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Review Article

Histopathological variations of Sclerosing Polycystic Adenoma: A systematic review

Syeda Areeba Rehan, MPhil, Oral Pathology [a,*], Zainab Niazi, PhD, Oral Pathology [a], Saeed Alam, FCPS [b], Tamoor Khan Wazir, FCPS [c] and Fatimah Imran, BDS [d]

[a] *Department of Oral and Maxillofacial Pathology, Islamabad Medical & Dental College, Islamabad, Pakistan*
[b] *Department of Histopathology, Akbar Niazi Teaching Hospital, Islamabad, Pakistan*
[c] *Department of ENT, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, Pakistan*
[d] *Department of Dental Materials, Army Medical College, Rawalpindi, Pakistan*

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الملخص

في هذه المراجعة المنهجية، هدفنا إلى تقييم الاختلافات النسيجية المرضية لورم الغدة النكفية المتعدد الكيسات المصلب. تم البحث بشكل شامل في قواعد البيانات، بما في ذلك "بيميد"، و "ساينس دايركت"، و "أوفيد" ومصادر الأدبيات غير الرسمية. تم تحديد ما مجموعه ١٣٧ حالة من ورم الغدة النكفية المتعدد الكيسات المصلب من خلال ٦٦ مقالة مختارة. يؤثر ورم الغدة النكفية المتعدد الكيسات المصلب بشكل رئيسي على الغدد النكفية لدى البالغين، بمتوسط عمر ٤٥،١ عاما، وله غلبة طفيفة لدى الإناث. سريريا، يظهر ورم الغدة النكفية المتعدد الكيسات المصلب على شكل كتلة صلبة وغير مؤلمة ذات فترة تطور طويلة. من الناحية النسيجية، كانت آفات الورم الغدي المتعدد التكيسات المصلب محددة بوضوح، وتتميز بفرط تنسج قنوي وعنقي، وتكوين كيسات، وتليف كثيف في النسيج الضام. ومن النتائج الملحوظة تباين مورفولوجيا الخلايا الظهارية، وخصائص النسيج الضام، ووجود تكاثر داخل القناة. تؤكد هذه المراجعة على ضرورة فهم الطيف النسيجي المرضي للورم الغدي المتعدد التكيسات المصلب لتحسين دقة التشخيص وإدارة المريض. على الرغم من طبيعته الحميدة، فإن النسيج المرضي المعقد للورم الغدي المتعدد التكيسات المصلب يتطلب تشخيصا تفريقيا شاملا، مما يؤكد على أهمية اتباع نهج منهجي في التقييم النسيجي المرضي.

الكلمات المفتاحية: حميد؛ علم الأمراض النسيجي؛ الكيمياء المناعية؛ ورم الغدد اللعابية؛ الورم الغدي المتعدد التكيسات المصلب;

Abstract

In this systematic review, we evaluated the histopathological variations of sclerosing polycystic adenoma (SPA). Databases including PubMed, ScienceDirect, OVID (MEDLINE), and grey literature sources were searched comprehensively. A total of 137 cases of SPA were identified across 66 selected articles. SPA predominantly affects the parotid glands of adults, with a mean age of 45.1 years, and has a slight female predominance. Clinically, SPA presents as a firm, painless mass with a prolonged evolution period. Histologically, SPA lesions were well demarcated, featuring ductal and acinar hyperplasia, cyst formation, and dense stromal fibrosis. Variability in epithelial cell morphology, stromal characteristics, and the presence of intraductal proliferation were notable findings. This review underscores the necessity of understanding the histopathological spectrum of SPA to enhance diagnostic precision and patient management. Despite its benign nature, SPA's complex histopathology necessitates extensive differential diagnosis, emphasizing the importance of a systematic approach in histopathological evaluation.

Keywords: Benign; Histopathology; Immunohistochemistry; Salivary gland neoplasm; Sclerosing polycystic adenoma

* Corresponding address: Department of Oral and Maxillofacial Pathology Islamabad Medical & Dental College, Islamabad, Pakistan.
E-mail: areeba.rehan@imdcollege.edu.pk (S. Areeba Rehan)
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Introduction

Smith et al. (1996) were the first to describe sclerosing polycystic adenoma (SPA), a rare and benign salivary gland condition.[1,2] This intriguing pathology usually affects the major salivary glands, especially the parotid and submandibular glands, presenting as a lobulated mass.[3,4] However, despite its benign nature, SPA's etiology and pathogenesis remain unclear even though current literature supports its classification as a neoplastic growth rather than a reactive process.[5,6]

Ductal and acinar hyperplasia, along with cyst formation and dense stromal fibrosis, are key identifiable histologic features of SPA with lymphocytic infiltration being a common finding.[1,3] These characteristically distinct histopathological attributes help differentiate SPA from other salivary gland pathologies despite clinical presentation often mimicking more common conditions, making diagnosis difficult.[4,6]

Clinical behavior and long-term prognosis of this disease remain poorly understood because of the paucity of comprehensive studies, primarily due to its rarity.[5] Additionally, diverse presentations at the histopathological level often make its diagnosis very challenging; thus, a broad range of possibilities needs to be considered, including malignancies.[6]

In recent years, there has been increasing interest in delineating the histopathological spectrum of SPA to improve diagnostic accuracy and patient management.[5] Although some reports and small case series have made important observations, no comprehensive systematic review of histopathological variants has been conducted.[3,4] This systematic review provides an extensive analysis of the spectrum of histopathologic changes observed in SPA by pooling data from various studies. To this end, this review consolidated and analyzed available literature to enhance our understanding of the histopathological characteristics of SPA, which may help pathologists and clinicians better diagnose and manage this rare condition.[5,6]

Materials and Methods

This systematic study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was entered into the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42024536153).

Eligibility criteria

We used papers that evaluated patients with SPA from the head and neck region according to the World Health Organization's histopathological diagnostic criteria.[7] The inclusion criteria were observational studies, case series, and case reports published in English, with no restrictions on the publication period. Book chapters, conference abstracts, letters, personal comments, reviews, *in vitro* and *in vivo* research, studies with inaccessible full versions, and studies focused on SPA in regions other than the head and neck region were excluded.

Search strategy

An electronic search was conducted on May 10, 2024, using databases including PubMed, ScienceDirect, OVID (MEDLINE), and grey literature sources such as Google Scholar. The reference lists of selected articles were manually reviewed to identify additional relevant studies. The search strategy is summarized in Appendix 1. The search string included Medical Subject Headings (MeSH) terms, subject terms, and synonyms related to SPA, and was designed and executed by the author SAR. There were no restrictions on publication type or date. The authors SAR and ZN performed deduplication of the search results, and manual checks of the reference lists and supplementary searches were conducted by the authors SAR and SA.

Study selection and data collection process

The selection process was executed across four phases. Phase 1 involved SAR downloading search results into Endnote version 21, followed by deduplication using the Centre for Research in Evidence-Based Practice Systematic Review Accelerator algorithm (SR accelerator) for enhanced accuracy. Phase 2 included the independent screening of titles by SAR and ZN in Endnote and the identification of potential studies for full-text retrieval based on predefined criteria. In Phase 3, ZN and SA retrieved the full texts of relevant articles, with SAR and ZN conducting manual citation searches. Phase 4 involved SAR and ZN reviewing full-text articles for final eligibility determination and resolving discrepancies through discussion or consultation with a third author as needed. The selection process was meticulously recorded to facilitate the creation of a PRISMA flow diagram (Figure 1) and a comprehensive list of included and excluded studies (Appendix 1).

Data extraction

Data extraction was conducted by SAR and verified by ZN for accuracy. The extracted information included author(s), year of publication, study type, demographic data, sample characteristics clinical features and histological features, molecular data/mutation, immunohistochemical panel, and variations in features. In cases where data were duplicated across multiple case series,[8–10] duplicate cases were identified and excluded from the final analysis.

Risk of bias in individual studies

Each included study's risk of bias was evaluated using the Joanna Briggs Institute Critical Appraisal technique. The risk of bias for each domain was evaluated based on extracted data and categorized as "high risk," "low risk," or "unclear risk." Two authors independently assessed the risk of bias, and any disagreements were resolved through discussion, with consultation from a third author if necessary. The overall risk of bias for each study was classified as follows: "high risk" for up to 49 % of "yes" responses to the assessed parameters, "moderate risk" for 50–69 % of "yes" responses, and "low risk" for more than 70 % of "yes" responses. For

visualization, the Robvis tool was utilized. The data were compiled in Excel sheets and uploaded to the Robvis website to generate visual representations of the risk of bias assessments.

Analysis of evidence and statistics

The statistical data were organized using Microsoft Excel (Microsoft Office LTSC Professional Plus 2021; Microsoft Co., Redmond, WA, United States) to create a database containing relevant variables. To summarize the research methods, the authors conducted a narrative synthesis to provide general information about the studied population and sample characteristics, including clinical, histological, molecular, treatment, and follow-up details. Additionally, they performed a quantitative synthesis based on percentages using Jamovi software, version 2.3 (The Jamovi Project 2023, Sydney, NSW, Australia).

Results

Study selection and characteristics

We conducted a comprehensive literature search, identifying a total of 347 articles published between 1996 and 2024. After removing duplicates using a deduplication tool on the SR accelerator, 304 articles remained for further analysis. Then these articles were screened based on their titles and abstracts, resulting in 55 articles selected for detailed evaluation based on the specific criteria.

After reviewing the full texts, several articles were excluded based on the established eligibility criteria. Additionally, we identified 11 more relevant articles through manual tracking of references and grey literature. In total, 66 articles were included in the qualitative synthesis, as summarized in Table 2 (Appendix 1).

The PRISMA flowchart, presented in Figure 1, illustrates the study selection process and the reasons for excluding each article are detailed in Table 3 (Appendix 1).

Demographic and clinical characteristics

The 66 selected articles included a total of 137 cases of SPA, consisting of 54 case reports, 7 case series, and 5 observational studies. The mean age of the patients was 45.1 ± 20.0 years, with a slight majority being older than 45 years (55.5 %). More females (53.3 %) than males (46.7 %) were affected. The most frequently affected salivary gland was the parotid, accounting for 78.5 % of the reported cases. Other sites included the submandibular gland and various minor salivary glands, which collectively made up 15.6 % of the cases. Clinically, most patients presented with a mass (94.8 %), which was typically nontender (40.7 %) or firm (37.0 %). Different treatment modalities were employed. Recurrence was observed in a minority of patients, and the majority had no evidence of disease at follow-up. Table 1 shows brief clinical details of the patients included overall.

Histopathological features

Histopathological examination of SPA revealed a diverse array of characteristic features across the reviewed patients, as summarized in Table 2. The lesions were typically well-demarcated, with preserved lobular architecture, and were

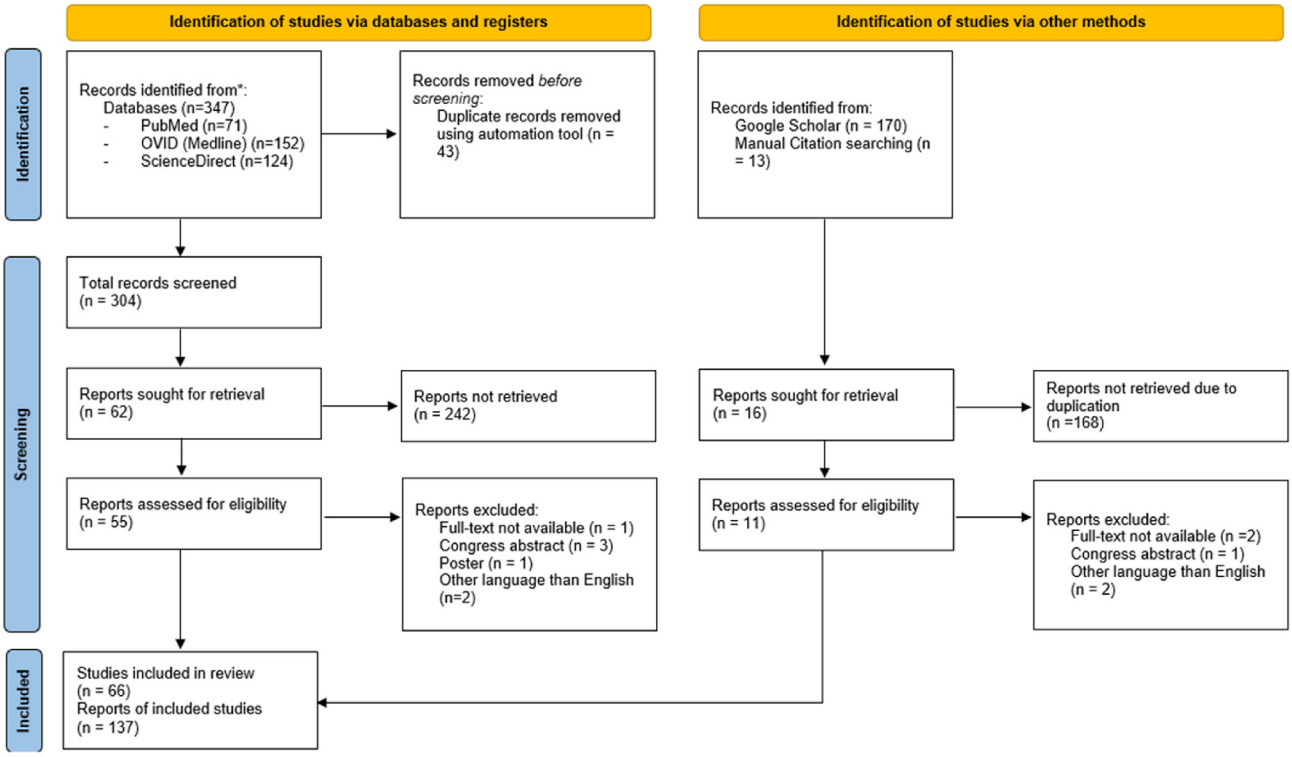

Figure 1: PRISMA flowchart.

Table 1: Clinical data summary.

Variable	N (%) (Total n = 137)
Site	
Major salivary gland	
Parotid	107 (78.1 %)
Submandibular	8 (5.8 %)
Minor salivary gland	
Hard palate	4 (2.9 %)
Buccal mucosa	4 (2.9 %)
Retromolar pad	3 (2.2 %)
Lower lip/labial mucosa	4 (2.9 %)
Oral mucosa	2 (1.5 %)
Floor of mouth	1 (0.7 %)
Tongue	1 (0.7 %)
Other	
Nasal region	2 (1.5 %)
Lacrimal gland	1 (0.7 %)
Clinical presentation	
Presence of Mass	130 (94.9 %)
Normal appearance	1 (0.7 %)
NA	6
Symptom characteristics	
Tender	21 (15.3 %)
Nontender	56 (40.9 %)
NA	60
Mass consistency	
Firm	48 (35.0 %)
Hard	9 (6.6 %)
NA	80
Treatment modalities	
Surgical excision	40 (29.2 %)
Parotidectomy − Superficial	39 (28.5 %)
Parotidectomy − Total	18 (13.1 %)
Surgical excision + neck dissection	6 (4.4 %)
Surgical excision + Radiotherapy	2 (1.5 %)
Surgical excision + neck dissection + Radiotherapy	1 (0.7 %)
NA	31
Recurrence	
Yes	13 (9.5 %)
No	94 (68.6 %)
NA	30
Patient status	
No evidence of disease	102 (74.5 %)
Alive with disease	1 (0.7 %)
NA	34

*NA: Not available.

Table 2: Histological Features.

Feature	Number	Percentage
Well circumscribed	122	89.1 %
Preservation of lobular architecture	100	72.9 %
Hypocellular hyalinized collagenous tissue/sclerotic stroma	132	96.3 %
Proliferation of ducts and acini	121	88.3 %
Sebaceous-like appearance	70	51.1 %
Ducts with cystic changes	122	89.1 %
Intraluminal material	32	23.3 %
Apical snouting	62	45.2 %
Acinar cells with eosinophilic cytoplasm granules	96	71.8 %
Lymphocytic and/or chronic infiltrate	102	70.1 %
Adipocytes	34	24.8 %
Periductal fibrosis	51	37.2 %
Cellular atypia	77	56.2 %
Capsule		
Encapsulated	2	1.45 %
Nonencapsulated	38	27.7 %
Pseudo capsule	45	32.8 %
Intraductal epithelial proliferation	87	63.5 %
Cribriform	64	46.7 %
Solid	60	43.8 %
Micropapillary	43	31.4 %
Epithelium cells		
Flattened	92	67.1 %
Cuboidal	79	57.6 %
Foamy	79	57.6 %
Vacuolated	72	52.5 %
Mucous	71	51.8 %
Clear	33	24.1 %
Squamous	65	47.4 %
Apocrine metaplasia	69	50.3 %
Oncocyte-like	37	27.0 %

mostly partially capsulated, usually by normal salivary gland parenchyma, in 45 (32.8 %) patients.

The predominant histological feature was the presence of sclerotic stroma in 132 patients, of whom 106 (80.3 %) had hypocellular hyalinized collagenized tissue, 24 (18.2 %) had paucicellular fibro myxoid stroma, 1 (0.8 %) had mucomyxoid stroma with focal sclerotic stroma, and 1 (0.8 %) had pronounced stromal distortion that mimicked invasive carcinoma. Almost all of the patients showed a proliferation of ducts and acini. Three patients exhibited ductal adenosis and acinar degeneration or a lack of acini (2.5 %). Ducts showed cystic changes in 122 patients. Small cystic areas or dilated cystic linings were the most common changes, and one patient had cystic spaces with a lattice-like appearance (0.8 %). No cystic changes were present in one (0.8 %) patient. Intraluminal material was observed in cystic spaces in 32 (23.3 %) patients. Cell debris was detected in 2 (6.3 %) patients, eosinophilic hyaline globules in small cystic spaces were detected in 9 (28.1 %) patients, eosinophilic material was detected in 19 (59.3 %) patients, intraluminal eosinophilic crystalloids were detected in 1 (3.1 %) patient, and central eosinophilic necrosed coagulum was detected in another patient (3.1 %). Concentric layers of hyalinized stroma around ducts were identified in 51 (37.2 %) patients.

Overall, varying epithelial cell morphologies were observed within the lesions. The different types of ductal lining epithelium are shown in Table 2. Intraductal epithelial proliferation was noted in 87 (63.5 %) patients and varied in architectural pattern, with cribriform formations being the most common, followed by solid and micropapillary growth patterns. Among the cribriform patterns, interconnecting rigid bridging (95.3 %) was the most common. In comparison, 'Roman' bridge formation (3.1 %) was observed in two patients, and a pseudocribriform pattern (1.6 %) was also observed in one patient. One patient (0.7 %) had a focal ductal *in situ* carcinoma pattern within a solid nest. An organoid pattern was observed in one (0.7 %) patient. One patient (0.7 %) exhibited a pseudoinfiltrative pattern. The epithelial lining showed the transformation of epithelial cells into cells with

Table 3: Immunohistochemical Expression of Markers in SPA.

Marker Category	Marker	Expression Type	Positive Cases (n)	Percentage
Epithelial	AE1/AE3	Cytoplasmic	36	26.3 %
	EMA	Cytoplasmic	18	13.1 %
	CAM5.2	Cytoplasmic	11	8.0 %
	Cytokeratins	Cytoplasmic	54	39.4 %
Myoepithelial markers	S100	Cytoplasmic	55	54.7 %
	p63	Nuclear	46	35.8 %
	α-SMA	Cytoplasmic	35	42.3 %
	Calponin	Cytoplasmic	41	44.5 %
	Muscle-specific actin	Cytoplasmic	18	13.3 %
Special stains	PAS	Intraductal mucin	35	25.5 %
	Mucicarmine	Intraductal mucin	15	10.9 %
Others	GFAP	Cytoplasmic	10	7.3 %
	GCDFP-15	Cytoplasmic	17	13.1 %

α-SMA: Alpha smooth muscle actin; AE1/AE3; Pan cytokeratin; CAM5.2; Anti-cytokeratin; EMA: Epithelial membrane antigen; GCDFP-15: Gross cystic disease fluid protein-15; GFAP: Glial fibrillary acidic protein; PAS: Periodic-acid Schiff; SPA: Sclerosing polycystic adenoma.

intraluminal projections or 'snouting,' resulting in decapitation-like sections, such as apocrine glands in 62 (45.2 %) patients, or a sebaceous gland-like appearance, characterized by ballooned cells with pale reticulated cytoplasm, which was often observed in 70 (51.0 %) patients. Acinar cells frequently exhibited eosinophilic intracytoplasmic zymogen granules (67 patients, 70.1 %). One (1.8 %) patient reported having binuclear vacuolated granular acinar cells. Paneth-like acinar cells with prominent cytoplasmic granules were identified in one (1.8 %) patient.

The cells showed varying degrees of cellular abnormalities. The majority of cases (84.4 %) exhibited mild atypia, which was defined by the presence of ductal epithelial cells with specific morphological features. These included round to oval nuclei, variably prominent nucleoli, and a low nuclear-to-cytoplasmic ratio. Moderate atypia (3.89 %) with nuclear pleomorphism and prominent nucleoli was observed in three patients. Severe atypia was observed in nine (11.69 %) patients.

Perineural entrapment (0.7 %) and nerve compression (2.19 %) were observed. Chronic inflammatory cell infiltration was observed in 102 patients (74.5 %), with lymphocytes and polymorphonuclear cells being the most common. High eosinophil counts were reported in one (0.98 %) patient.

Collagenous spherulosis was the predominant finding and was observed in 10 (17.5 %) patients, characterized by small hyaline globules of basement membrane-like material within cribriform areas. Atypical acinic cell hyperplasia was noted in six patients. Compression atrophy of the surrounding lobules of mucous glands was present in one (1.8 %) patient. Acinar cells with serous differentiation were uncommon. Periductal hyalinization was observed in one patient. One patient had cribriform intraductal proliferation that resembled secretory carcinoma-like features.

Rare nodules of myxoid tissue with a haphazard spindle cell component were identified in two (3.5 %) patients. Additionally, oval and elongated, somewhat distorted ducts resembling radial scar-like changes within a desmoplastic stroma were observed in one (1.8 %) patient. A hyalinized matrix in sclerotic collagen, demonstrating fibromyxoid quality with pale, degenerative acinar cells, was also observed in one (1.8 %) patient, and loose myxomatous features were noted in another (1.8 %) patient.

Calcifications were present in two (3.5 %) patients, including multifocal dystrophic calcification in one (1.8 %) patient and calcification with foreign body reaction at the lesion periphery in another patient (1.8 %). Siderophage-like small cells were noted in one (1.8 %) patient. Cholesterol clefts were specifically observed in three (3.5 %) patients.

More severe pathological findings included intermediate- to high-grade intraductal carcinoma (IDC) with foreign body giant cell reaction (1.8 %) and invasive carcinoma arising from atypical epithelial cells growing in a solid, infiltrative pattern, either in a sheet-like arrangement or as isolated cells (1.8 %). These cells exhibited eosinophilic cytoplasm and pleomorphic nuclei. Tumor cells undergoing degeneration and necrosis were noted in one patient (1.8 %), and focal areas of necrosis were observed in another two (3.5 %) patients. Additionally, tiny cell aggregates in the stroma, reminiscent of stromal invasion, were detected in nine (15.8 %) patients.

Several cases demonstrated notable associations: a bifocal, paucicystic variant with ductal carcinoma *in situ* (DCIS) in one (1.8 %) patient; coexistence with dysgenetic polycystic disease featuring pale eosinophilic secretion and mineral deposits in one (1.8 %) patient; invasive salivary duct carcinoma (SDC) in one (1.8 %) patient; and co-occurrence with Warthin tumor in another patient (1.8 %).

Immunohistochemical and special stain analysis

Immunohistochemical analysis of 137 patients with SPA revealed varied expression patterns of markers, reflecting the complexity of the condition. The main markers are summarized in Table 3.

Among the 54 cytokeratin (CK)-positive patients, CK14 was specifically positive in three (2.2 %) patients, with one (0.7 %) patient showing mosaic expression of CK14. CK7 was positive in 28 (20.4 %) patients, CK5/6 in 2 (1.5 %) patients, and CK5/8/18/19 in 1 (0.7 %) patient. Other immunohistochemical markers included collagen IV in 12 (8.8 %) patients and antimitochondrial antigen 113-1 in 11

(8.0 %) patients. Additional immunohistochemical markers showed variable results in a few patients. B-cell lymphoma 2 was positive in four (2.9 %) patients, and cluster of differentiation 117 (CD117) was positive in two (1.5 %) patients. The rare expression of markers such as BNC-5, CD10, Epstein–Barr virus positivity, carcinoembryonic antigen, vimentin, adipophilin, SRY-box transcription factor 10, GATA-binding protein 3, and mammaglobin was identified in only one (0.7 %) patient. These findings highlight the diverse immunohistochemical profiles of SPA. The Ki67 index ranged from 1 % to 15 % among the patients.

Special stains such as Periodic acid-Schiff (PAS), PAS-Diastase, and mucicarmine also showed positive results in a subset of cases, indicating varied staining patterns. Masson's trichrome stain highlighted fibrosis in one (0.7 %) patient.

Hormone receptor expression analysis revealed estrogen receptor (ER) positivity in 14 (10.2 %) patients, with focal or weak positivity observed in a small percentage of these patients. Progesterone receptor expression was detected in 11 (8.0 %) patients, with varying degrees of positivity noted.

Molecular profile

Molecular profiling of the SPA samples revealed the presence of various genetic alterations. It was determined using fluorescence *in situ* hybridization (FISH) and next-generation sequencing (NGS). Additionally, a PCR-based examination of X chromosomal inactivation patterns using the human androgen receptor (HUMARA) locus, was done, which revealed the monoclonality of cells in all female patients studied.[9] Mutations in the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) gene were detected in 16 patients,[5,10,11] phosphatase and tensin homolog (PTEN) in 10 patients,[5,10,11] Harvey Rat sarcoma virus (HRas) in 5 patients,[10,12] and AKT1 in 2 patients.[10] In one specific example, both PIK3R1 and the androgen receptor gene were involved for the first time.[12] By contrast, another investigation did not find mutations in PTEN, PIK3CA, or PIK3 regulatory subunit 1 (PIK3R1).[13] ETS variant transcription factor 6 FISH revealed no evidence of gene rearrangement.[14]

Risk of bias within studies

As part of our assessment, we evaluated the risk of bias for the included studies using the Joanna Briggs Institute classification. The majority of studies, comprising 52 articles (47 case reports, 3 case series, and 2 cross-sectional studies), were categorized as having an overall low risk of bias. Additionally, 10 studies (5 case reports, 3 case series, and 2 cross-sectional studies) were classified as having a moderate overall risk of bias. Finally, four studies (2 case reports, 1 case series, and 1 cross-sectional study) were observed to have a high overall risk of bias. The individual risk of bias assessments for each study are detailed in Appendix (Figs. 1–6).

Discussion

SPA is a rare salivary gland condition that resembles fibrocystic disease of the breast.[6,7] Patients often present with a painless, slow-growing tumor in the parotid gland.[7] SPA can occur across a wide age range, from 9 to 84 years, with a mean age of 45.1 years and a slight female predominance.

Diagnosing SPA via fine-needle aspiration cytology (FNAC) might be challenging due to the diverse cytologic features. No study has used FNAC alone to diagnose SPA.[13] Several patients have been diagnosed with pleomorphic adenoma or other benign lesions.[13,15–23] Nevertheless, FNAC is effective in determining the absence of malignant features in the majority of cases.

Histologically, SPA is distinguished by distinct mostly nonencapsulated lesions consisting of ductal and acinar components with diverse cytomorphological characteristics.[5,13] Epithelial cells have various morphologies such as apocrine metaplasia, foamy, cuboidal, mucous, squamous, columnar, and oncocyte-like cells.[13,24] Notably, SPA is marked by giant acinar cells with numerous eosinophilic cytoplasmic granules and a highly collagenized stroma with persistent inflammatory infiltrate.[13]

Immunohistochemically, ductal cells in SPA exhibit strong positivity for CKs, whereas both myoepithelial and ductal cells show high expression of S-100 protein.[6,13] Gross cystic disease fluid protein-15 is abundantly expressed in acinar cells. Positive staining for calponin, p63, alpha smooth muscle actin, and glial fibrillary acidic protein confirms that myoepithelial cells surround the acino-ductal components.[25] Human epidermal growth factor receptor 2 and p53 are negative, and the Ki-67 proliferation index is low (<1–15 %) in acinar and ductal components.[13,25]

Recent molecular studies have provided valuable insights into the nature of salivary SPA.[6] Skálová et al.[9] conducted the first investigation to investigate the clonal nature of SPA, demonstrating monoclonality using the HUMARA locus, suggesting that SPA is a neoplasm rather than a reactive process. These findings, however, should be viewed cautiously due to the variability in the inactivation of X-chromosomes between patients and cells.[6] Nevertheless, the authors noted that the lack of control tissues in this methodology led to descriptive rather than comparative findings.[6]

Several studies have identified mutations in PI3K pathway genes in SPA. Bishop et al.[5] found mutations in PTEN, PIK3CA, and PIK3R1, whereas Hernandez-Prera et al.[11] reported mutations in PIK3R1 and PTEN. Skálová et al.[10] recently discovered PTEN mutations as well as unique HRas and AKT1 mutations in SPA that had not previously been recorded. However, a recent study by Bhamad et al.[12] identified HRas and AR gene changes associated with SPA of the parotid gland for the first time. PTEN changes have been linked to neurological disorders; however, PIK3CA, KRAS, and PTEN expression may not always indicate neoplastic development.[26] Additional research is needed to examine the nonneoplastic characteristics of SPA.

Uemura et al.[13] described SPAs that underwent comprehensive NGS testing without revealing any mutations, and it was unclear if the SPA was a neoplasm or a non-neoplastic lesion. The authors stated that other molecular abnormalities may not be examined by NGS.[11,13,27] Additionally, PI3K pathway mutations can also be seen in non-neoplastic conditions such as hamartomatous syndromes and vascular malformations, suggesting a wide

clinical spectrum of PI3K gene expression that requires further analysis in SPA.[5,6,11]

In summary, while recent studies have identified PI3K pathway mutations in SPA, including novel HRas and AKT1 alterations, the heterogeneity of findings and the presence of similar mutations in non-neoplastic conditions warrant additional investigation to fully understand the molecular pathogenesis of this rare salivary gland disorder.[10–12] These findings are significant as mutations in the PI3K pathway are commonly observed in other salivary gland neoplasms, such as IDC and SDC.[6,28] SPA can also be diagnosed as pleomorphic adenoma, polycystic dysgenetic disease, acinic cell carcinoma, or mucoepidermoid cancer.[5,11] In SPA, the presence of eosinophilic cytoplasmic granules is considered distinctive among diagnostic possibilities.[6]

Interestingly, some SPA cases exhibit intraductal epithelial proliferations with cellular atypia, ranging from mild to invasive carcinoma, which has led some authors to conclude that SPA is a neoplasm rather than a reactive inflammatory lesion.[2,4,6,8,10,15,17,22,29] The shared mutations in the PI3K/AKT pathway among SPA, apocrine IDC, and high-grade SDC indicate a close relationship, indicating that SPA might serve as a precursor to these more aggressive forms.[10]

In addition to its histological characteristics, minimally invasive techniques may improve SPA therapy. Conservative treatments for chronic obstructive sialadenitis, including intraductal mucolytics, steroids, and antibiotic treatments, have recently been studied. These strategies could also provide useful knowledge for SPA management.[30]

This systematic review revealed several limitations inherent in the included studies, primarily stemming from the rarity of SPA and the retrospective nature of many reports. Variability in reporting standards and diagnostic criteria across studies may have influenced data interpretation and synthesis. Moreover, the limited molecular characterization and long-term follow-up data preclude a comprehensive understanding of SPA pathogenesis and natural history.

Future research directions should focus on elucidating the molecular underpinnings of SPA and identifying potential biomarkers for improved diagnostic accuracy. Longitudinal studies with standardized reporting guidelines are essential to further delineate the clinical behavior of SPA and optimize treatment algorithms.

Conclusion

In conclusion, this systematic review provides a comprehensive overview of the histopathological variations in SPA, emphasizing the importance of meticulous histological examination in achieving accurate diagnosis and guiding clinical management. Enhanced awareness of SPA's diverse histopathological spectrum is essential for clinicians and pathologists to mitigate diagnostic challenges, ultimately improving patient outcomes and quality of care.

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Conflict of interest

The author(s) have no conflict of interest to declare.

Ethical approval

This systematic review was registered with the PROSPERO database (CRD42024536153) before being conducted. Hence, there is no ethical issue.

Author contributions

Conceptualization: SAR, ZN, SA. Data curation: SAR, ZN, Investigation: SAR, ZN, SA, T. Writing – original draft: SAR, SA, TKW, FI. Writing – review & editing: ZN, SA, TKW, FI. Approval of final manuscript: All authors.

Declaration of Generative AI in scientific writing

During the preparation of this work, the author(s) used ChatGPT to improve readability and language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtumed.2025.06.005.

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