Cataract surgery in patients with chronic severe graft-versus-host disease

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PURPOSE: To evaluate the surgical outcomes of cataract extraction with phacoemulsification and intraocular lens implantation in patients with severe chronic ocular graft-versus-host disease (GVHD).

SETTING: University of South Florida Eye Institute, Tampa, Florida, USA.

DESIGN: Retrospective case study.

METHODS: A chart review was performed to identify patients with clinically severe, biopsy-proven chronic ocular GVHD who had cataract extraction. Outcome parameters included preoperative and postoperative corrected distance visual acuity (CDVA), type of cataract, postoperative complications, type of underlying malignancy, and time from bone marrow transplant to cataract extraction.

RESULTS: This study comprised 10 eyes of 6 patients with severe GVHD. Posterior subcapsular cataract accounted for all cataracts that were surgically removed in this patient cohort. The mean preoperative CDVA was 20/84, which improved to 20/30 at the 1-month postoperative visit and remained stable at 20/28 at the final visit noted in the charts (both $P < .05$). Two patients developed postoperative corneal melting. All but 1 patient had improved visual acuity after surgery.

CONCLUSIONS: With meticulous preoperative biometric measurements and calculations and aggressive assessment and treatment of dry-eye syndrome, patients with severe ocular GVHD who had cataract extraction had excellent postsurgical refractive outcomes. Postoperative corneal melting was a complication seen with greater frequency than anticipated in this patient cohort.

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Graft-versus-host disease (GVHD) is a complication that arises in patients who have bone marrow transplantation. Ocular symptoms of GVHD are a leading contributor to patient morbidity and are often associated with the chronic subtype of GVHD. Ophthalmic manifestations include moderate to severe ocular surface disease from lymphocytic infiltration of lacrimal glands, keratinization and squamous metaplasia of the conjunctiva and corneal epithelium, and secondary keratoconjunctivitis sicca.[1–5]

Cataracts, however, are the most common cause of vision loss in patients with GVHD.[6] Researchers have studied the visual outcomes of patients having phacoemulsification and have found excellent postoperative refractive outcomes once the preoperative ocular surface disease is managed.[7–9] However, these studies did not classify the severity of ophthalmic manifestations in their GVHD patients, nor did they ascertain the postoperative refractive outcomes specific to this patient subset.

Several factors unique to this patient population can contribute to poor refractive outcomes after cataract extraction. These include an irregular corneal surface, heightened susceptibility to infection, medical morbidity, chronic systemic immunosuppression, and poor wound healing.[10] Surgical planning is difficult, and intraocular lens (IOL) measurements often have to be repeated.

The purpose of this study was to assess the cataract surgery outcomes in eyes with a known (biopsy-confirmed) diagnosis of severe ocular GVHD and possibly identify postoperative complications unique to their underlying disease process.

PATIENTS AND METHODS

This retrospective study was initiated after institutional review board approval from the University of South Florida was granted. A chart review was performed to identify patients who had been evaluated by the cornea service after having bone marrow transplantation at the Moffitt Cancer Center, Tampa, Florida, USA. All patients had a clinical diagnosis of systemic GVHD confirmed by biopsy. Pathologic confirmation was either through excisional skin biopsy, gastrointestinal biopsy, or liver biopsy. Systemic GVHD was managed closely by the medical oncology team, and all patients were treated with immunosuppressive therapy, the most common being sirolimus and tacrolimus. Medical clearance for surgery was obtained once GVHD symptoms were deemed stable by the bone marrow team.

Exclusion criteria included pediatric patients, patients who had more than 1 procedure at the time of cataract surgery, patients with previous intraocular surgery, and patients with optic neuropathy, retinopathy, or any other intraocular pathology that may limit visual outcomes postoperatively.

All patients were evaluated at the University of South Florida Eye Institute. Patients were evaluated periodically, and follow-up was based on the severity of ocular surface disease. Ophthalmic manifestations of GVHD were confirmed through ancillary testing, including but not limited to evaluation of the tear film/tear meniscus, conjunctival and corneal staining with 10 μL lissamine green 1.0% (Leiter's compound pharmacy), Schirmer testing, tear osmolarity, and tear breakup time. To limit the study to those with severe ocular chronic GVHD, the International Chronic Ocular GVHD Consensus Group classification criteria were used for grading.[11] Grading criteria were based on a point scale from results of Schirmer testing, corneal fluorescein staining, conjunctival hyperemia, and the ocular surface disease index (OSDI). For instance, patients with a Schirmer test result of 5.0 mm or less at 5 minutes received a maximum of 3 points. Conjunctival hyperemia was graded on a 0 to 2 scale in which 0 points denoted no injection and 2 points indicated diffuse injection. Corneal fluorescein staining patterns were rated on a 0 to 3 scale for mild disease, moderate disease, and severe disease, respectively. Finally, the results of the OSDI were also categorized on a 0 to 3 scale based on patient response scores. Patients with a total of 9 or more points were classified as having severe chronic GVHD and were included. Figure 1 shows external slitlamp photographs of some of the patients included.

To obtain repeatable and accurate IOL measurements, patients were aggressively managed with topical and noninvasive treatments to lubricate and stabilize the ocular surface. Patients did not have cataract surgery unless surface disease had been maximally treated. Preoperative measurements, including partial coherence interferometry (IOLMaster, Carl Zeiss Meditec AG) and corneal topography (Atlas, Carl Zeiss Meditec AG), were obtained at least at 3 different times to confirm IOL measurements.

Some patients had surgical repair of cicatricial ectropion and/or epilation of lashes before cataract extraction. All cataract surgeries were performed by the same cornea specialist (E.M.E) from the University of South Florida Eye Institute using a 2.7 mm temporal clear corneal incision with phacoemulsification and implantation of a single-piece acrylic monofocal IOL in the capsular bag. Topical nonsteroidal antiinflammatory drugs were used postoperatively only in diabetic patients. All patients were treated aggressively with a combination of topical preservative-free artificial tears, lubricating ointments, and punctual occlusion before scheduled cataract extraction, and a majority was continued on their regimen after surgery.

Data collected included type of cataract, corrected distance visual acuity (CDVA) at preoperative and postoperative visits (1 month and final visit at time of chart review), and postoperative refraction (spherical equivalent [SE]). Postoperative complications were recorded if present. Toric, multifocal, and accommodating IOLs to eliminate astigmatism and spectacle independence were not offered to any patient.

Statistical analysis of the CDVA was performed after conversion of Snellen visual acuity into the logMAR equivalent to calculate the mean CDVA. Comparison of the preoperative CDVA and postoperative CDVA was performed at 1 month and at the final visit and was tested using the paired t test for continuous measures. A 2-sided P value less than 0.05 was considered statistically significant. Other significant data from the patient cohort, such as the occurrence of posterior subcapsular cataract and postoperative complications, were expressed as a proportion of total eye interventions.

RESULTS

The final analysis included 10 eyes involving 6 patients. Of these, 4 patients were men and the 2 were women. Table 1 shows baseline patient characteristics. The mean age at cataract extraction was approximately 59.3 years (range 55 to 68 years). The most common predisposing malignancy in GVHD patients was leukemia followed closely by lymphoma. The mean time from bone marrow transplantation to cataract surgery was 27.4 months (range 7 to 41 months). The mean follow-up after cataract surgery

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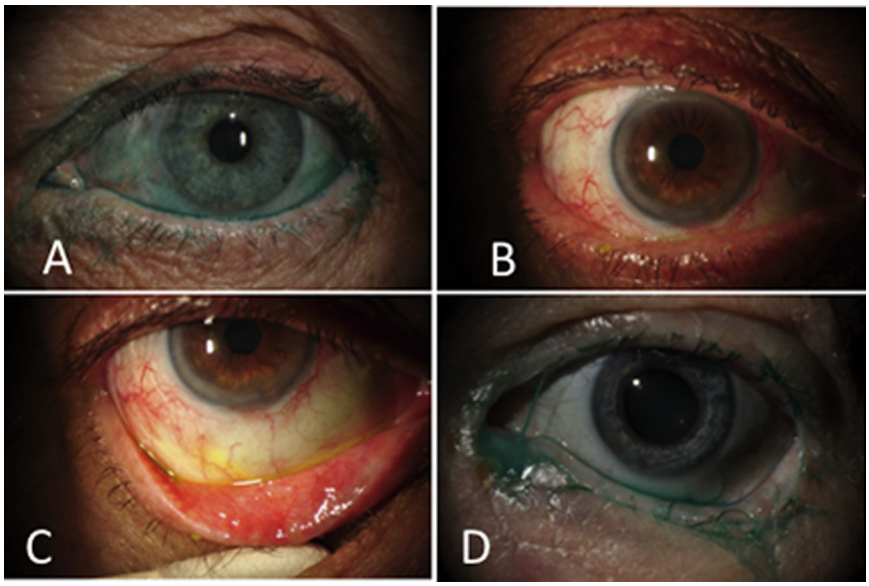

Figure 1. Common findings in severe chronic ocular GVHD include diffuse lissamine green conjunctival staining (*A*), noticeable conjunctival injection (*B*), cicatricial palpebral conjunctival changes (*C*) and lower lid ectropion (*D*).

was 11.6 months (range 3 to 56 months). The mean OSDI was 36.7.

Figure 2 shows the preoperative management of ocular surface disease. Table 2 shows an overview of the medical and surgical intervention to mitigate ocular surface disease in each patient before cataract extraction. Conjunctival histology confirmed a decrease in goblet cell density and squamous metaplasia of the epithelium on biopsy (Figure 3).

Posterior subcapsular cataract was the most common cataract type, occurring in all 10 patients. Table 3 shows the CDVA over time. The mean preoperative Snellen CDVA was 20/84 (0.63 logMAR). One month after cataract extraction, the mean CDVA improved to 20/30 (0.017 logMAR) and remained stable at 20/28 (0.14 logMAR) at the final visit. One patient lost lines of CDVA after surgery. The improvement in the average CDVA from before cataract surgery to 1 month and the final visit was statistically significant (both $P < .05$). There was no statistically significant improvement in CDVA from 1 month to the final visit.

There were no postoperative hyperopic surprises in any eye. The mean postoperative SE refraction was −0.66 diopter (D) (range −0.25 to −2.25 D). Figure 4 shows the attempted SE versus achieved SE. In general, the postsurgical refractions were fairly close to the desired target; however, overall there was no consistent hyperopic or myopic pattern. One patient had a moderately higher myopic refractive outcome than expected (−2.25 D).

Intraocular complications, including posterior capsule rupture, dropped nucleus, vitreous loss, and

Table 1. Baseline patient characteristics.

Patient/ Eye	Sex	Underlying Malignancy	Age at CE (Y)	Time from BMT to CE (Mo)	Systemic Immunosuppression	Schirmer Testing (mm)	Corneal Fluorescein Staining	OSDI	Conjunctival Injection
1/R	M	Acute lymphoblastic leukemia	60	20	Mycophenolate, tacrolimus, sirolimus	<4.0	Moderate	36	Moderate
2/R	F	Chronc lymphocytic leukemia	57	41	Tacrolimus	<2.0	Severe	28	Severe
2/L	F	Chronic lymphocytic leukemia	57	39	—	<2.0	Severe	28	Severe
3/R	M	Acute myeloid leukemia	57	9	Sirolimus, tacrolimus	<4.0	Moderate	39	Moderate
3/L	M	Acute myeloid leukemia	57	7	—	<4.0	Moderate	39	Moderate
4/R	M	Acute lymphoblastic leukemia	68	36	Sirolimus	<2.0	Severe	34	Severe
4/L	M	Acute lymphoblastic leukemia	68	34	—	<2.0	Severe	34	Severe
5/R	F	NK T-cell lymphoma	57	25	Sirolimus	<4.0	Moderate	42	Moderate
5/L	F	NK T-cell lymphoma	57	23	—	<4.0	Moderate	42	Moderate
6/L	M	Lymphoma	55	40	Tacrolimus	<4.0	Moderate	45	Moderate

BMT = bone marrow transplantation; CE = cataract extraction; NK = natural killer; OSDI = Ocular Surface Disease Index

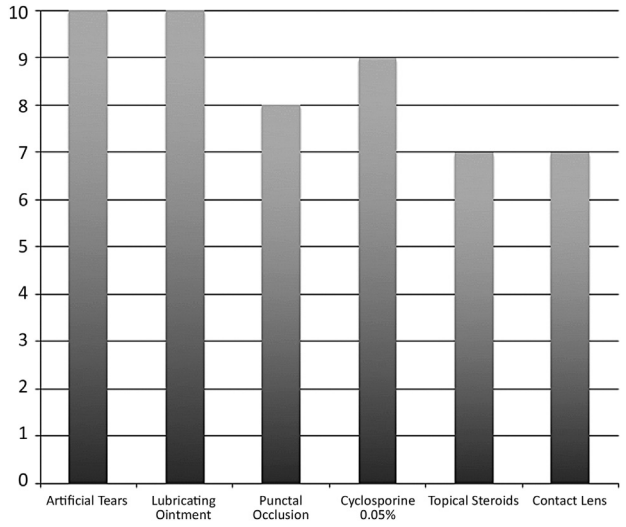

Figure 2. Preoperative management of ocular surface disease in the patient cohort before surgery. The *y*-axis represents the number of eyes.

choroidal hemorrhage or effusions, were not observed in any eye. Two patients developed moderate corneal melting in the operated eye postoperatively; however, there were no cases of endophthalmitis.

DISCUSSION

Cataract formation in chronic GVHD causes significant patient morbidity and a reduction in the quality of life.[12] Our results parallel those obtained by others, who achieved excellent postoperative refractive outcomes.[7,9] The goal of this study was to gain information to help surgeons obtain excellent outcomes in patients with severe ocular GVHD, provide analysis of refractive outcomes, and describe complications unique to this patient subset.

Posterior subcapsular cataract was the most common subtype of cataracts in our GVHD patient cohort. This was likely the result of the high incidence of steroid use and total body irradiation in these patients who had bone marrow transplantation. Their axial location predisposes these patients to a greater decline in visual acuity than nuclear sclerotic and cortical lens opacities.[13,14] On average, the cataracts did not become clinically significant until several years after the bone marrow transplantation, suggesting that cataract formation is not a common ophthalmic finding in acute GVHD.

Our study confirm that with meticulous preoperative calculations and prompt treatment of ocular surface disease, patients with severe ocular GVHD can achieve excellent visual acuity after cataract surgery. All patients had evidence of aqueous tear deficiency on clinical examination and required aggressive management with preservative-free artificial tears, lubricating eyedrops, punctual plugs, topical steroids, and cyclosporine. This not only allowed safer results but also more predictable IOL calculations. These treatment modalities were continued indefinitely postoperatively. Furthermore, meticulous preoperative axial length and keratometry measurements were obtained and repeated to avoid postoperative refractive surprises, which did not occur in our cohort.

Our refractive outcomes show that although the attempted SE was correlated with the achieved postsurgical refractions, there was no definitive pattern. The 1 outlier of a −2.25 D postsurgical myopic result likely represents a combination of poor preoperative measurements, surface irregularity from a healed corneal melt, and a dependency on scleral lenses.

Despite the excellent postoperative CDVA and thorough management of systemic immunosuppression by a highly experienced bone marrow transplantation team, 2 patients developed moderate postoperative

Table 2. Medical and surgical intervention to mitigate ocular surface disease in each patient before cataract extraction.

Patient	Eye	Preservative-Free Tears	Lubricating Ointments	Punctal Plugs	Cyclosporine 0.05%	Topical Steroids	Contact Lens
1*	L	Yes	Yes	Yes	No	No	Scleral
2	R	Yes	Yes	Yes	Yes	Yes	Bandage
2	L	Yes	Yes	Yes	Yes	Yes	Bandage
3	R	Yes	Yes	No	Yes	No	None
3	L	Yes	Yes	No	Yes	No	None
4	R	Yes	Yes	Yes	Yes	Yes	Bandage
4	L	Yes	Yes	Yes	Yes	Yes	Bandage
5	R	Yes	Yes	Yes	Yes	Yes	Scleral
5	L	Yes	Yes	Yes	Yes	Yes	Scleral
6	L	Yes	Yes	Yes	Yes	Yes	None

*Patient 1 also had lid surgery before cataract surgery

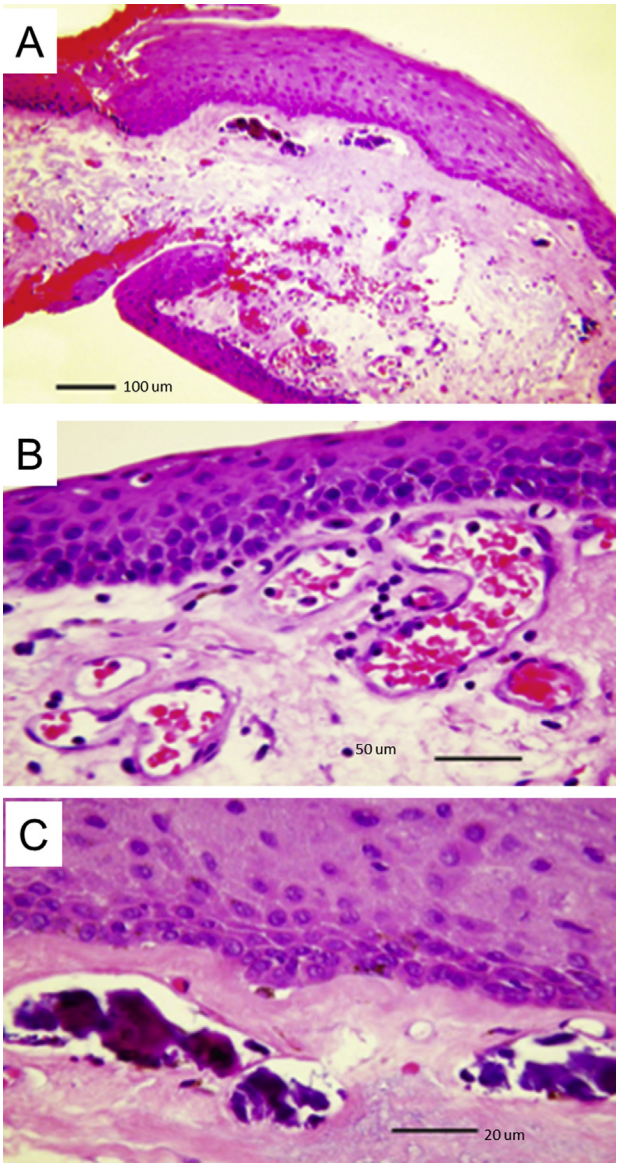

Figure 3. Conjunctival biopsies showing findings consistent with severe ocular surface disease. Squamous metaplasia and decreased goblet cell density or depletion are seen. *A*: Depletion of goblet cells is seen in the conjunctival epithelium. *B*: Higher magnification photograph showing mild squamous metaplasia and sparse goblet cells. *C*: Highest magnification photograph showing mild metaplasia of the squamous epithelium.

corneal melt in the pseudophakic eye in the setting of presumed stable systemic GVHD (Figure 5). Rarely, ocular surface complications, such as postoperative corneal melting, punctate keratitis, filamentary keratitis, and recurrent corneal epithelial defects, have been associated with systemic rheumatologic conditions.[15] The incidence of postoperative corneal melts in our chronic GVHD cohort was much higher than that reported in patients with collagen vascular disease (0.01%).[16] In both patients, the corneal melts

Table 3. Preoperative and postoperative CDVA at 1 month and at final visit.

			Corrected Distance Visual Acuity		
Pt	Eye	Cataract Type	Preop	1 Mo Postop	Final Visit
1	L	PSC	20/50	20/60	20/70
2	R	PSC	20/60	20/25	20/25
	L	PSC	20/60	20/25	20/25
3	R	NSC, PSC	20/70	20/30	20/20
	L	NSC, PSC	20/60	20/25	20/25
4	R	PSC	20/40	20/25	20/25
	L	PSC	20/50	20/25	20/30
5	R	PSC, cortical	20/400	20/20	20/20
	R	PSC	20/400	20/50	20/20
6	L	PSC	20/80	20/30	20/40

NSC = nuclear sclerotic cataract; PSC = posterior subcapsular cataract; Pt = patient

developed months after cataract surgery and were paracentral, away from the main cataract incision. Neither patient developed persistent epithelial defects after the initial surgery. Furthermore, in patient 1 the melting also occurred in the unoperated eye. Both patients improved after aggressive management with corneal cultures (which were negative), prophylactic topical antibiotics, and aggressive lubrication. Surgery was not necessary; however, both patients required an increase in immunosuppression after levels were found to be subtherapeutic by the bone marrow transplantation team.

This postoperative corneal melt accounted for the 1 patient (#6) with worsening CDVA after surgery. It is strongly recommended that a thorough review of systems and a systemic immunosuppressive level be performed preoperatively. We believe that management of these patients under continuous supervision by the bone marrow transplantation team is essential to achieve surgical success. Aggressive

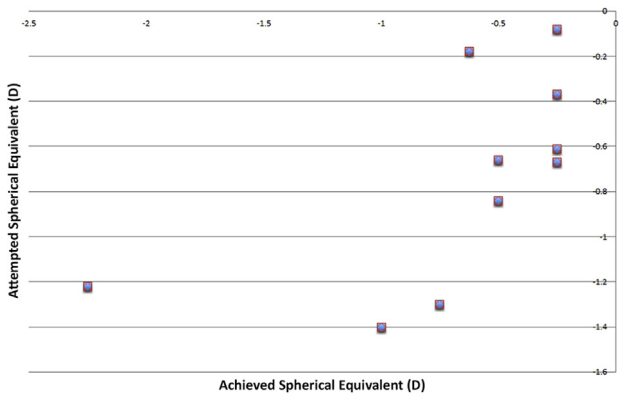

Figure 4. Attempted SE versus achieved SE.

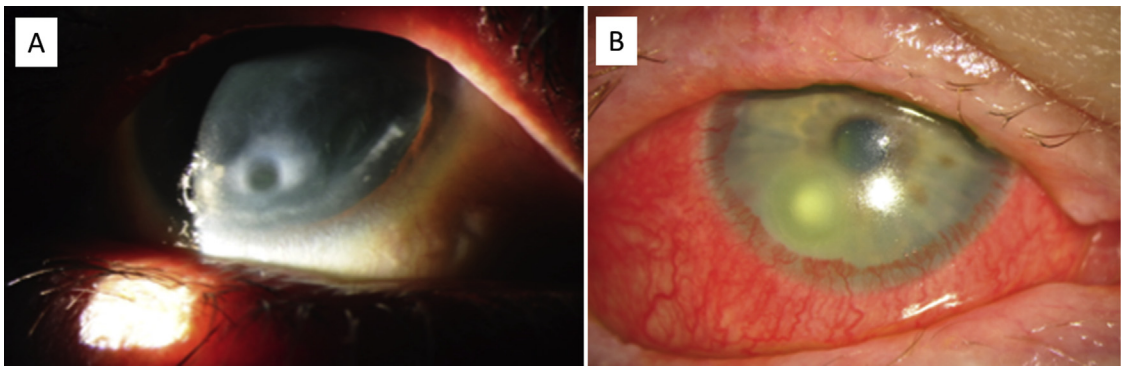

Figure 5. Postoperative corneal melts in 2 patients in this series. *A*: Patient 1 developed a corneal melt in the unoperated eye after cataract surgery. *B*: Patient 6 developed bilateral corneal melt a few weeks after cataract surgery.

management of sterile corneal melts should include precautionary cultures, topical antibiotics, lubricants, a bandage contact lens, temporary tarsorrhaphy, amniotic membranes, and, if necessary, therapeutic keratoplasty.

Several inherent limitations to the study might have contributed to the low incidence of postoperative complications. These include a short postoperative follow-up (mean ~11 months) and a small patient cohort (10 eyes; 6 patients). Such a variable postoperative follow-up was related in part to the retrospective nature of our study and in part because of the strict inclusion criteria set forth for the study. Adequate follow-up is difficult in many patients who have a high incidence of hospitalization and numerous conflicting appointments with medical providers. Furthermore, our study design restricted patient inclusion to a limited timeframe and a single primary surgeon. Despite such limitations, we are satisfied with the surgical outcomes in this challenging patient cohort.

WHAT WAS KNOWN

- Management of cataract in patients with GVHD presents unique challenges to postoperative care and yields satisfactory postoperative outcomes in those with mild disease.

WHAT THIS PAPER ADDS

- Overall, the postoperative CDVA was excellent in patients with severe GVHD despite a higher than previously reported incidence of postoperative corneal melt.
- A thorough review of systems and systemic immunosuppression should be considered preoperatively to identify patients at risk for developing postoperative complications.
- There was no standard pattern to the target SE and postoperative SE.

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