Obstructive sialadenitis of a transplanted submandibular gland: chronic inflammation secondary to ductal obstruction

Jia-Zeng Su,[1] Ning-Yan Yang,[1] Xiao-Jing Liu,[1] Zhi-Gang Cai,[1] Lan Lv,[2] Lei Zhang,[1] Li-Ling Wu,[3] Deng-Gao Liu,[4] Wen-Ge Ren,[4] Yan Gao,[5] Guang-Yan Yu[1]

[1]Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, Beijing, PR China
[2]Department of Ophthalmology, Affiliated Beijing Tong Ren Hospital, Capital University of Medical Science, Beijing, PR China
[3]Department of Physiology and Pathophysiology, Peking University Health Science Center and Key Laboratory of Molecular Cardiovascular Sciences, Ministry of Education, Beijing, PR China
[4]Department of Oral Radiology, Peking University School and Hospital of Stomatology, Beijing, PR China
[5]Department of Oral Pathology, Peking University School and Hospital of Stomatology, Beijing, PR China

Correspondence to
Professor Guang-Yan Yu, Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, 22 Zhong Guan Cun South St., Beijing 100081, PR China; gyyu@263.net

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ABSTRACT

Aims To determine the pathological basis and clinical features of obstructive sialadenitis in transplanted submandibular glands (SMGs).

Methods A total of 161 patients (174 eyes) with keratoconjunctivitis sicca underwent microvascular SMG transplantation. Patients were followed up at approximately 1 and 4 months and annually thereafter. Clinical data, including dry eye discomfort, symptoms of ductal obstruction, and Schirmer test, were recorded. Sialography was performed in six patients. In addition, SMG autotransplantation was performed in 22 rabbits. Salivary flow was recorded and the morphology of glands was examined at 6 months postoperatively by light microscopy.

Results Among the patients, 16 out of 172 glands during the latent period (0–3 months) and 2 out of 154 glands with long-term follow-up (>1 year) showed obstructive sialadenitis. Typical manifestations were continuous small volumes of viscous secretions, recurrent gland swelling, decreased Schirmer test values, and irregular dilation of the main duct on sialography. The transplanted SMGs eventually showed no secretion in five cases. Of the 22 rabbit SMGs, 4 had obstructive sialadenitis. Morphological examination showed chronic inflammatory infiltration with salivary deposits.

Conclusions Obstructive sialadenitis of transplanted SMGs is a chronic inflammation secondary to ductal obstruction, which leads to insufficient ocular lubrication and potential treatment failure.

INTRODUCTION

Keratoconjunctivitis sicca (KCS) is a multifactorial disease of the tears and ocular surfaces that results in discomfort, visual disturbances and tear-film instability with possible damage to the ocular surfaces.[1] Despite the generally efficient pharmaceutical tear substitutes, cyclosporin eyedrops or occlusion of tear drainage for the patients with mild or moderate KCS,[2 3] severely affected individuals cannot achieve adequate relief.[4] Microvascular autologous submandibular gland (SMG) transplantation provides a continuous, endogenous source of ocular lubrication.[4–7] The secretions from all viable transplanted SMGs maintain stable function for at least 5–10 years after surgery.[8 9] The uncomfortable symptoms resolve or are obviously relieved, and the application of pharmaceutical lubricating substances is reduced to a large extent. Ophthalmological examinations show significant improvements in tear films and other ocular-surface features, such as the break-up times of tear films, corneal fluorescein and rose bengal staining.[8–11]

The transplanted SMG is completely disconnected from the normal nerve supply and its secretory function changes after surgery. In most patients, secretions of the transplanted glands decrease within 5–7 days and recover spontaneously for 3 months after transplantation, with a 3-month period of low-level secretions known as the latent period.[5] However, in some patients, the transplanted SMGs have different secretory patterns. Low levels of secretions are accompanied by recurrent swelling of the gland and this course could be prolonged, resulting in insufficient ocular lubrication and even the failure of treatment. These secretory abnormalities, which might represent a new complication, have only been addressed by a few publications.[5 6] Therefore, more research is required to improve our understanding of this complication and the long-term outcomes of SMG transplantation.

The present study was designed to investigate the clinical and sialographic features of the transplanted SMGs, to understand the essence of this secretory abnormality and to propose diagnostic criteria for this complication. Moreover, we established a rabbit model of SMG transplantation to explore the pathological basis of this secretory abnormality.

MATERIALS AND METHODS

Patients

The study was approved by the Ethics Committee for Human Experiments of Peking University Health Science Center and was conducted in accordance with the Declaration of Helsinki guidelines for human research.

We enrolled 161 consecutive patients (81 men; median age, 31 years; range, 7–71 years) with severe KCS at Peking University School of Stomatology between August 1999 and October 2012. A total of 148 patients underwent unilateral microvascular autologous SMG transplantation and 13 patients underwent bilateral procedures (174 eyes; 82 right eyes). The inclusion criterion was a viable transplanted SMG as confirmed by ^{99m}Tc scintigraphy. All patients were followed up during the latent period (0–3 months), after the latent period (4 months) and over a long-term period (>1 year).

Subjective evaluation

At follow-up visits, the patients completed a questionnaire to evaluate the degree of dry eye

discomfort, the presence of viscous secretions and any recurrent swelling of the transplanted SMG.

Secretory flow measurement

Secretory flow of the transplanted SMG was measured by Schirmer test as described previously.[12] The length of the filter paper (120 mm×5 mm) moistened by the secretion of transplanted SMG over 5 min was recorded. Measurements were performed initially during a resting condition (recorded as basal secretion) and then after physical exercise (climbing six flights of stairs for 30 s, recorded as post-exercise secretion).

Sialography

Morphological appearance of Wharton's duct was evaluated by sialography in a subgroup of six patients (six eyes). The technique used for sialography was similar to that used for normal salivary glands.[13]

Animal experiments

Healthy male New Zealand white rabbits (weighing 2.4±0.3 kg) were used. For 12 h before the experiment, the rabbits were deprived of food but had free access to water. All experimental procedures were approved by the Ethics Committee for Animal Research of the Peking University Health Science Center.

SMG autotransplantation was performed as described previously.[14] In brief, the left SMG of rabbits was isolated and transplanted into the right temporal region. The free gland was revascularised by an anastomosis of the lingual artery branch to the external carotid artery and the facial vein branch to the temporal vein. Wharton's duct was implanted into the conjunctival fornix of the right eye. The animals were followed up for 180 days postoperatively.

Secretory flow measurement in rabbits

Secretory flow was measured by Schirmer test in resting and conscious rabbits on postoperative day 1, 3, 7, 30, 90, 120, 150 and 180. A tube was inserted into Wharton's duct and the length of filter paper (35 mm×5 mm) moistened by the secretion from the tube was recorded for 5 min, as described previously.[14 15]

Histology

The transplanted glands were removed 180 days postoperatively. SMG specimens were fixed in 10% formaldehyde, paraffin embedded, sectioned into 5 µm slices, stained with H&E and examined using light microscopy (BX53; Olympus, Tokyo, Japan).

Statistical analysis

Data were presented as the number (%), mean±SE or median (IQR). Comparisons between the two groups were performed using the Mann–Whitney U test (for the independent samples), Wilcoxon signed-rank tests (for the paired samples) or χ^2 tests (SPSS V.17.0; SPSS Inc., Chicago, Illinois, USA). A p value <0.05 (two tailed) was considered statistically significant.

RESULTS

Clinical assessment in the latent period (0–3 months)

The results of the postoperative evaluation during the first 3 months were obtained in 172 vital transplanted SMGs (159 patients, with 2 patients lost to follow up). Of the 172 transplanted glands, 156 showed the typical secretory manifestations of the latent period[4 5] at approximately 1 month postoperatively (normal group). They had very low secretion (median Schirmer test value, 1 (0–2) mm/5 min) and sometimes viscous fluid in the resting condition, but gland swelling was not observed. After physical exercise, the volume of saliva increased (median Schirmer test value, 4 (2–6) mm/5 min, p<0.001, Wilcoxon signed ranks test) and became more clear (table 1). However, the remaining 16 glands (9.3%; 16 patients; 8 men; median age 28.5 years; range 18–62 years) showed different secretory patterns and were collected as the abnormal group. These transplanted SMGs were suspected to have developed a secretory abnormality. The average flow rates of both basal and post-exercise secretions were significantly lower than those of the normal individuals (table 1). Viscous secretions were expressed upon milking the swollen transplanted SMGs (figure 1A, B). Recurrent swelling of the transplanted glands was reported by 13 patients. The median time of onset of the complication was postoperative day 28 (range 10–90 days).

Clinical assessment after the latent period (4–12 months)

At the beginning of the fourth month after surgery, secretory flow spontaneously increased in the normal patients (n=156), with complete resolution or obvious relief of dry eye symptoms in most patients (table 2).

The 16 glands with secretory abnormalities were treated using different methods. From 1999 to 2002, six transplanted SMGs were simply monitored to await the spontaneous recovery of secretory function (the so-called 'wait and see' approach), and they were defined as the earlier cases of the abnormal group. From 2003 to 2012, the remaining 10 glands were treated more promptly with individualised treatments to relieve the ductal obstruction, and they were defined as the later cases of the abnormal group.

The earlier cases were followed up for more than 4 months (range 4–14 months; median 6 months). The secretory abnormalities were unremitting and the patients complained of no improvement in dry eye discomfort (table 2). All of these patients eventually underwent surgery and ductal obstruction was confirmed intraoperatively (figure 1C). In response to surgical treatment, three patients successfully regained sufficient ocular lubrication and their salivary flow rates increased to 7, 12 and 18 mm/5 min, respectively. The surgery failed in the other three patients (3/6, 50%) and their transplanted glands lost secretory function as the main ducts were irreparable.

Table 1 Clinical assessment of transplanted submandibular glands during the latent period (0–3 months)

	No amelioration of dry eye (%)	Viscous secretions (%)	Gland swelling (%)	Basal secretory flow (mm/5 min), median (IQR)	Post-exercise secretory flow (mm/5 min), median (IQR)
Normal group (n=156)	82.1	83.3	0	1 (0–2)	4 (2–6)
Abnormal group (n=16)	100*	100*	81.3*	0 (0–0)†	0.5 (0–1)†
p Value	0.077	0.135	<0.001	0.004	<0.001

*χ^2 test.
†Mann–Whitney U test.

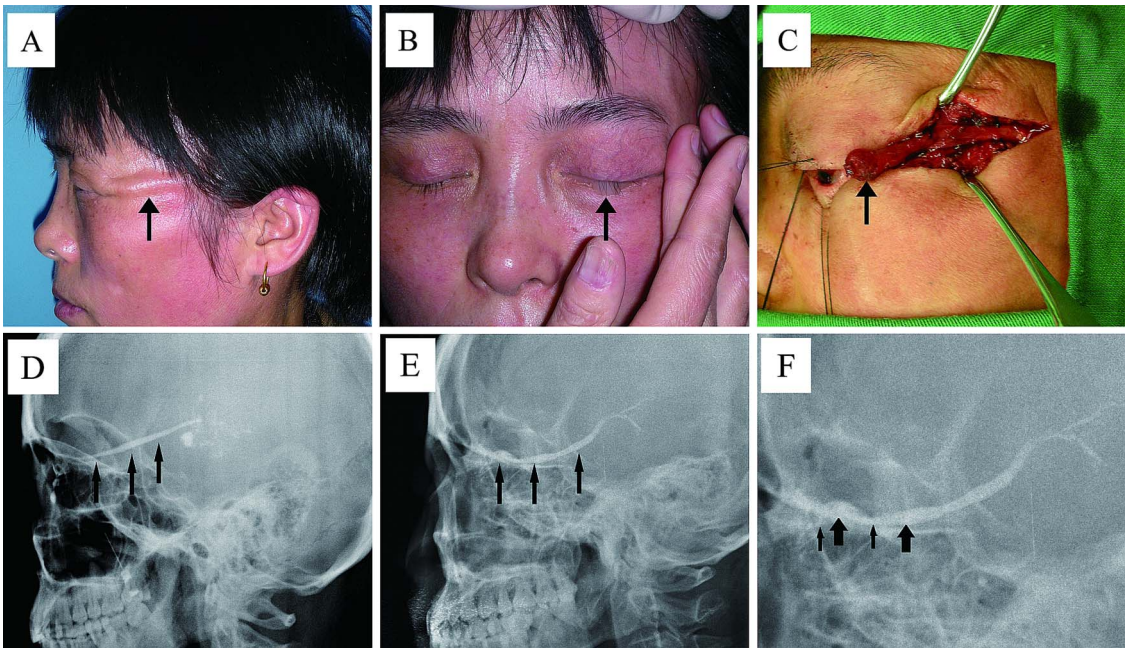

Figure 1 Clinical and sialographic manifestations of obstructive sialadenitis of the transplanted submandibular glands. (A) The main duct (arrow) is swollen. (B) Viscous secretion (arrow) is discharged after the gland is milked. (C) Dilation of the main duct (arrow) is confirmed intraoperatively. (D) Representative image of a patient with suitable secretions, which showed the uniformity and smooth curve of the main duct (three arrows). (E) Representative image of the patients with abnormal secretions. Cardinal features were irregular dilation and stricture of the main duct (three arrows). (F) Figure 1E at higher magnification. Dilation and stricture of the main duct were marked with two thick arrows and two thin arrows, respectively.

Based on the results of the earlier cases of the abnormal group, individualised treatments were performed in a timely manner (range 10–90 days after transplantation; median 42 days) from 2003 to 2012 in the 10 later cases of the abnormal group. In 8 of the 10 glands, the ductal obstruction was successfully removed and the average salivary flow of the glands was 13 (8–22) mm/5 min at 4 months after transplantation, with no further episodes of viscous secretion or gland swelling (table 2). However, surgery failed in two glands (2/10, 20%) and the secretory function was lost. As a final result, five transplanted glands lost secretory function due to secretory abnormalities and they were left in situ without further treatment.

Clinical assessment in the long term after transplantation (>1 year)

Of the 174 vital glands, 154 (144 glands of the normal cases, 3 glands of the earlier abnormal cases and 7 glands of the later abnormal cases) were followed up for more than 1 year (range 1–14 years; median 7 years). Although the secretory flow rate was higher during the summer and lower during the winter, 141 glands produced sufficient secretion to lubricate the ocular surface throughout the year. Thirteen glands, none of which had ductal obstruction during the early phase, occasionally secreted insufficient fluid to lubricate the ocular surface when the temperature was very low (usually less than 5°C). This seasonal insufficiency would spontaneously vanish after winter in 11 glands. However, two glands developed continuously decreased and viscous secretions with recurrent gland swelling that persisted for 4 and 6 months, respectively. In both glands, secretory function recovered after external irrigation with normal saline.

Sialographic findings

To identify the reasons for the abnormal secretions, two patients with low viscous secretion and swollen transplanted glands were

Table 2 Clinical assessment after the latent period (4 months)

	No amelioration of dry eye (%)	Viscous secretions (%)	Gland swelling (%)	Basal secretory flow (mm/5 min), median (IQR)
Normal group (n=156)	4.5	0	0	19 (13–25)
Earlier cases of abnormal group (n=6)	100*	100*	100*	1 (0–1)†
Later cases of abnormal group (n=8‡)	0*	0	0	13 (8–22)†
p Value				
Earlier cases	<0.001	<0.001	<0.001	<0.001
Later cases	1.0	NA	NA	0.162

*χ^2 test.
†Mann–Whitney U test; data were respectively compared with the normal group.
‡Two glands of later abnormal cases underwent unsuccessful surgery, after which the secretory function was completely lost and did not return by 4 months postoperatively.
NA: p value was unavailable as both rates equalled zero.

selected and subjected to sialography between December 2009 and October 2011. At the same time, another four patients with normal levels of secretion were randomly selected as the controls. A uniform and smooth curve was observed in the Wharton's duct of the four normal glands (figure 1D), which showed no glandular swelling and produced sufficient ocular lubrication. However, the two abnormal transplanted SMGs, which had continuous viscous excretion and recurrent glandular swelling with Schirmer test results of <3 mm, showed mild dilation with distal stenosis of the main duct (figure 1E, F), which resembled the appearance of chronic obstructive sialodochitis on sialography.

Animal experiments

SMG autotransplantations were performed in 22 rabbits. Before transplantation, saliva flow of SMGs of the rabbits was 1.25 ±0.06 mm/min. Saliva secreted from the transplanted glands increased on postoperative day 1, decreased on day 3 and was barely detectable on day 7. The pattern was similar to the clinical latent period.[4 5] The salivary flow of 18 transplanted SMGs increased spontaneously to a high level at 3–6 months after transplantation. However, the saliva flow of the remaining four glands was continuously less than 1 mm/min with viscous secretion and recurrent swelling lasting for 6 months (figure 2). The latter four glands were considered to be the abnormal group, and the former 18 glands the normal group.

Histological findings

At 6 months postoperatively, the transplanted SMGs were removed and observed under light microscopy. SMGs of rabbits that did not undergo transplantation showed mixed glands that contained more mucous acini (figure 3A), as reported previously.[15] Similar morphological manifestations were observed in the transplanted glands with normal levels of secretion (figure 3B). In the glands of the abnormal group, intraductal solid salivary deposits were observed in the luminal system, which showed irregular areas of dilation. Inflammatory cells infiltrated the periductal region and parenchyma. The acini were atrophic and were replaced by hyperplastic ducts in some areas (figure 3C, D).

DISCUSSION

Chronic obstructive sialadenitis is a common clinical condition and one of the major disorders that can cause salivary hypofunctioning.[16] Although its pathogenesis is currently unclear, the primary pathogenic event is believed to be a decreased rate of saliva production or salivary flow, resulting in stasis of the saliva and ascending infection.[17 18] Repeated exacerbations of the inflammatory process lead to ductal wall damage. This damage results in fibrosis and stricture formation, further decreasing salivary flow rates and perpetuating the obstructive process.[17 18]

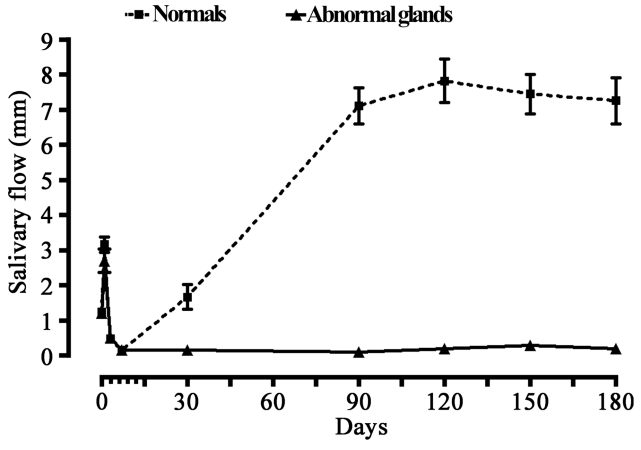

Figure 2 Salivary flow in the transplanted rabbit submandibular glands (mean±SE). Secretory flow of the transplanted gland was measured by Schirmer test.

Microvascular autologous SMG transplantation is an effective approach for the treatment of severe KCS, but a few patients had abnormal secretions postoperatively. The abnormal secretions could also be reproduced in a rabbit model. According to the results of the present study, we presumed that the transplanted SMGs of the 16 human patients and the 4 experimental rabbits that developed secretory abnormalities in our study had suffered from chronic obstructive sialadenitis. First, the affected transplanted glands showed the typical symptoms of viscous secretion with intermittent swelling of the gland, which is the essential feature of obstructive sialadenitis.[16 19 20] Second, histological examinations in the rabbit model demonstrated that the transplanted SMGs with abnormal secretions had a mild inflammatory cell infiltration surrounding the duct and salivary stagnation in the ductal lumens, and these are the typical histopathological manifestations of chronic obstructive sialadenitis.[20 21] Clinically, sialography remains the gold standard in the diagnosis of obstructive sialadenitis.[17 19 22] The characteristic manifestation of sialography is irregular dilation of the ductal system.[17 20 21] In the present study, the affected transplanted SMGs also showed irregular dilation of the main duct, which is very similar to that seen in chronic obstructive parotitis.[21] Therefore, we termed this complication chronic obstructive sialadenitis of the transplanted SMG.

This complication could lead to insufficient lubrication of the treated eyes. The incidence of this disorder was 9.3% (16/172) in the early phase (0–3 months) and 1.3% (2/154) with long-term follow-up durations of >1 year after transplantation. On the basis of the present study, we propose the following diagnostic criteria for chronic obstructive sialadenitis of transplanted SMGs: vital transplanted SMG as confirmed by ^{99m}Tc scintigraphy; no secretion or viscous fluid secreted with swelling of the transplanted SMG (>3 months); secretory abnormality not improved by stimulation; Schirmer test value <3 mm; and irregular dilation of the main duct on sialography.

The diagnosis of chronic obstructive sialadenitis of transplanted SMGs should be differentiated from the typical low secretory flow observed during the latent period. This complication would last for a long duration (6 months on average in the present study) without specific interventions and could even result in the failure of treatment. Hyposecretion during the latent period can be significantly increased by secretory stimulation and usually recovers spontaneously at the beginning of 4 months after transplantation.[4 5]

Treatment for chronic obstructive sialadenitis of transplanted SMGs should be performed without delay, as secretory function of the affected glands cannot recover without removing the ductal obstruction. Early intervention had a higher rate of success than delayed treatment (80% to 50% in the present study). If the transplanted glands finally lost secretory function, they can be left in situ in the recipient. Therefore, it was impossible to obtain clinical samples for histological examinations and animal experiments were performed in the present study to explore the pathological basis of this complication.

The pathogenesis of chronic obstructive sialadenitis of the transplanted SMG remained unclear. During transplantation

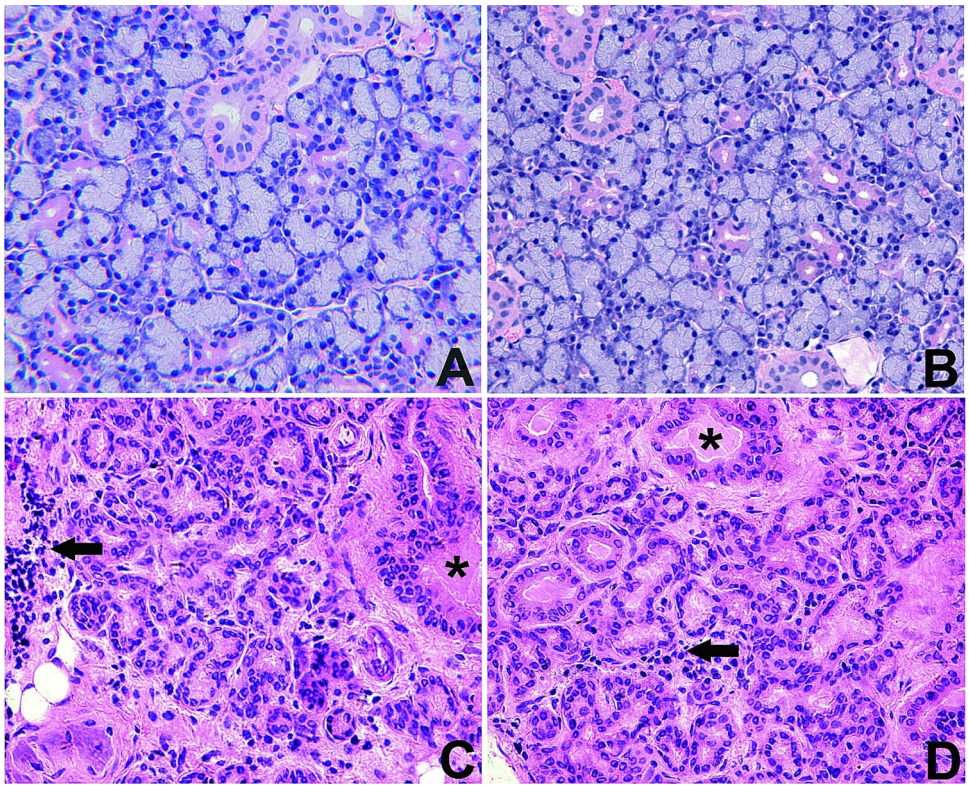

Figure 3 Histological appearances of the rabbit submandibular glands. (A) The glands of non-transplanted rabbits showed mixed glandular tissues containing more mucous acini. (B) Similar manifestations were observed in the normal cases. (C and D) The glands with abnormal secretions showed salivary deposits (*) and chronic inflammatory cell infiltration (arrow). H&E; magnification ×400.

surgery, the orifice of Wharton's duct of the gland is fixed in the conjunctival fold to form a new opening. Surgical scar formation of the incision between Wharton's duct orifice and the conjunctiva might be one of the reasons for the chronic obstructive sialadenitis of the transplanted SMG. Clinically, some cases of ductal obstruction were located in the orifice of Wharton's duct. However, surgical scarring was not the only reason for this complication. During the operation, Wharton's duct is harvested together with the mucosal cuff around the ductal orifice. The mucosal cuff is sutured to the conjunctiva and a polyethylene tube is then intubated into Wharton's duct for more than 7 days to prevent scar formation. Some cases of obstruction were in the central part of the duct. Furthermore, all cases of obstructive sialadenitis of the transplanted SMGs occurred during the latent period or in winter when the rate of salivary secretion shows a marked idiopathic decline. This finding suggested that salivary hypofunctioning of the transplanted glands might be the primary pathogenic event underlying obstructive sialadenitis. The repeated exacerbations of the inflammatory process within the gland lead to tissue damage, fibrosis and stricture formation of the ductal wall. The ductal stricture aggravates the salivary stasis, ductal dilation and glandular swelling. Therefore, promotion of the secretion of the transplanted SMGs, especially during the latent period, may be helpful in the prevention of chronic obstructive sialadenitis of transplanted SMGs.

In summary, we propose a new complication of transplanted SMGs named chronic obstructive sialadenitis. As a chronic inflammatory condition, it is characterised by continuous viscous secretions with decreased flow rates and intermittent gland swelling. The complication leads to insufficient lubrication of the treated eyes and can cause treatment failure. Schirmer test and sialography are helpful in making the diagnosis, whereupon prompt treatment should be performed to remove the ductal obstruction.

Contributors J-ZS and G-YY: conceived and designed the study. J-ZS, N-YY, X-JL, Z-GC, LL, L-LW, LZ, D-GL, W-GR and YG: contributed to data collection. J-ZS, N-YY, L-LW, D-GL, YG and G-YY: analysed and interpreted the data. J-ZS, L-LW and G-YY: prepared the manuscript or revised it critically for important intellectual content and approved the final version to be submitted.

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Competing interests None.

Patient consent Obtained.

Ethics approval Ethics Committee of the Peking University Health Science Center; Ethics Committee for Animal Research of the Peking University Health Science Center.

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