



Adipose tissue grafting for management of persistent anastomotic leak after low anterior resection

W. J. Tan¹ · B. J. Mehrara¹ · J. Garcia-Aguilar¹ · M. R. Weiser¹ · G. M. Nash¹

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Abstract

Background An anastomotic leak is the most dreaded complication after low anterior resection. Adipose tissue grafting may induce healing in a persistent anastomotic defect. The aim of the present study was to report retrospectively reviewed outcomes for a series of patients who were managed with heterotopic grafted adipose tissue to facilitate anastomotic healing.

Methods Patients with anastomotic leakage after low anterior resection sequentially treated with grafting of adipose tissue were included in the study. All patients had pelvic radiation during treatment and had a diverting ileostomy in situ. The cohort had a persistent defect despite being treated with available modalities such as suture repair, fibrin glue, Endo-Sponge and surgical debridement. The outcomes were reviewed and reported.

Results There were 11 patients (8 males and 3 females) with a median age of 54 years (range 33–72 years). Five patients experienced complete healing of the anastomotic defect with successful reversal of the diverting ileostomy. The anastomotic defect of one other patient in the series appeared to have healed and hence his diverting ileostomy was reversed. However, he presented with a recurrent leak, which ultimately necessitated an abdominoperineal resection. Another patient had a persistent defect after an attempt at adipose tissue grafting and opted to proceed with a takedown of the anastomosis. In the remaining four patients, the outcome after adipose tissue grafting remains unknown, as two patients succumbed to metastatic disease, one was lost to follow-up and the remaining patient developed a recurrence which required pelvic exenteration. Procedural associated morbidity occurred in one patient who developed fat embolism, which was treated expectantly.

Conclusions Adipose tissue grafting is safe and feasible, though its effectiveness remains uncertain. It may be useful selectively in the management of persistent anastomotic leak after radiation and low anterior resection.

Keywords Anastomotic leak · Adipose tissue grafting · Lipoaspirate · Adipose tissue-derived mesenchymal cells

Introduction

An anastomotic leak (AL) remains the most dreaded complication after proctectomy. Its incidence has been described to range from 1 to 20%. It is a significant source of morbidity and mortality, and many of its risk factors remain unknown [4, 12, 14, 15]. Despite advancements in surgical technique, the treatment of colorectal AL remains a management

conundrum. While fecal diversion, percutaneous drainage and intravenous antibiotics constitute the initial management strategy in most patients with a contained AL, a significant proportion of patients remain with a persistent anastomotic defect requiring long-term fecal diversion despite these interventions. In these patients, endoscopic negative-pressure therapy is commonly employed at our institution and elsewhere, and this has been demonstrated to be successful in approximately 80% of selected patients [1, 5]. However, success rates with endoscopic negative-pressure therapy are lower in the post-irradiated rectum [1]. This is likely related to radiation-induced ischemia, which precludes the generation of granulation tissue to seal the anastomotic defect [10]. In these patients, nonradiated lipoaspirates may help to induce healing, as they have the capability to enhance self-renewal of colonic epithelium and accelerate structural recovery after radiation injury [2, 3]. Lipoaspirate has been

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✉ G. M. Nash
NashG@mskcc.org

¹ Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065, USA

demonstrated to improve anastomotic healing in irradiated colon [18]. They are abundant in the adipose tissue and can easily be harvested for therapeutic purposes.

In our institution, we selectively graft adipose tissue as an adjunct for the management of AL after low anterior resection. The aim of the present study was to report retrospectively the reviewed outcomes for a series of patients who were managed with heterotopic grafted adipose tissue to facilitate anastomotic healing.

Materials and methods

Between March 2014 and April 2018, patients who developed AL after low anterior resection and were sequentially treated with grafting of adipose tissue were included in the study. All patients had received neoadjuvant or adjuvant radiation to the rectum prior to the grafting procedure and received a diverting ileostomy either during the index surgery or after the anastomotic leak was diagnosed. The median duration from surgery to the diagnosis of anastomotic leak was 47 days (range 3–570 days). At the time of diagnosis of AL, patients were initially managed by percutaneous drainage and intravenous antibiotics. After adequate source control and treatment of sepsis, the Endo-Sponge device (B. Braun Medical, Melsungen, Germany) was applied whenever feasible using the technique previously described [19]. Once the defect was deemed too small and no longer amenable to Endo-Sponge treatment, patients were observed and re-evaluated after 6–8 weeks for a persistent defect via awake endoscopy or examination under anesthesia. Adipose tissue grafting was then performed if a persistent defect was identified after the cavity was debrided to viable tissue. The abscess cavity related to the anastomotic defect should be debrided at least once, with specimens sent for pathology to assess for local recurrence, before proceeding with adipose grafting.

The anastomosis was re-evaluated for healing via flexible sigmoidoscopy and/or water-soluble enema approximately 6 weeks after each attempted adipose tissue grafting procedure. Reversal was performed at least 3 months after successful grafting. Healing of the AL was defined as absence of a defect on endoscopy and/or water-soluble enema, followed by successful closure of the diverting ileostomy.

Harvesting of the lipoaspirate was performed by the Plastic Surgery Service. Briefly, the lower abdomen was prepped and draped in a sterile fashion, and the area of choice injected with a solution containing 1:500,000 epinephrine and 50 mg of lidocaine. Approximately, 10–20 cc of fat was harvested using a 4.0-mm cannula and a power-assisted liposuction machine (MicroAire, Inc., Charlottesville, VA, USA). The donor site wound was then closed in layers.

The harvested lipoaspirate was injected by an attending colorectal surgeon into the tissue surrounding the bowel wall along the length and width of the anastomotic defect using a 7-cm Style I Coleman Infiltration Microinjection Cannula (Mentor Corp., Irvine, CA, USA). The procedure was done under general anesthesia in the lithotomy position. Bowel preparation was not performed as most patients had a diverting ileostomy in situ and antibiotic prophylaxis was generally not required. The harvested lipoaspirate was not injected into the defect itself, nor was it injected into an adjacent organ or the sacrum. There was some mass effect of the grafted tissue on the fistula tract; however, the opening of the fistula tract remained patent after completion of the injection. The procedure was performed using a blunt tip needle in all but one case to mitigate the risk of fat embolism during injection [20].

This study was approved by the Institutional Review Board of Memorial Sloan Kettering Cancer Center.

Results

During the study period, 11 patients (8 male and 3 females) with a median age of 54 years (range 33–72 years) underwent adipose tissue grafting for a persistent anastomotic defect. The median duration from diagnosis of an anastomotic leak to the first attempt at adipose tissue grafting was 5 months (range 1–15 months). The demographic and pathologic characteristics of the study cohort are illustrated in Table 1. Ten of the patients in the series had received preoperative radiotherapy prior to proctectomy; the other patient received adjuvant radiation.

Among the 11 patients in the series, 5 experienced complete healing of the anastomotic defect with successful reversal of the diverting ileostomy and no subsequent AL. The gastrografin enema images of patient 1 before and after adipose tissue grafting are provided in Fig. 1.

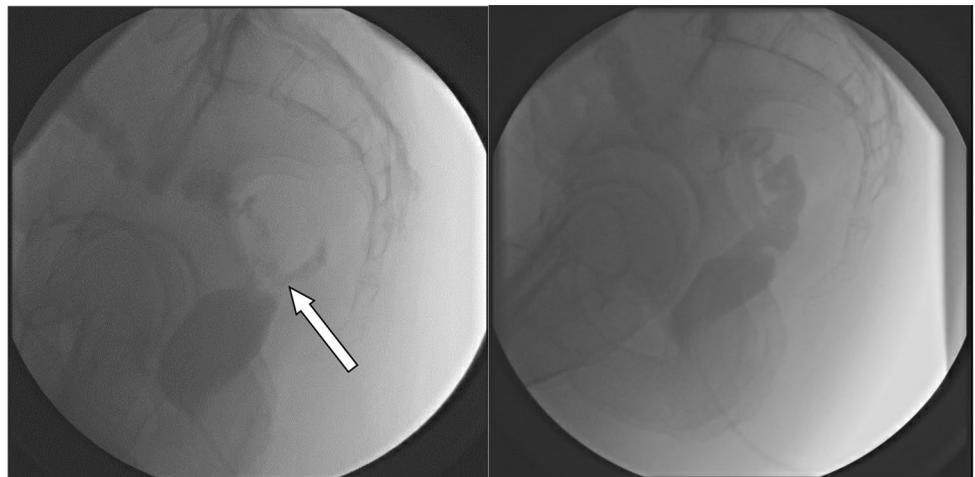
One patient (patient 6) in the series had no visible anastomotic defect during endoscopic examination and a normal water-soluble enema and hence had his diverting ileostomy reversed. The patient unfortunately developed large bowel obstruction at the coloanal anastomosis and recurrent AL 2 weeks after the procedure, which necessitated rectal tube decompression and subsequent abdominoperineal resection for persistent symptoms. Another patient (patient 10) had a persistent defect after an attempt at adipose tissue grafting and opted to proceed with a takedown of the anastomosis instead of further attempts at adipose tissue grafting. In the remaining four patients, the outcome after adipose grafting remains unknown. Two patients (patient 2 and 4) were diagnosed with metastatic disease 10 and 16 months, respectively, after grafting and no further effort was made to assess the anastomotic defect given the lack of pelvic symptoms

Table 1 Demographic and pathologic characteristics of the study cohort

Patient	Age (years), sex	Anastomosis	TNM stage	Margins	Size of defect (width × depth, cm)	Prior treatment	No. of injections	Final outcome
1	54, male	Colorectal	ypT0N0M0	Clear	0.2 × 3	Endo-Sponge 4 ×, surgical debridement 3 ×, advancement flap 1 ×	1	Success
2	54, female	Colorectal	ypT3N2aM1	Clear	2 × 1	Endo-Sponge 14 ×, surgical debridement 1 ×	1	Unknown; died of recurrent disease
3	69, male	Colorectal	ypT0N2bM0	Clear	NM × 4	Fibrin glue 2 ×	1	Success
4	47, female	Colorectal	ypT3N2aM0	Clear	NM	Surgical debridement 1 ×	1	Unknown; died of recurrent disease
5	72, male	Colorectal	ypT3N0M0	Clear	2 × 4	Surgical debridement 1 ×	2	Unknown; lost to follow-up
6	35, male	Coloanal	ypT2N0M0	Clear	NM	Endo-Sponge 4 ×	2	Failure; required abdominoperineal resection
7	57, male	Colorectal	ypT3N1cM0	Clear	1 × NM	–	1	Success
8	33, male	Colorectal	ypT3N2bM1	Clear	NM	Surgical debridement 1 ×	1	Unknown; developed recurrence requiring exenteration
9	54, female	Coloanal	ypT1N0M0	Clear	NM × 2	Surgical debridement of abscess cavity 7 ×	3	Success
10	69, male	Colorectal	ypT0N0M0	Clear	0.5 × 1	Suture repair 1 ×	1	Failure; required takedown of anastomosis
11	56, male	Coloanal	ypT2N1bM0	Clear	0.5 × 4	Endo-Sponge 3 ×	1	Success

NM not mentioned

Fig. 1 Gastrografin enema images of patient one prior to (left) and after (right) adipose tissue grafting. The anastomotic defect is indicated (arrow)



and the need for systemic therapy. One patient (patient 5) was lost to follow-up 7 months after grafting with evidence of persistent AL at last evaluation, and the remaining patient (patient 8) developed a pelvic recurrence 2 months after adipose grafting, which necessitated a pelvic exenteration.

Procedure-related morbidity occurred in one patient (patient 7) who was grafted with a sharp needle. The patient

presented with pleuritic chest pain 4 days after lipoaspirate injection and was diagnosed with a fat embolism on computed tomography imaging. He was treated expectantly and discharged after 2 days of observation.

The median duration of follow-up (after closure of the diverting ileostomy) for the five patients successfully treated with adipose grafting was 21 months (6–56 months). None

of these five patients developed a recurrent AL. Among these five patients, the median time to confirming healing of the anastomosis after the final attempt at adipose tissue grafting was 6 months (2–7 months).

Discussion

Neoadjuvant radiation therapy is currently a component of standard treatment of locally advanced rectal cancer. While this reduces risks of local recurrence, it compromises tissue healing, and hence prior radiation therapy is an established risk factor for AL [8]. Radiation induces stem cell depletion, endothelial cell activation and chronic inflammation associated with persistent oxidative stress, which contributes to tissue fibrosis and leads to structural and functional alterations [7]. This makes the management of AL after prior irradiation particularly challenging.

Lipoaspirate contains mesenchymal stem cells and has been successful in tissue regeneration and promoting wound healing [11]. They can ameliorate tissue inflammation and accelerate angiogenesis, which are important factors in the management of AL. They have also been shown to improve anastomotic healing in irradiated colon [18]. This prompted us to perform adipose tissue grafting to facilitate anastomotic healing in patients who have a persistent anastomotic defect despite optimization of current available therapies.

In our series, 5 of 11 patients experienced healing with the use of adipose tissue grafting. This seems promising, as all the patients in the series had a persistent defect despite 10 out of 11 patients being treated with other modalities such as suture repair, fibrin glue, Endo-Sponge and surgical debridement. If adipose tissue grafting was not attempted, these patients may have required resection of the anastomosis and possibly even a permanent end colostomy. In our series, one patient developed a pulmonary fat embolism that was expectantly managed. This was related to lipoaspirate injection using a sharp needle instead of a blunt tip needle. In all the other cases where a blunt tip needle was utilized for lipoaspirate injection, no morbidity was encountered. This is consistent with literature on autologous fat grafting, which is generally accepted to be a low-risk procedure [13]. Adipose tissue grafting may thus be a useful addition to the armamentarium for the selective treatment of colorectal AL.

A natural concern with this technique lies in its possible effects on oncological outcome. Exfoliation of malignant cells to the distal bowel is a known entity, and hence an anastomotic defect may present an avenue for malignant cells to seed the exposed mucosa [6]. It is thus unsurprising that local recurrence risk has been associated with AL in some series even though distant recurrence does not seem to be affected [9]. The inoculation process of the adipose tissue may thus theoretically introduce malignant

cells into systemic circulation. Hence, we exercise great care to debride the abscess cavity related to the anastomotic defect at least once, with specimens sent for pathology to ascertain that there is no local recurrence, before proceeding with adipose grafting. Even then, we failed to detect the presence of local recurrence in one patient (patient 8) in our series who was diagnosed with local recurrence 2 months after adipose grafting.

To our knowledge, this is the only reported experience on adipose tissue grafting for the treatment of colorectal AL in human subjects. Prior studies which have demonstrated the benefits of adipose tissue grafting in anastomotic healing were predominantly done on mice, with the study by Van de Putte et al. focused mainly on the postirradiation setting [17, 18]. Adipose tissue grafting has, however, been reported in humans for the treatment of anal fistulas and appears efficacious and well tolerated with minimal morbidity [16].

The main limitation of our study lies in the heterogeneity of our patient cohort. Our cohort of patients varied in terms of the size and location of the anastomotic defects as well as the type of interventions that were attempted prior to adipose tissue grafting. This is, however, a factor common to studies performed on AL, as the initial intervention instituted would vary based on the defect's anatomic location, dimensions and the prior experience or expertise of the attending surgeon. It was also possible that the successful cases demonstrated could have healed regardless of adipose tissue grafting. This is, however, unlikely as adipose tissue grafting was attempted at a median duration of 5 months after an anastomotic defect was diagnosed, allowing sufficient time for spontaneous healing of the AL prior to the procedure in the majority of cases. Nonetheless, this represents the first reported series on adipose tissue grafting for the treatment of colorectal AL and would be an invaluable addition to the literature on the management of this challenging condition.

Conclusions

Adipose tissue grafting may facilitate healing of persistent colorectal anastomotic defects. It ought to be considered for management of colorectal AL.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

Ethical approval This study was approved by the Institutional Review Board of Memorial Sloan Kettering Cancer Center.

Informed consent For this type of study, no informed consent is required.

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