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CASE REPORT

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Syringomatous adenoma of the nipple: A case series and systematic review

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Key Clinical Message

SAN should be considered in the setting of nipple discharge or morphology changes with typical histological findings. There are limited published cases of SAN, and workup of this pathology is still not clear to date.

Abstract

Syringomatous adenoma of the nipple (SAN) is known to be a rare benign breast neoplasm. With a few cases documented in the literature, preoperatively diagnosing this tumor is a challenge, which often leads to invasive procedure such as mass excision with nipple removal. This study was aimed at presenting a case report of SAN and to conduct a review of published cases. Literature search was conducted through PubMed databases. Articles published from year 1983 to March of 2022 were included. Only histologically confirmed cases of SAN were included. The review was performed according to the PRISMA guidelines. Twenty-eight cases, including the newly reported case, were included in the review after going through inclusion criteria. The mean age at diagnosis was 44 ± 16 years. 7% were male. The most common presentation was palpable mass. Preoperative biopsy was done for 9 cases, out of which 7 did not indicate typical histopathological characteristic of SAN. Most common treatment was wide local excision with nipple removal. Immunohistochemical staining of the resected tumor was performed in 16 cases postoperatively. 32.1% (9/28) utilized p63 in constellation with histologic findings. Five cases that utilized staining also used Estrogen Receptor (ER) marker, while three used progesterone receptor (PR) marker. SAN should be considered in the setting of nipple discharge or morphology changes with typical histological findings. There are limited published cases of SAN, and workup of this pathology is still not clear to date. The case presented here and our comprehensive literature review suggest that pathohistological findings of SAN can be heterogeneous. Clinicians would also benefit from recognizing these variances. Further research and reported cases are needed to confidently diagnose SAN, which may open doors for less aggressive surgical treatment or surveillance option for asymptomatic patients.

KEYWORDS

breast lesion, keratinous cysts, nipple discharge, Syringomatous adenoma of the nipple

1 | INTRODUCTION

Syringomatous adenoma of the nipple (SAN) was first described in 1983 by Rosen.[1] It is widely believed that these tumors arise from sweat glands, specifically within the nipple-areolar complex.[1–3] Some of the presentations include mass associated with pain, itching, ulceration, and nipple discharge or inversion.[4] Imaging tools such as mammogram and ultrasound are not specific to distinguish SAN from other breast etiologies. Histologically, they are known to be glandular structures surrounded by myoepithelial layer which infiltrates the smooth muscle stroma containing keratinous cysts, providing a characteristic comma appearance in a dense stromal background.[1,3] Achieving the definitive diagnosis of this pathology in the preoperative setting is still unclear to date; thus, most patients undergo surgical excision. We present a case of 68-year-old female with left nipple inversion without a palpable mass, who had inconclusive diagnosis via mammography and core needle biopsy. She was confirmed to have SAN after undergoing surgical excision of the lesion with nipple removal. A systemic review of the published literature on SAN was also conducted. This case series presents common clinical and histopathological findings of SAN seen on biopsy in the last 25 years in hope to aid diagnosing SAN prior to making more invasive surgical decisions.

2 | METHODS

2.1 | Consent statement

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy. The case report and systematic review component of the study did not meet criteria for IRB review.

2.2 | Search strategy

Due to paucity of literature from first being described in 1983, no limitations were placed on the year of publication. Literature search was conducted through PubMed of reported cases until March 2022 for all histologically confirmed cases of SAN. Three of the authors (SP, SS, and CW) independently performed a literature search using the keywords “Syringomatous Adenoma of the Nipple”. The search was limited to human case reports, case series, English language, and full text. Abstracts without full texts were excluded. This review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.

2.3 | Selection criteria

All case reports and series involving patients with histological confirmation of SAN were included in the review.

2.4 | Data extraction

All selected articles were reviewed, and the following data were retrieved: age, gender, screening imaging, diagnostic imaging, presence of palpable mass on presentation, presence of nipple discharge on presentation, biopsy method, if SAN histology was present on biopsy results, final immunohistochemical analysis, and type of surgery patients underwent. The authors' names and year of publication as well as DOI were collected.

2.5 | Statistical analysis

Descriptive statistics were used to present the demographic, clinical, and pathologic features of the pooled data from all selected studies. Continuous variables were presented as mean with standard deviation, while categorical variables were presented as proportions. Statistical analysis was performed using Microsoft Excel version 2021.

3 | CASE PRESENTATION

The patient is a 68-year-old female with no history of breast lesion who underwent screening mammography. She was found to have subtle left nipple inversion associated with suspicious microcalcifications within the left areolar-nipple complex measuring 0.8 cm (Figure 1). The patient recalled a few episodes of nipple discharge and pruritus but denied any palpable concerns. Ultrasound-guided core needle biopsy was performed (Figure 2). The patient's case was reviewed at our multidisciplinary meeting. The review of the biopsy demonstrated atypical ductal proliferation favors cutaneous adnexal origin, in a background of breast tissue with keratin cysts with associated calcifications and foreign body-type giant cell reaction. The differentials were SAN versus low-grade microcystic adnexal carcinoma. Surgical resection was recommended to make a definitive diagnosis. The patient then underwent left central lumpectomy with the removal of the nipple. A mass measuring 1.0 cm × 0.9 cm × 0.6 cm was resected. The final pathology confirmed syringomatous adenoma of the nipple with characteristics described as keratinous cysts associated granulomatous response; small solid nests and cords with squamous differentiation that have a tadpole or comma-like shape (Figure 3). The mass was resected

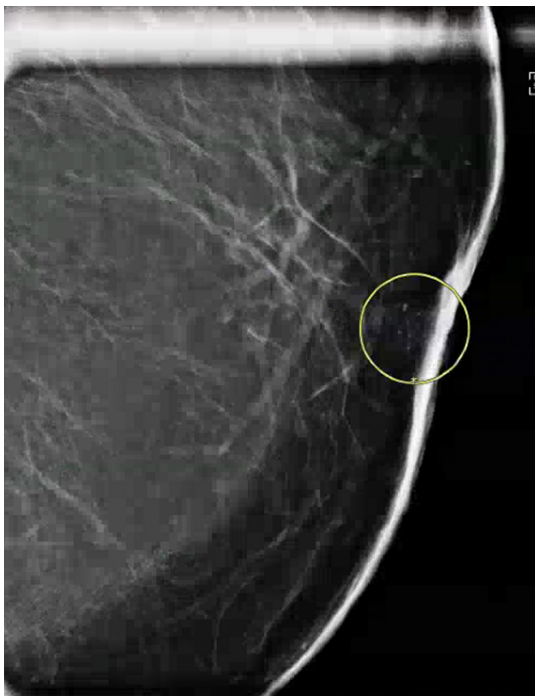

FIGURE 1 Mammography demonstrating microcalcifications of the left nipple-areolar complex.

with clear margins. Postoperatively, she had no complications. Repeat mammogram performed 3 months after the surgery demonstrated no suspicious masses, calcifications, or areas of architectural distortion.

4 | SYSTEMATIC REVIEW

After reviewing the 41 articles, 26 met our selection criteria. Excluded articles were one literature review, three in non-English, and 11 abstracts without full text. From the selected papers, there were 27 cases altogether. With inclusion of the case discussed above, the total number of cases in this review is 28. These reported cases are summarized in Table 1. Of the articles included in this review, two cases were male (2/28). The overall mean age was 44.4 years old, ranging from 11 to 71. Six cases were found during pregnancy (21.4%). The most common clinical presentations included palpable mass (67.9%), followed by nipple retraction (32.1%), discharge (25%), and erythema (7.1%). Nine cases (32.1%) did not use any diagnostic imaging prior to surgical excision. 7.1% (2/27) of cases had mammography as an only imaging modality, 7.1% (2/27) used only ultrasound and 53.6% (15/28) utilized ultrasound with mammography. Of those who had used imaging, 52.6% (10/19) had imaging findings of microcalcifications. Two cases used MRI; however, only one case had a mass detection when it had not been demonstrated on US or mammography.[5]

Nine cases out of 28 (32.1%) utilized a biopsy prior to surgery. The types of biopsy used were fine-needle aspiration, punch biopsy, core needle biopsy, and stereotactic biopsy. 77.8% (7/9) of these biopsies demonstrated nonspecific histopathological characteristics. Common biopsy findings from this group were aggregates of atypical epithelial cells, clusters of ductal epithelial cells, granulomatous inflammation, hamartoma, and foreign body giant cell reaction. Based on these biopsies, differential diagnoses included DCIS, tubular carcinoma, nipple adenoma, invasive squamous cell carcinoma, and inclusion cyst. One case demonstrated characteristic keratinizing cysts with double layer of epithelial cells on biopsy.[6] However, this case report did not comment if the diagnosis of SAN was known prior to definitive surgery. Therefore, not a single case reviewed discussed a diagnosis of SAN prior to surgical excision. In our presented case, the preoperative biopsy mentioned of atypical ductal proliferation in a background of breast tissue with keratin cysts with associated foreign body-type giant cell reaction. Although SAN was on the differential, the definitive diagnosis was uncertain at this stage. Out of 28 cases, only one case reported nipple-sparing excision.[7] The most common intervention performed was local excision with nipple removal.

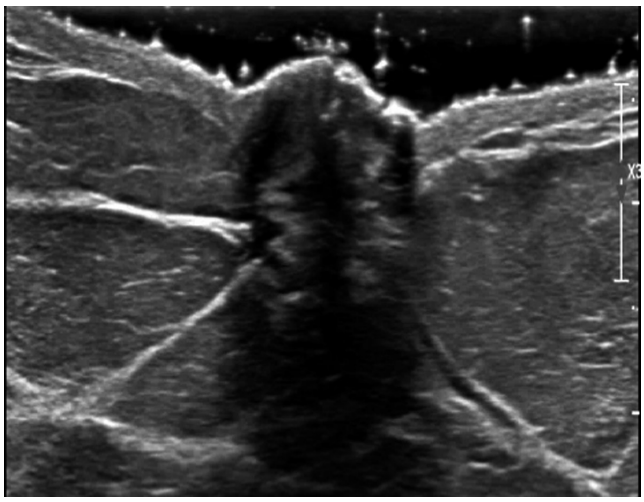

FIGURE 2 Ultrasound with suspicious calcifications within flattened left nipple.

All final histopathologic descriptions were analyzed and compared with Rosen's initial description.[1] 50% (14/28) had description of keratinous cysts. 39.3% (11/28) had mentioned invasion of smooth muscle bundles. 82.1% (23/28) described duct-like structures and proliferation intermixed throughout the lesion. 57.1% (16/28) described the stroma as fibrotic, desmoplastic, or dense. 64.3% (18/28) of cases observed the double layer of epithelial cells that lined the ducts and tubules. 50% (14/28) commented on a characteristic teardrop or comma-like appearance. One should be mindful of variance in histopathologic descriptions from each case report as each pathologist may review individual sample differently based on their experience and the quality of sample.

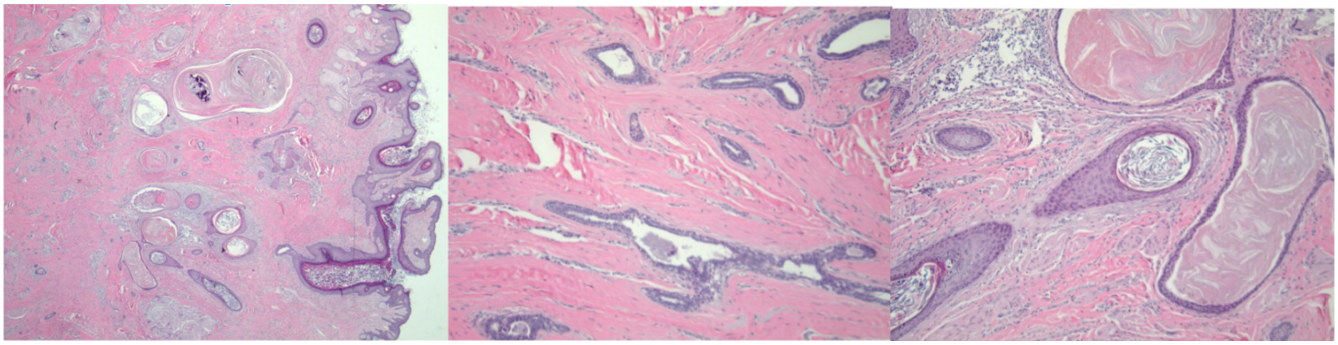

FIGURE 3 Demonstration of keratin cysts giving the characteristic teardrop or comma-like shape, duct proliferation, and double layer of epithelial cells.

To aid in diagnosis, several cases utilized immunohistochemistry. A histological marker, p63 can be used to identify myoepithelial cells and subsequent invasion.[8] Of the nine papers discussed p63, they demonstrated myoepithelial cells with no invasion from epithelial strands surrounding the tubules. Five cases tested for estrogen receptors (ER). Of those, 80% were ER negative (4/5). Of the three cases tested for progesterone receptors, all (3/3) were negative. Above findings are summarized in Table 2.

5 | DISCUSSION

SANs are rare breast lesions. Although it is known to not metastasize, it can recur if not excised to negative margins.[3] To our knowledge, about little over 40 cases of SAN have been reported in the literature. It is possible the prevalence of SAN is higher but incorrectly diagnosed as another entity due to sharing many nonspecific features with other types of neoplasm. In this series, we have summarized unique pathological and histological features of SAN, which may improve preoperative diagnosis.

SANs can often present with nipple discharge, pruritus, and retraction. These lesions are believed to arise from sweat glands, providing the glandular structures and proliferation that infiltrate smooth muscle bundles along with keratin cysts creating the characteristic comma appearance.[1] Imaging modalities such as mammography and ultrasound are not as specific and needle biopsies rarely assist in diagnosis, with only 7.1% (2/28) of cases seen during literature review demonstrated typical characteristics of SAN preoperatively. Among cases reviewed, most needle biopsy results were uncertain or misdiagnosed as low-grade adenosquamous carcinoma or ductal hyperplasia.[3,4,9] Due to this difficulty, patients are usually referred for excisional biopsy or surgical excision to achieve a diagnosis.

Our case presented is no exception, initially demonstrating nonspecific microcalcifications on screening mammogram with an inconclusive core needle biopsy result. However, the biopsy noted keratin cysts, one of the common histologic findings of syringomatous tumor. The differentials were SAN versus low-grade microcystic adnexal carcinoma. Due to uncertainty of diagnosis, the patient elected to undergo lumpectomy with nipple excision. Syringomatous tumors on immunostaining have strong immunoreactions for keratin cysts as observed by Rosen.[1,10] These cysts are seen among duct-like structures bound by double-layered epithelial cells in the setting of a dense stroma, which provides the characteristic comma shape as seen by 50% of cases reviewed. Also, use of immunohistochemistry such as p63 can demonstrate intact myoepithelium.[8]

The limitation of this review is that not as many published case reports met our inclusion criteria. In addition, not all groups obtained preoperative biopsy, imaging, or final immunohistochemistry study. Histopathologic descriptions mentioned above are qualitative assessment and as each pathologist would review samples differently based on their experience and quality of sample, the variance in their description is inevitable.

It would be ideal if full diagnosis of SAN can be offered before undergoing invasive intervention such as surgical excision with nipple removal. This is especially true for younger patients or those who wish to preserve the nipple for cosmesis. Nipple sparing or watchful waiting may be an alternative option for asymptomatic patients if the features of SAN can be confidently noted on the preoperative workup. However, care must still be taken to discuss the risk of recurrence or other types of malignancy. Ishikawa et al demonstrated a case of a patient with SAN, who underwent nipple-sparing excision of the lesion, and there was no recurrence of the disease at 1.5 year from the surgery.[7] Currently, the data on this method are limited but it is potentially an alternative option for those wanting to spare the nipple. Further studies on long-term surveillance of this method would be helpful to determine its true efficacy.

6 | CONCLUSION

Syringomatous adenoma of the nipple is known to be rare, and it is difficult to diagnose preoperatively via imaging and biopsies. Due to this uncertainty, many patients

TABLE 1 Reported cases of syringomatous adenoma of nipple.

Authors	Year	Age	Sex	Mass on Presentation	Nipple Retraction	Nipple Discharge	Imaging	Biopsy type	Biopsy Findings	Pre-Op Diagnosis	Surgical procedure	Stains
Abeciunas et al[3]	2020	60	F	Yes	Yes	No	US, mammography	FNA, Core needle	Myoepithelial cells, hamartoma	Hamartoma	Wide local excision	p63, CK5/6
AlSharif et al[12]	2014	39	F	No	No	No	US, mammography	NR	NR	Ductal carcinoma in situ +/− Paget, Papilloma, Adenoma	Lumpectomy	NR
Azita N, Hana S[22]	2011	11	F	Yes	NR	NR	None	NR	NR	NR	Excision (unspecified)	NR
Carter et al[20]	2004	33	F	Yes	No	Yes	None	NR	NR	NR	Wide local excision	NR
Hwang et al[13]	1987	51	M	No	No	Yes	None	NR	NR	NR	Mastectomy	NR
Ichinokawa et al[28]	2012	48	F	Yes	NR	NR	mammography	NR	NR	Nonmalignant tumor	Excision (unspecified)	AE1/AE3, CK7, CAM5.2, p63, SMA, S-100, p63, ER, PR
Ishikawa et al[7]	2015	48	F	No	Yes	Yes	US, mammography, MRI	NR	NR	NR	Excision, nipple sparing	Ki-67
Kim et al[11]	2010	36	F	No	No	No	US, mammography	NR	NR	Suspicious for malignancy	Wide local excision	NR
Ku et al[17]	2004	71	F	Yes	NR	Yes	US	NR	NR	Infected Sebaceous cyst.	Wide local excision	NR
Kubo et al[19]	2004	58	F	Yes	NR	Yes	US	NR	NR	NR	Wide local excision	NR
Montgomery et al[27]	2014	44	F	Yes	NR	NR	mammography	NR	NR	Invasive squamous cell carcinoma arising from epidermal surface	Mastectomy	SMA, p63, cytokeratin, 34BE12, CK5/6
Mrklic et al[14]	2012	33	F	No	NR	NR	US, mammography	FNA	Aggregates of atypical epithelial cells and microcalcifications	Tubular carcinoma, nipple adenoma, low-grade adenosquamous carcinoma	Wide local excision	CK5/6, CK7, p64, E-cadherin, ER, PgR, Her-2/neu, CK20, CD117, S-100, p53
Niakan et al[2]	2021	32	F	Yes	No	No	US, mammography	Punch biopsy	Keratinous debris with foreign body giant cell reaction	Ruptured epidermoid inclusion cyst, nipple adenoma	Wide local excision	NR
Odashiro et al[24]	2009	68	F	Yes	NR	NR	US, mammography	NR	NR	NR	Excision (unspecified)	34BE12, CK8, ER, S-100, SMA
Oliva et al[23]	2007	43	F	Yes	Yes	NR	None	NR	NR	Infection	Wide local excision	p63

(Continues)

TABLE 1 (Continued)

Authors	Year	Age	Sex	Mass on Presentation	Nipple Retraction	Nipple Discharge	Imaging	Biopsy type	Biopsy Findings	Pre-Op Diagnosis	Surgical procedure	Stains
Paramaguru R, Ramkumar S[25]	2021	20	F	Yes	Yes	No	None	FNA	Numerous cohesive clusters of ductal epithelial cells with fine chromatin, inconspicuous nucleoli, and moderate cytoplasm.	Proliferative breast lesion without atypia	Wide local excision	ER, PR, and CD15, smooth muscle myosin, p63, and CK5/6
Sarma et al[18]	2009	66	F	Yes	No	No	None	NR	NR	Leiomyoma, dermatofibroma, dermal cyst, breast tumor	Excision (unspecified)	NR
Senger et al[21]	2015	46	F	Yes	Yes	No	US, mammography	Stereotactic biopsy	Irregular groups of metaplastic atypical squamous epithelial cells with granulomatous inflammation and calcifications.	Microinvasive carcinoma	Mastectomy	NR
Suarez et al[6]	2022	33	F	No	No	No	US, mammography	Punch biopsy	Infiltrating bland small ductular proliferation lined by double layer comprised of small, cuboidal cells with scanty cytoplasm. Squamous metaplasia of the tubules and keratinizing cysts. Tumor cells infiltrated the stroma between the smooth muscle bundles.	NR	Wide local excision	p63
Toyoshima et al[9]	1998	59	F	Yes	Yes	No	US, mammography	Core needle biopsy	NR	Low-grade adenosquamous carcinoma	Mastectomy	NR
Wadhwa et al[16]	2003	41	F	Yes	NR	Yes	None	NR	NR	NR	Wide local excision	S100

TABLE 1 (Continued)

Authors	Year	Age	Sex	Mass on Presentation	Nipple Retraction	Nipple Discharge	Imaging	Biopsy type	Biopsy Findings	Pre-Op Diagnosis	Surgical procedure	Stains
Ward et al[15]	1989	34	F	Yes	NR	NR	None	NR	NR	NR	Wide local excision	CEA, S-100
Ward et al[15]	1989	43	M	Yes	No	No	None	NR	NR	NR	Mastectomy	CEA, S-100
Wilsher et al[4]	2020	33	F	No	NR	No	US, mammography	Core needle biopsy, Nipple punch biopsy	Cysts containing calcium oxalate crystals, adenosis, and columnar cell change, hyperplasia and papillary structures within lactiferous ducts	Nipple adenoma	Wide local excision	calponin, myosin heavy chain, p63, ER
Yosepovich et al[26]	2005	23	F	Yes	No	No	US, mammography	NR	NR	NR	Excision (unspecified)	SMA, ER, PR
Yu et al[5]	2020	35	F	No	Yes	No	US, mammography, MRI	NR	NR	NR	Wide local excision	p63
Zhong et al[29]	2013	68	F	Yes	Yes	Unknown	US, mammography, CT	NR	NR	NR	Excision (unspecified)	p63, Ki-67, calponin, M-CEA, CD117, CK8/18, S-100
Present case	2022	68	F	No	Yes	Yes	US, mammography	Core needle biopsy	Atypical ductal proliferation favors cutaneous adnexal origin, in a background of breast tissue with keratin cysts with associated calcifications and foreign body-type giant cell reaction	SAN vs low-grade microcystic adnexal carcinoma	Lumpectomy	None

Abbreviation: NR, not recorded.

TABLE 2 Results from the systematic review.

Characteristic	Number of patients (percentage)
Age	
<50 years	19 (67.9%)
>50 years	9 (32.1%)
Mean age	44.4 years ± 16
Median age	43 years
Gender	
Male	2 (7.1%)
Female	26 (92.9%)
Symptoms	
Palpable mass	19 (67.9%)
Nipple retraction	9 (32.1%)
Nipple discharge	7 (25.0%)
Erythema	2 (7.1%)
Ulceration	2 (7.1%)
Pain	3 (10.7%)
Itching	2 (7.1%)
Edema	1 (3.6%)
Bilateral	1 (3.6%)
Treatment	
Excision (unspecified)	6 (21.4%)
Excision (nipple sparing)	1 (3.6%)
Wide local excision	14 (50%)
Lumpectomy	2 (7.1%)
Mastectomy	5 (17.9%)
Final histopathologic descriptions	
Keratinous cysts	14 (50%)
Invasion of smooth muscle	11 (39.3%)
Duct-like structure	23 (82.1%)
Fibrotic/dense stroma	16 (57.1%)
Double layer of epithelial cells	18 (64.3%)
Teardrop/comma-like appearance	14 (50%)
Immunohistochemical stains	
p63	9 out of 9 demonstrated intact myoepithelium
SMA	3 out of 4 tested positive
S-100	5 out of 7 tested positive
ER	4 out of 5 tested negative
PR	3 out of 3 tested negative

undergo invasive surgical interventions such as lumpectomy or mastectomy with nipple excision. In our series, we have reviewed demographics, clinical presentations, and common pathohistological findings of SAN. The series demonstrate typical pathological finding of characteristic comma shape, which stems from keratinous cysts along duct-like structures composed of multilayered epithelial cells in a fibrotic stroma invading smooth muscle bundle.[3] Immunohistochemistry such as p63 may be used to demonstrate intact myoepithelium.[9]

While there are multiple causes of nipple shape changes, SAN should be considered in the differential diagnoses when initial diagnostic workup reveals common pathological features. We propose that also recognizing variances in pathohistological finding of SAN would benefit clinicians considering SAN as part of their differential. The clinical features should also allow excluding other lesions. If SAN can be confidently diagnosed, this would favor less aggressive treatment such as nipple-sparing excision and promote surveillance of asymptomatic lesion if patient wishes to avoid surgery. Regardless, discussion of the risk of recurrence and other types of malignancy should be addressed. More research and reported cases of this rare lesion along with unique characteristic findings would facilitate better understanding of the disease and translate to prompt diagnosis and more treatment options.

AUTHOR CONTRIBUTIONS

Sean K Park: Conceptualization; data curation; formal analysis; methodology; project administration; writing – original draft; writing – review and editing. **Sajjaad H Samat:** Data curation; investigation; validation; writing – review and editing. **Courtney M Whitelock:** Data curation; methodology; validation; writing – review and editing. **Thais Fortes:** Conceptualization; investigation; validation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

DATA AVAILABILITY STATEMENT

The raw data that support the findings of this study are available in this article, Table 1.

REGISTRATION OF RESEARCH STUDIES

N/A.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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