



# Association between the COVID-19 pandemic and granuloma formation following lower blepharoplasty

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## ARTICLE INFO

### Keywords:

Granuloma formation  
Blepharoplasty  
Lower blepharoplasty  
COVID-19  
Eyelid granuloma  
Foreign body reaction

## ABSTRACT

**Purpose:** We hypothesize that lower blepharoplasty post-operative granuloma formation increased during the COVID-19 pandemic.

**Observations:** Retrospective consecutive case series of first-time lower blepharoplasties performed at an academic private practice. Odds ratios of post-operative granuloma formation before and after the onset of the COVID-19 pandemic were analyzed using a logistic regression model controlling for age, gender, and surgical approach. 547 subjects underwent lower blepharoplasty between 2018 and 2023. Their average age was 64.6 ( $\pm 10.3$ ) years, 73 % were women. 222 (40.6 %) subjects underwent lower blepharoplasty by transconjunctival surgical approach with 290 (53.0 %) by transcutaneous approach. The odds of developing post-operative granuloma during the pandemic period were 2.188 (95 % CI 1.061, 4.513,  $p = 0.03$ ) times higher than prior to the lockdown period. Increased age was associated with higher odds of post-operative granuloma formation: OR 1.085 (95 % CI 1.05, 1.122,  $p < 0.0001$ ). Finally, a transconjunctival surgical approach was associated with a 2.525 (95 % CI: 1.415, 4.507,  $p = 0.01$ ) times higher odds of granuloma formation than was the transcutaneous approach.

**Conclusions and Importance:** We observed an increased odds of post-operative granuloma formation following lower blepharoplasty during the COVID-19 pandemic period. This signal may guide future surgical approaches to reduce post-operative granuloma such as utilizing intraoperative steroid injection and limiting fat manipulation. Further scientific investigation is warranted to evaluate etiology and avoidance.

## 1. Introduction

Lower blepharoplasty is performed to reduce familial fat herniation or age related skin laxity and localized adiposity. In this procedure, loose eyelid skin and/or lower lid orbital fat herniation are addressed.<sup>1</sup> Major complications associated with lower blepharoplasty are rare.<sup>2</sup> Minor complications occur in 3.5–12.7 % of cases, including post-operative granuloma formation.<sup>3</sup> The diagnosis of postoperative granuloma is typically made clinically, when a patient displays palpable, firm subcutaneous nodule(s) in the area of previous surgical manipulation presenting as late as 6 weeks postoperatively.<sup>3</sup> Occasionally, these granulomas may also cause visible erythema and edema of the tissues (Fig. 1). The granulomas may arise as a form of foreign body reaction to surgical materials including suture, glove material, cosmetics, ointment, or cauterized native fat tissue.<sup>4,5</sup> Histopathologic analysis of these nodules reveals segmented foci of inflammation containing collections of multinucleated giant cells, histiocytes, plasma cells, lymphocytes, and

polymorphonuclear cells within droplets of lipid.<sup>6</sup> However, histological evaluation is not routinely performed, as clinical diagnosis is typically sufficient to guide successful treatment. When infectious causes can be ruled out, these inflammatory lesions are commonly treated with topical, intralesional, or rarely systemic steroids.

The novel coronavirus 2019 (COVID-19) pandemic began on December 2, 2019<sup>7</sup> and quickly spread to California where a state of emergency was declared on March 4, 2020. COVID-19 healthcare impacts including ocular effects of the virus as well as its prevention and treatment warrant ongoing careful examination.<sup>8</sup> Eyelid inflammation has previously been reported in association with the COVID-19 pandemic.<sup>9</sup> Moreover, there is mounting evidence of systemic granulomatous inflammation being linked to COVID-19.<sup>10–13</sup> This study sought to evaluate the potential relationship between post-operative granuloma formation and lower blepharoplasty before and after the COVID-19 lockdown period. We hypothesize that the risk of post-operative granuloma formation following lower blepharoplasty significantly increased

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<https://doi.org/10.1016/j.ajoc.2024.102219>

Received 19 July 2024; Received in revised form 15 October 2024; Accepted 2 November 2024

Available online 5 November 2024

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during the pandemic period.

2. Methods

Our study was a retrospective consecutive case series of first-time lower blepharoplasties performed at an academic private practice (Silkiss Eye Surgery, San Francisco, CA). Electronic medical records were queried from January 2018 to December 2023, identifying all patients who underwent lower blepharoplasty during the study period. Charts were reviewed for the development of postoperative granuloma, a diagnosis that the surgeon consistently screened for and recorded throughout the time period of this study. This diagnosis was made clinically, defined as a firm, palpable subcutaneous mass located in the area of resected fat pads which developed after one week or more following an uncomplicated lower blepharoplasty in which the lower lid surface was initially smooth postoperatively. Surgical characteristics and date of granuloma formation were recorded. Two surgical approaches to lower blepharoplasty were performed according to patient preference and preoperative planning: transcutaneous or transconjunctival. Fat transposition procedures were excluded from the study because of the increased fat manipulation, periosteal dissection, and use of sutures for securing the fat, which could confound the data.

All surgeries were performed by a single surgeon (RZS) at one of 4 outpatient fully accredited surgery centers. The surgeon, technique, and materials were consistent across surgical centers. In the transcutaneous approach, after sedation, a 50:50 mixture of 2 % xylocaine with 1:100,000 epinephrine, 0.5 % Marcaine with 1:200,000 epinephrine, sodium bicarbonate, Hylenex and tranexamic acid was injected subcutaneously into right and left lower eyelids. Forceps were used to delineate the skin to be excised. A 5-0 silk suture was placed in the lid margin and the lid placed on upward tension. A #15 Bard-Parker blade was used to incise the skin. Monopolar cautery was used to excise the ellipse of skin and orbicularis. A skin flap was developed anteriorly and inferiorly. The orbital septum was buttonholed and each of the 3 lower lid fat pads were trimmed and smoothed according to the plan outlined prior to surgery. The cutaneous incision was closed with a 6-0 plain gut suture.

In the transconjunctival approach, following sedation, an identical local solution was injected into the eyelids via the conjunctival approach. Protecting the globe with a plastic Jaeger lid plate and retracting the eyelid with a Desmarres retractor, the cutting mode of cautery was used to make an incision through the conjunctiva and lower lid retractors, prolapsing each of the 3 lower lid fat pads into the surgical field. These pads were then trimmed according to the plan outlined prior to surgery. The incision was allowed to close spontaneously without suture.

Baseline characteristics including surgical approach were compared using chi-squared test for categorical variables and Wilcoxon test for continuous variables. Odds ratios of post-operative granuloma formation before and after the onset of the COVID-19 pandemic were analyzed using a logistic regression model controlling for age, gender, and

surgical approach.

Study oversight and approval was obtained from the IRB of Sutter Health. This study adhered to the principles of the Declaration of Helsinki and all research activities were HIPAA compliant.

3. Results

547 subjects underwent lower blepharoplasty between 2018 and 2023. Their average age was 64.6 ( $\pm 10.3$ ) years, 73 % were women. None of the patients had a history of autoimmune disease. Other baseline characteristics are summarized in Table 1. There was no significant difference with respect to baseline characteristics comparing the pre- and post-pandemic groups. 222 (40.6 %) subjects underwent lower blepharoplasty by transconjunctival surgical approach and 290 (53.0 %) by transcutaneous approach. In 35 (6.4 %) difficult medical record retrieval prevented definition of the approach. The overall rate of post-operative granuloma formation was 11.5 %, increasing from 6.7 % prior to the COVID-19 lockdown to 13.4 % after. The odds of developing post-operative granuloma during the pandemic period were 2.188 (95 % CI 1.061, 4.513,  $p = 0.03$ ) times higher than prior to the lockdown period (Table 2).

Increased age was associated with higher odds of post-operative granuloma formation: OR 1.085 (95 % CI 1.05, 1.122,  $p < 0.0001$ ).

Table 1  
Baseline characteristics, N (%) or mean  $\pm$  SD, unless noted.

Category N (%) unless otherwise specified	Overall	Pre- Pandemic	Post- Pandemic	P value <sup>a</sup>
N	547	150	397	
Age, years, mean $\pm$ SD	64.6 $\pm$ 10.3	65.0 $\pm$ 10.4	64.5 $\pm$ 10.3	0.54
Gender, n (%)				0.99
Female	401 (73.3 %)	110 (73.3 %)	291 (73.3 %)	
Male	146 (26.7 %)	40 (26.7 %)	106 (26.7 %)	
Approach, n (%)				0.09
Transconjunctival	222 (40.6 %)	56 (37.3 %)	166 (41.8 %)	
Transcutaneous	290 (53.0 %)	79 (52.7 %)	211 (53.2 %)	
Unknown	35 (6.4 %)	15 (10.0 %)	20 (5.0 %)	
Granuloma				0.03
Yes	63 (11.5 %)	10 (6.7 %)	53 (13.4 %)	
No	484 (88.5 %)	140 (93.3 %)	344 (86.6 %)	

<sup>a</sup> Chi-square test for categorical variables, and Wilcoxon test for continuous variables.



Fig. 1. Clinical presentation of a lower lid granuloma following bilateral blepharoplasty.

**Table 2**

Adjusted odds ratio (OR) of having granuloma from the logistic regression controlling for period, age, gender, and approach, n = 547.

	OR (95 % CI)
Period	
Before Pandemic	Reference
After Pandemic	2.188 (1.061, 4.513)
Age, years	1.085 (1.05, 1.122)
Gender	
Female	Reference
Male	0.637 (0.329, 1.234)
Approach	
Transconjunctival	2.525 (1.415, 4.507)
Transcutaneous	Reference
Unknown	0.69 (0.151, 3.143)

**Footnote** OR = (odds of the event in the exposed group)/(odds of the event in the non-exposed group) A confidence interval is the mean of your estimate plus or minus the variation in that estimate. This is the range of values you expect your estimate to fall between if you redo your test, within a certain level of confidence. Confidence, in statistics, is another way to describe probability.

There were no differences with respect to baseline characteristics comparing the two groups by surgical approach. The transconjunctival surgical approach was associated with a 2.525 (95 % CI: 1.415, 4.507, p = 0.01) times higher odds of granuloma formation than was the transcutaneous approach.

4. Conclusions and Importance

Consistent with the previously reported risk of post-operative granuloma formation following lower blepharoplasty, our study demonstrated an overall probability of 11.5 %. Age and surgical approach were identified as risk factors for granuloma formation. Additionally, there was a significantly increased risk of granuloma formation after the beginning of the COVID-19 lockdown (6.7 % prior, to 13.4 % after). These findings have not been previously reported and merit further investigation.

Both older age and transconjunctival surgical approach were found to be significant risk factors for granuloma formation. Although the use of ointment has been associated with transconjunctival blepharoplasty granuloma formation, the surgeon in this study avoids the use of ointment in post operative transconjunctival surgery. It is also conceivable that Vicryl or gut sutures could induce granuloma formation, however this surgeon does not place any sutures with the transconjunctival approach. Perhaps the finding is related to increased fat manipulation with the transconjunctival approach compared to the transcutaneous approach. Of note, no cases with fat transposition were included in this study.

Although age and approach were risk factors for granuloma formation, they remained stable across pre- and post-pandemic periods. Surgeon, surgical technique, and surgical sites/equipment remained stable during this time. The only variation was the addition of tranexamic acid into the local anesthetic, which began in 2021/2022. Tranexamic acid has been found to have both pro- and anti-inflammatory properties.<sup>14</sup> The literature reveals only a single report of a patient who developed a foreign body granuloma after intradermal injections of hyaluronic acid, vitamin C, and tranexamic acid,<sup>15</sup> which the authors attribute to tranexamic acid as the patient was previously treated with hyaluronic acid/vitamin C without issue. Although there is a theoretical risk of tranexamic acid inducing granuloma in our cohort, the literature overwhelmingly supports the use of tranexamic acid in plastic surgery.<sup>16</sup>

Mask wear must be considered as a plausible causative factor. In San Francisco, Los Angeles, New York, and other cities there have been reports of significantly increased inflammatory chalazion formation in the COVID-19 era attributed to face mask wear.<sup>9,14</sup> Face mask wear results

in changes to the ocular microbiome and microenvironment which becomes increasingly exposed to warm air and oral microbes. This change could contribute to an increase in inflammatory reactions following lower blepharoplasty.

Given the increased risk of granuloma formation in the post-COVID era, COVID-19 infection should be considered as a potential contributor to granuloma formation. COVID-19 infection has been associated with increased ocular inflammation including ocular surface dysregulation exceeding the effect of mask wear alone.<sup>17–19</sup> Infectivity of the SARS-CoV-2 virus requires interaction of its spike protein with the angiotensin converting enzyme (ACE) 2 receptor. Polymorphisms in the gene encoding ACE2 are implicated in the granuloma-forming disease pulmonary sarcoid<sup>40</sup> and there have been reports of COVID-19 infection preceding the development of this granulomatous autoimmune disease.<sup>11,13,20</sup> COVID-19 vaccination is another possible etiology for the increased odds of granuloma formation. Granulomatous skin reactions after COVID-19 vaccination have been reported, and are attributed to inflammatory reaction to either spike protein or the vaccine vehicle.<sup>21</sup> Sarcoidosis onset following COVID-19 vaccination has also been previously reported.<sup>20</sup> There have been reports of hypersensitivity reactions to cosmetic fillers following COVID-19 vaccination.<sup>22,23</sup> Some potential haptens eliciting an immunologic response to the vaccine include lipid nanoparticles, polyethylene glycol, and polysorbates.<sup>24</sup> As a subset of individuals likely exhibit an immune reaction to these vaccine components, they may also be at increased risk not only for inflammation at the site of injection but also for delayed reaction elsewhere. Further investigation into the role COVID infection and/or vaccination may have in inciting granulomatous inflammation is warranted.

This surgical case series has certain limitations. As a retrospective study, surgical approach could not be assigned randomly although the study groups were well-balanced with respect to baseline characteristics. There is potential for observation bias in this study, as perhaps investigators may have been looking more closely for postoperative granuloma formation in the post-pandemic group. However, these granulomas are not subtle and were examined for in both pre- and post-pandemic cohorts. Although speculation regarding the impact of COVID-19 was discussed, this study did not assess infection or vaccination amongst our cohort. It is possible that the increased odds of granuloma is random or related to issues other than COVID.

By analyzing a large series of consecutive cases, we demonstrated a statistically significant increase in the odds of post-operative granuloma formation during the pandemic period. Further scientific investigation will be necessary in order to fully elucidate the scope of this finding as well as its potential causes. We encourage surgeons to perform similar investigations, and potential collaboration, in order to improve the generalizability of these findings.

CRediT authorship contribution statement

**Shane Griffin:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Samantha Butterfield:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Rona Z. Silkiss:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Formal analysis, Data curation, Conceptualization.

Patient consent

Patient consent was obtained for the publication of all identifiable information including clinical photographs. De-identified data was used elsewhere and deemed by the Sutter IRB to be exempt.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

## Claims of priority

After conducting a literature review (7/14/24) on Google scholar, we did not find any previous reports of this case series.

## Funding

Pacific Vision Foundation.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements and Disclosures

No author has financial disclosures related to this work. The authors would like to thank Qiwen Huang and Sylvia Sudat for their statistical expertise.

## References

- Murri M, Hamill EB, Hauck MJ, Marx DP. An update on lower lid blepharoplasty. *Semin Plast Surg.* 2017;31:46–50.
- Sniegowski M, Davies B, Hink E, Durairaj VD. Complications following blepharoplasty. *Expet Rev Ophthalmol.* 2014;9:341–349.
- Pacella SJ, Codner MA. Minor complications after blepharoplasty: dry eyes, chemosis, granulomas, ptosis, and scleral show. *Plast Reconstr Surg.* 2010;125:709–718.
- Fryer RH, Reinke KR. *Pyogenic Granuloma: A Complication of Transconjunctival Incisions: Plastic & Reconstructive Surgery.* vol. 105. 2000:1565.
- Belinsky I, Patel P, Charles NC, Lisman RD. Ointment granulomas following sutureless transconjunctival blepharoplasty: diagnosis and management. *Ophthalmic Plast Reconstr Surg.* 2015;31:282–286.
- Heltzer JM, Ellis DS, Stewart WB, Spencer WH. Diffuse nodular eyelid lipogranuloma following sutureless transconjunctival blepharoplasty dressed with topical ointment. *Ophthalmic Plast Reconstr Surg.* 1999;15:438–441.
- World Health Organization. *Novel Coronavirus (2019-nCoV): Situation Report.* vol. 22. Geneva: World Health Organization; 2020. Available at: <https://iris.who.int/handle/10665/330991>.
- Bertoli F, Veritti D, Danese C, et al. Ocular findings in COVID-19 patients: a review of direct manifestations and indirect effects on the Eye. *J Ophthalmol.* 2020;2020:1–9.
- Silkiss RZ, Paap MK, Ugradar S. Increased incidence of chalazion associated with face mask wear during the COVID-19 pandemic. *Am J Ophthalmol Case Rep.* 2021;22, 101032.
- Calender A, Israel-Biet D, Valeyre D, Pacheco Y. Modeling potential autophagy pathways in COVID-19 and Sarcoidosis. *Trends Immunol.* 2020;41:856–859.
- Behbahani S, Baltz JO, Droms R, et al. Sarcoid-like reaction in a patient recovering from coronavirus disease 19 pneumonia. *JAAD Case Rep.* 2020;6:915–917.
- Song X, Shao F, Lan X. The onset of Sarcoidosis after COVID-19 vaccination revealed by the 18F-FDG PET. *Clin Nucl Med.* 2022;47:869–871.
- Monte-Serrano J, García-Gil MF, García-García M, et al. Granuloma annulare triggered by SARS-CoV-2 infection: immunohistochemical staining. *Dermatol Ther.* 2021;34:9–11.
- Barrett CD, Moore HB, Kong YW, et al. Tranexamic acid mediates proinflammatory and anti-inflammatory signaling via complement C5a regulation in a plasminogen activator-dependent manner. *J Trauma Acute Care Surg.* 2019 Jan;86(1):101–107. <https://doi.org/10.1097/TA.0000000000002092>. PMID: 30575685.
- Zhang Q, Yang L, Yang F, Liu L, Jiang X. Mesotherapy-Induced cutaneous foreign body-type granulomatous reaction in the face treated with minocycline: case report and literature review. *Clin Cosmet Invest Dermatol.* 2023 Apr 3;16:861–867. <https://doi.org/10.2147/CCID.S403601>. PMID: 37033786; PMCID: PMC10081525.
- Elena Scarafoni E. A systematic review of tranexamic acid in plastic surgery: what's New? *Plast Reconstr Surg Glob Open.* 2021 Mar 23;9(3), e3172. <https://doi.org/10.1097/GOX.0000000000003172>. PMID: 33907653; PMCID: PMC8062149.
- Lin M, Godfrey KJ, Segal KL, Lelli GJ. Chalazion frequency during the COVID-19 pandemic. *Invest Ophthalmol Vis Sci.* 2023;64:OD21. OD21.
- Gambini G, Savastano MC, Savastano A, et al. *Ocular Surface Impairment after Coronavirus Disease 2019: A Cohort Study.* vol. 40. 2020.
- Mertz P, Jeannel J, Guffroy A, et al. Granulomatous manifestations associated with COVID19 infection: is there a link between these two diseases? *Autoimmun Rev.* 2021;20, 102824.
- Somboonviboon D, Wattanatham A, Keorochana N, Wongchansom K. Sarcoidosis developing after COVID-19: a case report. *Respirol Case Rep.* 2022;10:1–5.
- Magro C, Crowson AN, Franks L, et al. The histologic and molecular correlates of COVID-19 vaccine-induced changes in the skin. *Clin Dermatol.* 2021;39:966–984.
- Niebel D, Novak N, Wilhelmi J, et al. Cutaneous adverse reactions to covid-19 vaccines: insights from an immuno-dermatological perspective. *Vaccines.* 2021;9.
- Kalantari Y, Sadeghzadeh-Bazargan A, Aryanian Z, et al. First reported case of delayed-type hypersensitivity reaction to non-hyaluronic acid Polycaprolactone dermal filler following COVID-19 vaccination: a case report and a review of the literature. *Clinic Case Rep.* 2022;10:1–5.
- Liu L, Ledin W. COVID-19 infection-associated hypersensitivity reaction to dermal filler—a case report and review of the histologic features. *J Cosmet Dermatol.* 2022; 21:3673–3674.