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Histologic case series of human acellular dermal matrix in superior capsule reconstruction

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Background: Acellular dermal matrix (ADM) allografts are commonly used in the surgical treatment of complex and irreparable rotator cuff tears. Multiple studies report that superior capsule reconstruction (SCR) using ADM has resulted in short-term clinical success as assessed via radiographic and patient-reported outcomes. However, limited information is available regarding the biologic fate of these grafts in human subjects. This case series describes histologic results from 8 patients who had reoperations, during which the previously implanted ADMs were removed. These explanted ADMs were subjected to histologic analysis with the hypothesis that they would have evidence of recellularization, revascularization, and active remodeling.

Methods: Eight patients, 38-82 years old, underwent reoperation 6-38 months after undergoing SCR. ADM explants were voluntarily shipped to the manufacturer for histologic analysis. Each graft's structure and composition were qualitatively evaluated by 1 or more of the following histologic stains: hematoxylin and eosin, safranin O, and Russell-Movat pentachrome. Pan-muscle actin staining also assessed the level of neovascularization, potential myoblast or myocyte infiltration, and muscle tissue development in the graft, and was analyzed to determine the proportion of graft that had been recellularized in situ.

Results: Grafts showed varying levels of gross and microscopic incorporation with the host. An uneven, but high, overall degree of recellularization, revascularization, and active remodeling was observed. The degree of remodeling correlated with implant duration. These results are consistent with successful biologic reconstruction of the superior shoulder capsule.

Conclusions: The present histologic analysis suggests that ADMs used in SCR undergo active recellularization, revascularization, and remodeling as early as 6 months after implantation, and that graft recellularization positively correlates with duration of implantation. These results represent a significant advancement in our knowledge regarding biologic incorporation of ADMs used in SCR.

Institutional review board approval was not required for this basic science study.

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Irreparable rotator cuff tears can result in pain, limited range of motion, and diminished strength. They are challenging to treat, and historical treatment options, such as patch augmentation, partial repair, tendon transfers, or reverse total shoulder arthroplasty, have the potential for high failure and complication rates.[14] Superior capsule reconstruction (SCR) was originally described by Mihata as a reconstructive technique for irreparable tears of the rotator cuff using autograft fascia lata, which yielded good clinical results.[12] SCR using human acellular dermal matrix (ADM) is a newer alternative that has grown in popularity.[8] In this modified version of Mihata's technique, ADM reinforces the superior capsule of the glenohumeral joint to restore the normal fulcrum of the shoulder. Clinical outcomes have shown that the SCR procedure can alleviate pain and restore range of motion.[12] Multiple studies report that SCR using ADM has resulted in short-term clinical success as assessed via radiographic and magnetic resonance imaging (MRI) and patient-reported outcomes.[3,6,10,15] However, there is limited information regarding the extent of biologic integration of the graft.[7,16]

Opportunities to examine graft integration are limited because, once implanted, grafts typically remain in the patient undisturbed. Second-look arthroscopy can provide an occasion to obtain biopsies from select regions of the graft, but the assessment is still limited to small, specific areas.[16] Reoperation, on the other hand, presents a rare opportunity to assess patterns of integration within recipient tissue in the entire graft. This case series presents the histologic evaluation of explanted ADMs used in SCR procedures for 8 patients in a wide age range, as well as from a multitude of time points after implantation. The authors' hypothesis is that SCR with an ADM graft will show recellularization, revascularization, and active remodeling of the ADM graft.

Materials and methods

Patients

All patients provided consent for participation, which included use of deidentified tissue samples. IRB approval was not sought as results from this small case series would not be considered generalizable and therefore 45 CFR part 46 does not apply.[20] Exclusion criteria included lack of patient consent or unwillingness of surgeon to be an author. Otherwise, this study included all specimens sent to the manufacturer from 2016-2019. Six different surgeons in different practices performed the 8 reoperations, explanted the ADMs, and placed the specimen in formalin for shipment to the manufacturer. Methods of explantation may have differed among surgeons. All patients received ArthroFLEX ADM (Arthrex, LifeNet Health, Virginia Beach, VA, USA) between 2016-2019.[11] This human ADM was decellularized using the patented and validated Matracell technology.[13] Matracell is validated to reduce DNA content, as a marker of intact cells, by $\geq$97%,[13] and therefore it can be assumed the grafts were acellular on implantation. Histology of grafts preimplantation have been published elsewhere.[13,16]

Histology

The explanted specimens were placed in 10% neutral buffered formalin for fixation and sent to the LifeNet Health R&D Laboratory (Virginia Beach, VA, USA) or Bon Secours DePaul Medical Center Histology Laboratory (Norfolk, VA, USA) for further histologic preparation and analysis. On receipt of the specimens, the formalin fixative was replaced at a 1:10 weight-volume ratio of tissue to fixative. The duration of fixation at room temperature was 7 or more days because of the size of the specimens.

Specimens varied in size and condition depending on how they were surgically removed. Most specimens consisted of the entire graft in 1 piece, although 3 specimens were approximately half of the original graft size and 2 of these 3 arrived in multiple pieces. Any attached bone was debulked before processing, and each specimen was cut into multiple segments that were numbered for identification (Fig. 1). The goal was to crosscut specimens along the vertical (glenoid-humerus, lateral) axis and multiple horizontal (anterior-posterior) planes to enable the histologic observation of the graft as a whole, wherever possible. In addition, the crosscut sections provided images from the bursal to the articular side of each graft. Each piece was processed and stained for histologic analysis, as previously described.[7] Tissue pieces were then sectioned at 7 μm thickness with a microtome. The level of neovascularization and presence of myoblasts or myocytes were assessed using immunohistochemical staining for pan-muscle actin (MA5-11874, 1:100 dilution; Thermo Fisher Scientific, Waltham, MA, USA), incubated for 1 hour at room temperature. Hematoxylin 2 (Richard Allan Sci.; Thermo Fisher Scientific) was used as a counterstain, whereas mouse IgG (ab91353; Abcam, Cambridge, UK) acted as a negative control. Histologic staining was performed for hematoxylin and eosin (H&E), safranin O, and Russel-Movat pentachrome following the manufacturer's protocol (catalog no. KTMTR; American MasterTech, Lodi, CA, USA) for assessment of tissue remodeling.

Merged multiple images of each piece of specimen were captured using a Zeiss Axio Observer Z1 microscope (Carl Zeiss AG, Oberkocken, Germany) equipped with 5×, 10×, and 20× objectives, a Zeiss camera AxioCam MRc, and software Zen 2.3 pro.

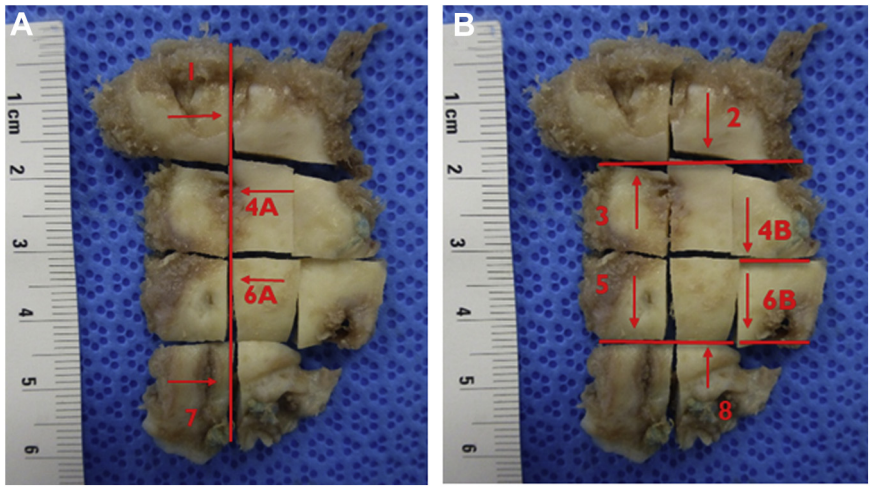

Figure 1 Representative images of specimen preparation. (**A**) Multiple cuts to specimen along vertical (glenoid-lateral direction); (**B**) horizontal planes (anterior-posterior direction). *Red arrow* indicates embedding or sectioning surfaces*.

The total graft area and recellularized area were assessed by observing pentachrome and immunohistochemical-stained tissue sections. On the pentachrome-stained sections, the borders between host tissue, remodeled graft, and graft were identified by locating elastin fibers, which are found in allograft, but not in surrounding host tissue, and by organized collagen fiber pattern around the graft and inside the remodeled portion of the graft. Recellularization was determined by observing immunohistochemical-stained slides counterstained with hematoxylin. Area of graft and area of recellularization were manually traced on jpg images. These images were loaded into Image J software tools (version 1.46r; National Institutes of Health, Bethesda, MD, USA) for measuring the total graft area and recellularized area. The level of recellularization was calculated as the percentage of the recellularized area in the total graft area for each graft's piece as follows:

$$\%\ \text{of recellularization} = \left[\frac{\text{Recellularized area}(\text{mm}^2)}{\text{Total allograft area}(\text{mm}^2)}\right] \times 100$$

Statistics

Minitab 18 software was used to calculate the Pearson correlation coefficient of the strength and direction of the linear correlation between duration of graft implantation and level of recellularization. A strong positive correlation between variables was considered if the value of Pearson coefficient was between $r = 0.5$ and 1. Statistical significance was assessed at the 0.05 alpha level.

Results

Relevant baseline patient characteristics were collected and summarized (Table I). For the reoperations, 6 of 8 patients were converted to reverse total shoulder arthroscopy, 1 had a débridement and graft removal, and 1 had revision SCR. In 7 of the 8 patients, the graft was disrupted. Two of these were related to direct traumatic events, and 5 were

Table I Patient information

Patient	Age, yr	Sex	Reason for explant	Duration of implant, mo	Reoperation type	Number of prior surgeries
1	38	F	Traumatic graft failure (water skiing)	13	Débridement and graft removal	5
2	65	M	Atraumatic graft failure	20	RTSA	2
3	57	F	Atraumatic graft failure	13	RTSA	0
4	65	M	Atraumatic graft failure	8	RTSA	0
5	50	M	Atraumatic graft failure	33	Revision SCR	1
6	82	M	Atraumatic graft failure	26	RTSA	0
7	68	F	Traumatic graft failure (fall)	38	RTSA	0
8	71	M	Humeral head collapse/intact graft	7	RTSA	2

F, female; *M*, male; *RTSA*, reverse total shoulder arthroplasty; *SCR*, superior capsular reconstruction.

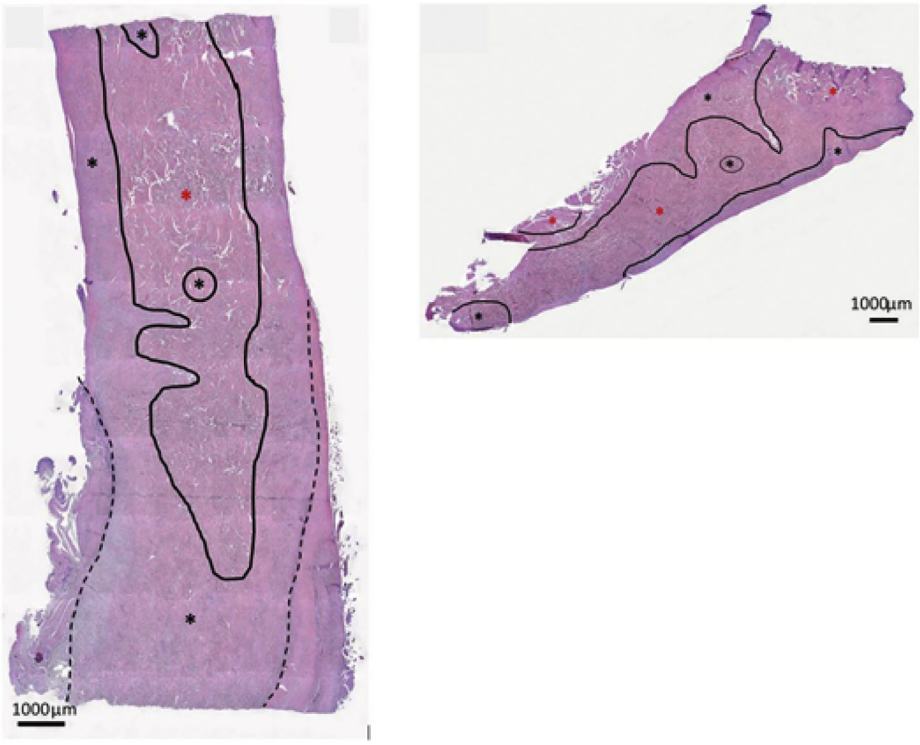

Figure 2 Representative image of recellularization measurement. (**Left**) Piece 8 of this explant from a 57-year-old female patient whose implant was removed after 13 months because of continued discomfort showed 60.45% recellularization, primarily along the periphery of the implant. (**Right**) Piece 9 from the same patient showed 35.15% recellularization. *Black solid lines* demarcate the border between nonrecellularized and recellularized areas. *Indicates areas of recellularization. *Indicates nonrecellularized area. *Dashed lines* demarcates the border between host tissue in-growth and allograft. H&E staining, original magnification × 5; merged images. *H&E*, hematoxylin and eosin.

nontraumatic failures. The 1 remaining patient failed as a result of humeral head collapse, requiring revision 7 months after SCR. The graft was intact in this patient. For the atraumatic failures, it is unknown whether the failure could be directly attributed to the graft, surgical technique, or patient-related factors.

Recellularization and neovascularization

All grafts showed some level of recellularization, with the lowest being an average of 31% after 6 months of implantation and the highest being an average of 79% after 38 months of implantation (Fig. 3). Recellularization was concentrated on the periphery and diminished toward the center of most grafts, which remained acellular and avascular, but without any signs of necrosis (Fig. 2). A strong positive correlation between the implantation time and graft recellularization was found with a Pearson correlation coefficient of $r = 0.758$ ($P < .05$) (Fig. 3).

The highest cell density and neovascularization were found in the suture areas at the glenoid and greater tuberosity attachments (Fig. 4, *A* and *C*). The articular side of the grafts consistently showed high levels of cellularity, whereas the bursal side was inconsistent. Infiltrated cells appeared to have mostly fibroblast-like morphology, with some chondrocyte-like cells mostly found on the articular sides (Fig. 5). In general, more cellular infiltration was found in areas where hair follicles were removed or where

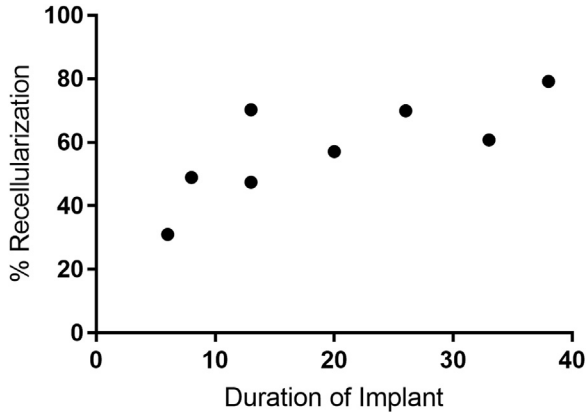

Figure 3 Summary of average recellularization with increasing duration of implant. Average recellularization was higher in patients with longer implant duration. Pearson correlation coefficient of $r = 0.758$ ($P < .05$).

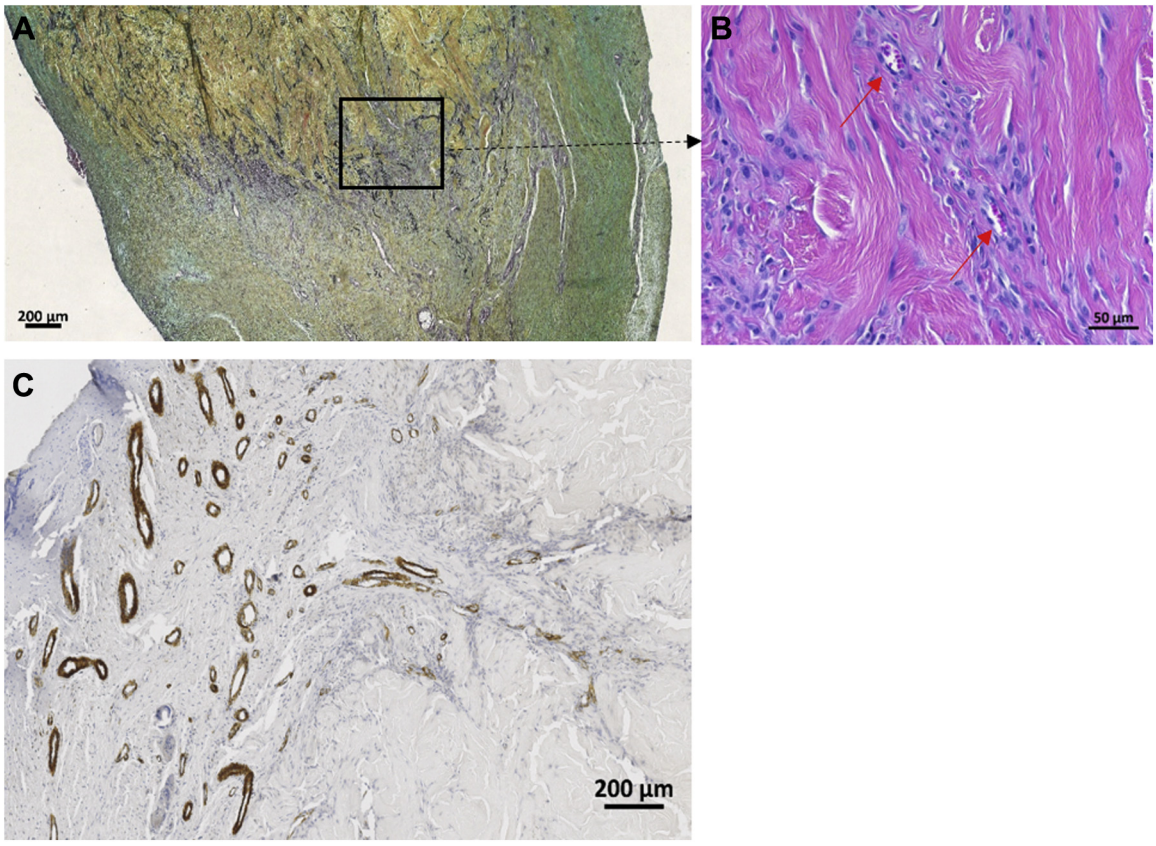

Figure 4 Cell infiltration and neovascularization at the sutured area. Both panels are histologic samples from a 65-year-old male patient whose implant duration was 8 months. (**A**) Black-stained elastin fibers on pentachrome-stained section demonstrate difference between host tissue and the allograft. (**B**) H&E-stained tissue section. *Red arrow* indicates blood vessels. (**C**) Immunohistochemical staining with hematoxylin counterstaining indicates area with numerous blood vessels near the lateral attachment in surrounding host tissue as well as inside the graft. Merged images, original magnification × 10 (**A**, **C**); original magnification × 20 (**B**). *H&E*, hematoxylin and eosin.

the graft was sutured, indicating that the greater porosity in these areas was beneficial for cellular migration.

Like fibroblast recellularization, neovascularization appeared to originate at the periphery of the graft first, and then developed toward the interior. Neovascularization was also observed in newly developed host tissue on the graft surface in some areas (Fig. 4, *C*). None of the explants showed signs of necrosis.

Tissue remodeling

Russell-Movat pentachrome staining gave insight into tissue remodeling by differentiating allograft from host tissue. By comparing elastin staining (black staining) from the preimplanted graft to the explanted grafts, it was evident that elastin fibers remained present in the graft even after 3 years of implantation, indicating that the graft served as a long-term scaffold for tissue remodeling (Fig. 6). Despite the differences in patients' ages and duration of implant, a remodeling pattern emerged. In general, it was noted that the articular side of the explants was more remodeled than the bursal side. The articular side of most specimens showed immature cartilage tissue (safranin O staining; Fig. 7) when the graft was implanted with the basement membrane facing the articular side. The exceptions were 2 grafts implanted with the basement membrane side toward the bursal side, which demonstrated a slightly different remodeling pattern with cartilage-like tissue evenly distributed on both sides. Areas of immature cartilage were not vascularized.

Both the glenoid and humeral regions of bone attachment were generally more remodeled than the central portions of the grafts. Histologic findings confirmed that the allografts were intact and remained firmly attached to the patient bone at the time of the explantation procedure. H&E results showed that the area of the graft attached to humerus or glenoid bone had collagen fibers aligned in a uniform direction along with elongated fibroblast-like cells, indicating an advanced state of tissue remodeling (Fig. 8). Additionally, pentachrome staining showed cartilage-like tissue above the bone surface (Fig. 9, *B*). The orientation of graft implantation did not appear to affect tissue remodeling of this area (Fig. 9). Some chondrocyte-like cells stained positively for pan-muscle actin, and were found on the bursal surface, indicating that the graft was in an active remodeling phase in which the infiltrated cells

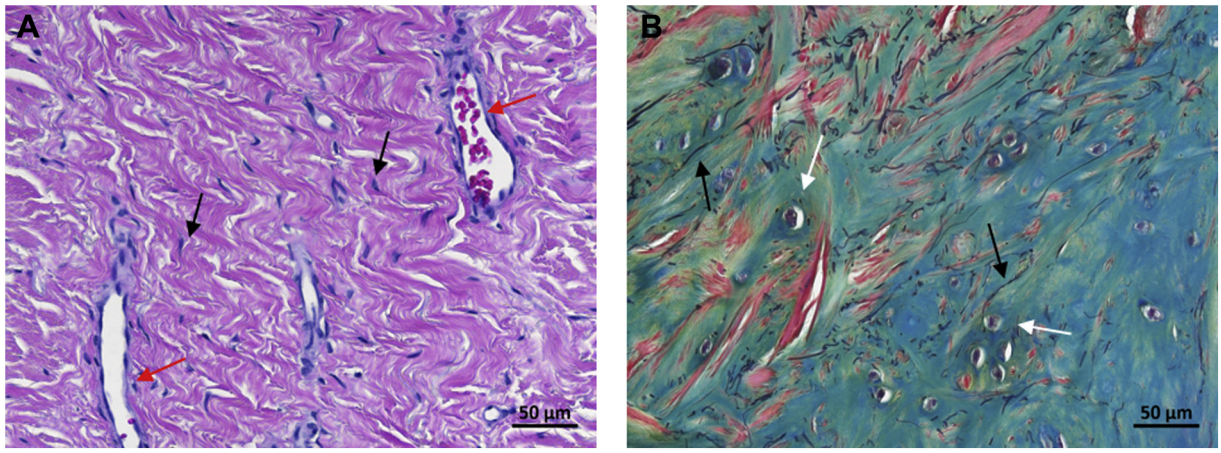

Figure 5 Representative cell morphology in the grafts. (**A**) H&E staining shows fibroblast-like cells (*black arrows*) and blood vessels (*red arrows*) seen in a specimen from a 65-year-old male patient with implant duration of 20 months. (**B**) Pentachrome staining in specimen from a 57-year-old female patient, implantation duration of 13 months, shows chondrocyte-like cells (*white arrows*) as well as black-stained elastin fibers in the allograft (*black arrows*). Original magnification × 20. *H&E*, hematoxylin and eosin.

were still in the process of differentiating into their committed cell type (Fig. 10).

Discussion

This histologic analysis study confirmed our hypothesis that SCR with an ADM graft demonstrated recellularization, revascularization, and active remodeling. Numerous studies have confirmed that SCR is a successful treatment for irreparable rotator cuff tears in the short term based on patient-reported outcome scores, MRI, and plain radiographs.[3,7,8,10,15] Aside from a few case reports, there has been a paucity of direct confirmation regarding the integration and recellularization of the ADM.[2,7,16,17] This case series examined the histology of whole or large segments of SCR explants from 8 patients of a wide age range, as well as from a multitude of time points after implantation. It represents a significant advancement in our knowledge regarding biologic incorporation of ADMs used in SCR.

The consistent recellularization and revascularization observed indicates that graft integration occurred regardless of age within this group of patients. Within 6 months after implantation, cellular infiltration was observed on the periphery of each graft, with infiltration diminishing toward the center. From these observations, it appears that remodeling begins at the periphery and moves inward. These results are in agreement with previously published histology results from ADMs used in rotator cuff

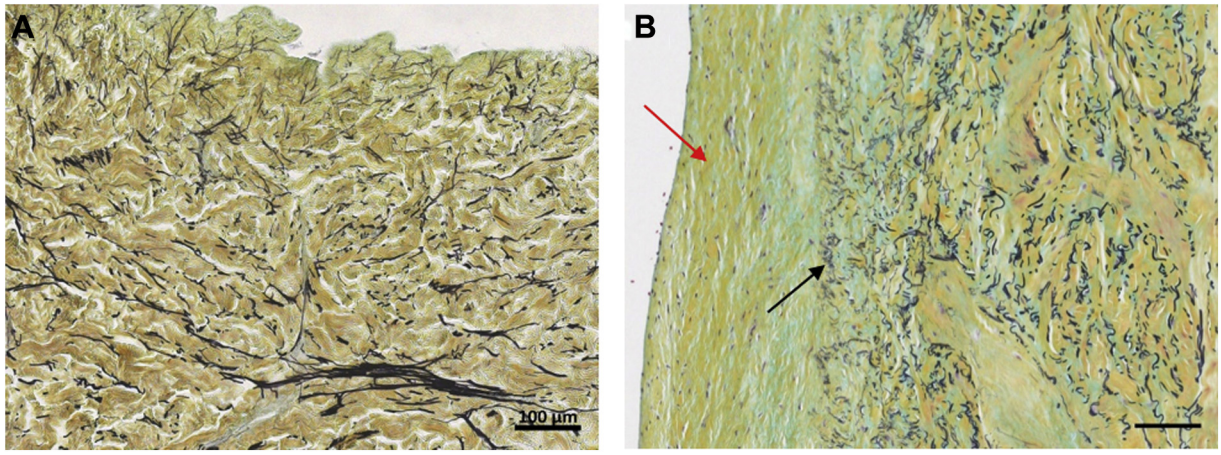

Figure 6 Representative Russell-Movat pentachrome staining. (**A**) Arthroflex preimplantation. (**B**) A 68-year-old female patient with implant duration of 38 months. Black staining of elastin fibers demarcates the border between the host tissue ingrowth and graft. Staining confirmed that elastin fibers of the graft are present after implantation; graft: *black arrow*, and host tissue ingrowth: *red arrow*. Original magnification × 10.

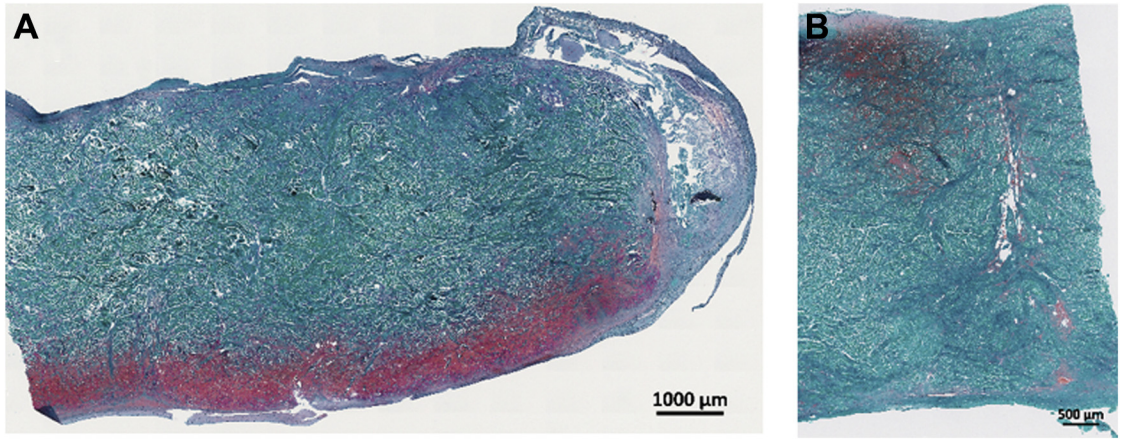

Figure 7 Representative image of safranin O staining. Explants from (**A**) 38-year-old female patient, implant duration 13 months with cartilage development concentrated on the articular side; allograft implanted with basement membrane toward the joint. (**B**) An 82-year-old male patient, implant duration 26 months, with more cartilage development on the bursal side; allograft implanted with basement membrane toward the skin. Merged images, original magnification × 10.

repair.[7,16,19] Remodeling patterns also suggest that graft orientation may be important. In 2 of the atraumatic failures, the grafts were implanted with the basement membrane surface facing the bursal side. In explanted grafts from these 2 male patients, 50 and 82 years old, with implant durations of 33 and 26 months, respectively, histology showed an even distribution of immature cartilage along both the bursal and articular sides of the graft. In explanted grafts with the basement membrane surface facing the articular side, histology showed a higher degree of remodeling and immature cartilage formation favoring the articular side of the graft. These are the first histologic findings showing that graft orientation may affect remodeling. Although it is unknown whether the difference in remodeling might affect clinical outcomes, these findings are intriguing and warrant further study.

Early studies[1,4,5,18,21] using animal models showed that ADMs provide a scaffold for robust host cell infiltration and remodeling. Human data are limited, but results have been consistent among several publications. Plachel et al[16] performed second-look arthroscopy 6 months after the initial procedure on a 51-year-old patient who continued to have pain after SCR, despite MRI showing an intact ArthroFlex graft. The authors obtained and histologically examined 6 biopsy samples from various locations on the graft. Four biopsies were used for histologic analysis: H&E, Russel-Movat pentachrome, and Alcian blue were used to assess residual graft tissue, evidence of chondral metaplasia, cellular infiltration, and blood vessel formation. Consistent with the data presented here, cellular infiltration and neovascularization were most abundant on the periphery of the graft. The center did not show cellular

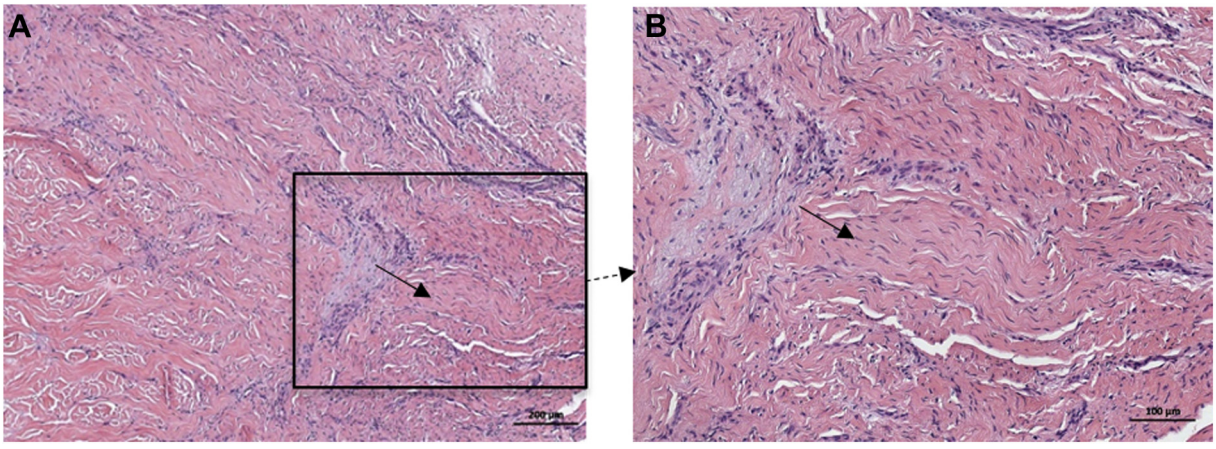

Figure 8 Representative images of remodeling phase. H&E staining of specimen from 38-year-old female patient, implant duration 13 months; near glenoid attachment. Note the aligned collagen fibers, indicating advanced remodeling (*black arrows*). Merged images, (**A**) original magnification × 5 and (**B**) original magnification × 10. *H&E*, hematoxylin and eosin.

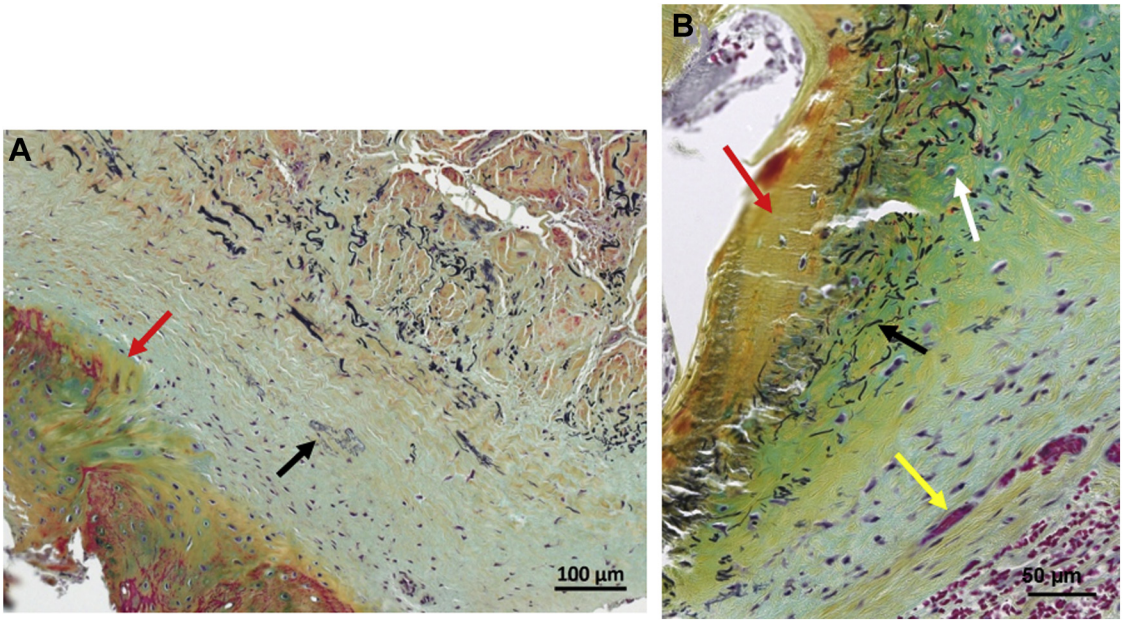

Figure 9 Representative pentachrome staining of graft in active remodeling phase attached to humeral bone. Elastin fibers (*black arrow*), bone (*red arrow*), blood vessel (*yellow arrow*), chondrocyte like cells (*white arrow*). (**A**) A 57-year-old female patient with implantation duration of 13 months, graft implanted with basement membrane side toward the bone. (**B**) An 82-year-old male patient with implantation duration of 26 months, graft implanted with basement membrane side toward the skin. Original magnification × 10 and × 20.

infiltration but also did not show any signs of necrosis. The authors also noted that immature cartilage had formed near areas of native cartilage, such as the humeral head. These results are also consistent with the present findings of immature cartilage, particularly located near the presence of native cartilage on the articular side, indicating that the ADM acts as a scaffold for infiltration of nearby host cells.

Additionally, the authors used the other 2 biopsy samples for gene expression analysis. The authors reported high expression of scleraxis (SCX) and tenolodulin (TNMD), both of which are associated with tendon maturation. In another second-look arthroscopy case in non-SCR rotator cuff repair, Snyder et al[19] also found that ADM biopsies (GraftJacket MaxForce Extreme; Wright Medical

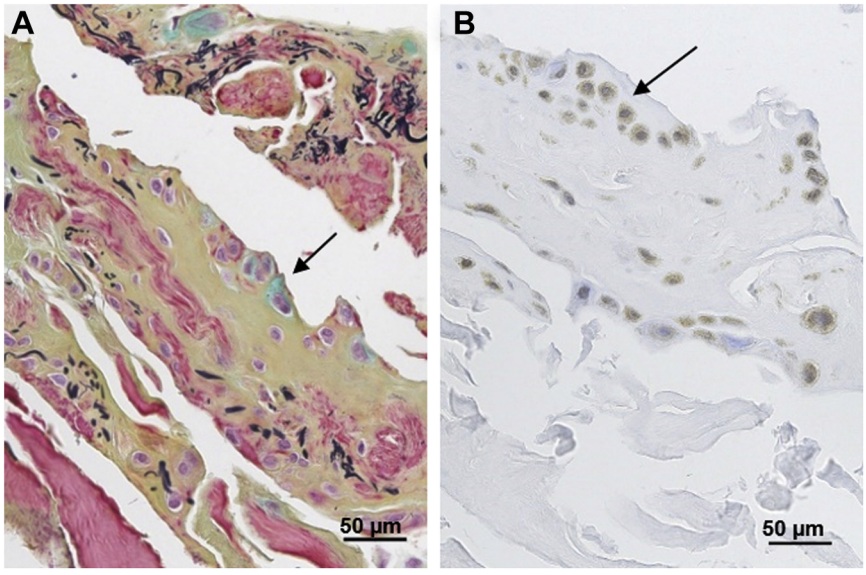

Figure 10 Representative images of active remodeling. (**A**) Russell-Movat pentachrome-stained graft from a 57-year-old female patient with implant duration of 13 months showed chondrocyte-like cells in the bursal side. (**B**) Positive pan muscle actin staining of the same graft's area. Original magnification × 20.

Technology, Arlington, TN, USA) showed cellular infiltration, evidence of graft remodeling, and neovascularization 3 months after implantation. Although the biopsies from these studies can provide some information regarding graft incorporation, studies examining the entire graft, such as done here, provide a clearer picture of graft fate.

Hartzler et al[7] examined an explanted, intact ADM from a 72-year-old patient who had undergone SCR. Radiographic imaging showed that the graft was intact and appeared to be healed at 7 months postoperation; however, the patient's humeral head had avascular necrosis, resulting in conversion to reverse total shoulder arthroscopy. The explanted ADM showed evidence of abundant recellularization, particularly near sutured areas on the humeral side. The authors speculated that bone marrow cells may have entered and contributed to healing in this area through the cannulated suture anchors used in the procedure. Similar to the cases in the present series, they reported immature cartilage formation and suggested that this speaks to the potential for ADMs as vehicles for tissue regeneration. The authors also noted positive pan-muscle actin staining in chondrocyte-like cells, which is unexpected. Similar results were seen in the present study, indicating the presence of highly active remodeling because the cells had not yet fully differentiated. In their case study, Altintas et al[2] also reported a patient who had undergone SCR with ADM, but showed little improvement at 4.5 months postoperation despite computed topography showing an intact graft. The patient opted for reverse total shoulder arthroplasty, at which time the graft was removed and subjected to biomechanical and histologic testing. Histologic results showed cellular infiltration in the graft, with the most cellular content found in the medial section and the least in the lateral section. The authors noted that Herovici's staining revealed highly crosslinked collagen as well as newly formed collagen in the medial and middle sections. The authors interpreted these findings as being similar to tendon morphology and hypothesized that the ADM incorporates in a similar manner to ADM used in skin and hernia repair. They suggested that the differences in cellularity between the medial and middle portions compared to the lateral portion may be accounted for if these sections were in different phases of remodeling. The authors speculated that the lateral side was in the first phase, which is represented by hypocellularity. The medial and middle sections may have been in the proliferative phase, given the high cellular content and neovascularization, or early third phase, which would lead remodeling to a tendon-like morphology, as suggested by the Herovici staining.

Finally, in a small case series, Ravencroft et al[17] followed 27 total patients who had SCR in 2016-2017. During follow-up MRIs, 5 procedures were labeled as failures. Two of these 5 patients reported good clinical outcomes despite MRI findings and did not seek reoperation. The authors histologically examined grafts from the other 3 patients; 1 graft had an intra-substance tear whereas the other 2 had anchor failure at the glenoid insertion. The results showed that the 3 grafts had fibroblast infiltration as well as evidence of bony integration and neovascularization near the periphery. These findings suggest that in surgeries that failed to relieve symptoms, the mechanism of failure may not always be graft related. It has been suggested that in some cases of clinical failure in which the graft was intact, the failure was a result of improper tensioning, which failed to restore acromial-humeral distance.[9] Ravenscroft et al[17] concluded that these results provided evidence that the ADM used acted as a ''good biologic scaffold.'' Altogether, these findings from the literature support the use of decellularized dermal matrix as a bridging graft in SCR and suggest its utility as a scaffold for tissue regeneration.

Limitations of this study include its retrospective nature and the small number of patients included, indicating that the present results are not necessarily generalizable, in spite of their congruence with published reports. Seven of these explants were due to clinical failure and may not accurately represent tissue remodeling in a clinically successful surgery. Additionally, the cause of some patients failing to find relief, even when the graft is well incorporated (or alternatively, may find relief when the surgery is described as ''failed''), is beyond the scope of this article. These questions warrant investigation in future studies.

Conclusions

The findings of this study support the use of human ADM as a hospitable scaffold for host cell infiltration and remodeling. Regardless of patient age or time after implantation, all grafts had evidence of cellular infiltration, neovascularization, and active remodeling. The results of this case series also suggest that there is a relationship between implant duration and the extent of recellularization, and that human ADM can successfully incorporate into host tissue when used in SCR. This study advances our knowledge regarding the biologic incorporation of ArthroFlex ADM used in SCR.

Disclaimer

Julie B. McLean is an employee of LifeNet Health, a nonprofit organization, which processes ArthroFLEX. Amy L. Dorfman is an employee of LifeNet Health, a nonprofit organization, which processes ArthroFLEX. Davorka Softic is an employee of LifeNet Health, a nonprofit organization, which processes ArthroFLEX. Xiaofei Qin is an employee of LifeNet Health, a nonprofit organization, which processes ArthroFLEX. The other authors, their immediate families, and any

research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article. All histologic testing was performed at LifeNet Health's Institute for Regenerative Medicine.

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