의학석사 학위논문

The cause of capsular contracture in silicone-implant rhinoplasty: An immunohistochemical analysis of capsules associated with silicone implants.

실리콘 보형물 코성형 후 발생한 캡슐 구축의 원인: 면역조직화학염색법을 이용한 실리콘 캡슐 분석

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Abstract

Introduction

In this study, we attempted to identify the pathological processes underlying capsular contraction in silicone-implant rhinoplasty through immunohistochemical evaluation of the capsules.

Materials and Methods

Capsules were obtained from 12 patients (3 male and 9 female) who underwent revision rhinoplasty because of unsatisfactory aesthetic results or complications. The patients were segregated into 2 groups: capsular contracture group (CC; n=3) and non-capsular contracture group (NCC; n=9). The existence of capsular contracture was determined from the patient's history, preoperative photographs, previous surgical procedures, and present nasal status. Immunohistochemical analyses were performed to analyze the substance-P levels, and the number of mast cells, neutrophils, and myofibroblasts present in the capsules.

Results

The CC group showed a higher level of substance P than the NCC group (P = 0.006). However, mast cell and neutrophil counts

and staining grade of the myofibroblasts were not different between the 2 groups. There was a significant association between the staining grade of the myofibroblasts and chymase positive mast cell counts (P = 0.04) and tryptase positive mast cell counts on the borderline significance (P = 0.051), but not the neutrophil counts (P = 0.298).

Conclusion

Our results demonstrate that capsular contracture is associated with increased substance-P levels in the tissues and suggest that persistent neurogenic inflammation due to mechanical stimulation by the silicone implant is a possible cause of capsular contracture.

Keyword : Capsular contracture, rhinoplasty, silicone implants, mast cells, myofibroblasts, substance P
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List of abbreviation

α-SMA: alpha-smooth muscle actin

MPO: myeloperoxidase

SP: substance P

HPF: high-power field

ECM: extra cellular matrix

TGF-β1: transforming growth factor-β1

PDGF: platelet-derived growth factor

BoTA: Botulinum toxin A

CC: capsular contracture group

NCC: non- capsular contracture group

Chapter 1. Introduction

For major dorsal augmentation, alloplastic materials such as silicone, Gore-Tex, and Medpor are used frequently as an alternative to autogenous material owing to ease of acquisition and the technical simplicity of the procedure.[1,2] Among these materials, silicone has been used widely since the 1960's because of its nontoxic nature, chemical stability, simplicity of use, and inexpensiveness.[3] Nonporous silicone does not permit ingrowth of neighboring tissue and its presence results in the development of a thick fibrous capsule similar to a foreign body reaction, which is a part of the normal healing process. Capsule formation may help maintain the position of the implant and prevent adhesion with neighboring tissue; this also makes subsequent removal easier.[2] However, complications associated with the use of silicone implants are additionally thought to arise from the presence of the capsule. Noted complications include infection, mobility, and contracture of the nose.[1,4] Among these, contracted nose, which is represented by a short and upturned nose, is common in patients who have undergone silicone implant rhinoplasty.[5,6]

Contracted nose occurs in a variety of circumstances. Commonly, patients who develop a contracted nose have a history of multiple

rhinoplasties including silicone-implant augmentation and its subsequent removal. Repeated injuries to the nasal tissue, infection, absence of dorsal volume following silicone removal, and over-aggressive resection of normal cartilages are presumed to contribute to the development of nasal contracture. However, nasal contracture develops even with silicone *in situ* or with a history of one-time silicone removal. In summary, although contracted nose is not caused solely by capsular contracture, this process is presumed to play an important role in the development of this condition, especially in patients for whom the development of contracture cannot be explained otherwise.

The etiology of capsular contracture is not fully understood; however, the process is thought to be multifactorial.[7] Studies evaluating silicone capsular contracture have mainly been performed by cosmetic surgeons that specialize in breast augmentation and reconstruction. In these studies, the incidence rates of capsular contracture following breast augmentation range from 2.8% to 20.4%.[8-11] Despite the wide use of silicone for nasal augmentation, few studies have evaluated nasal silicone associated capsular contracture.[4,12-14] Kim et al. reported that 35% of revision rhinoplasty surgeries performed after silicone augmentation is due to capsular contracture.[4] To our knowledge, the incidence rate of

capsular contracture following augmentation rhinoplasty using a silicone implant has not been reported and the mechanism behind this process has not been evaluated.

In this preliminary study, we attempted to identify the pathological process underlying capsular contracture by evaluating and comparing capsules harvested during revision rhinoplasty.

Chapter 2. Materials and methods

From March of 2014 to September of 2016, capsules were obtained from 12 patients (3 male, 9 female) whom had a silicone implant removed during revision rhinoplasty due to unsatisfactory aesthetic results or complications. All patients were referred for revision rhinoplasty after augmentation rhinoplasty using a silicone implant was performed at an outside clinic. The study protocol was approved by our Institutional Review Board (IRB No. 16-2013-110-081).

2.1. Anthropometric measurement

Image analysis was performed using AutoCAD® (Autodesk Inc) (Figure 1). The lateral photographs were analyzed, which included measurement of nasal length and columellar-facial angle (CFA). Nasal length and CFA were measured using a previously described method.[6] Nasal length was calculated as a ratio of the length between nasion and tip-defining point (N-TDP) to the distance between pupil and anguli oris. The CFA was measured at the junction of a line drawn from the anterior columella to the subnasal

and the line perpendicular to the Frankfort horizontal. Park et al. reported values obtained from healthy Korean volunteers: nasal length ratio above 0.6, mean CFA 109.7° (M/F, 108.1°/111.6°).[6]

2.2. Capsule harvest

Capsule specimens were harvested when the silicone implant was removed during revision rhinoplasty by a single surgeon. Specimens were obtained mainly from the caudal part of the posterior surface of the implant because disruption of the anterior capsule could lead to vascular compromise and irregularities in the overlying skin.

2.3. Immunohistochemistry

Immunohistochemical staining was performed using 4-μm sections of formalin-fixed paraffin-embedded specimens. Sections were deparaffinized with xylene and rehydrated using a series of ethanol grades. If antigen retrieval was required, it was performed at this time as specified for each antibody below.

We used mouse monoclonal antibodies directed against tryptase (ab2378, Abcam; Cambridge, UK) and chymase (MA5-11717, Abcam; Cambridge, UK) for mast cell staining and against alpha-smooth muscle actin (α-SMA) (202M-95, Cell Marque; Rocklin,

California, USA) for myofibroblast staining. Goat polyclonal antibodies directed against myeloperoxidase (MPO) heavy chain (sc-34159, Santa Cruz Biotechnology; Dallas, Texas, USA) were used for neutrophil staining. Substance P (SP) was stained using rabbit monoclonal antibodies (ab133240, Abcam; Cambridge, UK). The sections were counterstained with hematoxylin.

We calculated the number of mast cells and neutrophils present per high-power field (HPF, 400x magnification). Five HPF's focused on the capsular tissue were counted for each specimen. The average number of tryptase-positive, chymase-positive, and MPO-positive cells were enumerated. Qualitative rather than quantitative measurements were used to interpret the results of α-SMA and SP staining. The degree of staining was graded on a 3-point scale: 0 = negative, +1 = low intensity, +2 = high intensity (Figure 2). Low intensity (+1) was defined as a staining intensity below that of reference staining. Normally, anti-α-SMA antibody stains smooth-muscle cells in vessel walls and anti-SP antibody stains nerve endings in healthy skin. For verification of the specificity of the SP antibody, we tested paraffin-embedded normal healthy skin and used this to set the reference intensity for SP staining.

All slides were examined by one independent investigator. All

histologic evaluations were performed using photographs taken by microscope (Olympus BX 51, Tokyo, Japan) with a digital camera system (Olympus DP 25, Tokyo, Japan).

2.4. Statistical analyses

For statistical analysis, the Mann-Whitney, Kruskall-Wallis, or Spearman's correlation test was used as appropriate for the analysis of data. In addition, Fisher's exact test or linear-by-linear association was used to analyze semi-quantitative data. All results were expressed as mean ± SD. Statistical significance was presumed at $P < 0.05$. All analyses were performed using SPSS Version 18 software (SPSS, Inc, Chicago, IL, USA).

Chapter 3. Results

3.1. Demographic findings and baseline

The main reason for silicone removal was displacement (5 patients), followed by nasal contracture (4 patients), dorsal skin thinning (2 patients), and unexpected high dorsum (1 patient). The mean age was 29.8 years (range, 21–46 years), and the mean number of previous surgeries was 2.1 (range, 1–7 years). Duration of silicone implantation was 7.5 years on average (range, 2–25 years). An L-shaped silicone implant, which extends from the radix to the tip, was used in 1 case, and an I-shaped silicone implant had been used in 11 cases. Demographic findings and baseline data are presented in Table 1.

Considering preoperative photographs, present nasal status, and previous surgical history, capsules from 3 patients (case no. 1, 2, and 12) were assigned to the capsular contracture group (CC; n = 3). Capsules from 9 patients (case no. 3 through 11) were assigned to the non-capsular contracture group (NCC; n = 9). No significant differences between the groups were considered for the baseline data (Table 2).

3.2. Immunohistochemical findings

The number of mast cells was 4.2 ± 4.2 per HPF as indicated by tryptase staining and 2.8 ± 2.2 per HPF as indicated chymase staining. The number of neutrophils as indicated by immunoreactive cells for MPO was 2.4 ± 3.0 per HPF. The grade of staining intensity for α-SMA was 0 in five capsules, +1 in five capsules, and +2 in two capsules (Table 1). Higher numbers of mast cells were observed in capsules with higher grades of α-SMA staining intensity (Table 3). The difference in mast cell number as indicated by chymase staining was significantly different for each grade of α-SMA staining intensity (P = 0.04, Kruskall-Wallis test). The difference in the number of tryptase positive mast cells also reached a marginal statistical significance (P = 0.051, Kruskall-Wallis test). In contrast, the number of MPO positive neutrophils was not significantly correlated with α-SMA staining grade (P = 0.298, Kruskall-Wallis test).

Substance-P staining was positive in five cases: grade +1 in 3 cases and grade +2 in 2 cases (Table 1). A higher level of substance P was measured in the CC group than in the NCC group (P = 0.006, linear by linear association). One case (33.3%) from the CC group and 1 case (11.1%) from the NCC group showed a +2

α-SMA staining grade, with no significant difference noted between the 2 groups (P = 0.507, linear by linear association).

Detailed data for case no. 1 is presented in Figure 3 as an example of capsular contracture. Because the patient had nasal contracture after a single augmentation rhinoplasty procedure using a silicone implant, but no tip manipulation, it is possible that silicone implant-related capsular contracture was responsible for the condition. Twenty-five years after the surgery, mast-cell hyperplasia was observed in the capsular tissue without any additional inflammation or injury as a possible cause. Figure 3 also shows that the staining intensities for α-SMA and SP were high within the same area of the fibrous capsule.

Chapter 4. Discussion

Capsule formation after implantation of non-biological materials is a type of wound-healing process that results in the formation of a barrier between the foreign material and the body. Under normal conditions, equilibrium between matrix synthesis and tissue remodeling is maintained to heal the wound and regain near-normal function. The hypertrophic scar theory postulates that capsular contracture is caused by an aberrant fibrogenic healing response arising from surgical insult to the tissue surrounding the implant such as formation of a seroma or a hematoma.[15] In pathogenic fibroproliferative conditions such as hypertrophic scars, there is excessive and disorganized collagen deposition, and profibrotic mediators contributing to this collagen imbalance are observed.[16] Recent studies on human subjects and some preclinical studies suggest that a neuroinflammatory axis mediated by neuropeptides and mast-cell signaling is an important fibrogenic stimulus.[16] This implies that fibrogenesis is governed by a maladaptive neuropeptide-mast cell-myofibroblast signaling pathway (Figure 3).

The mast cell is a key player in the initiation and propagation of

the inflammatory response. Our results showed that average count of mast cells, which was the same as tryptase positive cell counts in this study, in capsule was approximate 4 per HPF. In addition, the difference between CC and NCC group did not reach statistical significance (Mann–Whitney test: $P = 0.232$, unpublished data). In humans, almost every organ contains a small population of mast cells.[17] These are particularly abundant within the mucosa and connective tissues of the tongue, skin, and respiratory and gastrointestinal tracts.[18] Two to 8% of the cells in healthy skin are mature mast cells.[19] Activated mast cells induce changes in vascular permeability and cause vasodilatation. In addition, mast cells activate neighboring endothelial cells, leading to the expression of adhesion molecules and cytokines needed for leukocyte rolling, adhesion, activation, and transmigration.[20] Mast cell hyperplasia has been implicated in the development of chronic inflammatory processes such as fibrotic disorders and wound healing.[21–23] Histology reveals increased numbers of mast cells in keloids,[24] and an improvement in the appearance of keloids following intralesional cryotherapy was correlated with decreased numbers of mast cells.[25] In current study, it seemed to be that the field of exam close to the vessel containing subcutaneous tissues had more mast cells. Thus, if the thickness of fibrous capsule was thinner, the result could

show higher mast cells count.

Considering mast cell phenotype, the ratio of chymase positive cell count to tryptase positive cell count was 0.8 ± 0.2. Two phenotypes of human mast cells were initially classified by Schwartz based on the presence of chymase within their exocytotic granules.[26,27] Mucosal mast cells associated with allergic and parasitic diseases contain only tryptase (namely Mt) and are found mainly in the mucosa of the gastrointestinal system and the lamina of the respiratory tract. Conversely, mast cells in the connective tissue contain tryptase, chymase, cathepsin G, and carboxypeptidase (namely Mtc) and are localized within the submucosa of the gastrointestinal tract, skin, and peritoneum.[28] Although we did not use simultaneous double labeling technique in immunohistochemistry, our results also showed that Mtc had a tendency to be observed more often in capsule tissue. The mechanisms by which mast cells terminally differentiate into distinct phenotypes is probably governed by the cytokines present within the local microenvironment.[29]

In this study, an increased number of mast cells were observed in the capsules with a high content of myofibroblasts (α-SMA) in both groups. Immunohistochemical staining of the capsular tissue against chymase and tryptase showed that both phenotypes of mast

cells were associated with myofibroblast proliferation and differentiation. Actions of chymase include conversion of angiotensin I into angiotensin II, inactivation of bradykinin, and degradation of extracellular matrix (ECM) components such as collagen type IV and laminin.[30] Therefore, mast-cell secretory products other than chymase may promote a pro-fibrotic pathway in fibrous capsular tissue. Mast cell tryptase has been shown to be a potent fibroblast mitogen that can signal the phenotypic transformation of myofibroblasts. Tryptase has also been shown to be an upregulator of matrix synthesis.[31] However, the primary mediators from cutaneous mast cells responsible for pathologic fibrogenesis have not been clearly identified.

In the present study, although the grade of α-SMA was not significantly different between the two groups, capsules in NCC group had a tendency to show the negative result of α-SMA staining (44.4%). Activated fibroblasts become myofibroblasts, which, within connective tissue, are regarded as the principal effector cells in fibrosis. Myofibroblasts are mesenchymal cells that express α-SMA. They are responsible for collagen deposition, growth factor liberation, and mechanical wound contraction.[32,33] A variety of pro-fibrotic mediators produced by immune cells have been recognized, including transforming growth factor-β1 (TGF-

β1), platelet-derived growth factor (PDGF), and endothelin-1.[34] These cytokines play a critical role in fibroblast chemoattraction, induction of myofibroblast formation, and inhibition of myofibroblast apoptosis.[35] TGF-β1 appears to be constitutively expressed by mast cells and is also liberated into the local environment.[36] Elevated levels of TGF-β1 were commonly observed in previous animal models of peri-implant capsule formation.[37,38] Myofibroblast hyperplasia is also common in most fibroproliferative conditions such as hypertrophic scar formation.[39] The persistence of myofibroblasts results in excessive ECM synthesis. Because we analyzed the data using ordinal variables ranked as three-point grade and harvested only the small part of the silicone capsule for aesthetic purpose, the result did not prove the association between myofibroblast hyperplasia and capsular contracture.

In this study, SP immunoreactive staining was stronger in the CC group than in the NCC group. Similarly, elevated levels of SP have been observed in various fibrotic conditions including scleroderma, keloids, and hypertrophic scar formation.[40-43] Mast cells and fibroblasts are suddenly exposed to activating signals and growth factors during a surgery-induced injury. Under normal conditions, as soft-tissue healing progresses, fibroblast, myofibroblast, and mast cell numbers diminish. However, persistent noxious and

mechanical stimuli caused by the presence of the silicone prosthesis result in persistent neuropeptide synthesis and chronic activation of fibroblasts and mast cells. Caudal part of the silicone implant has higher mobility than the cranial part which places in subperiosteal space. Correspondingly, the caudal part of the implant may have a large impact on the fibrogenic process. Neuropeptides such as SP are a family of extracellular signaling molecules that play an essential role in wound healing.[16] Although significant relationships were not found between SP and mast cells numbers in the current study, SP has been called a mast cell secretagogue.[44] SP also stimulates fibroblast proliferation and impairs proapoptotic signaling in myofibroblasts.[45] Histamine is a well-known mast cell-derived mediator that accounts for 10-15% of the dry granule weight of mast cells.[46] Histamine causes the release of SP from type-C unmyelinated nerve fibers.[47] Substance P, in turn, potentiates histamine release. Thus, fibroproliferative stimuli persist and escape regulatory control. As mast cells and fibroblasts are activated, a vicious cycle is engaged whereby growth factors synthesized and liberated by these cell types function to maintain further cell recruitment, proliferation, differentiation, and neuropeptide synthesis. These events create an environment of

sustained myofibroblast hyperplasia resulting in disorganized collagen deposition (Figure 3).

Elucidating the biological mechanisms involved in the pathologic fibrosis leading to implant-related capsular contracture is a critical step in developing strategies to treat and control capsule contracture. Since, as this study suggests, a neuropeptide-mast cell-myofibroblast axis may play a role in capsule contracture, interruption of this pathway may be effective in preventing fibrosis-induced contracture. Mast-cell stabilizers such as ketotifen fumarate and sodium cromoglygate have been tested in various human and animal models.[22,48] However, it has been reported that ketotifen and cromolyn therapy cannot reverse existing fibrosis. Interventions targeting mast cell signaling will be more effective in preventing fibrosis. It has been reported that leukotriene is closely associated with myofibroblasts.[49] Leukotriene receptor antagonists (LTRA), namely zafirlukast and montelukast, have been used to reduce the occurrence of capsular contracture in breast-augmentation surgery.[50,51] However, the contracture grading score began to increase when treatment was discontinued. Zafirlukast has also been associated with hepatotoxicity. Recent reports suggest that Botulinum toxin A (BoTA) is effective in treating and reducing the size of keloids and hypertrophic scars.[52,53]

BoTA inhibits vesicular release of the neurotransmitter acetylcholine (ACh) at the neuromuscular junction.[54] Recent studies suggest that BoTA inhibits not only ACh release but also SP release from the autonomic nervous terminals.[55] SP is a major excitatory non-cholinergic neurotransmitter that causes depolarization of the membrane and thus induces contraction of smooth muscle.[56] In animal studies, it was shown that BoTA decreased mast cell activity, the formation of myofibroblasts, and capsule thickness.[37,57] These findings suggest that BoTA may be an option for the treatment and prevention of capsular contracture.

In contrast to breast augmentation surgery, complications from rhinoplasty also include deviation and skin problems in addition to contracture. Because silicone implants cannot adhere to neighboring tissue, capsule formation occurring because of a normal foreign body reaction helps to fasten the implant to the skin and maintain its position. Capsule formation can also improve the transparency of the silicone prosthesis seen through thin skin. Because capsule formation as a normal physiologic healing response does have its advantages, prevention of only abnormal fibrogenic activity causing contracture of the surrounding structure is the goal of future treatments.

With only 12 patients, our report must be considered preliminary. While our evidence supports a neuroinflammatory axis as the mechanism behind capsular contracture, further experiments with additional biomarkers and larger group of patients may reveal more information about the pathogenesis of capsular contracture.

Chapter 5. Conclusion

This preliminary histological study, although performed on only 12 patients, demonstrated that capsular contracture is associated with increased substance-P levels in the capsular tissue. Silicone-induced mechanical stimuli are thought to play a role in persistent neurogenic inflammation, which may be one of the causes of capsular contracture.

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Table 1. Raw data for 12 cases of revision rhinoplasty with implant removal

Case no	Sex/Age	Number of previous surgeries	Duration (years)	Type of implant	Main reason for revision	CFA (°)	Nasal length ratio	Immunohistochemical findings				
								Tryptase (Immunoreactive cell count/HPF)	Chymase (Immunoreactive cell count/HPF)	MPO (Immunoreactive cell count/HPF)	α-SMA grade	SP grade
1[a]	M/46	1	25	I-shape	Contracted nose	115	0.56	6.0	5.0	7.0	+2	+2
2[a]	F/22	1	2	L-shape	Contracted nose	125	0.51	4.0	3.0	1.0	0	+2
3	F/30	7	2	I-shape	Contracted nose	115	0.58	1.0	1.0	1.0	0	+1
4	F/22	1	3	I-shape	Displacement & Skin problem (tip)	106	0.67	4.0	4.0	1.0	+1	+1
5	M/43	3	17	I-shape	Displacement & Deviation	107	0.64	10.2	4.8	4.0	+1	0
6	F/28	5	2	I-shape	Skin problem (transparency)	115	0.60	14.0	7.6	3.0	+2	0
7	M/37	1	19	I-shape	Displacement	106	0.55	1.2	0.8	9.0	0	0

Table 1. Raw data for 12 cases of revision rhinoplasty with implant removal (continued)

Case no	Sex/Age	Number of previous surgeries	Duration (years)	Type of implant	Main reason for revision	CFA (°)	Nasal length ratio	Immunohistochemical findings				
								Tryptase (Immunoreactive cell count/HPF)	Chymase (Immunoreactive cell count/HPF)	MPO (Immunoreactive cell count/HPF)	α-SMA grade	SP grade
8	F/21	1	2	I-shape	Displacement	112	0.68	1.0	1.2	2.0	0	0
9	F/23	1	6	I-shape	Skin problem (transparency)	97	0.65	1.0	1.0	2.6	0	0
10	F/27	2	6	I-shape	Displacement	106	0.64	2.0	1.6	1.0	+1	0
11	F/27	1	4	I-shape	High dorsum	105	0.66	1.0	1.0	0.2	+1	0
12[a]	F/31	1	2	I-shape	Contracted nose & Deviation	112	0.55	4.8	2.3	0.4	+1	+1

CFA, columellar–facial angle; HPF, high power field; MPO, myeloperoxidase; SMA, smooth muscle actin; SP, substance P.

Shadowing indicates upturned and short nose as determined by reference values; CFA > 110, nasal length ration ≤ 0.6.[6]

[a] The capsular contracture group.

Table 2. Baseline data according to capsular contracture

	Patients, No. (%)			*P* value
	Total (n = 12)	Capsular contracture (+) (n = 3)	Capsular contracture (−) (n = 9)	
Male	3 (25%)	1 (33.3%)	2 (33.3%)	1.000†
Female	9 (75%)	2 (66.7%)	7 (77.8%)	
L−type	1 (8.3%)	1 (33.3%)	0 (0%)	0.250†
I−type	11 (91.7%)	2 (66.7%)	9 (100%)	
Number of surgeries (Range)	2.1 ± 2.0 (1 – 7)	1.0 ± 0.0 (1)	2.4 ± 2.2 (1 – 7)	0.187‡
Duration (years) (Range)	7.5 ± 8.1 (2 – 25)	9.7 ± 13.3 (2 – 25)	6.8 ± 6.6 (2 – 19)	0.773‡
Age (years) (Range)	29.8 ± 8.3 (21 – 46)	33.0 ± 12.1 (22 – 46)	28.7 ± 7.2 (21 – 43)	0.458‡

Values are given as mean ± standard deviation.

†Fisher’s exact test, ‡Mann-Whitney test.

Table 3. Comparison of mast cell and neutrophil count by α-SMA staining grade

Immunoreactive cell count (Average number per HPF)	α-SMA staining grade			*P* value*
	0 (n = 5)	+1 (n = 5)	+2 (n = 2)	
Tryptase (+)	1.6 ± 1.3	4.4 ± 3.6	10.0 ± 5.7	0.051
Chymase (+)	1.4 ± 0.9	2.7 ± 1.6	6.3 ± 1.9	0.040
MPO (+)	2.7 ± 3.7	1.1 ± 1.7	5.0 ± 2.8	0.298

HPF, high power field; SMA, smooth muscle actin; MPO, myeloperoxidase.

Values are given as mean ± standard deviation.

* Statistical significance was tested by Kruskall-Wallis test.

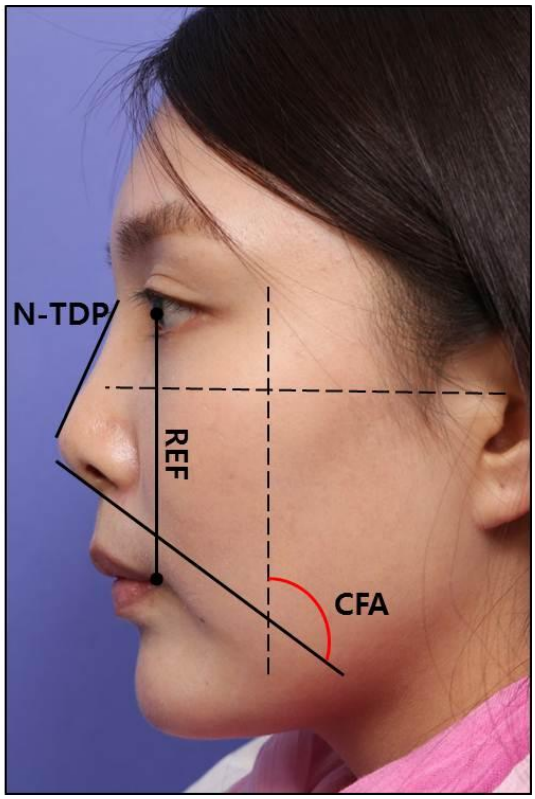

Figure 1. Anthropometric measurements for short nose evaluation. Nasal length was measured as the distance between the nasion and the tip-defining point (N-TDP). Reference length (REF) was measured as the distance from the pupil to the anguli oris.The columellar-facial angle (CFA) was measured as an angle between two lines: the line from the anterior columella to the subnasale and the line perpendicular to the Frankfort plane.

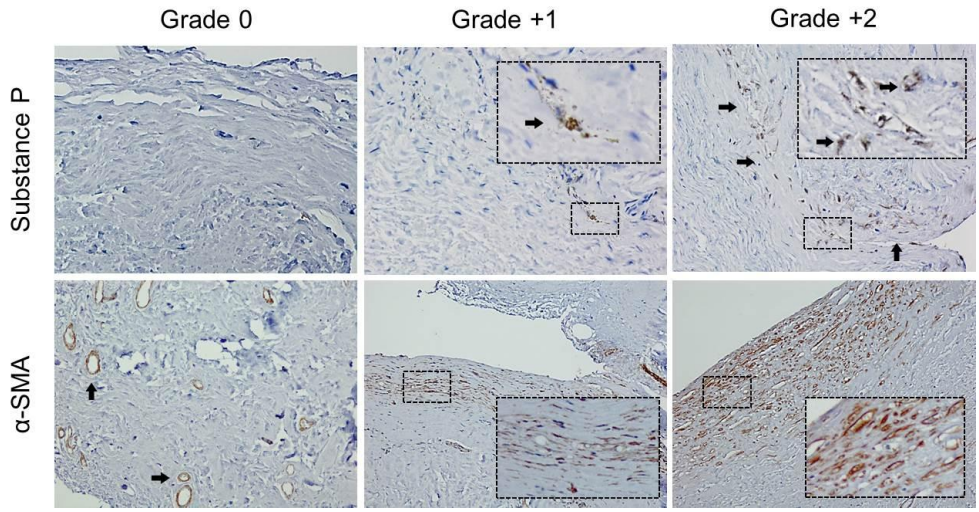

Figure 2. Grading system for staining intensity. Grade 0 = negative: below, not myofibroblast but smooth muscle cells in vessel walls stained with α-SMA are indicated by arrows. Grade +1 = low intensity or weak positive: above, substance-P staining can be observed only at high magnification. Grade +2 = high intensity or strong positive: below, myofibroblasts stained with α-SMA are present as strong as staining of the vessels. below, high levels of α-SMA are indicated by strong staining of the vessels. Magnification, 400x (above) and 200x (below).

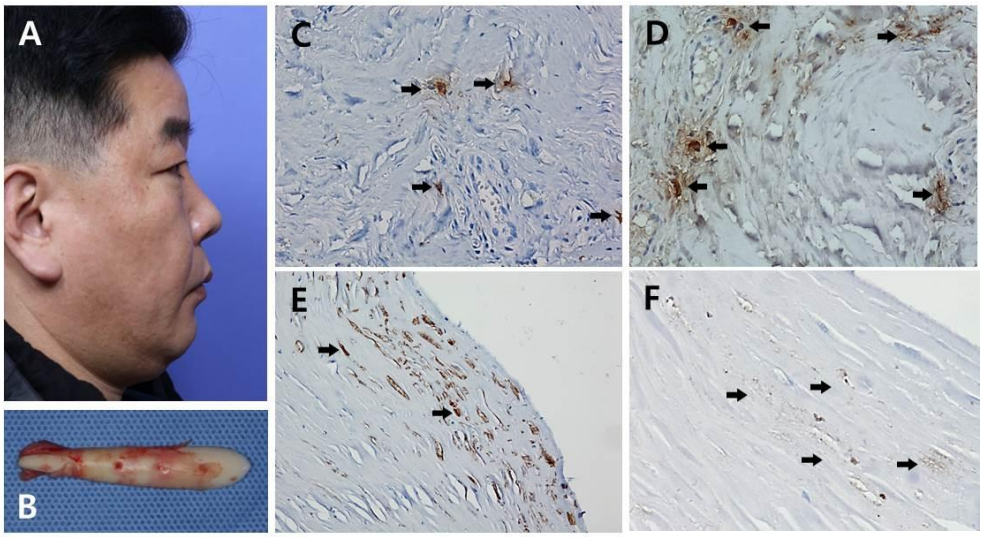

Figure 3. Contracted nose associated with a silicone implant. (A) Preoperative lateral view shows a short and upturned nose. (B) Fibrous capsule with silicone implant. (C) Chymase+ mast cells are present as shown with arrows. Magnification, 400x (D) Tryptase+ mast cells are stained with arrows. Magnification, 400x (E) α-SMA staining at 200x. Myofibroblasts are indicated by arrows. (F) Secreted substance P in the fibrous capsule is indicated by arrows. Magnification, 400x.

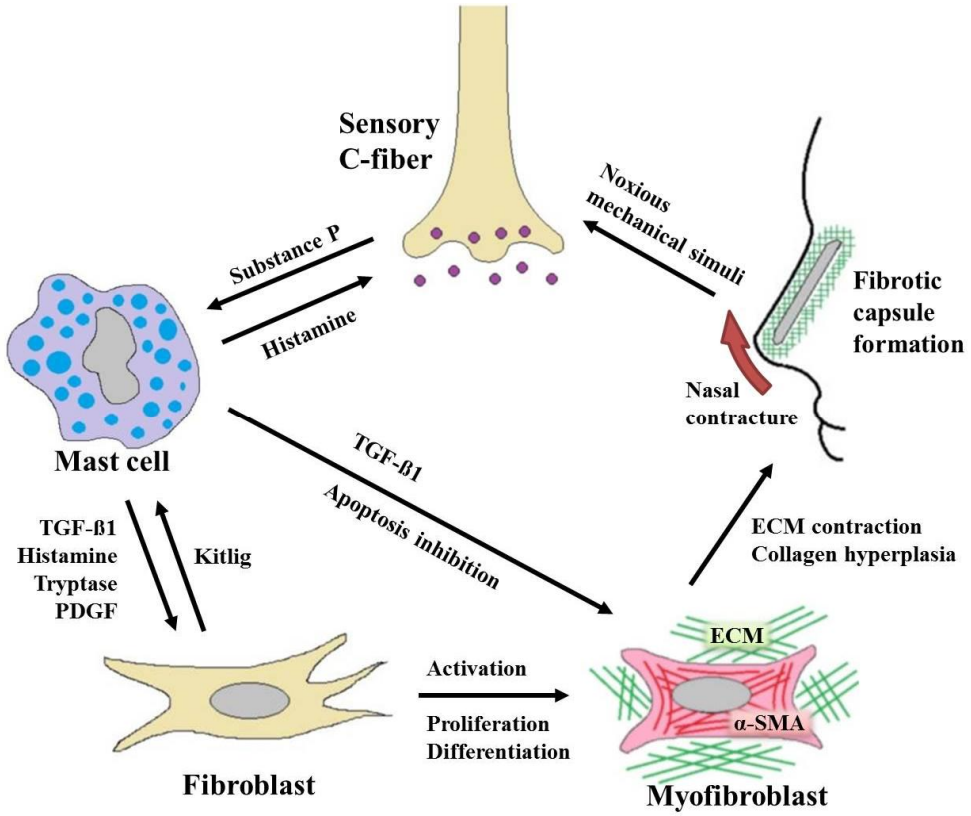

Figure 4. Neuropeptide-mast cell-myofibroblast signaling pathway. Surgery-induced injury activates mast cells and fibroblasts by neuropeptide signaling. In at-risk patients, persistent noxious and mechanical stimuli caused by the presence of a silicone prosthesis results in continued neuropeptide synthesis and chronic activation of myofibroblasts. Over time, collagen hyperplasia and ECM contraction results in nasal contracture. TGF-ß1, transforming growth factor-beta1; PDGF, platelet-derived growth factor; ECM, extracellular matrix; α-SMA, alpha-smooth muscle actin.

국문초록

서론: 비성형 후 제거된 실리콘 캡슐에 대하여 구축과 관련된 병적인 섬유화 진행 기전을 연구하고자 하였다.

재료 및 방법: 실리콘 삽입 비성형 후 미용적인 불만족으로 재수술을 시행한 환자 12명에서 얻어진 캡슐 조직을 대상으로 하였다. 남자가 3명, 여자가 9명 이었다. 수술 전 외관상 구축여부에 따라 구축군(3명)과 비구축군(9명), 두 군으로 분류하였다. 면역조직화학 염색을 이용하여 비만세포, 호중구, 근섬유아세포, 및 P물질에 대한 관찰을 시행하였다.

결과: 구축이 발생한 실리콘 캡슐에서 P물질 분비가 더 자주 관찰이 되었다. 하지만, 두 군을 비교하였을 때, 비만세포 및 호중구 수와 근섬유아세포 염색 정도에서는 유의한 차이가 없었다. 근섬유아세포 염색 정도와 비만세포 수는 트립타제 양성 및 키마아제 양성 비만세포 모두에서 유의한 상관관계를 보였으나, 호중구 수와는 뚜렷한 상관관계가 없었다.

결론: 본 연구 결과에서 구축변형을 일으킨 캡슐 조직에서 P물질 증가를 볼 수 있었다. 이번의 조직학적 예비연구는 삽입된 실리콘

보형물의 기계적 자극이 지속적인 신경 염증을 발생시키는 것이 캡슐 구축 발생의 원인일 가능성을 제시했다.

주요어: 캡슐 구축, 비성형, 실리콘 보형물, 비만세포, 근섬유아세포, P 물질

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