Causes of intrastromal corneal ring segment explantation: Clinicopathologic correlation analysis

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PURPOSE: To determine the main causes of intrastromal corneal ring segment (ICRS) explantation and the relationship with the microscopic findings on the ICRS surface.

SETTING: Vissum Corporation–Instituto Oftalmológico de Alicante, Alicante, Spain.

METHODS: This study evaluated ICRS that were explanted in centers in Spain from 2000 to 2008. Clinical data (reasons for explantation, date of implantation/explantation, tunnel creation technique, ICRS type) and scanning electron microscopy findings on the ICRS surface (adherent tissue-like material, cell deposits, protein) were documented.

RESULTS: Intrastromal corneal ring segments were explanted from 58 eyes (47 patients). The main cause was extrusion (48.2% of explanted segments), followed by refractive failure (ie, poor refractive outcome) (37.9%), keratitis (6.8%; 3.7% culture positive), and corneal melting and perforation (6.8%). Scanning electron microscopy showed cells and cell debris on the ICRS explanted by extrusion, a clean surface on the ICRS explanted for refractive failure, and bacteria (cocci) in the case of proven infectious keratitis.

CONCLUSIONS: The main cause of explantation was extrusion of the ICRS followed by refractive failure. There was a clear correlation between the cause of explantation and the microscopic findings on the ICRS. Extrusion was accompanied by inflammatory cells and cell debris on the ICRS surface. No inflammatory reaction was observed on the ICRS explanted for refractive failure.

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Implantation of intrastromal corneal ring segments (ICRS) is a promising and reversible refractive technique for keratoconus management.[1–3] It was designed to achieve refractive adjustment by flattening the central cornea curvature while maintaining clarity in the central optical zone and preserving corneal tissue. Poly(methyl methacrylate) (PMMA) devices have the shape of sections of a circumference and are inserted in semicircular channels between the stromal lamellae. The 3 main ICRS on the market are Intacs (Addition Technology, Inc.), Ferrara (Ferrara Ophthalmics Ltd.), and Keraring (Mediphacos Ltd.). During ICRS implantation, the tunnel is created by 1 of 2 techniques: mechanical dissection or use of a femtosecond laser.[4]

Intrastromal corneal ring segment implantation has been associated with intraoperative and postoperative complications. Intraoperative complications include segment decentration,[5] ICRS asymmetry,[5] inadequate channel depth,[5] superficial channel dissection with anterior Bowman layer perforation,[6] and anterior chamber perforation.[7] Several postoperative complications have been described, including ring segment extrusion,[5–10] corneal neovascularization,[2,11–16] infectious keratitis,[5,8,17,18] mild channel deposits around the ICRS,[2,11–14,19,20] segment migration,[5,15,21] and corneal melting.[7,10]

The present study sought to determine the leading causes of ICRS explantation and the relationship to microscopic findings.

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PATIENTS AND METHODS

Study Design

This multicenter nonrandomized consecutive case-series study evaluated ICRS that were explanted in centers in Spain from 2000 to 2008. Patient data and the explanted ICRS were reviewed and analyzed. Clinical data, including the cause of explantation, date of ICRS implantation, date of ICRS explantation, surgical technique, and ICRS type were documented based on the clinical reports supplied by the referring ophthalmic surgeons.

Scanning Electron Microscopy

A subgroup of explanted ICRS was studied by scanning electron microscopy (SEM). Immediately after the ICRS was extracted from the eye, it was placed in 2% (weight/volume) glutaraldehyde in a filter-sterilized 0.1 M sodium cacodylate buffer (pH 7.4). It was stored at room temperature for at least 2 hours. Then, the segment was rinsed 3 times for 15 minutes in a 0.15 M sodium cacodylate buffer. The technique was performed as described by Kodjikian et al.[22] with modification. Fixed segments were dehydrated, step by step, in ethanol. Samples were first soaked in ethanol–water mixtures with increasing ethanol concentrations (30%, 50%, 70%, 80%, and 95% by volume) for 7 minutes each. The samples were then soaked in pure ethanol for 5 minutes, 10 minutes, and 15 minutes. Once the ICRS were dehydrated, they were dried by critical point. The ICRS were then mounted on stubs and sputter coated with gold, after which they were examined by SEM (JSM-840 microscope, Jeol Ltd.). The type of ICRS and the presence of tissue-like material adhering to the ICRS surface, cell deposits, and protein were documented.

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RESULTS

During the study period, 250 ICRS implantations (not including center contributing single case) were performed and 57 ICRS (46 patients) were explanted. Including the single case from 1 center brought the number of explantations to 58 (47 patients; 23 women, 24 men). Table 1 shows the total number of ICRS implantations and explantations by center, the year of explantation, and the number of ICRS analyzed by SEM. The mean age of the patients was 36.7 years ± 9.75 (SD) (range 17 to 64 years). Of the 58 eyes, 46 (79.3%) had primary keratoconus, 7 (12.1%) had ectasia after laser in situ keratomileusis, 3 (5.2%) had marginal pellucid degeneration, 1 (1.7%) had previous keratoplasty, and 1 (1.7%) had myopia.

Tunnel creation in the ICRS explantation cases was by femtosecond laser in 26 eyes and by mechanical dissection in 32 eyes. All ICRS were inserted to 70% corneal depth. (The exact measurement after the implantation was not taken.)

Reason for Explantation

Table 2 shows number of ICRS explanted by year of implantation and the causes of explantation and method of tunnel creation by ICRS model (37 Intacs, 21 Keraring). Table 3 shows the causes of explantation by method of tunnel creation and the mean interval between implantation and explantation; the mean interval in all cases was 7.65 months (range 0.1 to 82.0 months). The main cause of explantation was extrusion (28 ICRS/48.3%), followed by refractive failure (poor refractive outcomes) (22 ICRS/37.9%), keratitis (4 ICRS/6.9%), corneal melting (3 ICRS/5.2%). There was 1 case (1.7%) of corneal perforation (segment perforated the endothelium).

Of extrusion cases (18 Intacs, 10 Keraring), 15 had tunnel creation by femtosecond laser and 13 by mechanical dissection. In eyes with ICRS extrusion, 5 had corneal melting, 3 had vascularization, and 2 were suspicious for infection, although the cultures were negative.

Of the cases of refractive failure (12 Intacs, 10 Keraring), 14 had tunnel creation by femtosecond laser and 10 by mechanical dissection.

Of the cases of suspected infection (3 Intacs, 1 Keraring), 3 had tunnel creation by femtosecond laser and 1 by mechanical dissection. The cultures were positive (*Staphylococcus aureus* and *Streptococcus mitis*) in 2 cases (3.4%) and negative in 2 cases. None of the eyes had corneal melting or ICRS extrusion.

In the cases of corneal melting (all Intacs), 2 had tunnel creation by femtosecond laser and 1 by mechanical dissection. In all cases, the clinician observed melting

Table 1. Number of ICRS explanted and number of ICRS analyzed by SEM by center and by year.

	Number of Cases				
Parameter	Vissum Alicante	Vissum Sevilla	Barraquer Barcelona	IOBA Valladolid	Vissum Madrid
Total ICRS implanted	215	10	19	NA*	6
ICRS explanted					
2000–2007	36	—	—	—	—
2008	15	3	2	1	1
SEM analysis	25	3	2	1	1

Barraquer Barcelona = Barraquer University Institute; IOBA Valladolid = Instituto Universitario de Oftalmobiología Aplicada; SEM = scanning electron microscopy; Vissum Alicante = Vissum Corporation–Instituto Oftalmológico de Alicante; Vissum Corporation–Instituto Oftalmológico de Madrid; Vissum Sevilla = Vissum Corporation–Instituto Oftalmológico de Sevilla
*Last case of explanted ICRS sent from the center

before extrusion occurred and extracted the ICRS to prevent further melting.

Scanning Electron Microscopy

Thirty-three explanted ICRS were studied by SEM. Figure 1 shows a photograph and SEM images of 1 of the 18 extruded segments evaluated by SEM. Biodeposits comprising extracellular matrix (ECM), cells, collagen, and exopolysaccharide were found on the surface of 68.8% of extruded segments. The deposits were on the proximal end of the segment, next to the incision. In most cases, the distal end did not extrude and was free of deposits. Three ICRS explanted by extrusion also showed vascularization (Figure 2, *A*); microanalysis showed a large amount of cells and debris along the segment (Figure 2, *B* to *D*). In these cases, both ends of the ICRS had the same appearance. In no case was vascularization the only cause for explantation.

Figure 3 shows a photograph and SEM images of 2 of the 13 segments explanted for refractive failure and evaluated by SEM. The surfaces of all ICRS were clean; that is, there was no cell debris or exopolysaccharide on either end of or along the segment.

Two ICRS explanted for suspected infection (keratitis) were analyzed by SEM. Figure 4 shows a photograph and SEM image of 1 segment for which the culture was positive (*S. aureus*) and the 1 segment for which the culture was negative. In the culture-positive case, cocci were found on the segment surface. In other case, exopolysaccharide was on the ICRS surface, although no bacteria were isolated. In both cases, the cocci and exopolysaccharide were located on the part of the ICRS at which infection was visible, regardless of the distal or proximal location.

DISCUSSION

Reported postoperative complications of ICRS implantation include segment extrusion,[5–10] corneal

Table 2. Number of ICRS explanted by year of implantation, and cause of explantation, ICRS model, and tunnel creation technique.

		Explantation Cause (n)					ICRS Model		
Year of Implantation	ICRS Explants (n)	E	RF	I	M	CP	Intac	Keraring	Tunnel Creation
2000	6	4	1	—	1	—	6	—	Manual
2001	4	1	3	—	—	—	4	—	Manual
2002	1	—	1	—	—	—	1	—	Manual
2003	8	5	3	—	—	—	8	—	Manual
2004	8	4	1	1	1	1	7	1	Manual
2005	1	—	—	1	—	—	—	1	Femtosecond
2006	8	4	3	1	—	—	3	5	Femtosecond
2007	15	7	7	1	—	—	6	9	Femtosecond
2008	5	2	2	—	1	—	2	3	Femtosecond
No date	2	1	1	—	—	—	—	2	Femtosecond

E = extrusion; CP = corneal perforation; I = suspected infectious keratitis; ICRS = intrastromal ring segment; M = corneal melting; RF = refractive failure

Table 3. Causes of explantation by tunnel creation technique channels and time between implantation and explantation.

	Tunnel Creation				Time from Implantation to Explantation (Mo)	
	Mechanical		Femtosecond			
Cause	Intacs	KeraRings	Intacs	KeraRing	Median	Range
Extrusion	12	1	6	9	7.5	0.1 to 82.0*
Refractive failure	8	0	4	10	8.0	2.0 to 24.0
Keratitis	1	0	2	1	2.4	0.25 to 6.0
Melting	2	0	1	0	7.0	3.0 to 14.0
Cornea perforation	1	0	0	0	0.5	—

ICRS = intrastromal ring segment
*Three ICRS extruded 42, 43, and 84 months after implantation; without these 3, the interval range 0.1 to 29 months.

neovascularization,[2,11–16] infectious keratitis,[5,8,17,18] mild deposits around the ICRS,[2,11–14,19,20] segment migration,[5,15,21] and corneal melting.[7,10] However, ICRS explantation is not necessary in some cases. In our study, extrusion, refractive failure, microbial keratitis, and corneal melting were the 4 leading reasons for ICRS explantation. The most common was extrusion (48.2%). In most cases, extrusion is accompanied by melting; vascularization also occurs in some cases. Although many studies[5–8,10] report that segment extrusion is more common when the tunnel is created by mechanical dissection, a femtosecond laser was used in half of the extrusion cases in our study. Our results support those in other studies[9,21] that found no significant differences between methods of tunnel creation.

In addition to ICRS extrusion,[6,7,9,10,14] patient dissatisfaction with visual outcomes (eg, decreased uncorrected and corrected distance visual acuity) is another important cause of ICRS explantation.[19] In our study, 37.9% of explantations were for refractive failure. In these case, the ICRS can be safely and easily explanted, with most visual, refractive, and topographic features returning to near preoperative levels.[23] Although the clinical effects of ICRS implantation have been studied extensively since Colin and Velou[24] performed the first ICRS placement for keratoconus, few data on the histopathologic changes after ring implantation[25–29] are available.

Histological reaction after ICRS insertion in the corneal stroma is difficult to study. Most available data come from keratoplasty specimens. Therefore, the number of eyes having evaluation is low and only corneas with advanced keratoconus are examined. However, analysis of the ICRS surface can be performed in

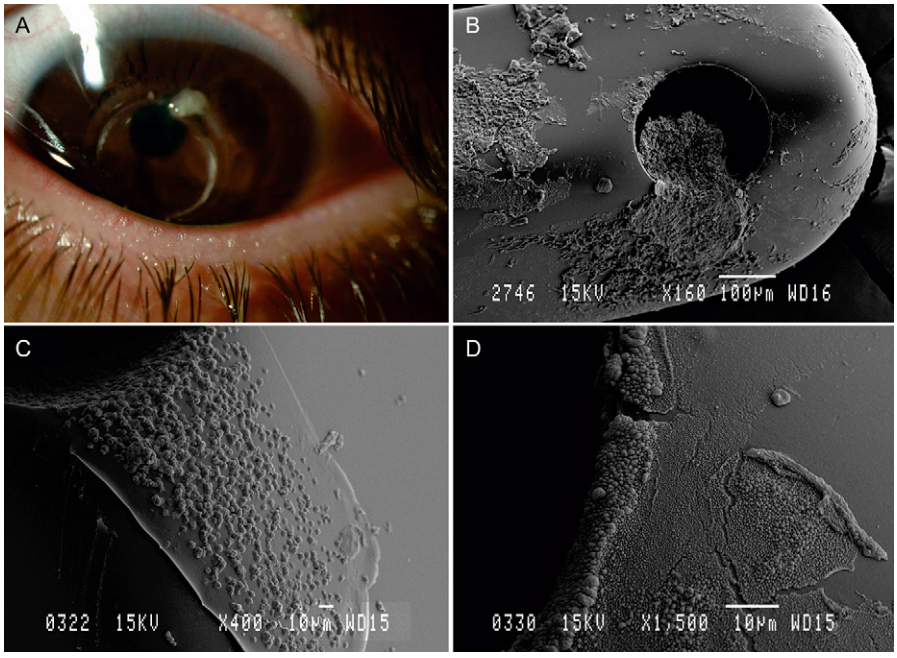

Figure 1. Findings in ICRS extrusion. *A*: Clinical photograph of spontaneous extrusion of the temporal ring's upper extremity. *B*: Cell debris and cells are seen on the surface of the extremity the ICRS (SEM). *C*: The surface of the extremity of the ICRS had multiple cell deposits (SEM). *D*: The surface also has lipid deposits (SEM).

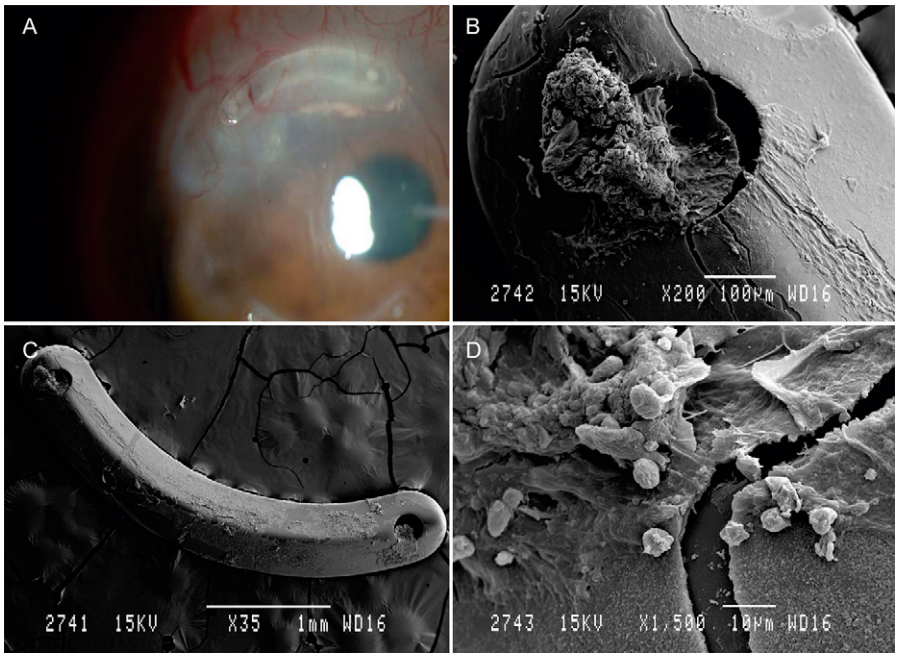

Figure 2. Findings in ICRS extrusion with vascularization. *A*: Clinical photograph of vascularization around of the temporal segment. *B*: Cell debris has adhered to the extremity of the ICRS (SEM). *C*: There are multiple cell deposits along the segment (SEM). *D*: Detail of the deposits on the ICRS surface (SEM).

virtually all eyes from which ICRS are explanted. Although this information may not be as complete as that obtained by histopathologic studies, it increases the number of cases evaluated and allows collection of specimens with different grades and types of corneal disease; that is, ranging from healthy corneas with poor refractive outcomes to cases of microbial keratitis. Scanning electron microscopy analysis of ICRS provides information on the biocompatibility of the ICRS material in the stroma, the corneal reaction when the ICRS extrudes, and whether neovascularization or infection is present. The results in our study agree with those in studies of keratoplasty specimens.

The results in our study shed light on tissue reaction after ICRS implantation. We found no inflammatory material on the surface of any ICRS explanted for refractive failure (poor refractive outcome), showing the biocompatibility of PMMA in the area of ICRS implantation. In our cases of ICRS explanation for refractive failure, there was no evidence of foreign-body reaction, as occurs in some cases of intraocular lens

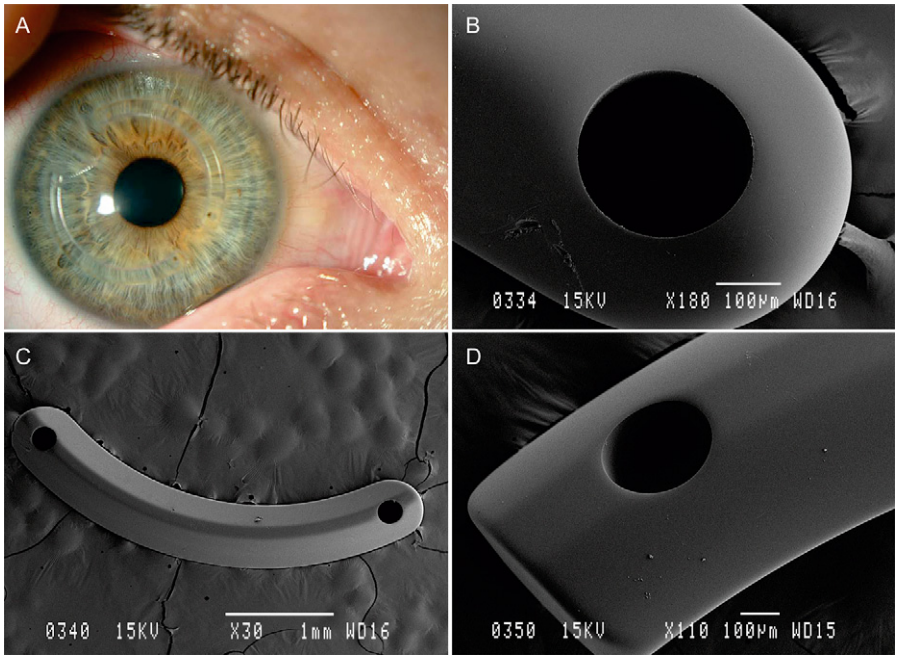

Figure 3. Findings in ICRS explantation for refractive failure. *A*: Clinical photograph taken before ICRS explantation. *B*: Scanning electron micrograph shows the clean surface of a Keraring ICRS. *C*: Scanning electron micrograph of the segment surface. *D*: Scanning electron micrograph shows the clean surface of the extremity of an Intacs ICRS.

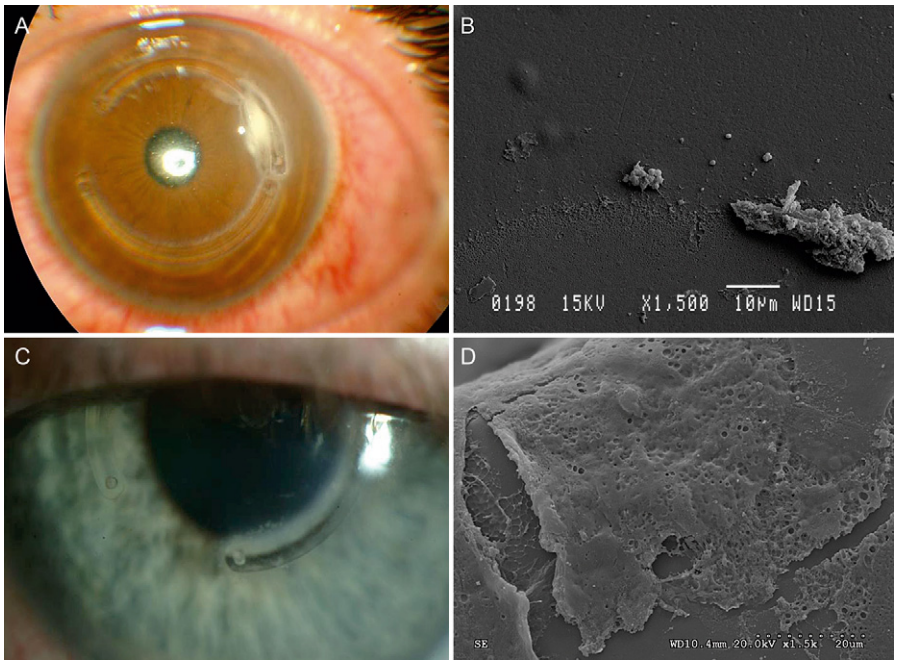

Figure 4. Findings in ICRS explantation for suspected infection. *A*: Clinical photograph shows an infiltrate around the extremity proximal to the superior segments, with pronounced stromal infiltration at the superotemporal incision. *B*: Bacterial deposits (coccus) are seen on the proximal extremity the ICRS (SEM). *C*: Clinical photograph shows an infiltrate around the distal extremity of ICRS and pronounced stromal infiltration. *D*: Scanning electron micrograph of biofilm deposits on the distal extremity of the ICRS.

(IOL) implantation. In the latter cases, the surgically induced inflammation produces a foreign-body reaction, which is expressed by the presence of macrophages and giant cells on the IOL surface.[30] We found macrophages only in cases of extrusion.

There were no lipid-like biodeposits on ICRS explanted for refractive failure, although biodeposits have been reported. Ruckhofer et al.[31] describe lamellar channel deposits after Intacs ICRS implantation and suggest they are caused by physical separation of stromal lamellae when they are dissected to create a channel for ICRS placement. This phenomenon has been seen with Intacs and Keraring ICRS,[26] and the incidence and density of deposits increase with segment thickness and duration of implantation.[31] Although the reported incidence of intrastromal lamellar deposits is as high as 60%,[31] we saw no deposits on clinical or SEM evaluation in any case of ICRS explantation for refractive failure. However, clinical examination in cases of segment extrusion showed deposits along the tunnel. The location and appearance of the deposits are different from those described in other studies.[31–33] In our cases, the deposits were in the inner curvature, along the ICRS (data not shown), or near the extruded end; in addition, the deposits appeared more diffuse. Twa et al.[25] observed 2 types of deposits on clinical microscopy. The first were translucent with an oil-droplet appearance, and they appeared earlier than the second type, which had a crystalline appearance. Our deposits were similar to the first type, and we believe they were probably related to a corneal lesion and the presence of a corneal foreign body (extruded part of ICRS).

In most cases (68.8%) of extruded segments, we observed inflammatory cellular reaction at the extrusion site; in some cases, the reaction surrounded the ICRS. The reaction was likely associated with corneal damage because the inflammatory infiltrate was larger near the wound, although deposits were seen at the segment edge. This indicates that epithelial breakdown and close contact between the corneal stroma and the tear film play a role in triggering this reaction. Migration of macrophages to the wound site, localized edema,[34] and activation of keratocytes to fibroblast and myofibroblast phenotypes would be consistent with the normal tissue response to surgical trauma.[35] We found numerous cells and cell debris on the surfaces of extruded ICRS. Although we presume these cells were macrophages and other blood cells, they are difficult to differentiate by morphology alone. Regarding cell debris, Samimi et al.[36] found ICRS-induced keratocyte apoptosis that probably developed through a switch to a collagenous synthetic phenotype. Therefore, we hypothesize cell debris corresponds to keratocytes or epithelial cells. We also found lipid drops on the surface of extruded ICRS. Lipid accumulation is reported to be a consequence of trauma during implantation surgery or corneal suturing.[37] Therefore, the inflammatory reaction does not occur when the segment is placed in stroma but rather is triggered when the epithelial barrier is broken. This reaction is amplified when a foreign body prevents wound closure. Three cases of ICRS extrusion in our study had vascularization. Corneal neovascularization after ICRS implantation is not frequently reported, and it is usually superficial and localized to

the site of the surgical wound. In our study, vascularization occurred near the extrusion wound in 2 cases and along the segment in the other case. Under SEM, all 3 segments were covered with ECM; the mechanism of the vascularization process has yet to be determined.

Scanning electron microcopy of ICRS explanted for suspected infection showed cocci over the surface of the segment with the positive culture; however, the cocci were not in aggregates or fixed to the surface by exopolysaccharide, nor did they form a biofilm on the ICRS. There were no inflammatory cells or any cell debris on the surface of the ICRS. In the case with a negative culture, there was a biofilm on the ICRS surface. Although no bacteria were identified, the microorganism may have been hidden under the exopolysaccharide, which contributed to the negative culture result.

Because extrusion was the principal cause of ICRS explantation and inflammatory response in our cases, we wonder whether this process is a result of host rejection or because the superficial part of the stroma thinned over time,[38] causing extrusion. Although the second option seems more probable, additional studies are required. We are processing new data from these cases to further our understanding of this pathophysiologic process.

In conclusion, the lack of inflammatory reaction in cases of ICRS explanted for refractive failure confirms the biocompatibility of PMMA segments in the corneal stroma. However, SEM analysis found evidence of an inflammatory process in cases of ICRS extrusion. We believe that this is the first study in which explanted ICRS were analyzed by SEM. Our results corroborate previous studies using histopathology and contribute new information about the causes and results of ICRS explantation.

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