Frequency, Distribution, and Outcome of Keratoplasty for Corneal Dystrophies at a Tertiary Eye Care Center in South India

Hijab Pandrowala, Aashish Bansal,* Geeta K. Vemuganti,† and Gullapalli N. Rao**

Purpose: To report the frequency, outcome, and atypical histology in corneal dystrophies.

Methods: Corneal buttons of patients diagnosed with corneal dystrophy as noted in the records of the ophthalmic pathology register over a period of 6 years were included in this study. The sections from formalin-fixed, paraffin-embedded tissues were reviewed specifically for the type of deposits, associated degenerations such as amyloid and spheroidal deposits, inflammation, and vascularization. Special stains including Masson trichrome, Congo red, and Alcian blue staining were used whenever required. The medical records were evaluated for demographics, clinical presentation, history of consanguinity, family medical history, and clinical outcome of keratoplasty, which was recorded as clear, recurrence of dystrophy, or graft failure. A clinicopathologic correlation was attempted.

Results: A total of 144 patients contributed 181 buttons, accounting for 8.1% of keratoplasties performed during the study period. The mean age of the patients was 34 ± 19 years (range 3–72 years) with a male:female ratio of 1.6 (89):1 (55). Consanguineous parentage was noted in 26% of cases. History of a similar problem in siblings and other family members was elicited in 33 (22%) and 14 (9.7%), respectively. Dystrophies included macular (29.3%), congenital hereditary endothelial dystrophy (34.8%), Fuchs (16.6%), and lattice (15%); the remaining 11% included granular, gelatinous drop-like, Reis-Bucklers, and posterior polymorphous dystrophy. Associated histologic changes were degenerations (15%), vascularization (4%), and inflammation (2%). At a mean follow-up of 42 months, the graft remained clear in 148 eyes (81.7%), failed in 33 eyes (18.2%), and recurred in 5 eyes (2.8%). Graft survival for all dystrophies at the end of 1 year was 94.3 ± 1.7%, and at the end of 5 years was 74.4 ± 4.5%. Atypical histologic features did not affect graft survival.

Conclusion: Consanguineous marriages possibly contributed to the increase in macular dystrophy and CHED in South India. The degenerative changes seen could possibly be related to late presentation or unknown environmental factors and do not have an effect on the ultimate graft outcome.

Key Words: corneal dystrophy, keratoplasty, granular lattice, amyloid, outcome, prognosis

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Corneal dystrophies are defined as primary, inherited, bilateral, heredofamilial disorders of the cornea affecting transparency or refraction, leading to varying degrees of visual disturbances.[1] They are generally said to be of early onset, axially symmetric, slowly progressive or stationary, free from vascularization, and not associated with other systemic conditions. These are reasonable guidelines for a clinical diagnosis of a corneal dystrophy. But there are exceptions to each of these characteristics, such as unilateral presentation in Meesman and lattice dystrophy, vascularization in gelatinous drop-like keratopathy, and delayed presentation in Fuchs dystrophy.[1,2] The dystrophies have been traditionally classified according to the primary layer of involvement into anterior membrane dystrophies (epithelium, epithelial basement membrane, and Bowman layer dystrophies), stromal dystrophies, and endothelial dystrophies (endothelium and Descemet membrane). But recent insights into the genetics of corneal dystrophies have changed the concept of dystrophies.[1,2] Multiple mutations in the BetaIGH3 gene, which codes for protein keratoepithelin, have been invoked to explain the phenotypic diversity of the classic stromal dystrophies,[1,2] thus indicating the need for a classification based on genotypic rather than phenotypic features. However, the 2 approaches are not mutually exclusive, and the phenotypic approach, based on the assessment of clinical and histologic features, will continue to provide the most comprehensive clinical account of these disorders for some time to come.

The frequency of dystrophies requiring penetrating keratoplasty in India is 8.4%,[3] and in other series it ranges from 4% to 24%.[4–7] The observation of atypical presentations, inflammation, and associated degeneration (spheroidal and amy-

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From the *Cornea and Anterior Segment Service, L. V. Prasad Eye Institute, Hyderabad, India; and †Ophthalmic Pathology Service, L. V. Prasad Eye Institute, Hyderabad, India.

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Reprints: Geeta K. Vemuganti, MD, Ophthalmic Pathology Service, L.V. Prasad Eye Institute, L.V. Prasad Marg, Banjara Hills, Hyderabad 500 034, India (e-mail: geeta@lvpeye.stph.net).

TABLE 1. Clinical Profile of Corneal Dystrophies at LVPEI

Dystrophy	No. of Buttons	Mean Age (years)	H/O Consanguinity	Siblings Affected	Other Family Members
Macular	53 (29.3%)	33	12 (27.3%)	16 (36.4%)	7 (15.9%)
Granular	4 (2.2%)	45	None	1 (25%)	2 (50%)
Lattice	15 (8.3%)	43	1 (6.7%)	2 (13.3%)	None
Gelatinous drop-like	8 (4.4%)	16	3 (60%)	2 (40%)	None
Reis-Bucklers	3 (1.7%)	36	None	1 (25%)	3 (75%)
Postpolymorphous	5 (2%)	52	3 (60%)	2 (40%)	None
CHED	63 (34.8%)	14	22 (35%)	11 (17%)	2 (3%)
Fuchs	30 (16.6%)	36	None	None	3 (7.5%)

loid) prompted us to review the frequency, distribution, and the outcome of keratoplasty in corneal dystrophies at a tertiary eye care center in South India. Moreover, to the best of our knowledge and based on an extensive literature search, there is no study comparing the frequency and characteristics of corneal dystrophies in India with that in other parts of the world.

MATERIALS AND METHODS

Corneal buttons from patients clinically diagnosed as having corneal dystrophy and who underwent penetrating keratoplasty over a period of 6 years (January 1995 to March 2001) were retrieved from the records of the ophthalmic pathology service and included in this study. The medical records of the patients were reviewed for demographics, family history, history of consanguineous marriage, presenting symptoms, duration of symptoms, and outcome of the graft after penetrating keratoplasty. There were multiple surgeons involved including consultants and corneal fellows. Graft size used was 8 or 8.6 mm depending on surgeons' preference. The suturing pattern was either interrupted 16 or 12 × 12 combined. Interrupted sutures were generally removed after 12–18 months unless loose, broken, or vascularized. Continuous sutures were left indefinitely. The clinical outcome of the penetrating keratoplasty at the last follow-up was recorded as clear graft, failed graft, or disease recurrence. The patients who lived far away and who could not afford frequent visits to the center were advised to follow up with trained and experienced corneal surgeons practicing in the local region, using state-of-the-art slit lamps. Graft survival was depicted in terms of the Kaplan-Meier survival analysis. The outcome of graft with and without secondary changes (identified clinically or by histology) was compared using Fisher exact test test.

The sections from formalin-fixed, paraffin-embedded tissues were reviewed specifically for the type of deposits, stromal scarring, inflammation, and vascularization. Presence of degenerative changes in stroma and Bowman layer in the form of secondary amyloid deposits, band-shaped keratopathy, and elastotic degeneration (spheroidal deposits) were noted. Special stains such as Masson trichrome, Congo red, and Alcian blue, which are specific for hyaline deposits of granular dystrophy, amyloid deposits of lattice dystrophy, and mucopolysaccharide deposits of macular dystrophy, respec-

TABLE 2. Histopathologic Profile of the Corneal Dystrophies

		Vascularization		Inflammation		Degeneration	
Dystrophy		Clinical	Histo	Clinical	Histo	Clinical	Histo
Macular	(53)	4 (7.5%)	—	—	—	1 (1.9%)	4 (7.5%)
Granular	(4)	—	—	—	—	—	—
Lattice	(15)	2 (13.3%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	3 (20%)	5 (33%)
Gelatinous drop-like	(8)	4 (50%)	4 (50%)	1 (12.5%)	1 (12.5%)	—	—
Reis-Bucklers	(3)	—	—	—	—	—	—
Postpolymorphous	(5)	—	—	—	—	—	—
CHED	(63)	2 (3.2%)	—	1 (1.6%)	3 (4.8%)	2 (3.2%)	6 (9.6%)
Fuchs	(30)	4 (13.8%)	4 (13.8%)	—	—	—	—
Total		16 (8.8)	9 (5%)	3 (1.7%)	5 (2.8%)	6 (3.3%)	15 (8.2%)

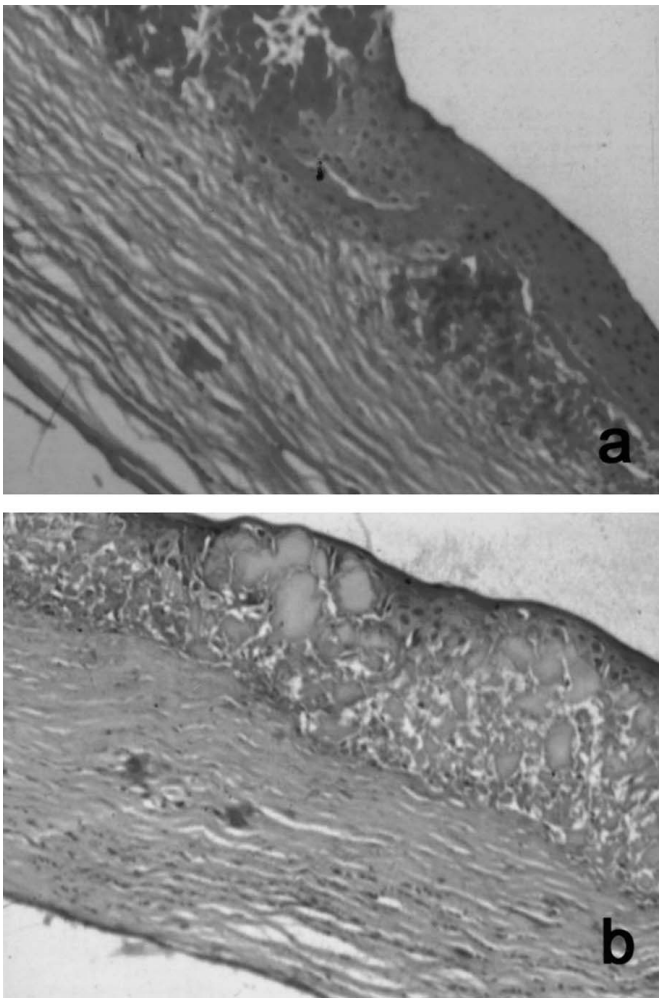

FIGURE 1. A, Section from a case of lattice dytrophy showing spheroidal degeneration in the superficial stroma (hematoxylin & eosin, ×250). B, The section from lattice dystrophy showing amyloid deposits in midstroma and spheroidal deposits in superficial stroma using Congo red.

tively, were performed whenever required. A clinicopathologic correlation was attempted.

RESULTS

During the study period, 2244 corneal buttons were received at the ophthalmic pathology laboratory, of which 181 corneal buttons from 148 patients were reviewed, accounting for 8.1% (181 of 2244) of the total keratoplasties. The mean age of the patients was 34 ± 19.4 years (range 3–72 years), with 62 patients (41.8%) under 30 years of age. There was a slight male preponderance with a female:male ratio of 1 (55):1.6 (89).

Clinical Profile

History of consanguineous parentage was noted in 38 (26%) cases. History of a similar problem in siblings and other members was elicited in 33 (22%) and 14 (10%) patients, respectively. The predominant presenting symptom was decreased vision in 174 (96%) eyes, followed by pain in 40 (22.7%), photophobia in 39 (21.5%), and redness in 26 (14%) eyes. The clinical profile and the frequency of each dystrophy is given in Table 1. Congenital hereditary endothelial dystrophy outnumbered the rest, contributing 63 buttons (34.8%) followed by macular dystrophy with 53 buttons (29.3%) and Fuchs dystrophy 30 buttons (16.6%); together they contributed 81% of the dystrophies. Superficial vascularization was observed in 16 eyes, including 4 cases each of macular, GDLK, and Fuchs and 2 each of lattice and CHED. Evidence of degeneration was noted clinically in 6 eyes. Inflammation was seen in 3 buttons, 1 each of GDLK, lattice, and CHED.

Histopathology

The final histologic diagnosis was based on the characteristic morphologic features found on light microscopic ex-

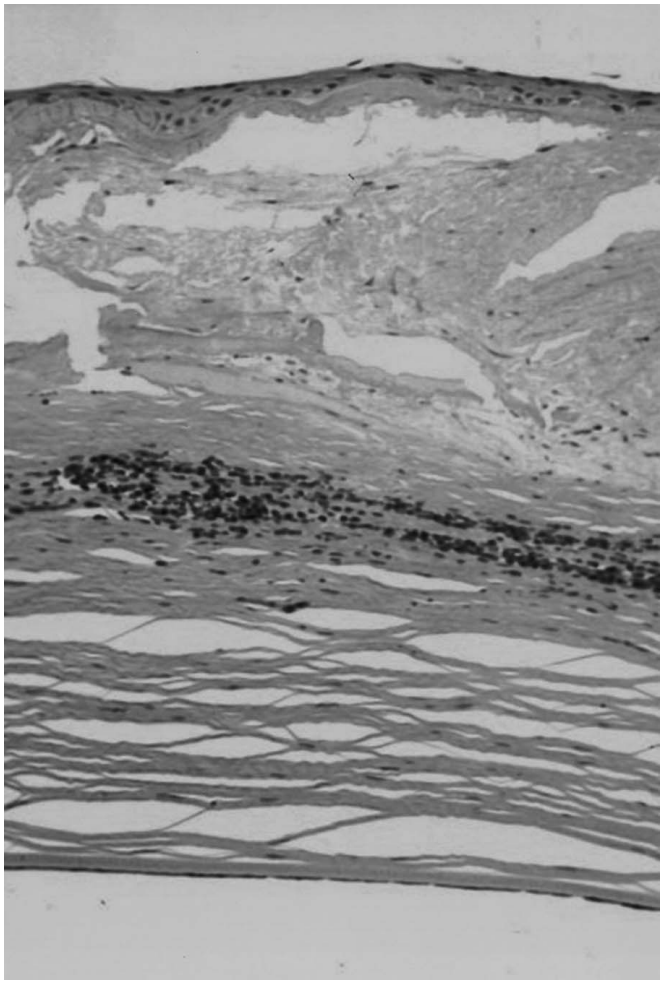

FIGURE 2. The section from a case of congenital hereditary endothelial dystrophy showing stromal scarring inflammation and amyloid deposits (×100, hematoxylin & eosin).

amination. Special stains such as per-iodic acid Schiff, Masson trichome, Congo red, and Alcian blue confirmed the diagnosis of endothelial dystrophy, granular, lattice, gelatinous-droplike dystrophy, and macular corneal dystrophy, respectively. The clinical diagnosis correlated well with histopathology in most of the cases except in 1 case of granular dystrophy, which was clinically diagnosed as Reis-Bucklers corneal dystrophy.

Associated secondary changes (Table 2) were noted in 36 (19.9%) cases with degeneration in 15 (8.2%), vascularization in 9 (5%), inflammation in 5 (2.8%), and amyloid in 7 (3.9%). Spheroidal degeneration in superficial corneal stroma was noted in 15 cases, including 6 buttons of CHED, 5 cases of lattice (Fig. 1), and 4 cases of macular dystrophy. Vascularization was noted in 9 buttons mostly in the superficial stroma, including 4 buttons each of GDLK and Fuchs and 1 of lattice dystrophy. Inflammation, predominantly consisting of lymphomononuclear cells, was noted in 5 buttons, 1 each of GDLK and lattice and 3 of CHED. Amyloid deposits were noted in 7 (3.9%) buttons of CHED (Fig. 2), which appeared clinically as whitish subepithelial deposits with underlying stromal edema.

Outcome of Grafts

The outcome of the penetrating keratoplasty is given in Table 3. With a mean follow-up of 42 months, the graft remained clear in 148 (81.7%) and failed in 33 eyes (18.2%), and recurrence of disease was noted in 5 (2.76%). Endothelial rejection was the most common cause of graft failure, accounting for 20 of 33 eyes (60.6%). Primary graft failure was noted in 3 (9%), glaucoma in 3 (9.1%), recurrence in 5 (15.2%), and graft infiltrate in 2 (6.1%).The Kaplan-Meier (Fig. 3) analysis showed a graft survival rate of 94.3 ± 1.7% at 1 year that progressively decreased to 88.8 ± 2.5% at 2 years, 83.2 ± 3.2% at 3 years, 79.2 ± 3.8% at 4 years, and 74.4 ± 4.5% at 5 years.

Correlation of Outcome with Histologic Features

Statistical significance of the difference in anatomic success and graft survival between the 2 groups was determined using Fisher exact test. One group included corneal buttons that did not have secondary changes, and the other included buttons that showed secondary changes of vascularization (16 of 165, 91.2%), spheroidal degeneration (15 of 166, 8.2%), inflammation (5 of 176, 2.8%), and amyloid changes (7 of 174, 3.9%) (Table 4). A P value less than 0.05 was considered significant. The presence of secondary changes did not have any significant effect on graft outcome.

DISCUSSION

Corneal dystrophies frequently require penetrating keratoplasty to restore vision, though the superficial ones can be treated with lamellar keratoplasty or phototherapeutic keratectomy. In this series, corneal dystrophies accounted for 8.1% of all keratoplasty surgeries performed during the study period; other series from the West, Middle-East, and Japan have shown a frequency ranging from 4% to 24.4% of the total keratoplasty surgeries,[3–7] but the distribution of the various types of dystrophies is unlike the Western literature.

A review of Western literature cites Fuchs dystrophy[4,7] as the most frequent dystrophy requiring keratoplasty. However, in our study, congenital hereditary endothelial dystrophy accounts for 63 (34.8%) and macular for 29% of the total dystrophies. These 2 together constitute nearly two thirds of all dystrophies. Lattice, granular, Reis-Bucklers, gelatinous droplike dystrophy, and posterior polymorphous dystrophy together constitute 19% of all cases. A similar distribution has been reported from Saudi Arabia,[6] where there is a high incidence of consanguineous marriages as in southern India. Because macular and CHED are inherited as autosomal recessive diseases, the high incidence in Saudi Arabia and South India are understandable. Therefore, genetic counseling is highly advisable among families that carry the trait of such vision-threatening inherited diseases.

Atypical histologic features in corneal dystrophies, namely vascularization and inflammation, have not, to the best of our knowledge and from our literature search, been reported earlier. Spheroidal deposits that have been noted earlier in lat-

TABLE 3. Outcome of Penetrating Keratoplasty in Total Cases of Corneal Dystrophy

Distribution		Clear Graft	Recurrence	Graft Failure	Mean Follow-Up (months)
Macular	(53)	49 (92.5%)	None	3 (6.8%)	28
Granular	(4)	3 (75%)	None	1 (25%)	28
Lattice	(15)	13 (86%)	None	2 (13.3%)	33
Gelatinous drop-like	(8)	3 (37.5%)	3 (37.5%)	2 (25%)	52
Reis-Bucklers	(3)	1 (33.3%)	2 (66.7%)	None	50
Postpolymorphous	(5)	4 (80%)	None	1	19
CHED	(63)	47 (74.5%)	None	16 (25.4%)	48
Fuchs	(30)	27 (90%)	None	3 (10%)	28

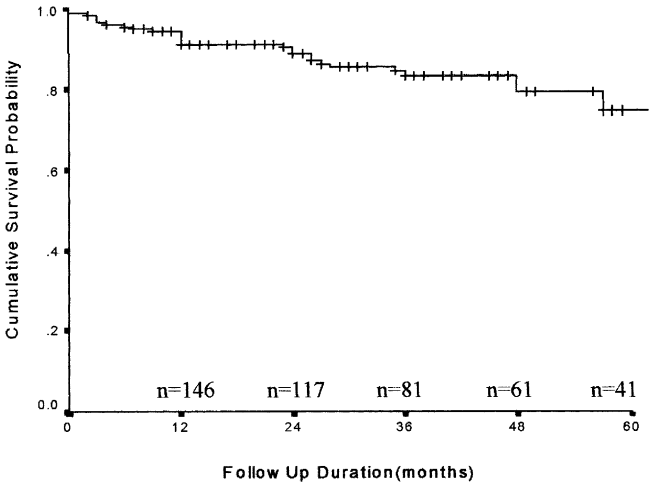

FIGURE 3.

tice dystrophy[5] were noted in this series in eyes with CHED and macular dystrophies as well. This possibly could be a degenerative response to the long-standing nature of the pathology. Because the degenerations are noted in many of the excised corneal buttons at our center (unpublished data), there is a possibility that it is an independent factor, unrelated to the corneal dystrophy. Vascularization was seen in 4 buttons of Fuchs dystrophy and 2 of CHED, which could be caused by long-standing corneal edema or repeated breakdown of corneal epithelial bullae. Vascularization was also seen in 4 buttons of macular and 2 of lattice, which could be secondary to the inflammation induced by recurrent epithelial breakdown, which is known to occur in these conditions. Amyloid deposits were seen in 7 buttons of CHED; this could be a degenerative response to long-standing corneal edema. In another study we demonstrated amyloid deposits, possibly secondary in nature, in 5 cases of CHED.[8] Inflammation documented in CHED, lattice, and GDLK could possibly be caused by recurrent epithelial breakdown. Further studies are required to confirm these changes in other dystrophies. Recurrence was seen in 5 eyes, 3 in gelatinous drop-like dystrophy and 2 in Reis Bucklers, both of which are known to recur.[5,9,10] The recurrence rate could possibly be low in this series because of a short follow-up of the patients at this institute.

Outcome in terms of clear grafts at last follow-up was best in macular dystrophy (92%), followed by Fuchs dystrophy (90%). Both of these dystrophies are known to have a very good prognosis with an 80% to over 90% chance of a clear graft.[11,12] Price and colleagues[11] reported a 5-year graft survival of 98% for keratoconus and Fuchs dystrophy combined; this was better than the outcome of keratoplasty done for other indications but not significantly different from each other. In our study, the overall graft survival taking into account all the dystrophies was 94.3 ± 1.8% at 1 year and 74.4 ± 4.5% at 5 years, which is similar to the 5-year graft survival of 75.8% for all corneal dystrophies cited in the Australian Graft Registry.[13]

Graft failure was highest in CHED 16 (25%). The graft survival, however, was 85% at 1 year and 81% at 2 years, which is comparable to that reported by Al-Rajhi and Wagoner.[14] They had operated on 56 eyes of 40 patients and reported a graft survival of 92% at 1 year and 72% at 2 years. The mean age of patients in their series was 11.8 years (ranging from 2 months to 35 years), whereas in this study it was 14 years, ranging from 3 months to 45 years of age. Endothelial rejection was the most common cause of failure in their study as well as in the present study. Penetrating keratoplasty in the pediatric age group is known to be a high-risk procedure.[15] The technical complexity of the procedure, the rapid and exuberant rate of rejection, the difficulties in patient follow-up and management, and the amblyogenic potential of corneal opacification in pediatric patients make for a less than desirable outcome.

Over the past 2 decades, new genetic information has become available, and about 10 chromosomal loci have been linked to specific corneal dystrophies.[1,2] The genotypic ap-

TABLE 4. Outcome of Grafts in Corneal Buttons With or Without Histologic Evidence of Secondary Changes

		Graft Status			
		Clear		Failed	
	Total	A	B	A	B
Vascularization	16/165 (91.2%)	12 (75%)	141 (85.5%)	4 (25%)	25 (14.5%)
Degeneration	15/166 (8.2%)	14 (93%)	139 (83.8%)	1 (7%)	27 (16.2%)
Inflammation	5/176 (2.8%)	4 (80%)	150 (85.3%)	1 (20%)	26 (14.7%)
Amyloid	7/174 (3.9%)	7 (100%)	148 (85.1%)	None	26 (14.9%)

A, cornea with secondary changes.
B, cornea without secondary changes.

proach will provide increasing understanding and, in the long term, increase the opportunity for medical intervention using conventional pharmocologic approaches or gene therapy. In view of paucity of information on genetics of corneal dystrophies from India, it would be worthwhile to undertake more studies in our population. Besides, in our study, as in previous reports, the prevalence and relative frequencies of various corneal dystrophies were based on the corneal buttons removed during penetrating keratoplasty. Population-based incidence calculated in terms of number of patients rather than cases undergoing keratoplasty would be more useful.

In summary, there is a high frequency of macular dystrophy and CHED in southern India, possibly related to consanguineous marriages, suggesting a need for genetic counseling. Recurrence was common with gelatinous drop-like dystrophy and Reis Bucklers dystrophy. Associated secondary degenerative changes were noted in 15% of cases. These could possibly be related to late presentation or other unknown environmental factors, and do not hinder graft survival.

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