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Original Article

Subepithelial Fibrinous Accumulation and Associated Epithelial Proliferation in Laryngeal Nodules

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ABSTRACT

Objective: Fibrinoid accumulation in the larynx and increase in the subepithelial collagenous connective tissue result in overgrowth. Mucosal epithelium may proliferate downward to organize and remove the fibrinoid accumulation. This downward proliferation may cause an invasive cancer-like image. This study focused on the pathogenesis of the accumulation of fibrinoid substance and the development mechanism of the associated squamous epithelium proliferation.

Methods: Five hundred and seventy-five laryngeal nodules were reexamined and 111 of them with varying degrees of irregular downward squamous epithelial proliferation were included in the study. Immunohistochemical staining of CK5/6, CK17, CK14, collagen type I, collagen type III, collagen type IV, and fibrinogen was performed. A modified Masson's trichrome method was used for the histochemical staining of collagen.

Results: Edema was present in 18% of the acute lesions and fibrin deposition in 42%. Relatively mature lesions mostly contain dense collagen fibers. The intensity of collagen type III was inversely proportional to the amount of fibrin accumulation. Collagen type IV was found in the epithelial and vascular basement membranes. A decrease in fibrin staining intensity and the presence of collagen type I and type III indicated the replacement of fibrin with collagen. Basal-type keratins showed more pronounced staining in the regenerated areas of the epithelium. As the laryngeal subepithelial fibrinoid accumulation was replaced with collagen, regression of the lesion became difficult.

Conclusion: Irregular squamous epithelial proliferation occurs independent of the stage of the lesion. Although the etiology is different, the resulting lesions are histologically similar to those seen in the ligneous mucosal disease.

INTRODUCTION

Laryngeal nodules are callous-like overgrowths of the laryngeal cords. Excessive use of voice and smoking cause these nonneoplastic protuberances. Continuous subepithelial edema and fibrin exudation followed by integration with collagen result in nonregressive lesions. Human proteins function in different cellular processes, and post-translational modifications may alter their function and structure.[1–4] Fibrinous exudation that cannot be fully lysed integrates with the connective tissue matrix due to its fibrillary structure. Then, accumulation becomes resistant to degradation without spontaneous improvement.[3,4] Overlying squamous epithelial hyperplasia and irregular downward proliferation are frequent in laryngeal nodules and may resemble invasive carcinoma. Hyperplasia of the overlying epithelium is a result of an effort to repair subepithelial excessive exudate. Fibrin exudation and fibrinolytic mechanisms activate the epithelium to ensure the integrity of the surface. The surface epithelium grows down and underlines, trying to limit the base of the exudate.[3] The epithelium, which tries to limit the base, tends to show more irregular development depending on the three-dimensional sphere-like structure in the polypoid structure, unlike the flat surface epithelial compartments. Similarly, the epithelial cells at the wound edge lose their apical–basal polarity and extend pseudopodia from their free basolateral sides into the wound.[3] Plasminogen de-

ficiency-related ligneous mucosal lesions contain similar fibrinous accumulations under the epithelium due to insufficient fibrinolysis.[1]

This study focused on the distribution of basal cytokeratins of the hyperplastic epithelium and types of collagen fibers to understand the pathogenesis of subepithelial homogenous deposits in the laryngeal nodules. The effect of healing delay due to excessive fibrin exudation and its relationship with irregular proliferation in the surface squamous epithelium was also studied. For this purpose, immunohistochemical staining of basal cytokeratins 5/6, 14, and 17, collagen types I, III, and IV, fibrinogen antibodies, and collagen was used. This study also aimed to draw attention to the irregular proliferation of squamous epithelium that may be confused with cancer in laryngeal nodules, which has not been highlighted before.

MATERIALS AND METHODS

All the procedures were approved by the Kartal Dr.Lütfi Kırdar City Hospital Ethics Committee (Project Approval Form Number: 2019/514/162/7). Five hundred and seventy-five laryngeal nodules, diagnosed in the Kartal Dr.Lütfi Kırdar City Hospital Department of Pathology and TOBB ETU Hospital Department of Pathology between 2011 and 2019, were included in the study. In all 575 nodules, age, sex, location of the nodules in the larynx, position of the vocal cord (anterior, middle, or posterior 1/3), and laterality were recorded. In our department, laryngeal benign vocal fold lesions are usually classified in accordance with Rosen's recommendation.[5] The presence of keratosis in the squamous epithelium, intraepithelial fibrin accumulation (vesicle formation), basal membrane thickness prominence, nodule type (dominant type and secondary type), presence of ulcer, fibrin deposition in the stroma, downward irregular epithelial proliferation, and presence of dysplasia were evaluated.

Immunohistochemical methods were applied to 111 nodules with varying degrees of irregular downward squamous epithelial proliferation. Immunohistochemical studies were performed using the Ventana BenchMark ULTRA IHC System (Ventana Medical Systems, AZ, USA). Included antibodies were CK5/6 (clone D5&16B4, dilution 1:100, Biocare Medical, CA), CK17 (clone E3, dilution 1:50, Thermo Scientific™, CA), CK14 (clone L002, dilution 1:100, Biocare Medical, CA), collagen type I (Polyclonal, dilution 1:600, Boster Bio, CA), collagen type III (Polyclonal, dilution 1:500, Boster Bio, CA), collagen type IV (clone PHM-12 + CIV 22, dilution 1:100, Thermo Scientific™, CA), fibrinogen (Monoclonal, dilution 1:50, Proteintech, IL). All antibodies were diluted with Ventana Antibody Diluent (251-018, Ventana Medical Systems, AZ, USA). A modified Masson's trichrome method was used for the histochemical staining of collagen (Trichrome Staining Kit-Blue, Roche Tissue Diagnostics, AZ, USA) at the VENTANA BenchMark® Special Stains platform (Ventana Medical Systems, AZ, USA).

RESULTS

Five hundred and seventy-five nodules were included after examining the reports and sections of the 476 cases in the study. Three hundred and eighty-eight cases were sin-

Table 1. Age and sex distribution of single and multiple nodules and nodules with irregular downward squamous proliferation according to the degree of proliferation

		Nodule number					Degree of downward irregular epithelial proliferation			
		1	2	3	4	5	Mild	Moderate	Severe	n
Male	Median	43.6	41.3	–	–	–	46.1	45.5	42.4	–
	Mean	44.2	44.3	–	–	–	44.5	46.1	41.0	–
	Min	17.4	17.3	51.2	49.9	51.9	17.3	21.1	21.8	–
	Max	79.3	72.4	60.6	–	–	62.6	79.3	57.5	–
	Total	277	52	2	1	1	48	49	4	101
Female	Median	41	37	50.5	–	–	43.0	58.8	–	–
	Mean	42.1	40.4	49	–	–	41.6	57.8	–	–
	Min	15.9	22	30.2	–	–	21.8	51.6	–	–
	Max	70.1	60.9	64.6	–	–	57.5	63.1	–	–
	Total	111	28	4	0	0	7	3	0	10
Total	Median	43	40.7	52.6	–	–	46.0	46.6	42.4	–
	Mean	43.6	42.9	51.3	–	–	44.1	46.8	41.0	–
	Min	15.9	17.3	30.2	–	–	17.3	21.1	21.8	–
	Max	79.3	72.4	64.6	–	–	62.6	79.3	57.5	–
	Total	95.2	89.7	94.8	0	0	55	52	4	111

gle, and 88 cases had multiple nodules. Eighty cases had 2 nodules, 6 cases had 3 nodules, 1 case had 4 nodules, and 1 case had 5 nodules. One hundred and eleven nodules (23.32%) with irregular downward squamous proliferation were included in the study. Age and sex distributions of single and multiple nodules and nodules with irregular downward squamous proliferation are presented in Table 1. It is noteworthy that male cases showing irregular squamous epithelial proliferation were ten times more than female cases, and the average age of males was higher than that of females. Localization of the nodules in the larynx, position of the vocal cord, laterality, presence of keratosis in the squamous epithelium, intraepithelial fibrin accumulation, basal membrane thickness, nodule type (dominant type and secondary type), presence of ulcer, fibrin deposition in the stroma, and downward irregular epithelial proliferation distribution of nodules are given in Table 2.

Table 2. Specification and distribution of laryngeal nodules

		M	F	Total
Keratosis	No	120	82	202
	Yes	273	104	377
Vesicle	No	315	175	490
	Yes	78	11	89
Basal lamina	No	203	79	282
	Yes	190	107	297
Type primary	Edematous	52	50	102
	Vascular	62	11	73
	Myxoid	132	88	220
	Hemorrhagic	36	8	44
	Hyalinized	100	28	128
	Fibrous	11	1	12
Type secondary	Edematous	1	1	2
	Vascular	95	45	140
	Myxoid	5	3	8
	Hemorrhagic	45	12	57
	Hyalinized	62	8	70
	Fibrous	6	1	7
Inflammation	None	254	152	406
	Mild	127	30	157
	Moderate	10	4	14
	Severe	2	0	2
Ulceration	No	361	180	541
	Yes	32	6	38
Fibrin deposition	None	196	135	331
	Mild	66	27	93
	Moderate	93	19	112
	Severe	38	5	43
Downward squamous proliferation	None	264	161	425
	Mild	73	20	93
	Moderate	52	5	57
	Severe	4	0	4
Laterality	Right	185	86	271
	Left	157	77	234
	Bilateral	2	2	4
Localization	Vocal cord	359	173	532
	False cord	6	1	7
	Anterior commissure	7	0	7
	Epiglottis	1	0	1
Sublocalization in vocal cord	1/3 Front	136	71	207
	1/3 Middle	26	12	38
	1/3 Back	1	2	3
	1/3 front–middle junction	12	8	20

The nodules showed two phenotypes according to the maturation stages of the lesions although there was no definite limit. More acute lesions with ulceration and surface-active fibrin outflow (Fig. 1a and 1f) and lesions that are more mature were stained with modified Masson's trichrome stain (Fig. 2a and 2b). While red staining was evident in acute lesions due to the predominant fibrin with TCS (Fig. 2d), it was observed that blue-stained collagen was formed in older lesions (Fig. 2b) or more mature areas of nodules. In some nodules, acute and more mature stages were observed together (Fig. 2c and 2d). Some parts of the nodule stroma were rich in fibrin, which was an early-stage finding, and they were stained red with TCS (Fig. 2d left), while the other part of the nodule was more mature and stained in blue with TCS (Fig. 2d right).

When fibrin immunohistochemistry was evaluated together with TCS and collagen immunohistochemical staining, it showed that accumulation still preserved the fibrin feature in a majority of cases (Fig. 1f). However, focal staining reduction, together with collagen type I and type III, were a finding that supported the replacement of fibrin with collagen. In this respect, in patients with collagen type III in the subepithelial area, the amount of fibrinogen and TCS was inversely proportional (Fig. 3a–3e). Similarly, collagen type I spread mostly in the subepithelial area (Fig. 3d). As expected, collagen type IV (Fig. 1i) was found in epithelial and vascular basement membranes. Apart from normal staining in basement membranes, staining in favor of accumulation was not observed with collagen type IV. Collagen type I and collagen type III were important components in the study, as fibrin was organized, it was replaced by newly formed collagen with its fibrillar structure. This showed that the lesion became mature in time and regression should not be expected (Fig. 2b). Collagen type I was more mature collagen, and as expected, it was a normal finding that the basal layer was located in the subepithelial area. Extending into subepithelial accumulation (Fig. 3d) was also a finding indicating that the lesion was mature and regression should not be expected.

Basal-type keratins showed more pronounced staining in the regenerated area as expected (Fig. 1b–1d). It supported the presence of collagen with TCS around the uneven downwardly proliferated epithelial groups (Fig. 2b and 2d). In these areas, collagen type I expression was almost nonexistent. These regions usually contain fibrinoid material accumulation and stromal cell density is also low.

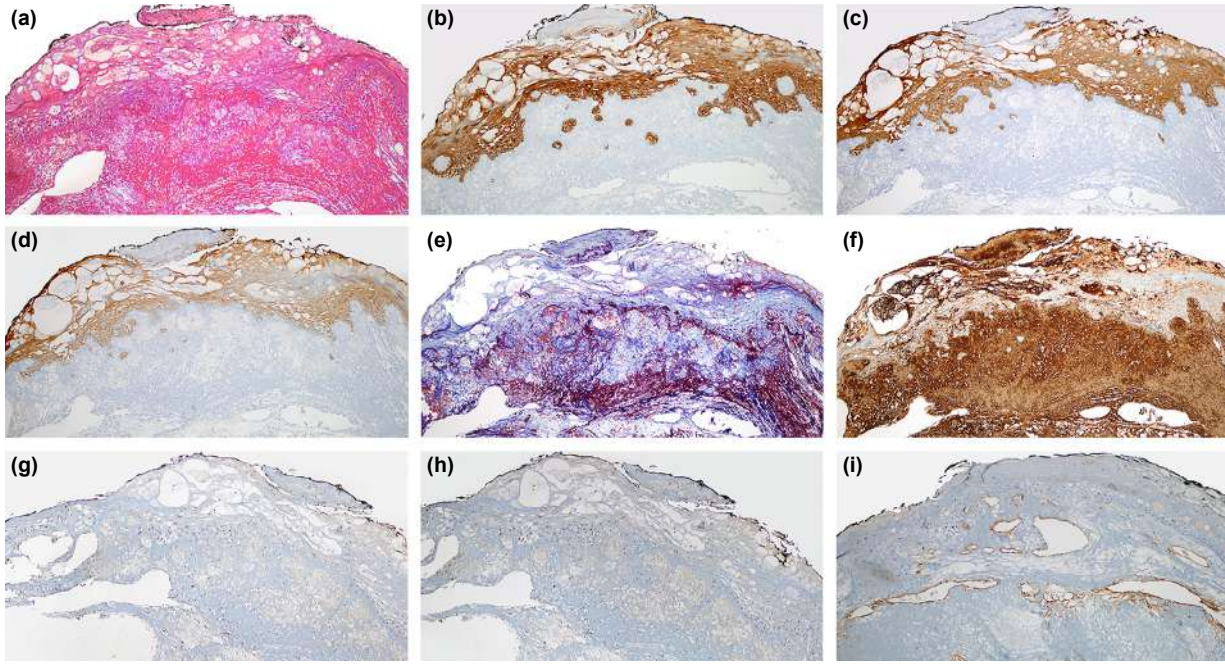

Figure 1. (a) Irregular proliferation, keratosis, intraepithelial, and stromal fibrin accumulation in the squamous epithelium on the larynx nodule and stromal edema (hematoxylin and eosin). **(b–d)** Immunohistochemical staining of CK5/6, CK14, and CK17. **(e)** Trichrome stain. **(f)** Dense fibrin accumulation in the stroma and the surface epithelium. **(g)** Collagen type I and **(h)** collagen type III do not have significant staining. **(i)** Staining vascular basal membrane with collagen type IV (magnification of all sections 200×).

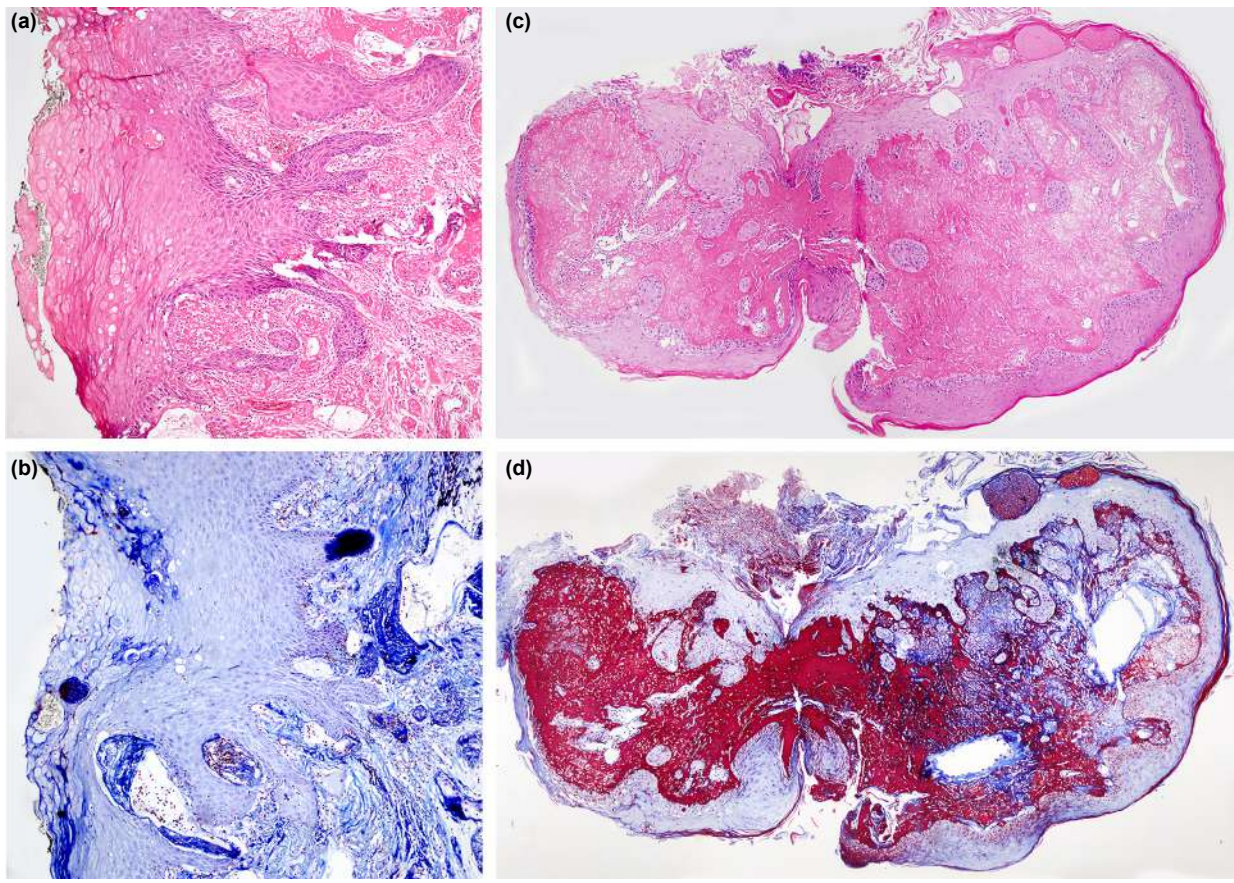

Figure 2. (a) More mature nodules have more coarse collagen bundles stained with hematoxylin and eosin (H&E) stain (400×) and **(b)** blue with trichrome stain (TCS) (400×). **(c)** Prominent downward irregular squamous epithelial proliferation (H&E, 100×). **(d)** More acute, less mature left side of nodule stained red with TCS, and blue on the right shows a more maturated region of the same nodule (100×).

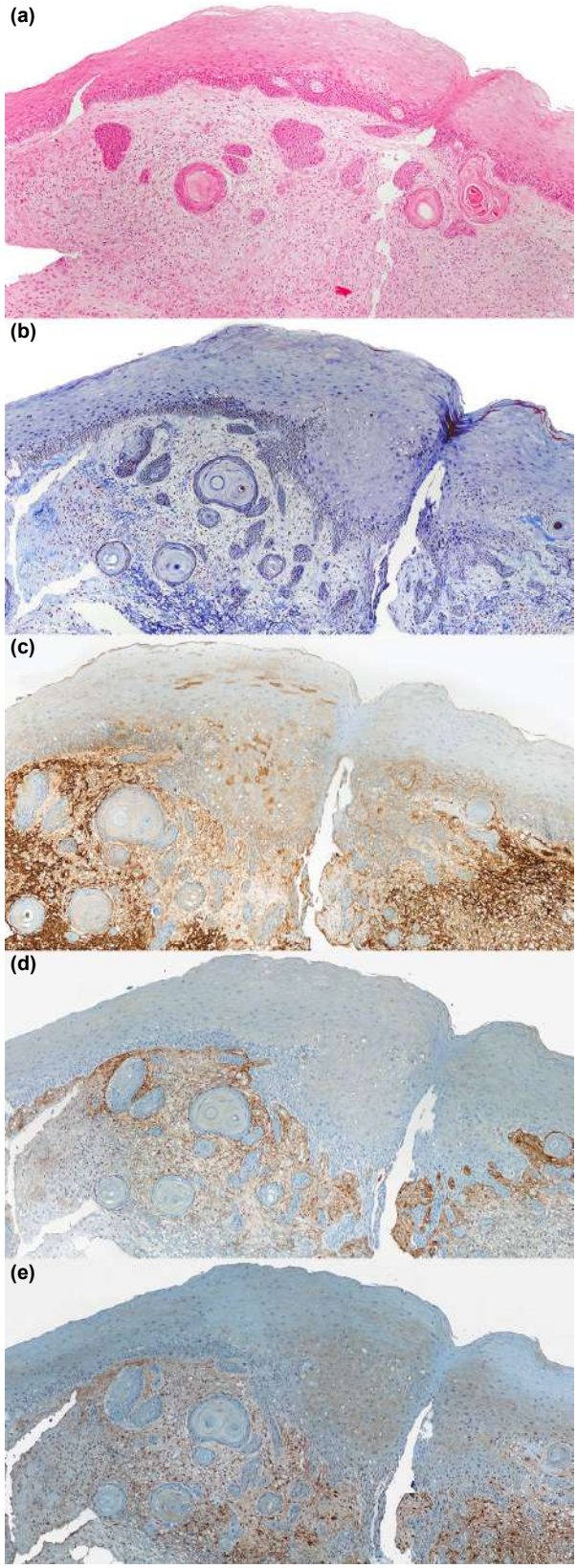

Figure 3. (a) Focal downward irregular squamous epithelial proliferation (H&E). **(b)** Blue staining of collagen in the stroma of the mature type nodule (TCS). **(c)** Fibrin is more pronounced in areas other than epithelial proliferation (fibrinogen). **(d)** Collagen type I and **(e)** collagen type III are a finding that supports the replacement of fibrin with collagen (100×).

In areas where the surface squamous epithelium was hyperplastic, it showed keratosis, and the basal membrane was thick in hematoxylin and eosin staining, subepithelial, and the collagen type I expression was evident, especially in the basal membrane and near the epithelial zone. No staining was observed around the downward irregular proliferated squamous epithelium with collagen type IV and weak expression was observed in the epithelial basement membrane (Fig. 1i).

DISCUSSION

Larynx nodules and polyps are frequent, similar lesions, and generally are distinguished by their size. Although the polyp stroma is more loose and edematous, the histological distinction is not always possible. Microtraumas in the pathogenesis of larynx nodules damage the squamous epithelium and its basement membrane. Surgical excisions are applied to the lesions that do not regress after medical procedures such as voice therapy.

In early-stage lesions, ulceration, regenerative epithelial changes, subepithelial fibrin extravasation, tissue edema, and bleeding are evident. In the late-stage or mature lesions, subepithelial fibrin accumulation contains fibroblasts and incorporates with surrounding connective tissues. The overlying mucosal epithelium is continuous and thin. While the early lesions are rich in fibrin and edematous, the late-stage lesions contain more collagen. Subepithelial accumulation of the fibrinoid material is associated with proliferative epithelial changes seen in both early and more mature lesions. The impairment of the basement membrane integrity of the surface epithelium may cause accumulation of the fibrin-rich exudate within the lamina propria. The breached stromal collagens results in the presence of a temporary matrix containing the fibrinogen.[1,3,4] Collagen type III is distributed throughout the whole lamina propria and does not form distinct fibrous structures and are not organized in a specific direction in normal vocal cords.[6] It does not show a distinct pattern similarly in vocal nodules, which supports the disruption of the laminar structure of the vocal cord lamina propria.

Collagen type I was found just beneath the basal membrane, in the deep layer of the lamina propria and the anterior and posterior maculae flavae.[7] Collagen type IV was present in the epithelial and endothelial basal membrane.[8] Collagen type III fibers were wavy, as previously observed in the vocal folds. Collagen type I fibers were thinner than type III fibers. These results suggest that collagen type III fibers help maintain the lamina propria structure and that type I collagen fibers provide the tensile strength required around the basal membrane and vocal ligament to maintain the vocal fold shape while withstanding vibratory forces.[6] Considering that vocal nodules occur predominantly with changes in the vocal cord lamina propria, it was demonstrated that there was no significant change in collagen types I, III, and IV in vocal nodules, which are the components that make up the normal vocal cord structure.

In the development of nodules, fibrin is the main material causing the formation of a bulge. Unresolved excessive and continuous fibrin deposition becomes permanent. It may also develop as a result of local fibrinolysis defect and the results of red staining with TCS support this. Tateya et al.[9] described that healing was slow and extended up to 2 months in the rat vocal cord. In our cases where the basement membrane was thick and protected, endophytic squamous proliferation forms wide anastomosing cords. An increase in the collagen type III related to the age and maturation of the nodule causes it difficult to regression. The squamous epithelium on the edge of the wound not only tries to cover the wound surface but also tries to separate the layer covering the surface from the living tissue.

Fibrinogen-rich clot covers the ulcerated skin of the body and forms a hard dry crust.[10–12] The dry crust is not seen in humid mucosal ulcerations. The epithelium at the edge of the defect would proliferate irregularly into the superficial fibrinoid mass and tries to limit the base. As re-epithelization progresses, basement membrane proteins reappear regularly from the edge of the wound.[10] Excessive fibrin accumulation in the lamina propria may also occur without an ulcerated surface epithelium (Fig. 2c). Epithelial proliferation starts with the contact of the epithelium with fibrin, regardless of the size of the lesion. Especially the loss of staining with collagen type IV in these areas indicates a lack of epithelial basal membrane. The epithelium comes into direct contact with the fibrinoid material and the proliferation mechanism is stimulated to exclude the fibrinoid substance and restore the epithelial barrier.[11] Then, squamous cells return to their normal phenotypes and once again firmly attach to the established basement membrane.[3] The fibrinoid accumulation due to the fibrin lysis defect in the ligneous mucosal diseases also causes apoptosis of epithelial cells and participates in the subepithelial accumulation.[2] This etiology does not apply to vocal nodules without fibrin lysis defect. Re-epithelialization of keratinocytes at the edge of the wound is stimulated and promotes migration and proliferation into the fibrin-rich matrix with cytokines.[13] We observed that the squamous epithelium in direct contact with fibrin shows more prominent irregular downward proliferation. Collagen replaces the unremoved excessive fibrin exudation over time. At the stage of the organization, the epithelium also tries to exclude and expel the fibrin by showing hyperplasia. All stages in the process of larynx nodules are quite similar to the ligneous mucosal disease. The ligneous mucosal disease may involve many places, especially the eyelids and mouth. Whereas laryngeal nodules are localized, nonsystemic lesions that exhibit chronic and excessive fibrin extravasation and cannot be lysed or regressed.

CONCLUSION

The accumulations in the ligneous mucosal disorder result from an abnormal healing process and are formed as a combination of organized fibrinogen, epithelial fragments, and connective tissue matrix. Our findings show that the pathogenesis of subepithelial deposits seen in the laryngeal nodule is similar to the ligneous mucosal disease. However, etiologically they are different lesions. Irregular epithelial proliferation toward the fibrinoid material is one of the main histological findings in both lesions. It is essential to clarify the etiology and pathogenesis of the lesion before deciding whether an epithelial proliferation is neoplastic.

Ethics Committee Approval

This study approved by the İstanbul Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (Date: 25.09.2019, Decision No: 2019/514/162/7).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: K.B., Ö.G.; Design: K.B.; Supervision: Ö.G., D.D.; Fundings: K.B., M.A., S.O.; Materials: K.B., Ö.G., M.Ç., Ş.S.A.; Data: K.B., Ö.G., M.Ç., Ş.S.A., M.A., S.O.; Analysis: K.B., Ö.G., D.D.; Literature search: K.B., Ö.G., D.D., M.Ç., Ş.S.A., M.A., S.O.; Writing: K.B., Ö.G.; Critical revision: K.B., Ö.G.

Conflict of Interest

None declared.

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Laringeal Nodüllerde Subepitelyal Fibrinöz Birikim ve İlişkili Epitelyal Proliferasyon

Amaç: Larinkste fibrinoid madde birikimi ve zamanla subepitelyal kollajenöz bağ dokusunun artması aşırı büyüme ile sonuçlanır. Mukozal epitel, fibrinoid birikimini sınırlamak ve ortadan kaldırmak için subepitelyal alana doğru çoğalabilir. Bu çoğalma, invaziv kanser benzeri bir görüntüye neden olabilir. Bu çalışmada fibrinoid madde birikiminin patogenezi ve ilişkili skuamöz epitel proliferasyonunun gelişim mekanizmaları üzerinde durulmuştur.

Gereç ve Yöntem: Beş yüz yetmiş beş laringeal nodül yeniden incelendi ve değişen derecelerde düzensiz skuamöz epitel proliferasyonu gösteren 111 tanesi çalışmaya dahil edildi. İmmünhistokimyasal olarak CK5/6, CK17, CK14, kollajen tip I, kollajen tip III, kollajen tip IV ve fibrinojen için immünohistokimyasal boyama yapıldı. Kollajenin histokimyasal boyamasında modifiye Masson trikrom yöntemi kullanıldı.

Bulgular: Akut lezyonların %18'inde ödem ve %42'sinde fibrin birikimi mevcuttu. Nispeten matür lezyonlar çoğunlukla yoğun kollajen lifleri içeriyordu. Kollajen tip III'ün yoğunluğu, fibrin birikimi miktarı ile ters orantılıydı. Kollajen tip IV epitelyal ve vasküler bazal membranlarda bulundu. Fibrin boyanma yoğunluğundaki azalma ve tip I ve tip III kolajen varlığı, fibrinin kolajen ile yer değiştirdiğini gösteriyordu. Bazal tip keratinler, epitelin rejenerasyon alanlarında daha belirgin boyama gösteriyordu. Laringeal subepitelyal fibrinoid madde birikimi kollajen ile yer değiştirdiği için lezyonun gerilemesi zorlaşmaktaydı.

Sonuç: Düzensiz skuamöz epitel proliferasyonu lezyonun evresinden bağımsız olarak mevcuttur. Etiyolojisi farklı olmakla birlikte, oluşan lezyonlar histolojik olarak lignöz mukoza hastalığında görülenlere benzerdir.

Anahtar Sözcükler: Fibrinöz birikim; kollajen; laringeal nodül; skuamöz proliferasyon.