing clinical trials [18]. *PIK3CA* encodes a catalytic subunit of the PI3K pathway that converts PIP_2 (phosphatidylinositol-4,5-bisphosphate) to PIP_3 (phosphatidylinositol-3,4,5-bisphosphate). All of the observed variants are well-studied gain-of-function variants [19]. *PTEN* encodes a phosphatase that converts PIP_3 back into PIP_2. Therefore, all loss-of-function mutations are expected to be oncogenic, and increase cellular PIP_3. All but one of our observed mutations were nonsense or frameshift. *PIK3R1* encodes a regulatory subunit of PI3K that stabilizes and inhibits that catalytic subunit. The p.L380del seen in case 1 has not been fully biochemically characterized, but is has been demonstrated to promote cell line proliferation in growth-factor depleted culture in vitro [20]. The p.Ser565lle variant seen in case 4 occurs in a region of *PI3KR1* where oncogenic variants cluster [21], but has not itself been functionally characterized.

It might be reasonably questioned if the NGS assay was merely detecting mutations confined to the apocrine ductal proliferations that resemble ductal breast neoplasia. Indeed, in the Skalova et al. HUMARA paper, it is mentioned that all 6 cases exhibited "apocrine atypia" [3]. However, 2 of the 4 SPA cases in this study had no areas of ductal hyperplasia or apocrine changes at all. Moreover, PTEN immunostaining demonstrated loss of protein expression throughout the SPA, not restricted to only the cases with apocrine changes. Taken together, these findings support the notion that SPA itself is indeed a neoplasm, and should be more correctly named "sclerosing polycystic adenoma."

PI3K pathway mutations are not novel in salivary gland neoplasia; they are commonly seen in salivary duct carcinoma [22–24]. Salivary duct carcinoma is a high-grade ductal malignancy that almost always demonstrates apocrine differentiation and is associated with a poor prognosis. Similar to our cases of SPA, salivary duct carcinoma also often harbors multiple, seemingly redundant, alterations in the PI3K pathway [22–24]. While they are genetically similar and the apocrine elements of SPA do bear resemblance to salivary duct carcinoma, the almost uniformly benign behavior of SPA is markedly dissimilar.

Interestingly, similar PI3K pathway alterations have also been described in the apocrine variant of intraductal carcinoma. Intraductal carcinoma is a non-invasive salivary gland tumor felt to be analogous to ductal carcinoma in situ of the breast [25, 26]. Emerging data has shown that intraductal carcinoma is actually comprised of at least two variants: (1) the intercalated duct-like type which is S100 protein-positive, negative for androgen receptor and usually harbors *RET* rearrangements, and (2) the apocrine type which is androgen receptor positive, S100 protein-negative, and has salivary duct carcinoma-like genetic changes [25, 27, 28]. The apocrine subtype was previously referred to as "salivary duct carcinoma in situ" because while its cells

are indistinguishable from salivary duct carcinoma, they are entirely surrounded by an intact, benign myoepithelial cell layer. Regardless of subtype, intraductal carcinoma of the salivary glands behaves in a very indolent manner when not associated with an invasive component. The histologic and genetic similarities, coupled with the finding that the myoepithelial cells in SPA retain PTEN expression and thus appear to be non-neoplastic, raise the possibility that SPA and apocrine intraductal carcinoma are closely related entities.

As mentioned above, the differential diagnosis of SPA is very broad, and the consistent finding of PTEN loss by immunohistochemistry suggests potential diagnostic utility in diagnosing SPA. *PTEN* mutations have not been reported in most of the entities in the differential diagnosis (e.g., pleomorphic adenoma, acinic cell carcinoma, mucoepidermoid carcinoma, obstructive sialadenitis), and so it would be anticipated that these lesions would not demonstrate PTEN protein loss, although further confirmation is required. On the other hand, as noted above, *PTEN* mutations are also common in salivary duct carcinoma, so PTEN immunohistochemistry has no role in separating SPA from that entity. In practical terms, the constellation of findings seen in SPA is so unique, especially its brightly hypereosinophilic cytoplasmic granules, that once familiar with the entity, it is a diagnosis rendered on routine histology alone.

Compliance with Ethical Standards

Conflict of interest All authors declare that he/she has no conflict of interest as it relates to this research project.

Ethical Approval All procedures performed in this retrospective data analysis involving human participants were in accordance with the ethical standards of the institutional review board (IRB #5968), which did not require informed consent.

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Affiliations

Justin A. Bishop[1] · Jeffrey Gagan[1] · Daniel Baumhoer[2] · Anne L. McLean-Holden[1] · Bahram R. Oliai[3] · Marta Couce[4] · Lester D. R. Thompson[5]

[1] Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX, USA

[2] Bone Tumor Reference Center at the Institute of Pathology, University Hospital Basel and University of Basel, Basel, Switzerland

[3] ProPath, Dallas, TX, USA

[4] Department of Pathology, University Hospital Cleveland Medical Center, Cleveland, OH, USA

[5] Southern California Permanente Medical Group, Woodland Hills Medical Center, Woodland Hills, CA, USA