CASE REPORT

Two cross-linked porcine dermal implants in a single patient undergoing hernia repair

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SUMMARY

A 50-year-old woman with a history of multiple recurrent incisional hernias and multiple comorbidities received two different porcine dermal implants during the same procedure due to the availability of products in stock. At 3.5 months following this procedure, the patient developed a secondary hernia inferior and lateral to the site of previous surgery. Both the implants were biopsied and sent for pathological evaluation. One implant was compliant and well integrated while the other was non-compliant and exhibited extensive foreign body reaction. In this case report, we examine the differences between the two porcine implants that may have caused them to react so differently in the same subject under the same conditions.

BACKGROUND

Acellular collagen implants have been developed for use in abdominal wall reconstruction. Crosslinking has been proposed to obviate problems with early degradation of non-cross-linked collagen implants. Little human histological data are available to assess the biocompatibility of these implants in the body. Here, we share our experience of two cross-linked porcine dermal implants, Permacol and CollaMend, used simultaneously in a single patient over a 3.5 months period. There are no published reports demonstrating the human histological response to CollaMend implants.

CASE PRESENTATION

A 50-year-old woman with a history of multiple recurrent incisional hernias and multiple comorbidities presented to our institution with abdominal pain and recurrent hernia following a previous incisional hernia repair. The patient's medical history was positive for breast cancer, hypertension, deep vein thrombosis, diabetes, smoking and fibromyalgia. Her surgical history included bilateral mastectomy and transverse rectus abdominus myocutaneous (TRAM) flap reconstruction, appendectomy, cholecystectomy, umbilical hernia repair and, as mentioned previously, multiple incisional hernia repairs.

During this particular incisional hernia repair, the patient received two different porcine dermal implants in the same procedure due to availability of products in stock. One piece was a 20 cm×40 cm hexamethylene di-isocyanate (HMDI) cross-linked implant (Permacol, Tissue Science Laboratories, Inc, Andover, MA, USA) and the other was a 20 cm×25 cm 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) cross-linked implant (CollaMend, Davol, Cranston, RI, USA). The devices

were implanted according to the manufacturer instructions. At 3.5 months following surgery, the patient developed a secondary hernia inferior and lateral to the site of the previous surgery. Biopsies of the two implants were obtained and sent for pathology evaluation.

INVESTIGATIONS

Gross examination revealed the CollaMend EDC cross-linked implant to be stiff and non-compliant, with little evident tissue ingrowth (figures 1 and 2). The Permacol HMDI cross-linked implant was compliant and well integrated. Both the implants were grossly intact. Histological examination of the CollaMend implant showed extensive foreign body reaction and avascular encapsulation, while the Permacol implant showed an organised fascia-like tissue and new blood vessel formation limited to the surface and pores of the device with evidence of mild chronic inflammation (figure 3).

TREATMENT

The CollaMend EDC cross-linked implant was removed.

OUTCOME AND FOLLOW-UP

The patient recovered from the procedure, but unfortunately continues to experience chronic abdominal pain. Since she has had a bilateral TRAM flap for reconstruction following breast cancer surgery, a component separation procedure would be quite difficult. The use of synthetic mesh was contraindicated in this case as the patient was suffering from multiple bowel perforations and undergoing the removal of infected mesh.

Figure 1 Intraoperative photo of removal of CollaMend implant. The implant was grossly intact and noncompliant.

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Figure 2 H&E stain of CollaMend implant at ×100. This figure illustrates the absence of remodelling and limited cellular infiltration.

DISCUSSION

The use of synthetic prosthesis for abdominal wall hernia repairs has dramatically reduced the rate of hernia recurrence.¹ The increased strength of the abdominal repair comes, in part, from scar tissue formation within and around mesh fibres secondary to the strong inflammatory response elicited by the mesh.^{2–3} Although this helps to reinforce the repair site, it also increases postoperative complications such as adhesions, bowel obstruction and fistula formation.^{4–6} In addition, poor neovascularisation of the mesh leads to an increased susceptibility to infection. A search for a biocompatible alternative with less infection risk has led to the use of acellular collagen matrices which promote cellular ingrowth and neovascularisation. Additional processing of dermal implants with either HMDI or EDC creates crosslinks between the collagen fibres changing the three-dimensional structure sufficiently to slow collagenase degradation of the implant.⁷ This prolongs the life of the implant enabling ample time for adequate tissue integration which had been a concern regarding previous, non-crosslinked, collagenous implants whose use in abdominal wall repairs lead to frequent reherniation due to premature implant degradation and loss of tensile strength.^{8–9}

Our understanding of the histological response to Permacol implants comes, in large part, from animal models. These studies show that the implants elicit a low-grade chronic

Figure 3 H&E stain of Permacol implant at ×100, illustrating orderly deposition of collagen and evidence of remodelling.

inflammation with cell infiltration, initially penetrating the implant through naturally occurring pores which are remnants of hair follicles left after processing. Neovascularisation follows a similar pattern with early vascular proliferation limited to the implant surface and along follicle remnants. The deposition of collagen occurs in an orderly fashion around the exterior of the implant with lines of deposition paralleling the surface of the implant and areas of cell infiltration.^{6–10–14} The presence of fibrous encapsulation varies with report, and its presence may be a manifestation of timing rather than an actual static indication of biocompatibility. Reports of encapsulation tend to come from short term studies.^{15–17} As study length increases both the presence of encapsulation and the overall impression of implant biocompatibility has been shown to improve with diminution of the capsule and significant improvements in cell infiltration, neovascularisation and extracellular matrix (ECM) deposition over time were observed.^{11–16}

The histological response to Permacol in our patient was similar to the response seen in animal models.¹⁸ Mild chronic inflammation was present in the absence of encapsulation with cell penetration into the graft limited to the pores. Organised fascia-like tissue was apparent on the surface of the graft with neocollagen deposition and vascular ingrowth occurring within the graft, localised to the areas of cell infiltration. The implant was found to be well integrated with the surrounding tissue and grossly intact. Our findings reflect a prospective pilot study of 15 patients undergoing loop stoma formation, where Permacol was placed in the anterior abdominal wall to prevent parastomal herniation. After stoma reversal occurred, at a median of 7 months (range 1–8 months), similar histological findings were identified.⁸

CollaMend elicited a more intense inflammatory reaction than Permacol displaying extensive foreign body reaction with avascular encapsulation and no indication of tissue integration. Petter-Puchner *et al*¹⁷ had similar findings of an extensive foreign body reaction with multinucleated giant cells surrounding the implant and no signs of cell penetration into the graft in a 2-month rat model. Similar findings at 1 month in a ventral hernia model using guinea pigs also found the CollaMend implants to be encapsulated.² Our experience illustrates the integrative process, may be very different between the two implants, with encapsulation and intense inflammation observed in the CollaMend implants persisting for 3.5 months with no indication of tissue integration.

The discrepancy between the responses elicited by these two cross-linked porcine dermal implants gives credence to the notion that long-term performance depends on individual processing conditions other than crosslinking.^{12–16–17–19} Variables of interest in the manufacturing process include the decellularisation process, method and extent of crosslinking and means of sterilisation.

Removal of cell material during the decellularisation process is critical to prevent host recognition of xenogeneic epitopes. Cell-associated epitopes are more easily removed than non-cell associated epitopes like galactose- α -(1,3)-galactose.^{19–20} Humans do not express α -gal epitopes due to a mutation in the α -(1,3)-galactosyltransferase gene.²¹ Exposure to intestinal bacteria expressing the α -gal epitope leads to anti- α -gal antibody production which accounts for up to 1% of the circulating human IgG.^{22–23} Decellularisation processes fail to remove the α -gal epitopes and their interaction with anti- α -gal antibodies has been shown in primates to cause a significant inflammatory response.^{24–25} This inflammatory response is mitigated by enzymatic removal of the α -gal epitope. In theory, cross-linked

acellular dermal implants should be less immunogenic than non-cross-linked acellular dermal implants because crosslinking masks the α -gal epitopes.²⁶ In vitro analysis of CollaMend implants shows widespread α -gal antigen staining while Permacol implants did not stain for α -gal.¹⁹ α -gal exposure could result from differences in either the level of crosslinking or in the fidelity of manufacturing process to preserve the implants' architectural integrity. Damage to the matrix before the cross-linking procedure could limit the efficacy of EDC cross-linking. Damage to the matrix after crosslinking could re-expose α -gal epitopes. Exposure of α -gal epitopes on CollaMend implants would be expected to elicit a more intense inflammatory response.²⁰ Although inflammation is a physiologic process following implantation of a foreign material, its nature and intensity may be critical towards acceptance or rejection of the graft.¹⁴ Severe inflammatory reactions predispose the implant to a rapid and disorganised deposition of collagen and fibrin which can compromise the integration process as well as the functional outcome.¹⁴ The CollaMend implant in our report demonstrated this characteristic disorganised collagen deposition and poor tissue integration which has also been shown in preclinical studies.^{2 17 18} The Permacol implant showed a regular pattern of collagen deposition along the surface of the implant with neocollagen deposition in areas of cell infiltration.

The efficiency of cell removal from a tissue is dependent on the specific physical, chemical and enzymatic methods used.²⁷ These treatments affect the biochemical composition, tissue ultrastructure and mechanical behaviour of the remaining ECM scaffold, which in turn, affects the host response to the material.²⁷ Preservation of matrix integrity during processing is necessary for effective tissue infiltration, collagen deposition and neovascularisation. In addition, disruption to the matrix could expose antigenic epitopes and incite a greater inflammatory response. The ability of the manufacturing process to maintain native matrix ultrastructure is essential for the graft to perform effectively.

Several published findings raise questions about the ability of CollaMend implants to retain their structural integrity during the manufacturing processes. CollaMend implants initially go through a process called liming to disinfect and remove hair from the dermis. Liming has been found to have a significant and dramatic negative effect on the mechanical strength and composition of the processed collagen, with subsequent deleterious effects on its ability to support cell growth in vitro.²⁸ Liming may help account for the in vitro findings of structural variations between individual CollaMend implants, and between the implants and native collagen prior to implantation.¹⁹ Disruption of the native collagen matrix may contribute to the widespread exposure of the α -gal epitope on CollaMend implants. Permacol implants were found to be structurally similar to native collagen and variation between implants was not seen.¹⁹ In addition Permacol did not stain for the α -gal epitope.¹⁹

The chemicals used to crosslink and sterilise CollaMend implants could also contribute to poor biocompatibility observed in our report. Ethylene oxide (EtO), the chemical used to terminally sterilise CollaMend implants, has long been known to be cytotoxic, but its many advantages as a sterilising tool have led to various means of reducing its potential toxicity rather than abandoning its use.^{29 30} Residual EtO that is not cleared from implant after sterilisation or persistence of toxic residues could provoke a greater inflammatory response by activating macrophages (M_1 -cytotoxic phenotype) and prevent implant integration by inhibiting fibroblast migration.^{29 31–33}

CollaMend implants are crosslinked using carbodiimide. A study investigating the macrophage polarisation profiles in small intestine submucosa-extracellular matrix (SIS-EMC) (Restore) and SIS-ECM crosslinked with carbodiimide (CuffPatch) found that the addition of carbodiimide crosslinks changed the population of macrophages elicited by each implant.^{32 34} The non-cross-linked SIS-ECM showed a predominantly M_2 phenotype which is the anti-inflammatory phenotype associated with tissue repair and constructive tissue remodelling.³² The addition of carbodiimide crosslinks resulted in predominantly M_1 population which is proinflammatory and cytotoxic. The author contributed these findings to the presence of crosslinks rather than the use of carbodiimide. If the inciting agents were the crosslinks, we would expect to find this response in other crosslinked implants. Pelvicol, a crosslinked porcine dermal implant also made by Tissue Science Laboratories, was shown to elicit a Th2 inflammation which does not stimulate M_1 macrophages and is thus associated with transplant acceptance rather than rejection.³² These findings appear inconsistent with each other and an alternative explanation for the M_1 to M_2 switch could be the use of carbodiimide in the cross-linking process.

Learning points

- Our case report illustrates that two biocompatible porcine dermal implants can react differently in a single subject.
- The long-term performance of these devices may depend on processing conditions, as well as crosslinking.
- Variables of interest in the manufacturing process include the decellularisation process, method and extent of crosslinking and means of sterilisation.

Competing interests None.

Patient consent Obtained.

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