The use of viable cryopreserved placental tissue in the management of a chronic rectovaginal fistula

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ABSTRACT

We present a case of a chronic recurrent rectovaginal fistula that initially arose from complications of haemorrhoid surgery and had failed multiple prior surgical repairs. The fistula was successfully managed using viable cryopreserved placental tissue.

KEYWORDS

Fistula – Rectovaginal – Perianal

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Case report

A 60-year-old woman presented with a past medical history significant for Barrett's oesophagus, irritable bowel syndrome, mitral valve prolapse, coronary artery disease, obesity, total abdominal hysterectomy and a long-standing and complex history of perianal disease. Her perianal disease initially manifested as a thrombosed external haemorrhoid in 2000, which was excised but was complicated by the formation of a left anterior ischioanal abscess. This abscess was drained but the patient subsequently developed a perianal fistula. The fistula did not heal with conservative management and she complained of stool drainage via the perineum in addition to faecal incontinence. Five further surgical interventions were attempted, including fistulotomy with sphincter repair, the use of fibrin glue and a diverting colostomy to allow for faecal diversion. Unfortunately, these interventions failed to fully manage her pathology and led to the development of a rectovaginal fistula.

In October 2010, the patient presented to our medical centre for a further opinion on the management of her chronic fistula. She was noted on examination to have a thin rectovaginal septum and a 5-mm anterior defect within the anterior mid-anal canal, which communicated with the left lateral introitus. Given the history of recurrent fistula formation, a colonoscopy was performed to exclude the possibility of inflammatory bowel disease. We concluded that the aetiology of this fistula was that of a chronic, failed wound. The patient was taken to the operating room in December 2016 for repair of the rectovaginal fistula with overlapping sphincteroplasty and a sheet of viable cryopreserved placental tissue (vCPT; Stravix®, Osiris Therapeutics Inc.) was used to buttress the repair at the time of surgery.

Intraoperatively, the fistula was easily identified using a fistula probe (Fig 1). An incision was made in the rectovaginal septum and the plane between the anal canal and the vagina

was established using the cut settings on electrocautery. The mucosa of the anal canal was lifted off the sphincter muscles around the fistula and beyond to the anorectal ring, and the anal sphincter muscle was dissected free of the vaginal mucosa. Once the fistula was isolated, the defects created by the fistula within the anal and vaginal mucosa were oversewn with 3-0 Vicryl® suture. The entire sphincter muscle complex was then divided in the midline, eliminating the tract through which the fistula had passed. Following irrigation, a 2 cm × 4 cm vCPT sheet was placed on top of the mucosa of the anus and secured with 5-0 nylon (Fig 2). The muscle was then overlapped using three horizontal mattress stitches with 2-0 Prolene® sutures (Fig 3). An additional piece of vCPT was placed on the inner vaginal mucosal side (Fig 4). The wound was irrigated and closed in layers using interrupted 3-0 Vicryl (Fig 5). Skin glue was used to seal the wound.

The patient was discharged the following day with instructions to avoid constipation and straining and to maintain soft bowel habits with the use of stool softeners. She was seen at two weeks postoperatively, with an intact repair noted despite breakdown of her perineal incision. The wound breakdown was managed with alginate packing for four weeks (Fig 6). Three months postoperatively, the fistula repair remained intact, the perineal wound had completely healed and there was no evidence of flatus or stool leakage from her perineum or vagina.

Discussion

A variety of management options exist for fistulas, ranging from primary fistulotomy, which is associated with healing in more than 90% of cases,¹ to ligation of the intersphincteric tract, anal advancement flaps and fistula plugs,² with the option of temporary stool diversion using a loop ileostomy or colostomy. Recent advances include the use of

Figure 1 The fistula was identified using a fistula probe.

Figure 3 The muscle was overlapped using three horizontal mattress stitches with 2-0 Prolene sutures.

Figure 2 A 2 cm × 4 cm viable cryopreserved placental tissue sheet was placed over the mucosa of the anus and secured with 5-0 nylon.

Figure 4 An additional piece of viable cryopreserved placental tissue was placed on the inner vaginal mucosal side.

Figure 5 The wound was irrigated and closed in layers using interrupted 3-0 Vicryl.

Figure 6 The wound breakdown was managed with alginate packing for four weeks.

bioprosthetic mesh, particularly in the case of recurrent chronic fistulas. More novel treatments continue to surface, with the current data from clinical trials suggesting a role for mesenchymal stem cell therapy.

Several clinical trials have investigated the use of expanded autologous or allogeneic mesenchymal stem cell therapy for the management of chronic perianal fistulas (Table 1). These non-hematopoietic, multipotent cells, which can be harvested from bone marrow, adipose tissue or placenta, are able to downregulate the local immune response and inflammation, and promote host tissue repair.³⁻⁵ Early trials and reports focused on mesenchymal stem cells harvested from a patient's adipose tissue preoperatively and cultured for use in the operating room, which were then injected into fistula tracts adjacent to inflamed tissue. Evidence from these trials has suggested that the use of mesenchymal stem cell injections can result in successful management, with resolution of the chronic fistula, in 50–71% of cases.⁶⁻⁸ A further trial investigated whether there was a dose-dependent effect for adipose-derived mesenchymal stem cells, with results suggesting that there may be a plateau, above which the number of cells does not have a significant impact upon healing rates.⁹ The use of mesenchymal stem cells appears to be a safe and feasible option in the management of complex perianal fistulas in patients who have not responded to conventional treatment modalities.⁶⁻¹⁰

More recent strategies include the use of viable cryopreserved human placental tissue, composed of umbilical amnion and Wharton's jelly. Such products have the benefit of retaining not only mesenchymal stem cells but also the native collagen and hyaluronic acid-rich extracellular matrix, endogenous growth factors and other endogenous cells found in placental tissue such as fibroblasts and epithelial cells.¹¹ As such, vCPT has low immunogenicity and exhibits import characteristics necessary for wound healing, including anti-inflammation, anti-microbial, anti-fibrosis and anti-scarring properties. The placental membrane sheet serves as a physical support structure, assisting in host cell adhesion and thus assisting with cell proliferation and differentiation during the healing process.^{12,15} vCPT is already being used commercially to assist in the repair of tendons, in wound healing following amputations and in ophthalmological and dermatological surgeries, and with the management of enterocutaneous fistulae.^{11,14}

Conclusion

The management of chronic perianal and rectovaginal fistulas can prove to be a great challenge to colorectal surgeons. The emergence and early evidence concerning stem cell therapy suggests that surgeons now have an additional effective weapon within their arsenal. Viable cryopreserved placental tissue appears to be an excellent alternative to aid in repair, due to its ability to conform to the affected area and be sutured into place, providing structural support in addition to the anti-inflammatory and immunomodulatory benefits of endogenous, viable stem cells. A vast scope exists for future research into the management of chronic fistulas with the assistance of vCPT.

Table 1 The key clinical trials related to fistula management with mesenchymal stem cells.

Study	Trial type	MSC tissue of origin	Participants (n)	Treatment/control	Key findings
Garcia-Olmo (2009) ⁷	Multicentre RCT, phase II, open label	Adipose	49	Fibrin glue + MSC (n = 25) vs. fibrin glue alone (n = 24)	71% healing in patients receiving fibrin glue + MSC, compared with 16% in glue alone at 8 weeks ($P = < 0.001$). A second dose of MSC was applied to 8% (2 patients) in the treatment arm. No significant difference in adverse outcomes.
Herreros (2012) ¹¹	RCT, single blind	Adipose	183	A: 20 million MSC (n = 64); B: 20 million MSC + fibrin glue (n = 60); C: fibrin glue alone (n = 59)	39.1% vs. 43.3% vs. 37.3% healing after 24 weeks ($P = 0.79$); 57.1% vs. 52.4% vs. 37.3% healing at 1 year ($P = 0.13$). A second dose of MSC (group A) or double dose of MSC + fibrin glue (group B) or additional fibrin glue (group C) was administered if healing was not observed at week 12. No significant difference in adverse outcomes.
De la Portilla (2013) ⁸	Open label, single-arm	Adipose	24	20 million MSC ± further 40 million MSC at week 12 if not healed	56.3% closure of treated fistulas by week 24. 15/24 patients (62.5%) received a second administration of MSC at week 12. One patient experienced a perianal abscess.
Molendijk (2015) ¹⁰	RCT, double blind	Bone marrow	21	MSC injections: group 1: 1 × 10 ⁷ (n = 5); group 2: 3 × 10 ⁷ (n = 5); group 3: 9 × 10 ⁷ (n = 5) vs. placebo (solution with no cells, n = 6)	66.7%, 85.7% and 28.6% healed at 24 weeks in groups 1, 2 and 3, respectively. 33.3% healing in the placebo group at 24 weeks ($P = 0.06$). No adverse events in any of the groups. Suggests low-dose MSC may be advantageous compared with higher doses.
Panes (2016) ⁹	RCT, double blind	Adipose	212	MSC alone (n = 107) vs. placebo saline solution (n = 105)	50% healing in MSC patients, compared with 34 in the placebo group ($P = 0.024$) at 24 weeks. Treatment adverse effects in 17% of treatment group, compared with 29% in the placebo group.
MSC, mesenchymal stem cells; RCT, randomised controlled trial.					

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