Sclerosing Polycystic Adenoma

Justin A. Bishop, MD[a,*], Lester D.R. Thompson, MD[b]

KEYWORDS

• Sclerosing polycystic adenoma • Sclerosing polycystic adenosis • Salivary glands • Parotid gland • PI3 kinase

Key points

- Sclerosing polycystic adenoma (SPA), formerly sclerosing polycystic adenosis, was originally believed to be analogous to breast fibrocystic changes.
- SPA is characterized by varying degrees of sclerosis, cystic changes, and proliferations of various salivary gland epithelial elements.
- SPA frequently exhibits apocrine intraductal proliferations resembling breast ductal carcinoma in situ.
- SPA is a neoplastic process harboring genetic alterations in the PI3 kinase pathway, similar to salivary duct carcinoma.
- SPA is benign, occasionally recurring locally. Cases of carcinoma arising in SPA are rare.

ABSTRACT

Sclerosing polycystic adenoma (SPA) is the more appropriate name for sclerosing polycystic adenosis. SPA is an uncommon salivary gland lesion with a constellation of unusual histologic findings that were originally interpreted as analogous to breast fibrocystic changes. The histologic findings in SPA include fibrosis, cystic alterations, apocrine metaplasia, and proliferations of ducts, acini, and myoepithelial cells in variable proportions. Because of its unusual mixed histology, SPA may be confused with a variety of lesions, ranging from reactive conditions to benign or even malignant neoplasms. The features of SPA are reviewed, with an emphasis on resolving its differential diagnosis.

INTRODUCTION

Sclerosing polycystic adenoma (SPA) is a salivary gland neoplasm first described as a distinct entity in 1996 as sclerosing polycystic adenosis, originally thought to be analogous to breast fibrocystic changes.[1,2] The concept of SPA being a nonneoplastic lesion persisted along with the adenosis terminology for more than 2 decades, and was included in the most recent World Health Organization (WHO) classification of salivary gland tumors.[2] However, there is now considerable evidence to suggest that SPA is a neoplasm, and is best regarded as an adenoma.[3,4]

SPA is rare, with fewer than 100 reported cases in the literature.[1,2,4–11] Most SPAs (around 70%) arise in the parotid gland, with occasional cases seen in the submandibular glands or oral cavity.[1,2,5–8,11,12] Rare SPAs have been reported to arise in the sinonasal tract or lacrimal glands.[9,13,14] SPA typically presents in patients as a painless, slow-growing mass. It develops over a wide age range (7–84 years), with a mean age of approximately 40 years at initial presentation.[1,2,5–12] SPA arises slightly more frequently in women than in men (1.3:1).[1,2,5–11]

[a] Department of Pathology, UT Southwestern Medical Center, 6201 Harry Hines Boulevard, Dallas, TX 75390, USA; [b] Department of Pathology, Kaiser Permanente, 5601 De Soto Avenue, Woodland Hills, CA 91365, USA
* Corresponding author.
E-mail address: justin.bishop@utsouthwestern.edu

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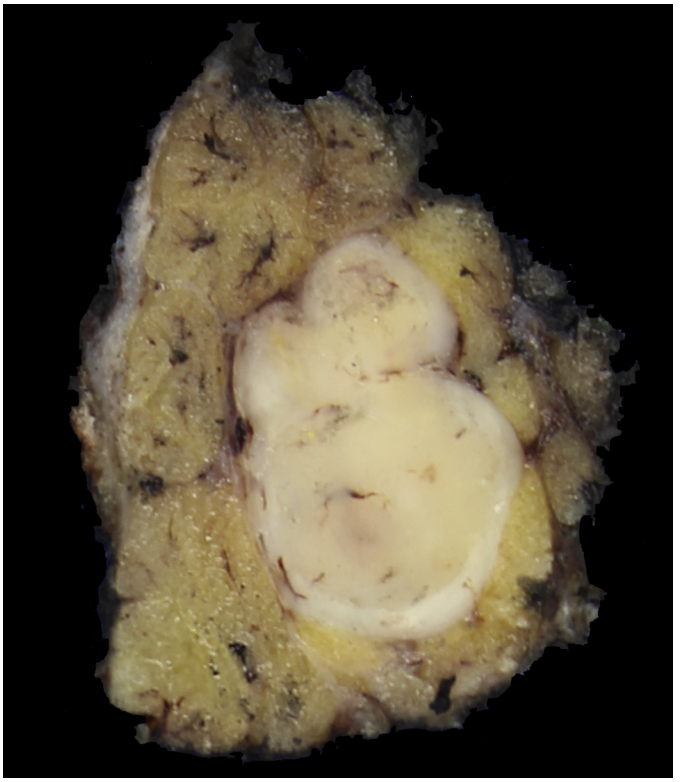

Fig. 1. The macroscopic appearance of SPA is nonspecific, usually consisting of a well-circumscribed tan-white nodule within the otherwise unremarkable parotid parenchyma.

GROSS FEATURES

Grossly, SPA is nonspecific. It consists of a well-circumscribed, firm, tan-white nodule ranging from 1 to 12 cm (**Fig. 1**). Lesions often have a multicystic gross cut surface.

MICROSCOPIC FEATURES

At low power, SPA usually appears well circumscribed and is often encapsulated (**Fig. 2**), frequently containing cystically dilated ducts (see **Fig. 2**A). Some cases have prominent fatty stromal metaplasia; when this feature is present, it may falsely give the impression of an infiltrative process (**Fig. 3**A). Most SPAs have bands of hyalinized fibrosis compartmentalizing the tumor into vague lobules (see **Fig. 2**B).

At medium and high power, SPA is characterized by its mixture of cell types. SPA contains various proliferations of ducts, myoepithelial cells, and acini. The ducts range from small ductules to large cystic spaces. The ductal cells often show apocrine or xanthomatous cytoplasmic alterations (**Fig. 4**). The tumor cysts frequently contain luminal secretions and/or foamy macrophages. The lesional myoepithelial cells are usually subtle, found surrounding the ductal spaces (**Fig. 5**A), but are occasionally more prominent (**Fig. 5**B). The lesional acini may appear normal, but are often filled with large, hypereosinophilic granules or hyaline globules (**Fig. 6**). These globules may represent altered zymogen granules. The acini of SPA often blend with small ductules (see **Fig. 5**A).

Most SPAs show intraductal neoplasia that is usually apocrine and, by itself, indistinguishable from apocrine forms of intraductal carcinoma. Usually the apocrine neoplasia is low grade, resembling breast atypical ductal hyperplasia or low-grade ductal carcinoma in situ with monotonous cells arranged in rigid bridges (**Fig. 7**A). However, the intraductal tumor is occasionally high grade with increased mitoses and comedo-type necrosis, resembling salivary duct carcinoma (**Fig. 7**B). Although they can be atypical or even frankly malignant, these ductal proliferations are almost always completely confined to the ductal system. Only 1 case of invasive carcinoma has been reported to have arisen from SPA.[10] Areas of intralesional sclerosis are common, and should not be misinterpreted as invasive carcinoma (**Fig. 8**).[15]

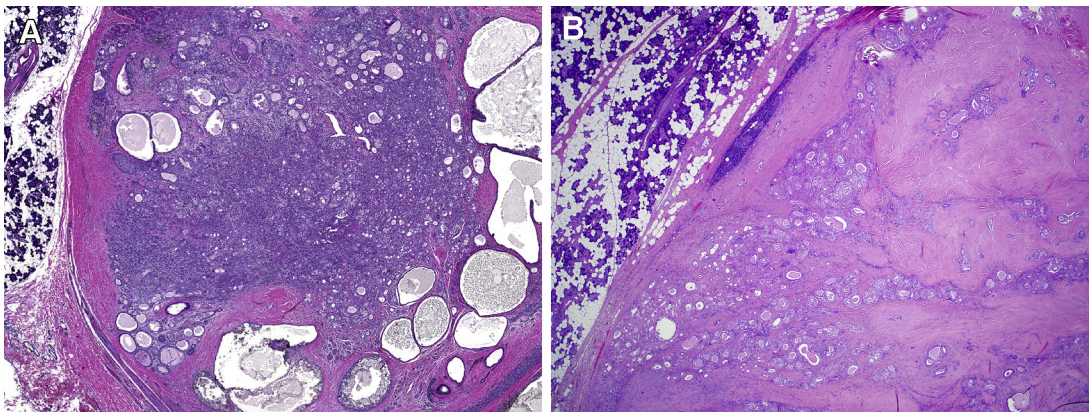

Fig. 2. (*A, B*) The typical low-power appearance of SPA is that of an encapsulated, well-circumscribed tumor with varying degrees of hyalinizing fibrosis and cystic spaces.

It must be emphasized that the histologic appearance of SPA is variable. There are cases that lack 1 or more of the classic features (eg, paucicystic SPA [see **Fig. 3**B], or SPA lacking fibrosis or apocrine changes).[15] The most helpful histologic features are the hypereosinophilic granules and the mixture of different cell types.

PATHOLOGIC KEY FEATURES

The key pathologic features are listed in **Box 1**.

ANCILLARY STUDIES

IMMUNOHISTOCHEMISTRY

Each cellular component (ductal cells, acinar cells, myoepithelial cells) of SPA generally shows its expected immunophenotype (**Fig. 9**). SOX10 highlights small ductules, myoepithelial cells, and acini. Interestingly, the acinar cell marker DOG1 is often weak and focal in the altered acini of SPA. Myoepithelial cell markers such as SMA, p40, calponin, and S100 protein are helpful to highlight the intact myoepithelial cell layer surrounding each duct and the apocrine ductal proliferations. As expected, the apocrine ductal tumor cells are positive for androgen receptor and GCDFP-15.

MOLECULAR TESTING

One study, by Skalova and colleagues,[6] reported X-chromosome inactivation in all tested cases using polymorphism of the human androgen receptor, suggesting that SPA is a neoplastic process. Because intraductal lesions are so common in SPA, this study left it unresolved as to whether the entire lesion was neoplastic or just the ductal proliferations.

More recently, Bishop and colleagues analyzed SPAs with next-generation sequencing and found that all, even those that lacked any intraductal

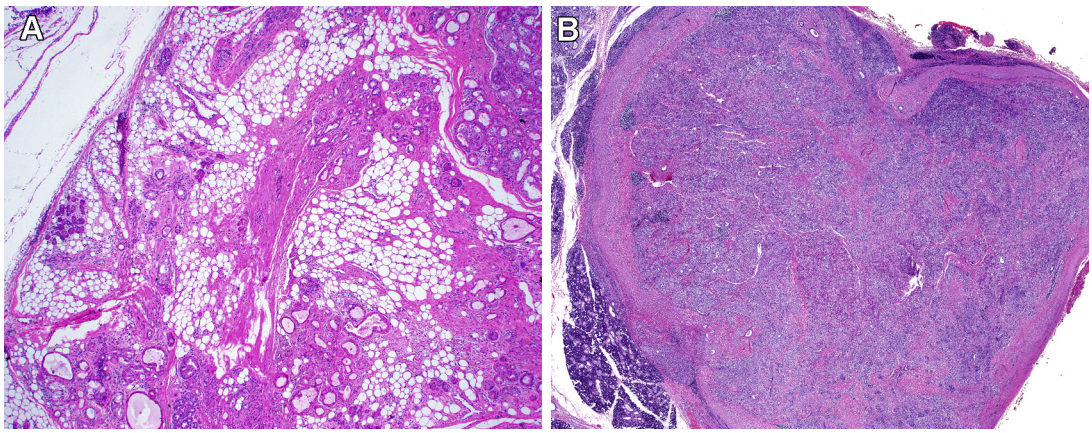

Fig. 3. Unusual cases of SPA may show prominent fatty stromal metaplasia (*A*) or may lack fibrosis or cystic changes (*B*).

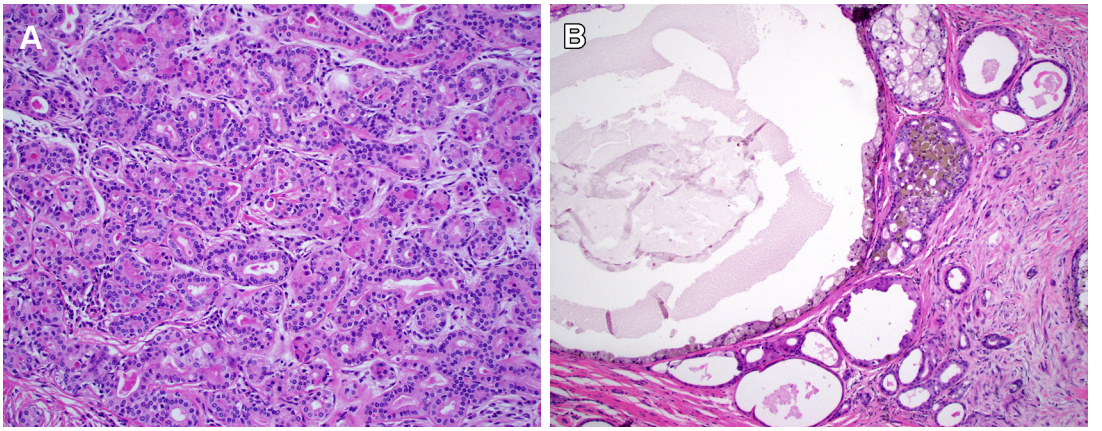

Fig. 4. The ducts of SPA range from small tubules resembling intercalated ducts (*A*) to variably sized cysts often lined by apocrine or xanthomatous cells (*B*).

proliferations, harbored mutations in the phosphatidylinositol 3 (PI3) kinase pathway, most frequently *PTEN*.[4] This finding is strong evidence that SPA is a neoplasm with genetics similar to apocrine intraductal carcinoma or salivary duct carcinoma. Interestingly, PTEN immunohistochemistry showed loss of expression in all ductal and acinar cell types, but expression was retained in the lesional myoepithelial cells. This finding suggests that the myoepithelial cells of SPA may be nonneoplastic, further tying SPA to apocrine intraductal carcinoma as possibly related entities.

DIFFERENTIAL DIAGNOSIS

SPA is confounding to pathologists unfamiliar with this rare tumor type because it shares features with nonneoplastic processes in benign or even malignant salivary gland neoplasms. Accordingly, its differential diagnosis is often broad.

The ductal dilatation and fibrosis seen in SPA frequently suggest polycystic/dysgenetic disease or nonspecific sialofibrosis with salivary duct cysts. In contrast with those processes, SPA is well circumscribed and does not involve the entire gland. Moreover, SPA is usually clearly proliferative. Further, polycystic/dysgenetic disease is usually bilateral and seen at a much younger age than most cases of SPA.[16]

In SPAs with a prominent lipomatous stroma, sialolipoma (a lipoma with entrapped salivary ducts, acini, and myoepithelial cells) is a consideration. However, in sialolipoma, the epithelial elements are either normal or atrophic in appearance, very different from the proliferative nature of SPA.[17]

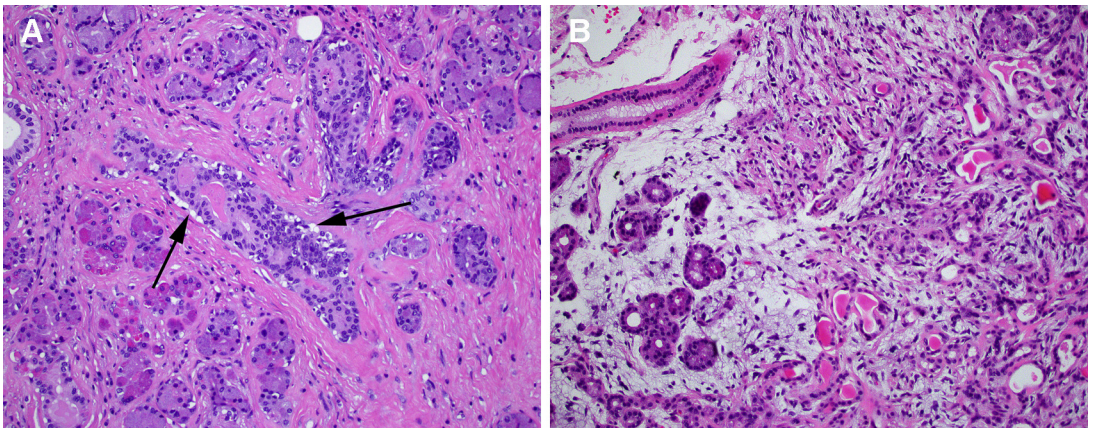

Fig. 5. The myoepithelial cells in SPA are situated around the ductal component and are typically subtle and indistinct (*arrows*). Note how the small ductules blend into lesional acini (*A*). On occasion, the myoepithelial cells (in this case, spindled cells in a myxoid background) can be focally prominent (*B*). The presence of abnormal acini (*left*) help distinguish this from pleomorphic adenoma.

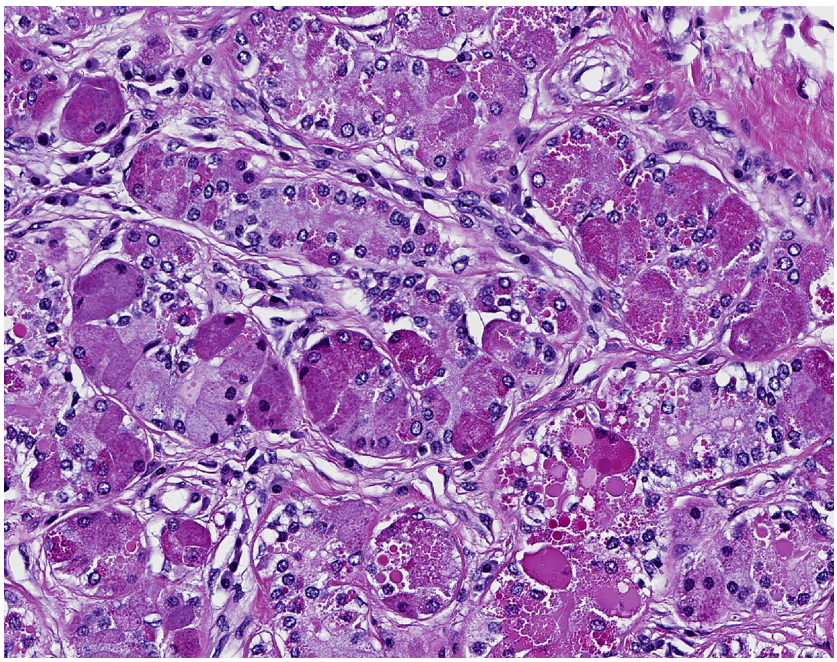

Fig. 6. Acinar cells are a classic histologic feature of SPA. Although some have a typical appearance with fine, basophilic granules (*left*), many of the granules are large and brightly eosinophilic (*right*).

SPA shows overlapping histologic features with pleomorphic adenoma, a much more common salivary gland tumor that is also circumscribed/encapsulated and may also give rise to apocrine intraductal proliferations. However, pleomorphic adenoma lacks acini and shows at least focal well-developed chondromyxoid stroma, a feature that is consistently absent in SPA. The tumors are molecularly distinct as well, with pleomorphic adenoma typically harboring fusions involving *PLAG1* or *HMGA2*.[18]

Intercalated duct lesions or adenomas develop predominantly in the parotid gland, frequently in conjunction with a basal cell adenoma, and are unencapsulated proliferations of intercalated ducts without significant stroma, blending with adjacent acinar cells, and showing few myoepithelial cells. The acinar cells frequently contain large, brightly hypereosinophilic cytoplasmic granules, similar to SPA. However, intercalated duct lesions/adenoma are usually a single, uniform population of cells.[19]

The presence of abnormal, disorganized serous acini within SPA raises the possibility of acinic cell carcinoma. Indeed, the presence of acinar differentiation in a salivary gland tumor is

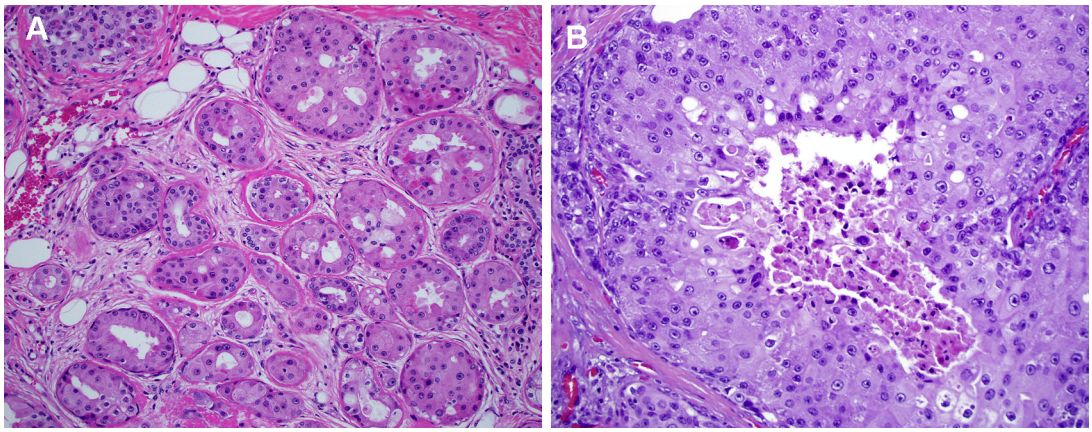

Fig. 7. Apocrine intraductal proliferations are common in SPA. These proliferations can be bland and low grade (*A*) or overtly high grade (*B*).

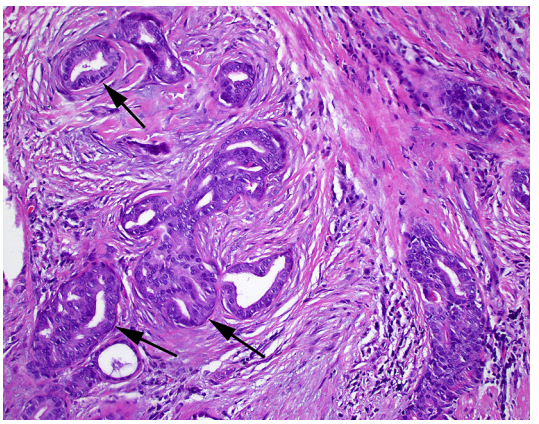

Fig. 8. Highly sclerotic areas of SPA can mimic an invasive carcinoma component. However, close inspection reveals a rim of small, compressed myoepithelial cells (*arrows*) around the glands, confirming that they are still intraductal.

usually diagnostic for acinic cell carcinoma. Showing the presence of myoepithelial cells by immunohistochemistry effectively excludes acinic cell carcinoma. Acinic cell carcinoma usually harbors *NR4A3* rearrangements and shows NR4A3 immunostaining, findings that would be absent in SPA.[20]

In cases of SPA with an apocrine intraductal component, salivary duct carcinoma may be considered. Immunostains for androgen receptor or gross cystic disease fluid protein (GCDFP)-15 are not helpful in distinguishing them, because apocrine elements of any tumor are uniformly positive for these markers. The intraductal elements of SPA, although very similar to salivary duct carcinoma, are entirely surrounded by myoepithelial cells, which can be demonstrated by immunohistochemistry. Moreover, the ductal elements of SPA are associated with other, benign ducts and acini, not seen in salivary duct carcinoma.

Box 1
Key pathologic features of sclerosing polycystic adenoma

- SPA is well circumscribed or encapsulated and often has large cysts
- Proliferative ducts, myoepithelial cells, and acini are present in SPA
- The presence of large, hypereosinophilic cytoplasmic granules is characteristic
- Most, but not all, cases show apocrine metaplasia and intraductal apocrine proliferations that are similar to intraductal carcinoma

As mentioned earlier, the apocrine intraductal proliferations seen in many SPAs are, by themselves, indistinguishable from the apocrine variant of intraductal carcinoma. In addition, next-generation sequencing has shown that these 2 tumors are very similar at the molecular level.[21] The additional proliferative ductules and altered acini seen in SPA are not present in pure intraductal carcinoma. Admittedly, the difference between these 2 lesions is not practically important, because they both behave in a benign manner in the absence of stromal invasion.

DIAGNOSIS

Most cases of SPA can be diagnosed based on morphologic features alone:

1. Well-circumscribed lesion with fibrosis and cystic changes.
2. Mixture of ducts, myoepithelial cells, and acini. The myoepithelial cell component may be indistinct and can be highlighted with immunostains for p40, S100 protein, calponin, etc.
3. Large, brightly hypereosinophilic cytoplasmic granules.
4. Ducts with apocrine metaplasia or intraductal carcinoma.

While the recent molecular features of SPA (ie, PI3 kinase pathway mutations and *PTEN* loss) are certainly interesting for classification purposes, they do not a have practical diagnostic role.

PROGNOSIS/TREATMENT

SPA is treated by surgical excision alone. It is not capable of metastasis, but it has been reported to recur in approximately 10% of cases, perhaps because of incomplete excision and persistence.[1,2,5–8,11,12] A single reported case transformed into invasive carcinoma after multiple recurrences over decades.[10]

SUMMARY

SPA is a rare salivary gland lesion that has an unusual constellation of histologic features that may be confused with a variety of reactive conditions, benign neoplasms, and malignant tumors. SPA is characterized by a circumscribed border, fibrosis, cystic changes, hypereosinophilic granules, and a mixture of cell types with frequent intraductal apocrine neoplasia. Even with markedly pleomorphic intraductal cells, SPA is benign and only occasionally recurs after surgical excision. Although originally thought to

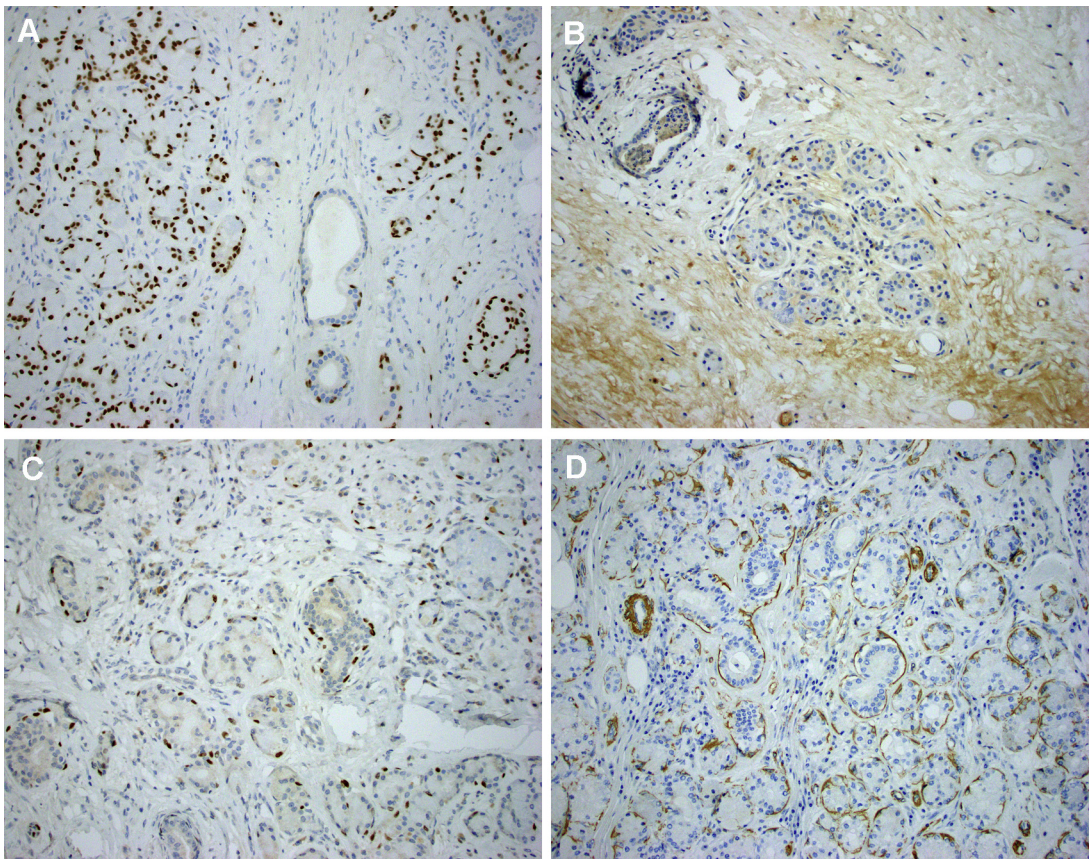

Fig. 9. In SPA, each cellular component has its expected immunoprofile: small ductules, acini, and myoepithelial cells are positive for SOX10 (*A*); acini are positive, albeit often weakly, for DOG1 in a luminal pattern (*B*); and myoepithelial cells are positive for p40 (*C*) and SMA (*D*).

be a nonneoplastic process, recent molecular evidence of clonality and PI3 kinase mutations has established it as a neoplasm.

CLINICS CARE POINTS

- SPA is a benign neoplasm with a mutational profile that is similar to apocrine intraductal carcinoma and salivary duct carcinoma.
- SPA is made up of acini, myoepithelial cells, and ducts that often become cystic and apocrine.
- Large, hypereosinophilic cytoplasmic granules are a helpful histologic clue for SPA.
- Intraductal proliferations are common in SPA, but have no bearing on its nearly uniform benign behavior.

DISCLOSURE

The authors have nothing to disclose.

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