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Refractory Gastrointestinal Fistula Healing with the Modena Tissue Healing Regeneration (MOTiHR) Method: Adaptation of an Existing Solution to a Complex Problem-A Case Series

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Abstract

Autologous fat grafting (AFG) has been successfully applied in to heal many types of human tissue, and mechanical activation of the lipoaspirate has been proven to increase anti-inflammatory activity and mesenchymal stem cell concentration. We report our preliminary experience of the MOTiHR method; a single, repeatable procedure (liposuction, activation, emulsion, dilution, and AFG injection) with activated AFG injection into healthy submucosal tissue surrounding the GI fistula orifice and any involved peri-orifice. Our case series of three patients demonstrate primary fistulae healing despite patient complexity and previous surgical failures, with no associated morbidity or obstacles to repeat procedures. Activated AFG in digestive endoscopy treatment of small (<15mm) refractory GI fistula seems promising.

Keywords: enteric fistula; enterocutaneous fistula; autologous fat grafting; mesenchymal stem cells; mechanical activation; gene activation.

Introduction

Gastrointestinal (GI) fistula is an abnormal communication between the gastrointestinal tract and the skin or other organs [1]. Despite advances in management, GI fistula remains challenging, due to complications such as sepsis, malnutrition, and electrolyte imbalance, all of which carry significant risks of mortality and morbidity [2-3].Most GI fistulae are iatrogenic (arising after surgery, endoscopic, or radiation therapies) [4], and their incidence varies depending on the type of intervention [5-10]. The primary goal of treatment is fistula closure [2,11], and a standardized protocol of care has been established to manage skin integrity, sepsis, nutrition, and define fistula anatomy [2, 12]. However, specific protocols for optimal interventions are yet to be developed.

A minimally invasive endoscopy approach is widely used for GI defect management; techniques include the application of clips (through the scope [TTS] or over the scope [OTS]), stents placement, novel suturing methods, vac therapy, and the use of glues [13-14]. However, challenges with nonhealing and recurrence have driven research into new modalities. Recently, attention has focused on the regenerative potential of autologous fat grafting (AFG) and associated therapies involving adipose-derived stem cells (ADSCs) [15]. The stromal vascular fraction (SVF) of lipoaspirate contains adipose tissue-derived stem cells (ADSCs) that stimulate neoangiogenesis, activate local stem cell niches, and modulate immune responses. Promising effectiveness and safety profiles have been reported in the treatment of neurological diseases [16], wound healing [17], systemic sclerosis of the hands [18], and anal fistulas [19].

Carelli et al. demonstrated that mechanical activation of Coleman lipoaspirate promotes anti-inflammatory activity and gene activation by stromal cells, supporting a healing mechanism [20]. This technique has shown success in chronic ulcer resolution [21], and has been experimentally applied to iatrogenic fistulae with upper GI leakage in rabbits [22]. However, no reports exist on the use of activated AFG in endoscopy of the GI tract of human patients.

Our center developed a standardized, multidisciplinary protocol using activated AFG for refractory GI fistula in patients unsuitable for surgery, with small fistula (orifice <15 mm). We report our preliminary results in a case series.

Material and Methods

Since no universally established protocol exists for activated AFG in digestive endoscopy, we developed a multidisciplinary protocol, the "Modena Tissue Healing Regeneration" (MOTiHR). This method was approved by the local ethics committee for compassionate cases (690/2023/SPER/AOUMO- SIRER 6947) and each patient signed an informed consent.

Under general anesthesia, the surgical area is disinfected, and an occlusive dressing is applied over a stoma (if present) before subcutaneous fat harvest. To minimize post-operative pain, local anesthesia (mepivacaine 2% with adrenaline) is administered before performing a 3mm microincision in the anterior superior iliac spine or subtrochanteric regions. A multi-port cannula is introduced for hydro dilatation (10 ml mepivacaine 2% with adrenaline) using a 16 G, 170 mm needle. After 15 minutes, adipose tissue (40-80ml) is aspirated with a 14 G Coleman collection cannula (200 mm long; Figure 1a) and transferred into a 10 ml syringe (Laboratorio Elea Phoenix S.A., Buenos Aires, Argentina). Plasma is obtained by centrifugation (2000 rpm for 2 minutes; Figure 1b). The surgical access is sutured with a non-absorbable monofilament 5/0 thread, and a compressive dressing is applied.

In the operating room, the adipose cells are transferred to 20ml syringes and placed in a Digital Vortex Mixer (ELEA System Surgere S.r.L. Trento - Italy; Figure1c) set to an orbital force of 2000 rpm for 8 minutes at room temperature, to achieve fat activation (Figure 1d). A physiological solution is added to the activated fat (emulsion) at a 1:1 ratio and mixed 25 times between two 3 or 5ml syringes (Pik solution, Pikdare, Milano, Italy; Figure 1e). The liposuction and emulsion phases take approximately 20-30 minutes.

The diluted solution is then aspirated by the distal end of the 19G endoscopic needle (US Endoscopy, Meditek Systems, New Delhi, India or Innova Medica, Rome, Italy), and at least 2 cc of the diluted solution is injected into each of the 4 submucosal quadrants of healthy tissue surrounding the fistula orifice. Activated fat tissue is also injected into the peri-orifice (enterocutaneous fistula) or involved abdominal organ. This second phase takes 15-20 minutes.

Patients continue parenteral nutrition until complete healing, defined as fistula resolution with no clinical, endoscopic, radiographic, or computed tomography (CT) evidence of output. Empirical broad-spectrum antibiotic theray is prescribed postoperatively for 3 days.

Case Presentation

Case 1.

A 34-year-old Asian male with a history of previous elective distal gastrectomy (*Roux-en-Y gastrojejunostomy*) for peptic duodenal stenosis in 2022 (performed in another hospital), and emergent treatment of an iatrogenic fistula at the duodenal stump (post-operative day 2) presented to our facility. A Kehr's T tube (Romson's Scientific and Surgical Pvt Ltd, Agra, India) had been incorrectly

positioned in the biliary tract, resulting in a secondary fistula of the common bile duct. We successfully resolved the fistulae with urgent endoscopic retrograde cholangiopancreatography (ERCP). Upon completion of the procedure, instrument withdrawal caused an intestinal perforation. On the same day, an urgent ileal-ileal anastomosis and laparostomy were performed. Negative pressure therapy of the abdomen (AbThera, GD Medica, Eindhoven, The Netherlands) was applied for 6 weeks.

Two months after the resection, CTA confirmed the presence of dehiscence that had caused a bilioperitoneum fistula (4.5mm, with approximately 75ml/day of enteral fluid output). An endoscopy with the application of an over-the-scope clip (OTSC, Ovesco Endoscopy AG, Tuebingen, Germany) was attempted, but resulting in an enterocutaneous fistula. Parenteral nutrition was maintained while awaiting spontaneous fistula healing by second intention. Four months later, an attempted repair of the perforation resulted in a chronic enterocutaneous fistula.

The multidisciplinary team decided to perform the first MOTiHR procedure. Accurate curettage of the cutaneous fistula was performed (Figure 2a). Autologous fat was collected from the patient's hips, activated, and injected into the submucosa at the four quadrants surrounding the fistulous orifice, with 8ml of autologous fat injected into the peri-orificial subcutaneous tissue (Figure 2b). The original subcutaneous fistula (Figure 2c) showed improvement postoperatively (Figure 2d). Following an initial increase, the output decreased from 150 ml to 20 ml per day after 2 weeks and remained stable. The MOTiHR procedure was successfully repeated 3 weeks later and at the check after 3 further weeks the healing of the cutaneous (Figure 2e) and subcutaneous fistula (Figure 2f).

No intra- or post-procedural complications were recorded. A reduction in fistula output was noted, and complete healing was confirmed, with no evidence of stenosis or luminal stricture. The patient resumed oral feeding and was discharged home 6 months after the initial ERCP procedure. At 1 year follow-up, there were no clinical signs or symptoms of bowel dysfunction.

Case 2.

A 77-year-old white male with chronic kidney disorders (CKD), a medical history of right nephrectomy for kidney cancer, anti-neutrophilic cytoplasmic antibody (ANCA)-associated vasculitis, and hypertension underwent endoscopic submucosal dissection of a 5cm laterally spreading tumor (LST) of the transverse colon in April 2022 (at another hospital). The colon was perforated, and a right hemicolectomy with a terminal ileostomy was performed. The postoperative course was complicated by wound infection and sepsis resulting in a hospital stay of 42 days.

In April 2023, the patient presented to our facility and we performed a surgical ileostomy closure. However, surgical dehiscence (4 mm) was revealed by postoperative CT scan on day 5. Several endoscopic attempts were performed (endoscopic double-pigtail catheter, OTSC) without success.

Forty-five days after the fistula presentation, the MOTiHR procedure was performed, with 12ml of autologous fat collected from the patient's thigh and injected into the submucosa at the four quadrants of the fistulous orifice. Enteral fluid output resolved, and fistula closure was confirmed by CT scan; the patient resumed oral feeding on postoperative day 12. Discharge was scheduled for postoperative day 21. However, the night before discharge, a nurse found the patient deceased in bed. Death was attributed to cardiac failure, but no post-mortem examinations were performed.

Case 3.

A 62-year-old white male with stage IV CKD (undergoing peritoneal dialysis since 2011) and a history of iatrogenic small intestine perforation (2012), was referred to our center in 2021. Previously, multiple surgical sessions, including exploratory laparotomy, protective jejunostomy, and recanalization, had been complicated by dehiscence of the anastomosis and enterocutaneus fistula, which were successfully treated with various surgical interventions.

In 2021, investigative endoscopy and CT scan (performed at another center) confirmed spontaneous anastomosis dehiscence and a 5mm enterocutaneous fistula. The patient was transferred to our hospital and an OTSC with subsequent cyanoacrylate injection was attempted without success.

One month later, enteral output averaged 100ml/day. The MOTiHR procedure was performed, with autologous fat collected from the patient's hips. Activated fat was injected into the four peri-orificial quadrants of the fistula and the periorificial subcutis (10ml). Fistula output reduced to around 40 cc within 4 weeks. A second MOTiHR intervention was performed: after accurate curettage, 10ml of activated fat was injected into the peri-orifice subcutaneous tissue. The visceral orifice was no longer visible. Two weeks later, fistula output further reduced (5-10ml). Laboratory examinations confirmed that the output was free from enteral material (containing only traces of serum). Complete fistula healing was confirmed by X-ray, with no evidence of stenosis or luminal stricture. Oral feeding was resumed. The patient was discharged home on postoperative day 16 in an acceptable general condition, consistent with his comorbidities.

On postoperative day 31, the patient developed a fever (39°), and an emergent CT scan (performed at another center) showed an infected abdominal-pelvic collection, located near the peritoneal dialysis site (distant from the MOTiHR site). The previous cutaneous fistula was confirmed as resolved, but a colonoscopy was not performed. Colleagues attempted an unsuccessful drainage of the enteral output; the brief postoperative course (12 days) reported sepsis and ended in a fatal outcome.

Figure 1: The MOTiHR Method. Adipose tissue is aspirated through a 14G Coleman collection cannula (a). The adipose tissue is transferred into 10 ml syringes, placed in the centrifuge (2000 rpm for 2 mins) to separate adipose cells from the plasma (b). The adipose cells are transferred to 20 ml syringes (c), and the fat is activated in a Digital Vortex Mixer (orbital force - 2000 rpm for 8 minutes) at room temperature (d). A physiological solution is added to the activated fat (1:1) and mixed 25 times between two 5 ml syringes (3 ml syringes can also be used)(e).

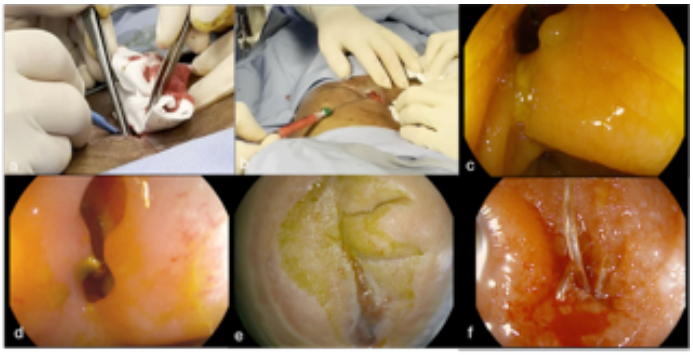

Figure 2: Case 1. Accurate curettage of the cutaneous fistula was performed (a) and autologous fat was injected into the peri-orificial subcutaneous tissue (b). Endoscopic image of the pre-operative fistula (c). At the repeat MOTiHR procedure, the fistula orifice appeared smaller and tissue repair was evident at the fistula distal extreme (d). After a second treatment, repeated 3 weeks after the first, fistula healing was evident at the cutaneous (e) and subcutaneous orifices (f) when the check was carried out 6 weeks after the first treatment.

Discussion

Our case series reports the successful resolution of small (<15 mm) GI fistulae, that were refractory to previous common endoscopic techniques, with the MOTiHR technique. A one-year follow-up confirmed ongoing fistulae healing in one young patient without comorbidities.

There are many methods for preparing harvested lipoaspirate for AFG. While evidence that lipoaspirate activation induces anti-inflammatory activity and increases mesenchymal stem cell concentration [20-21], this approach has not previously been applied to GI fistula repair. We developed a protocol that standardizes the optimal dilution (1:1) for suitable viscosity, allowing aspiration with a long 19 G needle (160 or 230 cm). Additionally, our protocol specifies an optimal orbital rotation. Other authors have reported rotations based on sample weight [20] and shorter rotation periods [22]. In contrast, our findings suggest that a rotation speed of 2000 rpm for 8 minutes yields optimal tissue density.

The MOTiHR procedure involves submucosal injection into healthy submucosal tissue surrounding the fistula orifice. Previous techniques, such as glue injection inside the defect, have often caused trauma and bleeding within the fistulous passage [23-25]. Where feasible, the MOTiHR procedure involves injecting activated AFG into both ipsilateral and contralateral areas around the fistula. We hypothesize that the best outcomes are achieved when tissue regeneration occurs from the “healthy” submucosal tissue rather than the fibrotic tissue surface or the fistula passage itself. Further investigations are warranted.

Despite the complexity of the selected patients reported in our case series, the MOTiHR procedure is quick (completed within 60 minutes), relatively easy to perform, cost-effective, and well-tolerated. All three patients had fistulae that had been refractory to other treatments, with cases 2 and 3 presenting multiple severe comorbidities. All patients achieved primary complete fistula healing, confirmed ongoing at 1-year follow-up in case 1. However, the premature deaths of patients 2 and 3 inhibit any meaningful assessment of the durability of healing. The preliminary results suggest that further studies are warranted to investigate MOTiHR as a potentially safer alternative to sometimes high-risk surgical repair.

We also report successful repeat MOTiHR procedures in patients 1 and 3, resulting in complete fistula healing. We recommend harvesting excess lipoaspirate during the primary liposuction procedure, as stored autologous fat used could reduce procedural time for potential repeat procedures. Furthermore, we confirm that MOTiHR can be repeated and does not preclude other interventions in the event of incomplete healing, as previously discussed in literature [19]. As post-operative imaging and complication management for case 3 were conducted outside our center, we cannot rule out an ongoing internal abdominal infection as a contributing factor.

The retrospective nature and heterogeneity of the patient sample inherently limit this preliminary report. Our results are generalizable to referral centers only, with high-level endoscopy and plastic surgical support and clinical experience in complex patient management.

Conclusions

We report primary fistulae healing in complex patients, with no morbidity or barriers to repeat procedures, underscoring the potential of activated AFG in treating small refractory GI fistula in digestive endoscopy. The MOTiHR protocol is performed in a single procedure (from liposuction to AFG injection) potentially avoiding additional surgical interventions and reducing hospital stay. Given that multiple treatments may be necessary, fat storage would be advantageous.

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Ethical Considerations:

The MOTiHR protocol was approved for compassionate cases by the local ethics committee (690/2023/SPER/AOUMO- sirer 6947) and each patient signed an informed consent.

Conflict of Interest:

The authors declare no conflict of interest.

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