Brief Report

Contiguous squamous proliferations in syringocystadenoma papilliferum: A retrospective study of 14 cases

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Abstract

Background: Syringocystadenoma papilliferum is a benign adnexal neoplasm. Contiguous squamous proliferation has been rarely described in syringocystadenoma papilliferum.

Aims: This study aimed to evaluate the spectrum and pathogenesis of contiguous squamous proliferation in syringocystadenoma papilliferum.

Materials and Methods: All cases of syringocystadenoma papilliferum diagnosed over the past 12 years were screened for contiguous squamous proliferation. Cases with associated nevus sebaceous were excluded from the study. Immunohistochemistry for GATA3, CK7, BRAFV600E and p16 was performed. PCR for human papilloma virus, type 16 and 18, was carried out.

Results: Of a total of 30 cases, 14 cases showed associated contiguous squamous proliferation which included four cases of verrucous hyperplasia, six cases with papillomatosis, two cases with mild squamous hyperplasia and one case each of Bowen's disease and squamous cell carcinoma. In the cases with non-neoplastic contiguous squamous proliferations, the squamous component did not express CK7 or GATA3. However, the squamous component of premalignant and malignant lesions expressed CK7 and GATA3 concordant with the adenomatous component. BRAF was positive in adenomatous component in five cases while the contiguous squamous proliferation component was negative for BRAF in all but one case. p16 was negative in both components of all cases and PCR for human papilloma virus was negative in all cases.

Limitations: Due to the rarity of disease, the sample size of our study was relatively small with two cases in the 2nd group, that is, syringocystadenoma papilliferum with malignant contiguous squamous proliferation. Detailed molecular studies such as gene sequencing were not performed.

Conclusion: Syringocystadenoma papilliferum with contiguous squamous proliferation is underreported, and most commonly displays verrucous hyperplasia. The premalignant and malignant contiguous squamous proliferations likely arise from syringocystadenoma papilliferum while the hyperplastic contiguous squamous proliferations likely arise from the adjacent epidermis. Relationship with high-risk human papilloma virus is unlikely. However, further molecular analysis of larger number of cases is required to establish the pathogenesis.

Key words: Contiguous squamous proliferations, Human papilloma virus, Immunohistochemistry, Syringocystadenoma papilliferum, Verrucous hyperplasia

Plain Language Summary

Syringocystadenoma papilliferum is a relatively uncommon skin disease. Sometimes, small growths occur alongside the tumour, which are called contiguous squamous proliferations, whose exact nature is unknown. The latter can be benign or cancerous. The authors aimed to study the origin of contiguous squamous proliferations in syringocystadenoma papilliferum. They studied 30 cases of the latter, of which 14 had contiguous squamous proliferations. Among these 14 cases, two had cancerous squamous proliferations while the remaining 12 were benign. The authors studied the expression of certain proteins in the tissue of these cases. They found that cancerous contiguous squamous proliferations have protein expression similar to that of syringocystadenoma papilliferum, while the benign ones have different protein expressions. So, the authors concluded that benign contiguous squamous proliferations seem to originate from the adjacent skin lining while the cancerous ones are likely to arise from syringocystadenoma papilliferum.

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Introduction

Syringocystadenoma papilliferum is a benign adnexal neoplasm derived from pluripotent cells.[1] Rarely, contiguous squamous proliferations appear in syringocystadenoma papilliferum. Contiguous squamous proliferations are squamous proliferations which appear adjacent to syringocystadenoma papilliferum.[2] The exact pathogenesis of contiguous squamous proliferations in syringocystadenoma papilliferum is unclear and this study is aimed to identify the morphological spectrum and frequency of contiguous squamous proliferation in syringocystadenoma papilliferum and to explore its pathogenesis.

Materials and Methods

The institutional histopathology database at Postgraduate Institute of Medical Education and Research, Chandigarh, India, was searched to identify all cases diagnosed as syringocystadenoma papilliferum over the past 12 years, that is, from January 2007 to July 2019. Cases with associated nevus sebaceous or those with insufficient tissue in the block were excluded from the study.

Demographic data, location and size of lesion were obtained from the requisition forms. The slides and blocks were retrieved for all cases. All cases were reviewed by three pathologists and were subdivided into two categories: cases with contiguous squamous proliferation and those without.

Immunohistochemistry for cytokeratin 7 (CK7, Dako, 1:100), GATA3 (Cell Marque, 1:300), BRAF (BRAF v600e VE1 clone, Ventana, ready to use) and p16 (Ventana, ready to use) was performed using Ventana autostainer in all cases of syringocystadenoma papilliferum with contiguous squamous proliferation. For BRAF, granular cytoplasmic positivity in >10% cells was considered positive.[3] Immunohistochemistry was assessed adenomatous component of syringocystadenoma papilliferum and in the contiguous squamous proliferation separately. DNA PCR (polymerase chain reaction) for human papilloma virus 16/18 was performed in all cases with contiguous squamous proliferation, using formalin fixed paraffin-embedded tissue.

The tissue was deparaffinized using xylene and ethanol in decreasing concentration. Genomic DNA was extracted using commercially available kit (Qiagen, Germany) as per manufacturer's protocol. Later, PCR was performed for the presence of human papilloma virus 16 and 18 by targeting the regulatory gene (271 bp) and E6 region (100 bp), respectively, using gene specific primers.[4]

Results

A total of 36 cases of syringocystadenoma papilliferum were identified, of which six were excluded as they had an associated nevus sebaceous. Among the remaining 30 cases, 14 cases (46.7%) had an associated contiguous squamous proliferation.

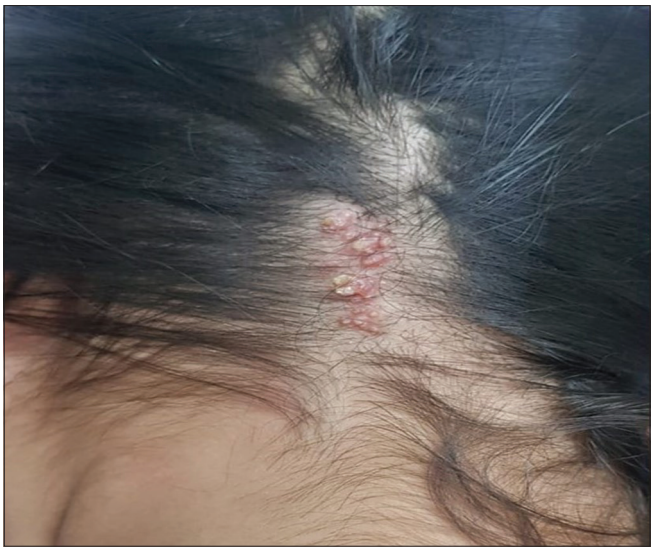

Figure 1a: A case of syringocystadenoma papilliferum with linearly arranged pinkish keratotic papules over occipital area

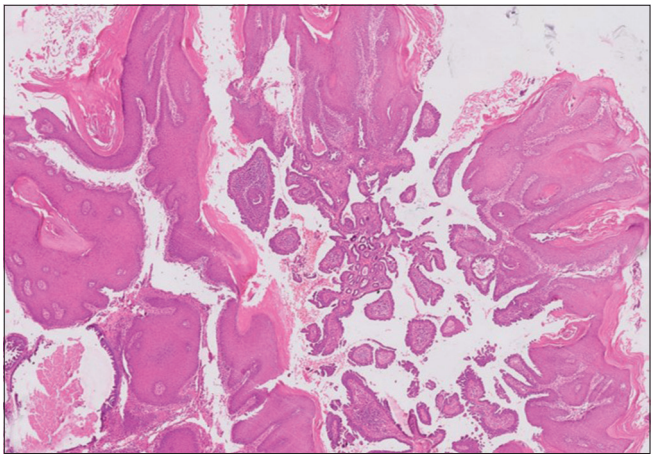

Figure 1b: Histological images of a case showing syringocystadenoma papilliferum with adjacent verrucous hyperplasia with no evidence of koilocytosis (hematoxylin and eosin, 40x)

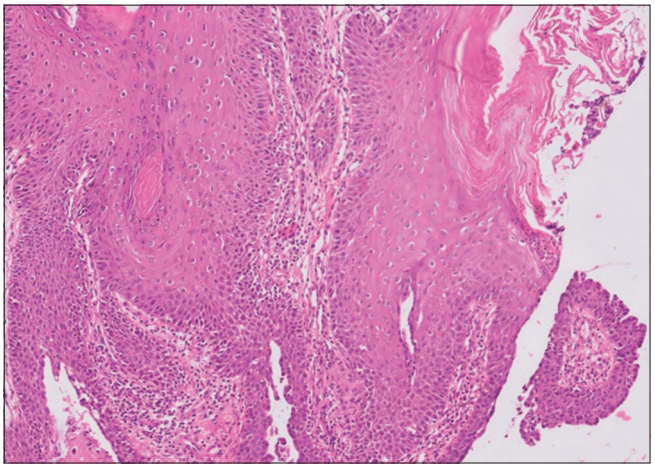

Figure 1c: Histological images of a case with adjacent verrucous hyperplasia with no evidence of koilocytosis (hematoxylin and eosin, 200x),

Table 1: Demographic data and clinical details of all patients of syringocystadenoma papilliferum with contiguous squamous proliferations

Case no.	Age (years)	Gender	Size of lesion (mm)	Site	Clinical presentation	Contiguous squamous proliferations
1	32	Male	12	Scalp	Well-defined nodule	Mild squamous hyperplasia
2	56	Female	50	Forehead	Ulceroproliferative growth	Squamous cell carcinoma
3	60	Male	15	Pre-auricular	Ulceroproliferative growth	Bowen's disease
4	61	Male	8	Scalp	Ulceroproliferative lesion	Verrucous hyperplasia
5	27	Male	15	Helix	Verrucous nodular lesion with aggregated keratotic papules	Papillomatosis
6	27	Female	5	Scalp	Nodular lesion	Mild squamous hyperplasia
7	11	Female	10	Scalp	Verrucous skin colored raised lesion	Verrucous hyperplasia
8	47	Female	15	Scalp	Ulcerated nodule with patch of hair loss	Papillomatosis with koilocytosis
9	40	Female	10	Cheek	Noduloulcerative lesion	Papillomatosis
10	25	Male	4	Scalp	Solitary nodular lesion	Papillomatosis with koilocytosis
11	70	Male	20	Scalp	Verrucous skin colored raised lesion	Verrucous hyperplasia
12	86	Female	15	Pre-auricular	Verrucous raised lesion	Verrucous hyperplasia
13	86	Female	4	Cheek	Well-defined nodule	Papillomatosis
14	66	Male	10	Forehead	Single well-defined nodule	Papillomatosis

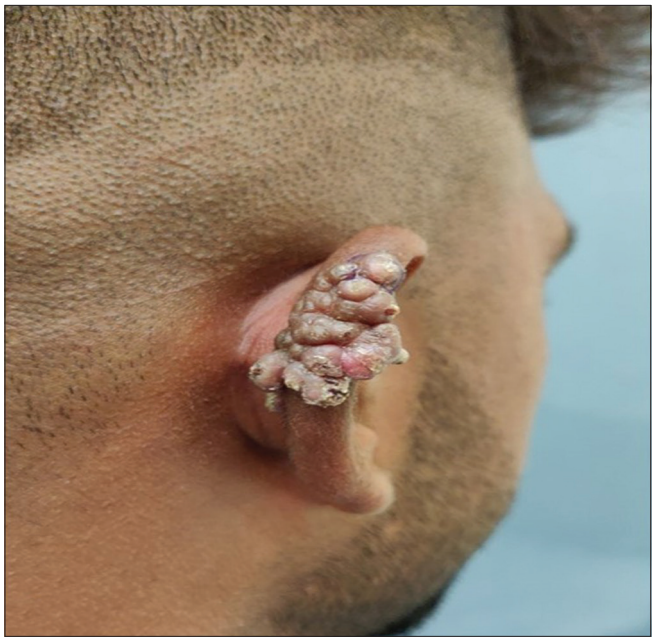

Figure 2a: Aggregated keratotic papules over outer helix

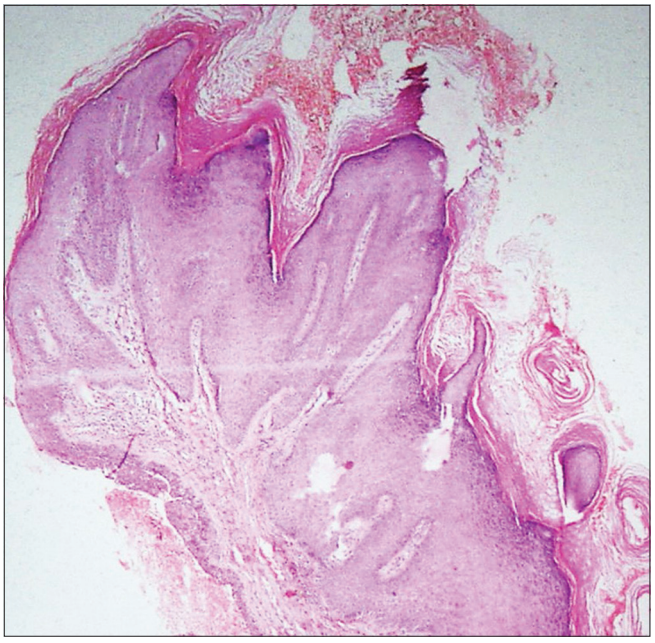

Figure 2b: Histological image showing syringocystadenoma papilliferum with verrucous hyperplasia (hematoxylin and eosin, 40x)

The mean age of patients with contiguous squamous proliferation (n = 14) was 50 ± 23 years with no gender predilection. Most common location was scalp (n = 8; 57.2%) followed by forehead, cheek and pre-auricular region (two each; 14.3%). The mean size of lesion was 13.1 ± 11.7 mm. The most common clinical presentation was skin colored to erythematous warty papules [Figures 1a and Table 1]. In patients of syringocystadenoma papilliferum without contiguous squamous proliferation (n = 16), mean age was 38.8 ± 12.6 years with a male: female ratio of 1:1.7. Scalp was the most common site (n = 12; 75%), followed by forehead, cheek, eyelid and neck (one each; 6.3%). The average size of lesion was 10.3 ± 11.6 mm. There was no significant difference in these two groups in terms of age, sex ratio, location or size of the lesion.

Based on histological examination, contiguous squamous proliferations were divided into two groups, Group 1 (n = 12) included hyperplastic or reactive conditions and Group 2 (n = 2) included pre-neoplastic and neoplastic conditions. In Group 1, papillomatosis was the most common finding (6/14, 42.9%) followed by verrucous hyperplasia (4/14, 28.6%) and mild squamous hyperplasia

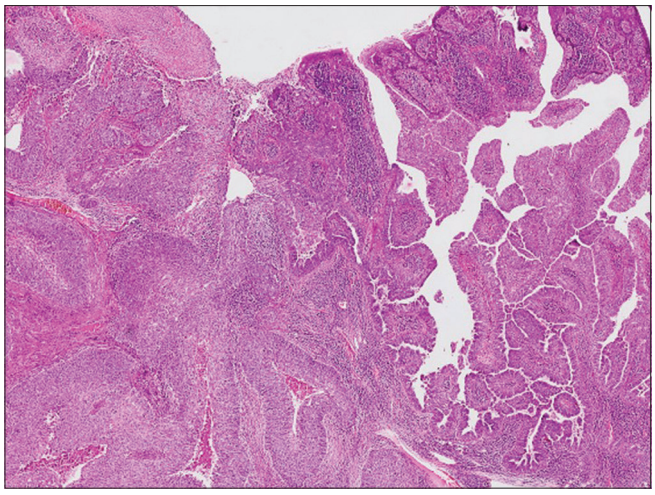

Figure 3a: Syringocystadenoma papilliferum with adjacent squamous cell carcinoma and necrosis (hematoxylin and eosin, 20x)

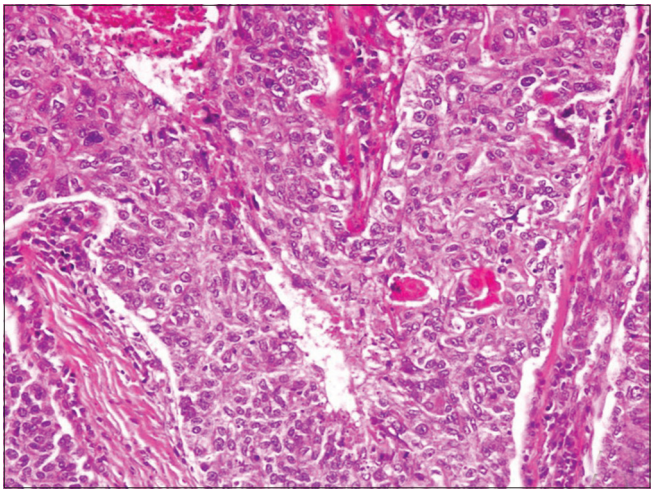

Figure 3b: A high-power image of syringocystadenoma papilliferum with adjacent squamous cell carcinoma and necrosis (hematoxylin and eosin, 400x)

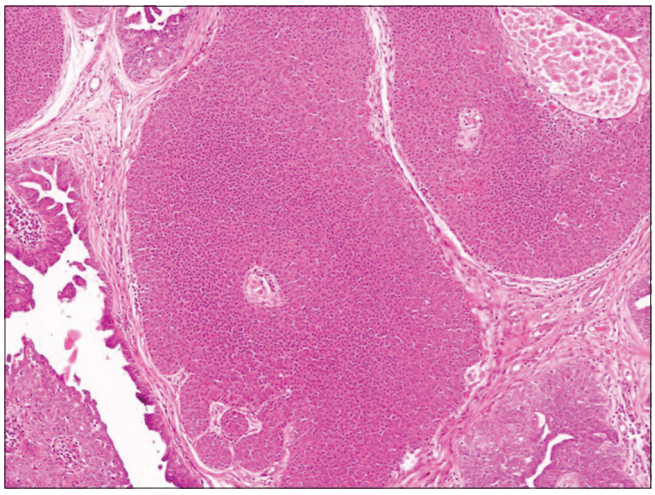

Figure 3c: Syringocystadenoma papilliferum with Bowen disease (hematoxylin and eosin, 100x)

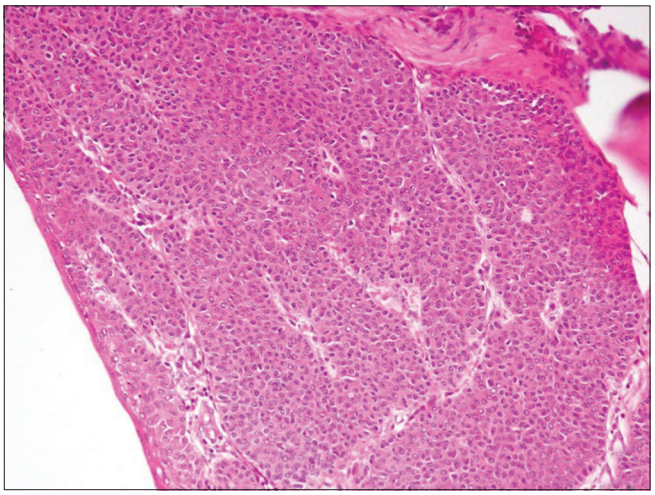

Figure 3d: Adjacent Bowen disease in a case with syringocystadenoma papilliferum (hematoxylin and eosin, 200x)

(2/14, 14.3%) [Figures 1b, 1c and 2]. Two out of four cases with papillomatosis showed wart-like morphology with the presence of acanthosis, hypergranulosis and koilocytic atypia. Group 2 included one (7.1%) case each of Bowen's disease and squamous cell carcinoma [Figure 3].

On immunohistochemistry [Figures 4 and 5], adenomatous component (syringocystadenoma papilliferum) showed positivity for CK7 in all cases [Figure 4a and 5b]. Hyperplastic contiguous squamous proliferations were negative for CK7 [Figure 4a] while neoplastic contiguous squamous proliferations were positive for CK7 [Figure 5b]. GATA3 expression was variable in the adenomatous component, as indicated in Table 2. The contiguous squamous proliferation component of the case with squamous cell carcinoma was positive for GATA3 while all other contiguous squamous proliferations were negative for GATA3 [Figures 4 and 5]. Adjacent normal epidermis was negative for CK7 and GATA3 in all cases. Immunohistochemistry for p16 was negative in all cases in both the components. PCR for human papilloma virus 16/18 DNA was negative in all cases.

Immunohistochemistry for BRAFV600E was positive in the adenomatous (syringocystadenoma papilliferum) component in five (35.7%) cases [all with hyperplastic contiguous squamous proliferation, Figure 4c]. The contiguous squamous proliferation component showed positivity for BRAFV600E in a single case which showed papillomatosis (adenomatous component was also positive). All remaining hyperplastic and neoplastic contiguous squamous proliferations were negative for BRAF. A summary is presented in Table 2.

Discussion

Syringocystadenoma papilliferum is a benign adnexal neoplasm which can either occur sporadically or within a pre-existing nevus sebaceous.[2] Without background nevus sebaceous, syringocystadenoma papilliferum not uncommonly demonstrates contiguous squamous

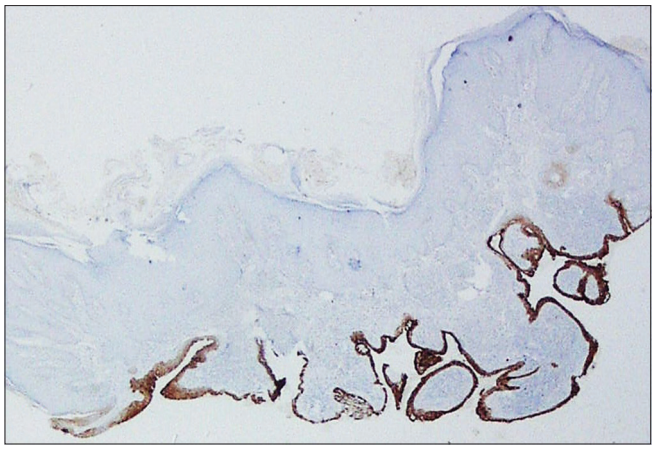

Figure 4a: Image showing CK7 positivity in adenomatous component while the contiguous squamous proliferation component is negative for all three markers (CK7, 40x)

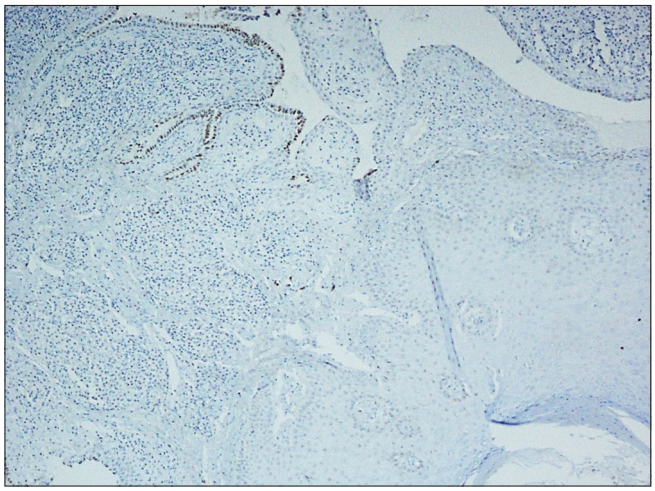

Figure 4b: Image showing GATA3 positivity in adenomatous component while the contiguous squamous proliferation component is negative for all three markers (GATA3, 200x)

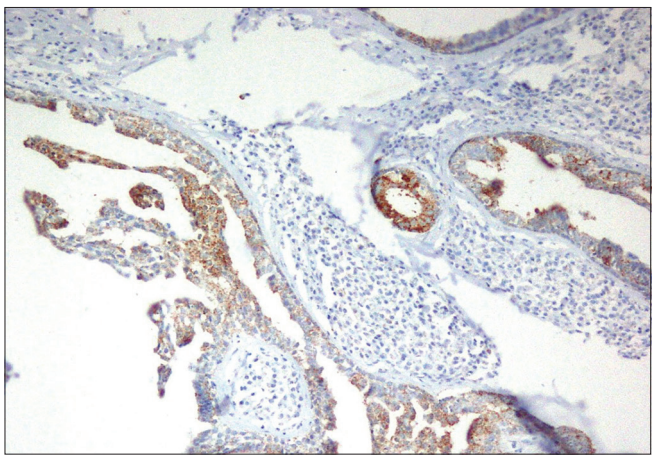

Figure 4c: Image showing BRAF positivity in adenomatous component while the contiguous squamous proliferation component is negative for all three markers (BRAF, 200x)

proliferations including metaplastic, hyperplastic and neoplastic proliferations.[1,2,5-12] Our study aimed to identify the spectrum and frequency of contiguous squamous proliferations in syringocystadenoma papilliferum and to explore their pathogenesis.

Among 30 syringocystadenoma papilliferum cases, 14 cases (46.7%) had contiguous squamous proliferations. Friedman *et al*. reported a higher incidence (9/12, 75% cases) of contiguous squamous proliferations.[1] Konstantinova *et al*. studied syringocystadenoma papilliferum of anogenital region where 10/16 cases (62.5%) had contiguous squamous proliferations.[2] The clinical appearance of the lesion is unable to predict underlying contiguous squamous proliferation. The mean age of patients of syringocystadenoma papilliferum with contiguous squamous proliferation in this study was higher than patients without contiguous squamous proliferation, although this difference was not statistically significant. It is possible that longer duration of syringocystadenoma papilliferum may be associated with the development of contiguous squamous proliferation, and thus, these lesions should be excised and subjected to histological examination.

The exact pathogenesis of these contiguous squamous proliferations in syringocystadenoma papilliferum remains unclear. The role of human papilloma virus 16/18 infection has also been suggested.[2,9] In this study, we found that the adenomatous component of contiguous squamous proliferations expressed CK7 and GATA3, whereas these markers were not expressed by hyperplastic contiguous squamous proliferation component. Interestingly, the neoplastic contiguous squamous proliferations showed concordant expression of CK7 and GATA3 in both adenomatous and contiguous squamous proliferation components while the normal adjacent epidermis was negative. Normal squamous epithelium and epidermis are known to express high-molecular-weight cytokeratin and not low-molecular-weight cytokeratin including CK7. Squamous cell carcinomas arising from skin or mucous membrane or Bowen's disease are also positive for high-molecular-weight cytokeratin and negative for CK7, similar to their normal counterparts. Both neoplastic contiguous squamous proliferations in our series showed strong CK7 expression, similar to adenomatous (syringocystadenoma papilliferum) component. These findings indicate that neoplastic contiguous squamous proliferations likely arise from the adenomatous component while hyperplastic contiguous squamous proliferations possibly originate from adjacent squamous epithelium/epidermis. We could not find any similar studies in literature, to make any valid comparisons with our results. We hypothesize that syringocystadenoma papilliferum undergoes squamous metaplasia which subsequently undergoes neoplastic transformation. Which factors actually trigger this neoplastic transformation is a matter of debate.

The role of human papilloma virus 16/18 in contiguous squamous proliferations in syringocystadenoma

Table 2: Summary of expression of immunohistochemical markers including CK7, GATA3 and BRAF in cases of Groups 1 and 2

Type of CSP	Number	CK7		GATA3		BRAF	
		Adenomatous	CSP	Adenomatous	CSP	Adenomatous	CSP
Mild squamous hyperplasia	2	Positive (2/2)	Negative (0/2)	Positive (2/2)	Negative (0/2)	Positive (2/2)	Negative (0/2)
Verrucous hyperplasia	4	Positive (4/4)	Negative (0/4)	Positive (3/4)	Negative (0/4)	Positive (1/4)	Negative (0/4)
Papillomatosis with koilocytes	2	Positive (2/2)	Negative (0/2)	Positive (2/2)	Negative (0/2)	Positive (1/2)	Negative (0/2)
Papillomatosis	4	Positive (4/4)	Negative (0/4)	Positive (2/4)	Negative (0/4)	Positive (1/4)	Positive (1/4)
Bowen's disease	1	Positive (1/1)	Positive (1/1)	Negative (0/1)	Negative (0/1)	Negative (0/1)	Negative (0/1)
Squamous cell carcinoma	1	Positive (1/1)	Positive (1/1)	Positive (1/1)	Positive (1/1)	Negative (0/1)	Negative(0/1)

*CSP: Contiguous squamous proliferation

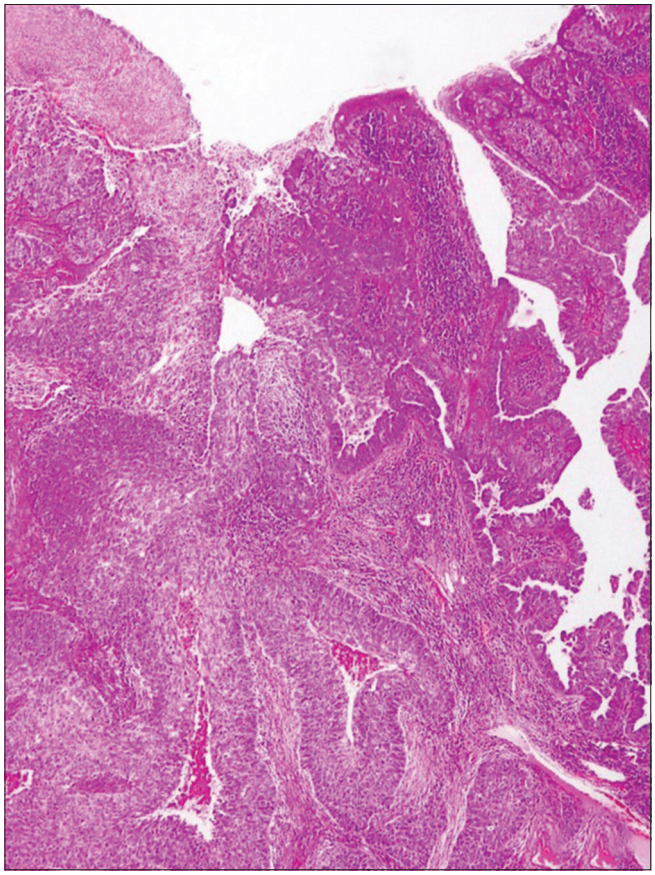

Figure 5a: Syringocystadenoma papilliferum with adjacent squamous cell carcinoma (hematoxylin and eosin, 20x)

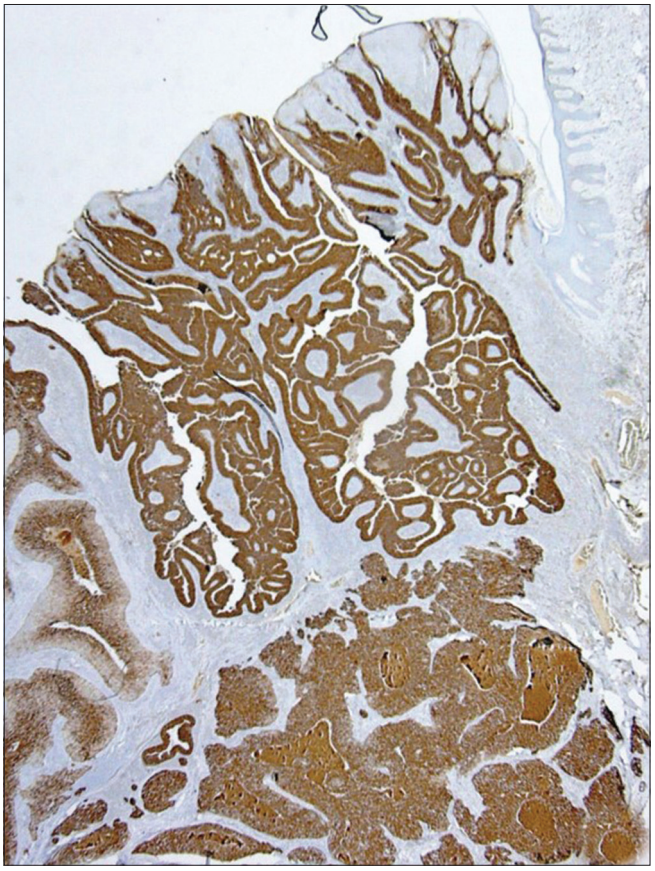

Figure 5b: Syringocystadenoma papilliferum with adjacent squamous cell carcinoma showing CK7 positivity in both adenomatous and contiguous squamous proliferations. The adjacent normal appearing squamous epithelium was negative (CK7, 10x).

papilliferum is disputed. A few authors have described occasional cases with human papilloma virus positivity. Konstantinova *et al*. reported a single case with human papilloma virus 16 positivity among ten cases showing contiguous squamous proliferation in anogenital syringocystadenoma papilliferum while none showed p16 positivity.[2] Skelton *et al*. reported a single case of syringocystadenoma papilliferum associated with condyloma acuminatum which was positive for human papilloma virus 6/11 by *in situ* hybridisation.[9] However, none of the four cases of syringocystadenoma papilliferum with verrucous carcinoma described by Alegría-Landa *et al*. showed any relation with human papilloma virus.[5] We performed PCR for human papilloma virus 16/18 since this is the most common high-risk human papilloma virus in Indian scenario. However, we could not perform PCR for low-risk human papilloma virus and other high-risk human papilloma viruses. None of our cases showing contiguous squamous proliferation (including two cases which showed koilocytic atypia on morphology) tested positive for human papilloma virus 16/18 or showed p16 positivity. Our findings corroborate those of other authors and it is unlikely that high-risk human papilloma virus plays a role in the pathogenesis of contiguous squamous proliferations.

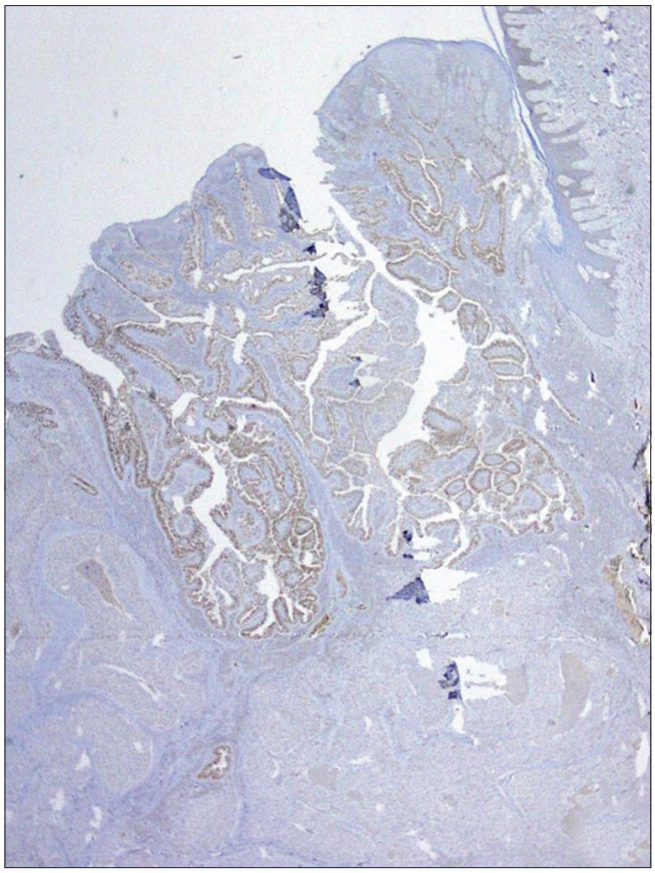

Figure 5c: Syringocystadenoma papilliferum with adjacent squamous cell carcinoma showing GATA3 positivity in both adenomatous and contiguous squamous proliferations. The adjacent normal appearing squamous epithelium was negative (GATA3, 10x).

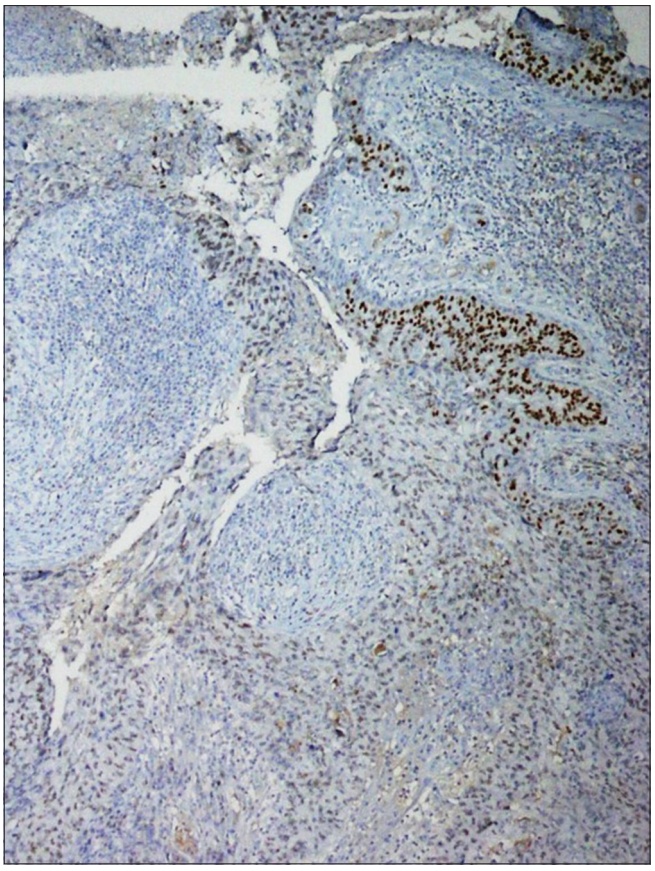

Figure 5d: Syringocystadenoa papilliferum with adjacent squamous cell carcinoma showing GATA3 positivity in both adenomatous and contiguous squamous proliferations (GATA3, 200x)

BRAFV600E expression in syringocystadenoma papilliferum has been variably reported by various authors and its role has been suggested in the pathogenesis of syringocystadenoma papilliferum. Friedman *et al*. reported BRAF expression in syringocystadenoma papilliferum and contiguous squamous proliferation component in seven and four out of nine cases, respectively.[1] Konstantinova *et al*. performed BRAF mutation analysis and five of their ten cases with contiguous squamous proliferations tested positive, although they did not perform BRAF mutation analysis in syringocystadenoma papilliferum and contiguous squamous proliferation separately.[2] Thus, it is not clear whether the contiguous squamous proliferation component also showed BRAF mutation. Half of the cases in a study by Alegría-Landa *et al*. showed BRAF immunohistochemistry positivity in both components, by immunohistochemistry and PCR.[5] Five of our 14 (35.7%) cases showed BRAF expression in syringocystadenoma papilliferum component and only one case showed BRAF positivity in contiguous squamous proliferation component. Syringocystadenoma papilliferum and contiguous squamous proliferation showing BRAF expression in our study are less as compared to that reported in literature. It could be because of the 10% positivity cutoff criteria that we used in this study or due to true biological variation of the disease. It is likely that BRAF mutation plays a role in pathogenesis of syringocystadenoma papilliferum, however, our findings as well as those of other authors do not indicate its role in contiguous squamous proliferation.

Due to the rarity of the disease, our study is limited by its small size. There were only two cases with malignant contiguous squamous proliferations associated with syringocystadenoma papilliferum, hence, the pathogenetic mechanisms can only be proposed and no firm conclusions can be drawn. Detailed molecular studies such as gene sequencing were not performed in this study. Human papilloma virus testing was done only for human papilloma virus 16/18 and testing for low-risk human papilloma virus and other high-risk human papilloma virus was not done. Further studies with larger sample size would be required for exploring these mechanisms.

Conclusion

Contiguous squamous proliferations in syringocystadenoma papilliferum are a relatively common but under-recognized phenomenon. Our findings indicate that high-risk human papilloma virus is unlikely to play a role in the pathogenesis of

contiguous squamous proliferations in syringocystadenoma papilliferum. It is likely that hyperplastic proliferations arise from the adjacent squamous epithelium as a reactive change while the adenomatous component gives rise to neoplastic proliferations, although the molecular mechanism could not be determined. However, this needs to be confirmed by larger studies with larger number of neoplastic cases. This study further reiterates that long-standing syringocystadenoma papilliferum may develop contiguous squamous proliferation, hence should be excised. In cases which are managed conservatively, close follow-up is advised.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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