Veterinary Ophthalmology (2001) **4**, 2, 147–153

The use of porcine small intestinal submucosa in ten cases of feline corneal disease

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Abstract

Porcine small intestinal submucosa (SIS) was used as a novel graft material in the management of 10 cases of feline corneal disease. Five cases had stromal ulceration associated with trauma, ocular foreign body and/or suspected infection and required a grafting procedure. Five cases had feline sequestra that were managed by a keratectomy prior to placement of SIS as a graft material. Eight eyes healed with minimal corneal scarring with a very good cosmetic and visual result. One eye with continued aqueous leakage in the immediate postoperative period required a conjunctival pedicle graft to reinforce the SIS graft site. One eye required enucleation 48 h following grafting due to progressive keratomalacia but the SIS material remained intact.

Key Words: cornea, corneal sequestrum, eye, feline, small intestinal submucosa, ulcerative keratitis

INTRODUCTION

Ulcerative keratitis is a common ocular disease that is potentially serious when both vision and the globe itself are threatened. Deep corneal defects should be managed surgically for optimum results and techniques available include conjunctival autografts,[1–5] cyanoacrylate tissue adhesive,[6–8] corneal–scleral–conjunctival transpositions,[9,10] lamellar keratoplasty,[5,11,12] and penetrating keratoplasty.[5,13] The use of tectonic corneal grafts has also been described.[12,14] Many of these techniques require specialist skills and equipment; the availability and storage of donor tissue can be difficult. Conjunctival pedicle grafts are practical and versatile and, as such, are widely and successfully used in veterinary ophthalmology.[2,3] However, conjunctival grafts can ultimately result in corneal opacities that can impair vision when the lesion is in the axial cornea. In the quest for an ideal graft material, numerous noncorneal materials have been employed to repair corneal defects with good results. These include split-thickness dermal grafts,[15] equine pericardium,[16] peritoneum,[17] equine amniotic membrane,[18] human amniotic membrane in rabbits,[19] equine renal capsule,[20] and expanded polytetrafluoroethylene (Gore-tex).[21,22]

The ideal biomaterial for the repair of corneal defects should achieve strict specifications for optical clarity, support of epithelial migration and adhesion, permeability to solutes, and stability to corneal proteases.[23] Potential biomaterials include collagen, collagen-hydrogel copolymers, bioactive synthetics, and coated hydrogels.[23] Different sources of collagen tissue in particular have been investigated as potential corneal biomaterials. Porcine collagen shields have been used as topical contact lenses in the management of corneal disease in man and in experimental models with variable results.[24–29] Examples of surgical implantation of collagen-based tissues include human type IV collagen, which supports corneal epithelialization *in vivo* in monkeys.[30] Allogenic aural cartilage tissue and dermal collagen have been successfully transplanted into corneal defects in rabbits.[31]

Small intestinal submucosa (SIS) is an example of a collagen-based material derived from the submucosal layer of porcine small intestine. It is a trilaminar material consisting of tunica muscularis mucosa, tunica submucosa and the stratum compactum layer of the tunica mucosa. It is biodegradable, acellular, nonimmunogenic, and xenogeneic. Extensive studies over the last decade have demonstrated its excellent regenerative capacities in multiple organ systems including bladder regeneration,[32] vascular graft studies,[33] anterior cruciate ligament repair,[34] Achilles tendon repair,[35] cartilage repair,[36] gastrointestinal studies,[37] dermatologic applications,[38] and dental/oral studies.[39] Histopathology has shown that SIS acts as a scaffold upon which host tissues can recreate a structure that is histologically similar to the original tissue.[32,33] Healing therefore occurs by regeneration rather than by simple scar formation. This property is site-specific; SIS biomaterial assumes the specialized microscopic and functional properties of the tissue into which it is grafted. For

example, all three layers of the bladder, grossly and microscopically indistinguishable from the normal tissue, were present at 48 weeks following the incorporation of SIS biomaterial into a full-thickness defect.[32]

The cornea owes its unique transparency to the precise organization of predominantly collagen type 1 fibrils, which are oriented in a parallel manner. During normal stromal healing, type 3 collagen is laid down and is less regularly arranged, thus resulting in corneal scarring and possible visual impairment. Although no specific studies for the surgical implantation of SIS into ocular tissues have been performed to the authors' knowledge, its unique ability to promote tissue healing with negligible scar formation in other tissues, including avascular tissues,[36] indicates its potential application in the management of ocular surface disease in which the preservation of a clear visual access is desired. It is translucent and thus offers advantages for corneal surgery as an alternative to conjunctival and other opaque tissues. As SIS is porous, it will allow the absorption of topical ophthalmic medications.

There are only a small number of recent reports which document the surgical use of SIS in ocular conditions in the veterinary field with good results. It was first described for the successful management of a full-thickness repair following excision of a canine limbal melanoma in 1999.[40] Its use in feline ulcerative keratitis was subsequently described by the authors[41,42] and was later proposed as a possible alternative to conjunctival grafts.[43] This article describes its use in 10 cases of feline corneal disease of varying etiology.

MATERIALS AND METHODS

Ten eyes of 10 cats with corneal disease of different etiologies were treated with SIS corneal graft biomaterial. The age range was 6 months to 13 ½ years old. There were five Persians, four Domestic short-haired cats, and one Domestic long-haired cat. The duration of treatment by the referring veterinary surgeon ranged from 5 to 90 days. Five eyes had stromal ulceration associated with suspected trauma and/or infection or ocular foreign body. Five eyes had ulcerative keratitis associated with feline sequestrum formation. Bacteriology for anaerobic and aerobic culture was performed in four cases and revealed no growth of microorganisms, including case 5 with 'melting' ulcerative keratitis.

Premedication with 0.2 mg/kg methadone (IM) (Glaxo Wellcome), 4 mg/kg carprofen (SC) (Rimadyl, Pfizer Limited, Kent, UK) and 8.75 mg/kg amoxycillin clavulanate (SC) (Synulox, Pfizer) was followed by induction with 6 mg/kg propofol (IV) (Rapinovet, Schering-Plough Animal Health, Middlesex, UK) and general anesthesia maintained with halothane, oxygen and nitrous oxide. In all cases surgery was performed with the aid of an operating microscope (Topcon OMS 600). In the five cases of stromal ulcerative keratitis, meticulous preparation of the recipient ulcer bed was performed by careful excision of nonviable corneal tissue prior to placement of the SIS biomaterial (VET BIOSIST, Cook (UK) Limited, Hertfordshire, UK). In the five cases of feline sequestra, the diseased cornea was completely excised by means of keratectomy up to two thirds of the stromal depth prior to placing a SIS graft. To prepare the SIS graft, the sheet was removed from the pouch using an aseptic technique. A Stiefel biopsy punch of appropriate diameter was used to construct a circular graft of the appropriate size. The graft was measured to overlap the corneal defect by approximately 1.0 mm. The graft was then rehydrated in sterile saline for a minimum of 3 min prior to placement into the corneal defect. The SIS graft was sutured into the corneal defect with a simple interrupted or continuous suture pattern with 8/0 or 10/0 polyglactin 910 (Vicryl, Ethicon, (Sanssen-Silag Limited), Buckinghamshire, UK). The graft and ocular surface were kept moist with the frequent application of sterile saline during the surgical procedure.

In cases 8, 9 and 10, soft bandage contact lenses (*i-protex*, Veterinary Speciality Products, Shropshire, UK) were placed to relieve immediate postoperative discomfort and were removed 3–5 days later. The use of contact lenses in selected cases was based on the temperament of the patient, the absence of ocular infection, and the preference of the surgeon. Routine postoperative medication included ketoprofen 1 mg/kg/day per os (Ketofen, Merial Animal Healthm, Essex, UK) for 3 days and 0.5% chloramphenicol eye drops (Schering-Plough Animal Health, Middlesex, UK) three times daily. Case 5 was treated every two hours with 0.37% disodium edetate (EDTA solution, Moorfields Eye Hospital, London, UK) and 0.3% ofloxacin (Exocin, Allergan Limited, Buckinghamshire, UK) in the perioperative period. Cases received follow-up for 7 days to 10 months.

RESULTS

With the exception of cases 4 and 5, all eyes appeared comfortable in the immediate postoperative period. Six of the 10 cases healed without complication and with minimal corneal vascularization and scarring (Figs 1 and 2); two of those cases presented with stromal ulceration (cases 1 and 2) and four with corneal sequestration (cases 6, 7, 8 and 10). Repeated sequential examinations with slitlamp biomicroscopy revealed gradual assimilation of the SIS graft material into the cornea with minimal vascular response. The long-term cosmetic effect and clarity of the visual access were very satisfactory in these cases. Case 3 had an intense corneal vascular response within the first few weeks, which then subsided without additional treatment; the final outcome was very good.

The discomfort observed in cases 4 and 5 was attributed to the ocular pathology (hypotony and keratomalacia, respectively) rather than the SIS graft material. Case 4 required a conjunctival pedicle graft 72 h after the initial operation due to continued aqueous leakage; the cornea then healed without further complications. In case 5, corneal 'melting' and stromal destruction continued for 48 h following surgery despite topical anticollagenase therapy, and enucleation was required; gross ocular pathology showed the SIS graft

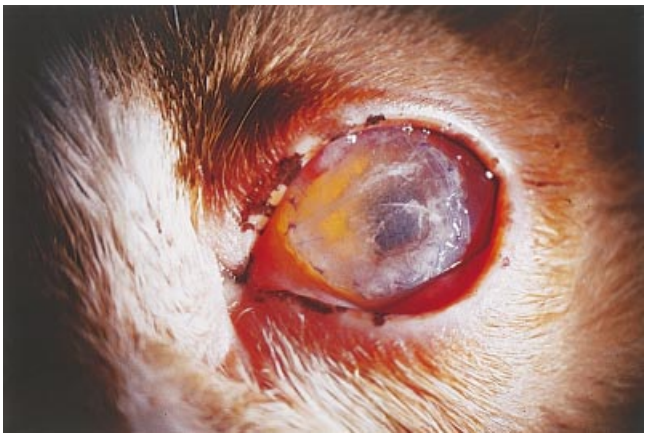

Figure 1. Left eye of an $8\frac{1}{2}$ year old, neutered male, Persian cat (case 2), 24 h post surgery. Normal pale appearance of SIS graft *in situ*.

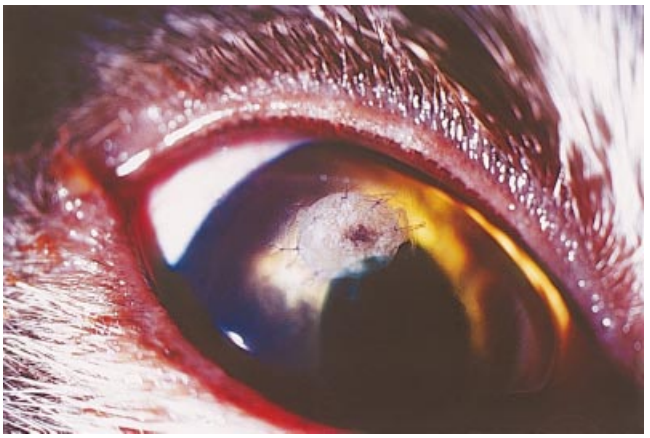

Figure 3. Left eye of a $4\frac{1}{2}$ year old, neutered male, Domestic short-haired cat (case 9), 24 h post surgery. Contact lens (central blue dot) *in situ*. Note focal hemorrhage in center of SIS graft – no remaining corneal pigment.

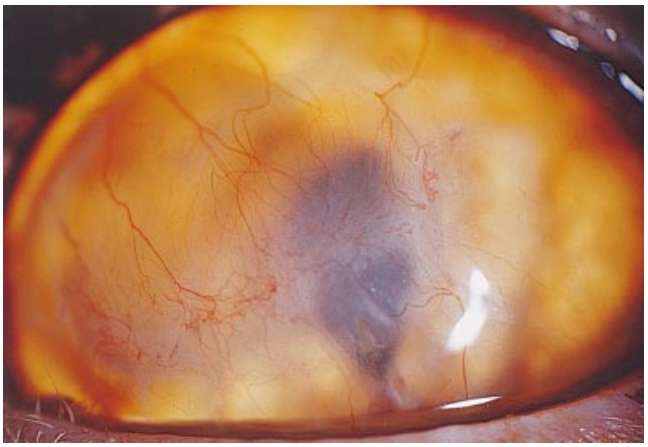

Figure 2. Left eye of an $8\frac{1}{2}$ year old, neutered male, Persian cat (case 2), 7 weeks post surgery, with mild diffuse corneal opacity and neovascularization.

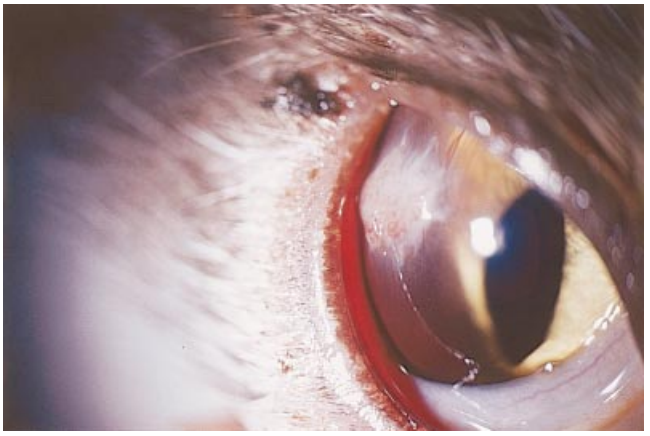

Figure 4. Left eye of a $4\frac{1}{2}$ year old, neutered male, Domestic short-haired cat (case 9), 4 weeks post surgery, demonstrating a focal granulation tissue response following SIS sloughing.

material to be intact despite extensive thickening and 'melting' of the entire cornea.

All five cases of feline sequestra resulted in a good long-term cosmetic and visual result with minimal corneal scarring and a relatively clear visual axis. In case 6, temporary brown discoloration of the SIS graft was observed, which subsided by 8 weeks. In case 8, faint brown stromal discoloration was noted 35 days postoperatively but there was minimal scarring and no sign of progression at 86 days. However, in case 9 the SIS graft appeared dark brown 6 days after surgery and then black at 17 days. There was mild ocular discomfort and localized superficial corneal neovascularization surrounding the SIS graft and surgical site (Figs 3 and 4) on postoperative days 17–28. At 28 days the blackened graft had disappeared, presumably sloughed from the corneal surface, and the cornea was healing with a moderate vascular response. There was negligible corneal scarring at the final check-up 10 months following surgery. There was no postoperative brown discoloration of the SIS graft or cornea in cases 7 and 10. See Table 1 for a summary of patients and postoperative outcomes.

DISCUSSION

Many methods have been described for the repair of deep corneal defects[1–12,14] but corneal opacification is often the final result, with the possible exception of penetrating keratoplasties.[13] Previous studies performed in a diverse range of vascular and avascular, nonocular tissues showed that SIS developed histological features consistent with the tissue into which it was implanted.[32,33,36] It is reasonable to assume that SIS biomaterial may remodel in a similar way over time when placed in corneal tissue. Histological examination of SIS graft sites is needed to complement clinical observations of assimilation of SIS into corneal tissue and to assess the precise nature of the healing environment and the type of collagen present.

Table 1. Clinical findings and postoperative results of cats with corneal disease treated with SIS grafts

Case	Breed	Age	Gender	OD/OS	Corneal lesion	Duration of treatment before presentation	Bacteriology	Surgical procedure	Follow-up period	Outcome	Comments
1	Persian	4 years	MN	OS	Deep stromal ulcer with perforation	7 days	NP	8 mm SIS graft	8 weeks	Excellent	No complications
2	Persian	8½ years	MN	OS	Deep stromal ulcer	5 days	NP	10 mm SIS graft	4 months	Excellent	No complications
3	DLH	6 months	F	OS	Traumatic ulcer with corneal penetration	24 days	NP	8 mm SIS graft	6 weeks	Good	Intense vascular response in first four weeks, which then subsided
4	DSH	9 months	FN	OS	Descemetocoele following foreign body	6 days	NEG	8 mm SIS graft	3 months	SIS – leaked CPG – good result	Conjunctival graft placed 72 h later – SIS graft insufficient, aqueous leak.
5	DSH	13½ years	MN	OS	Melting ulcerative keratitis	10 days	NEG	Double layer of 4 mm SIS graft + conjunctival pedicle graft	7 days	Enucleated at 48 h	Continued stromal destruction necessitated enucleation. Ocular pathology showed SIS to be intact.
6	Persian	8½ years	MN	OD	Sequestrum	10 days	NP	Keratectomy +8 mm SIS graft	8 weeks	Good	Temporary SIS discoloration that resolved
7	Persian	8 years	MN	OS	Sequestrum	60 days	NP	Keratectomy +8 mm SIS graft	3 weeks	Good	No complications
8	DSH	8 years	MN	OS	Sequestrum	90 days	NEG	Keratectomy +6 mm SIS graft + contact lens	7 months	Excellent	Faint discoloration at 35 days, no worse at 86 days.
9	DSH	4½ years	MN	OS	Sequestrum	20 days	NEG	Keratectomy +4 mm SIS graft + contact lens	10 months	Good	SIS graft became black and sloughed; corneal granulation response
10	Persian	8½ years	FN	OD	Sequestrum	42 days	NP	Keratectomy +6 mm SIS graft	6 weeks	Excellent	No complications + contact lens

DLH, Domestic longhair cat; NEG, Negative aerobic/anaerobic culture; DSH, Domestic shorthair cat; NP, Bacteriology not performed; F, Entire female; OD, Right eye; FN, Neutered female; OS, Left eye; MN, Neutered male.

Extensive research has been performed on the use of topical collagen shields[24–29] as well as the surgical implantation of collagen tissues.[23,30,31,44] Collagen shields and therapeutic contact lenses were found to be equally effective in the management of corneal wound healing in a rabbit model,[28] whereas 24-h collagen shields were ineffective in the treatment of persistent epithelial defects following penetrating keratoplasty in man when compared with bandage contact lenses.[27] Topical collagen shields did not reduce healing times following keratectomies in rabbits but a subacute inflammatory reaction associated with the collagen shields was observed when histological and immunochemical analysis was performed.[24] This suggests topical collagen should be used with caution.

Although the results have been variable and generally disappointing with topical collagen shields, there have been reported successes with surgical implantation of collagen tissue in experimental models[30,31,44] as well as in clinical veterinary ophthalmic patients.[40–43] SIS has both thrombogenic and thromboresistant properties, and initially stimulates a classical inflammatory response, which is modified with time to the extent that no remnant of foreign material can be found histologically.[32,33] It is noteworthy that cases 3 and 10 showed marked corneal vascularization, whereas six other eyes healed with a minimal vascular response. This difference may reflect individual host factors and the underlying corneal disease rather than a direct effect of SIS.

It is impossible to determine whether the corneal vascular response was incited by the SIS graft material or the braided suture material, polyglactin 910 (Vicryl, Ethicon). The size and nature of the suture material, as well as the suture pattern used, have important effects on the healing of grafted tissues. Polyglactin or nylon (9/0–10/0) are recommended suture materials for penetrating keratoplasty;[4] the latter is generally preferred as it is less reactive. Four cardinal stabilizing sutures followed by a simple interrupted, simple continuous, or double continuous pattern are recommended suture patterns for penetrating keratoplasty.[4] Wound healing is reportedly slower with nylon and with a continuous suture pattern, although the latter reduces both surgical time and the bulk of suture material within the wound.[4]

The SIS grafts were used in this study as an alternative to conjunctival pedicle grafts, in which simple interrupted 8/0 polyglactin 910 is an acceptable suture material and pattern. This would be considered suboptimal in transplantation studies and use of a different suture material and pattern could modify the clinical observations of the healing response associated with SIS grafts. Although corneal neovascularization is beneficial in the early healing stages of ulcerative keratitis, an excessive degree may cause ocular discomfort and corneal opacity. Vascularization, together with graft size (more than 8 mm) and proximity to the limbus, are important factors adversely affecting graft survival in penetrating keratoplasty.[45] It is noteworthy that the SIS grafts were 8 mm or greater in six of the cases in this study. SIS is nonimmunogenic and graft rejection has not been a complication in the studies in other tissues to date,[32–39] perhaps because the collagen molecule is structurally conserved between species. Whether sloughing of the graft in case 9 was due to graft rejection or a sequela of the underlying corneal disease is unknown.

The gross ocular pathology in case 5 showed that the SIS graft remained intact despite the continued keratomalacia evident clinically and was consistent with the pathological examination. It is well known that corneal stromal degradation can be caused by collagenolytic protease activity of bacterial, corneal or leukocytic origin. It is notable that SIS, a collagen-based material, appeared to be resistant to the collagenolytic activity in this case. Collagen shields applied to the corneas of patients with bacterial keratitis have been observed to degrade very rapidly until the infection is controlled; *in vitro* studies showed there was no evidence of adherence of microorganisms or inflammatory cells to the collagen graft and that collagen shields may actually inhibit corneal degradation in infectious ulceration and melting disorders by effectively competing for collagenase on the ocular surface.[26] However, other studies have shown that collagen shields can exacerbate corneal ulceration associated with alkali-burns in rabbit corneas.[25] Further work is clearly indicated, and SIS should perhaps be avoided in clinical cases where collagenolyic activity is evident.

Due to the serious nature of the presenting corneal pathology in case 5, standard surgical techniques may also have been unsuccessful. Indeed, a conjunctival pedicle graft performed in addition to the SIS graft also failed. The descemetocele in case 4 required further surgery due to postoperative aqueous leakage. This may represent a technical rather than graft failure, as cases 1 and 3 with concurrent corneal perforation and penetration healed without the need for ancillary surgery. SIS is porous in nature and may not provide sufficient strength for large corneal defects without additional supportive measures. For example, the full thickness corneoscleral defect created in a German shepherd dog in the management of a limbal melanoma was repaired by SIS in conjunction with a substantial conjunctival pedicle graft.[40]

This series of cases includes five with feline corneal sequestrum. Case 6 showed temporary brown discoloration of the SIS graft, which then subsided. Case 8 showed faint brown stromal discoloration postoperatively which did not progress in the follow-up period to 86 days. However, in case 9 the SIS became discolored very rapidly and was black at 17 days postoperatively, suggesting that the graft material had absorbed the same pigment responsible for that in feline sequestra. During this period there was mild ocular discomfort associated with a marked corneal vascular response until the blackened graft sloughed naturally from the corneal surface. Although subsequent healing was uncomplicated, the use of SIS did not improve the surgical result, which was equivalent to a keratectomy alone, followed by granulation of a sequestered graft. It has been noted that bandage contact lenses[46] and 72-h collagen shields (Zigler, personal

communication, 2000) can discolor when placed in eyes with feline sequestra so it is not surprising that the SIS material may also be affected in a similar way. This phenomenon of SIS discoloration following sequestrum surgery has also been noted by other colleagues (personal communication). As SIS is known to have the unique ability to histologically 'become the tissue in which it is placed', its use in feline sequestra, particularly following incomplete excision, should be carefully considered and probably avoided.

The risk of transfer of infectious agents is a concern with any tissue transplantation procedure and must be considered with SIS, although only limited detailed information is currently available. A serious risk of interspecies transmission of retroviruses during xenotransmission has been demonstrated with *in vitro* studies of porcine aortic endothelial cells.[47] The manufacturer of porcine SIS states that the naturally derived material is disinfected with peracetic acid prior to sterilization with ethylene oxide, so that the final product is free from bacterial and viral components.

CONCLUSION

This limited feline study utilizing porcine small intestinal submucosa in the management of stromal defects documents good results in eight of 10 patients. Careful case selection and consideration of the underlying corneal pathology is essential to minimize short-term complications and to optimize long-term success. As a graft biomaterial for corneal repair, SIS offers advantages in being inexpensive, readily obtainable, and technically straightforward to place surgically. Histology of grafted sites is clearly required to assess the precise nature of the healing process involved.

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