Biologic Orthopedic Journal

Original Article

REGENERATION OF FULL-THICKNESS SUPRASPINATUS ROTATOR CUFF TENDON TEAR AFTER TREATMENT WITH AUTOLOGOUS MESENCHYMAL STEM CELLS

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Submitted: May 19, 2020. Accepted: August 23, 2020. Published: September 2, 2020.

ABSTRACT

Rotator cuff tear (RCT) is primarily a disease of middle-aged and older patients. Observational data es-timated linear increment in the frequency of RCT over time due to the degenerative process. However, a good proportion of tears in older patients are asymptomatic and do not require any intervention. Sport and non-sport Injuries can contribute to RCTs. Many RCTs can be treated non-surgically with anti-inflammatory medication, steroid injections, and physical therapy for symptomatic relief and to restore shoulder strength and function. Rotator cuff tendon tears have limited ability to heal on their own and most often surgical repair is recommended in people failing non-operative therapy. The recovery time after surgery can be a lengthy process. There are no conclusive data to support the routine use of biologic therapy like mesenchymal stem cells (MSCs) or platelet-rich plasma (PRP) in the treatment of symptomatic RCTs. Herein we report a full-thickness supraspinatus tear (SST) in an elderly patient's shoulder following three injuries. The tear was confirmed by ultrasound scan (USS) and magnetic resonance imaging (MRI) with SST of 9 mm in length and 13 mm in width which was unresponsive to anti-inflammatory medicines, rehabilitation and steroid injections. The subject, however, did have a definitive clinical and radiological response to a single therapeutic injection using autologous adipose tissue-derived MSCs combined with PRP, the injections were performed by ultrasound guidance into the subacromial bursa, supraspinatus tendon and tendon insertion respectively. After five months an USS showed some healing of the SST. Eight months post-MSC therapy the subject had significant improvement in symptoms, and dramatic improvement of the Disability of the Arm, Shoulder and Hand (DASH) score from baseline of 88.3 prior to the therapy to 16.3 at the final visit. Follow-up MRI scan revealed complete healing of the SST indicating the possible successful outcome of MSC therapy as an alternative non-surgical treatment.

Key words: *Rotator cuff tear (RCT), regeneration, mesenchymal stem cells (MSCs), Platelet- Rich Plasma (PRP), stem cell therapy.*

INTRODUCTION

Rotator cuff tears (RCTs) are relatively common pathologies, they are prevalent with aging due to the degenerative process.[1] They can occur by or be aggravated by trauma. Many tears are asymptomatic and do not require any intervention but when they cause symptoms such as significant pain and functional impairment, medical and physical therapies are indicated to help symptoms. RCTs are unlikely to heal naturally thus surgical repair is suggested as a cost-effective approach for symptomatic cases.[2] A subacromial steroid injection can potentially help the symptoms but often that is short-lived.[3,4] There is a growing interest recently both in animal and human trials in the regenerative therapy including PRP (platelet- rich plasma) and MSCs (mesenchymal stem cells) as an alternative to surgical intervention to treat the RCT.[5–11]

CASE REPORT

A 70-year-old female presented with shoulder pain which she had suffered on a flight in June 2018 when a bag fell out of the baggage rack landing on her right shoulder. Conservative treatment with analgesia and physiotherapy were prescribed. An ultrasound scan (USS) revealed a small partial tear of SST with subdeltoid bursa thickened to 2.8 mm. An USS-guided subacromial steroid injection was administered by the radiologist with good effect. Soon after however, the patient developed another shoulder injury to the same area after catching her grandchild in October 2018. An USS at the same facility in December 2018 showed small rotator cuff tears in SST with recurrent sub-deltoid bursitis. A further USS-guided subacromial corticosteroid injection was given by the same radiologist two days following the scan.

Her condition was stable until she developed the third shoulder injury in April 2019 when a four-year-old child accidently jumped on her right shoulder resulting in extreme pain. The resulting pain greatly affected her sleep and significantly restricted her shoulder movements. After consultation with her family doctor she was referred to orthopedic surgeon for assessment and pain management.

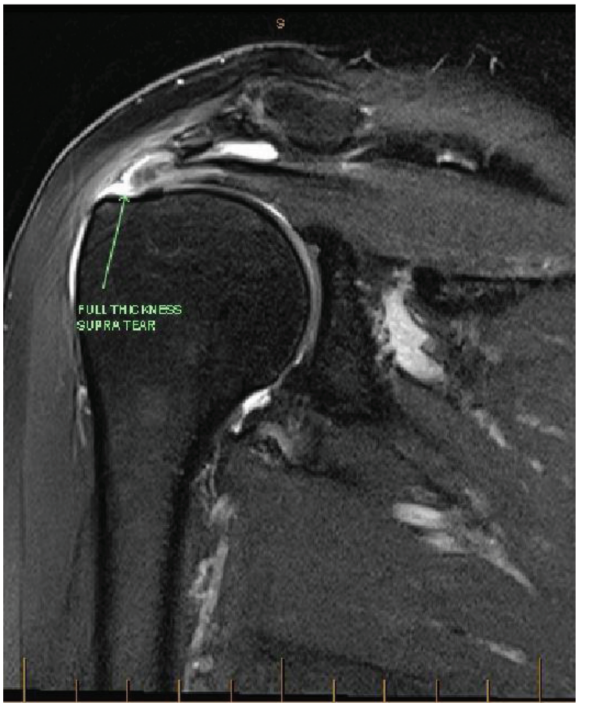
During that time conservative treatment with the use of NSAID once daily, shoulder brace and rehabilitation including manual therapy, exercises and several acupuncture sessions. Despite this, her injury deteriorated.

A repeat USS was performed on June 2019 and showed SST has progressed to a full thickness tear, anteriorly measuring 9 mm length, 13 mm width with the overlying bursa was swollen to 2.9 mm.

Magnetic resonance imaging (MRI) (1.5T, Seimens, Munich, Germany) revealed a full-thickness tear of supraspinatus tendon involving anterior, middle and posterior fibers with 7mm retraction from the footprint, 13mm AP width. There was a small glenohumeral joint effusion extends through the cuff tear into the subacromial space. There was no labral tear or MRI features of capsulitis (Figure1).

The patient was advised by the orthopedic surgeon to undergo a surgical repair of the SST and debridement of the subacromial bursa as further cortisone was unlikely to resolve her condition. The patient however was not keen on surgical intervention and wanted to

FIG. 1 Pre-treatment magnetic resonance imaging demonstrating evidence of full-thickness supraspinatus tear.



avoid general anesthesia and a lengthy post-operative rehabilitation.

In her research she tried to explore the option of an alternative therapy, she discovered a non-invasive treatment in New Zealand using adipose-derived expanded MSCs combined with PRP. Her assessment was carried out in August 2019 that highlighted the ongoing right shoulder antero-lateral deep sharp pain with loss of function. She tried various medicines including narcotics, NSAIDs, and analgesics daily to control the pain and she held her right arm in an adducted posture to lessen the constant discomfort. DASH score which is self-assessment measurement for symptoms and physical function, was administered, and the pre-treatment value was 88.3. The DASH is a brief self-administered measurement of both symptoms and functional status for the last one week. Symptoms include: pain, weakness, tingling and stiffness. Functional status addresses multiple physical tasks of daily living like preparing meals, opening jars, carrying heavy object, and gardening. It is recommended to measure DASH score before and after the therapy then compare it to assess the progress of intervention.

Physical examination revealed tender subacromial area and SST insertion with positive Hawkins-Kennedy and Neer's tests. Active range of movements were of the right glenohumeral joint was; flexion 0–80º, abduction 0–60º, and both external and internal rotation at the side of the body was 0–20º. The clinical picture was consistent with symptomatic full-thickness SST tear with associated shoulder stiffness.

After discussing the option of cellular based therapy utilizing culture expanded MSCs and PRP, she was happy to proceed for the adipose tissue harvesting, at that time she was not using any anti-inflammatory medicines for more than one week thus she was offered PRP for symptoms control while she is waiting for the tissue harvest and cell expansion. Two days later at our clinic, we performed the PRP procedure, patient gave informed consent before undergoing a blood draw for PRP. Forty mL of blood was taken, placed in anticoagulant ACD-A tubes, undergoing centrifugation 1500 RCF for 8 minutes producing good plasma separation with a total volume of 7.5 mL PRP, no characterization of the PRP was completed. The PRP was mixed with 0.5 mL of calcium gluconate 10% to a total volume of 8 mL and administered within 10 minutes under local anesthesia of xylocaine 1%, using anatomic landmarks and a portable, with linear L38, 15.6 MHz probe (Sonosite Inc, USA) to the right subacromial bursa (5 mL) and SST insertion (3 mL) utilizing an long axis approach. The procedure was done in a sitting position with right arm on her lap. She was advised to avoid anti-inflammatory medicine for up to a month after the injections to reduce any negative influence on PRP or MSCs functions.

Virtual follow up by email and phone was done for the first two weeks and she reported mild improvement of the symptoms but this was not persistent after one month. There were no complications of the PRP.

On 12.09.2019 after informed consent, the abdominal adipose tissue was harvested by a qualified general surgeon. The MSCs were extracted and expanded according to cGLP by licensed and registered provider (Regen Cellular, Queenstown, New Zealand) according approved protocol. The lipo-aspirate was washed and then digested with 0.2 U/mL collagenase. The stromal vascular fraction (SVF) was separated from the digested adipose tissue through density centrifugation. The SVF was plated down and cultured using Dulbecco's Modified Eagle Medium (DMEM) and 10% HPL to expand the MSCs population. Cells were grown to 90% confluency over a period of just under six weeks and then cryopreserved until injection date. Injections were prepared on the date of treatment. The cells were washed and filtered before being resuspended in Hartmann's solution with 10% HPL (human platelet lysate) in syringes for administration. Cell count was measured manually and confirmed by a haemocytometer and the viability was measured by trypan blue exclusion dye (Table 1).

Characterization of the MSCs was done by using Flow Cytometry for CD surface markers analysis and the results were consistent with MSCs per the International Society of Cellular Therapy (ISCT) guidelines (Table 2.)

On 23rd October 2019, we performed the stem cell injections, after informed consent and under aseptic technique we used 100×10^6 of MSCs (1.5 mL) combined with PRP (prepared on the day of the procedure, 10 mL, not characterized) in the same

TABLE 1 Cell Count and Viability

	Area	Cell number	Viability
Implant 1	Subacromial bursa	44 million	99 %
Implant 2	SST substance	35 million	99 %
Implant 3	SST greater tuberosity insertion	21 million	99 %

SST = supraspinatus tendon

TABLE 2 Flow Cytometry CD Surface Marker Analysis

	Positive markers			Negative markers			
	CD90 + %	CD73 + %	CD105 + %	CD14 + %	CD19 + %	CD34 + %	CD45+ %
% Percentage	93.7	99.9	65.6	0.11	0.02	10.29	0.42

syringe. Injection was performed under USS guidance. Of particular note in preparation of the PRP, 50 mL of blood was drawn and the same setting of PRP preparation was used, but this time was 10 mL of PRP without calcium gluconate to avoid gel formation. Three sites were injected, 5mls of the injectate was placed in the subacromial bursa at various depths to cover the SST, 4 mL was placed in the SST substance and 2.5 mL at the SST greater tuberosity insertion. We advised the patient to avoid direct heat or cold therapy to reduce any factors influencing the good function of the MSCs, also recommended shoulder immobilization for two weeks to avoid post-injections flare up. Physical therapy rehab program commenced with gentle massage and graduated shoulder passive and active exercises. We avoided heat or cold therapy in the first two weeks.

The patient was followed up virtually by phone and email every 4–6 weeks. There were no reported adverse events or complications of the therapy and a follow-up five months post injection in March 2020, showed "some healing of the tear occurring with some internal echoes now present and bursitis has resolved."

Seven months post injection, the patient reported stopping all pain medications and experiencing no pain. She was able to swim again, had pain-free sleep and was able to carry out normal daily functions.

On 25 June 2020, the patient reported the right shoulder was painless, The DASH score had significantly improved in both symptoms and functional status from 88.3 to 16.3. Glenohumeral active range of motion was measured revealing: flexion 0–170º; abduction 0–160º; external rotation in adduction, 0-70º; and internal rotation in adduction, 0–70º.

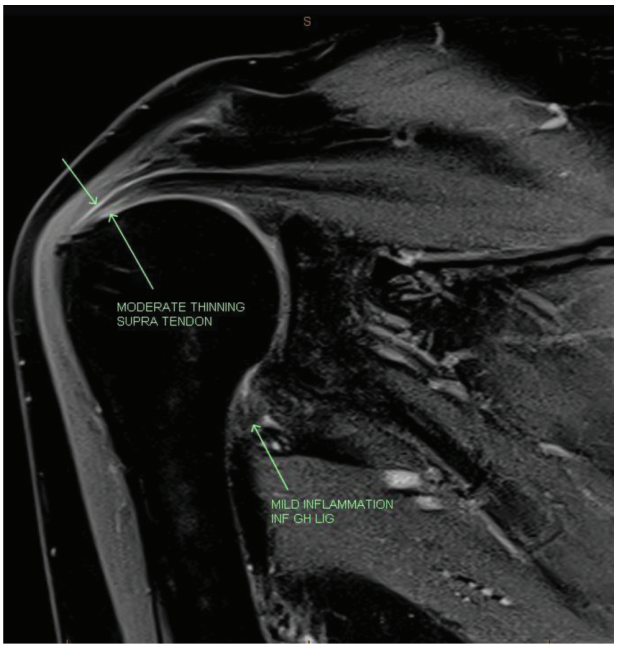
An MRI of the shoulder (1.5T, Seimens, Munich, Germany) showed moderate thinning at the supraspinatus tendon insertion, compatible with the previous tear. However, the supraspinatus tendon tear demonstrated on the last scan from one year ago had healed. There was no longer a full thickness tear or evidence of rupture, and the supraspinatus musculature is maintained. There is mild thickening of the inferior glenohumeral ligament suggestive of low-grade adhesive capsulitis (Figure 2).

DISCUSSION

Tendons are subjected to degenerative changes due a diminished regenerative capacity from reduced blood supply. Torn tendons often heal by forming scar tissue, which is structurally weaker than healthy tendon tissue, predisposing to mechanical failure. There is growing interest in providing biological stimuli to heighten the tendon reparative response. MSCs are a particularly exciting and promising science as they have potential to provide appropriate cellular signals in order to encourage new tendon formation (neotendon) during repair rather than scar tissue. Currently, this is being studied in various research facilities and clinical practices to determine both the efficacy and safety.[12,13]

Cellular based therapy is an evolving science which has been positively implicated in treating musculoskeletal conditions but still is considered

FIG. 2 Post-treatment magnetic resonance imaging demonstrating healing of the supraspinatus tear.



investigational.[14,15] It has been shown in meta-analysis that stem cells improved the rehabilitation of rotator cuff pathologies.[16] Biologic therapy of MSCs have been shown in some studies to help the outcome of orthopedics surgical procedures.[17]

A good outcome was achieved in our patient, and we believe that it was related to the placement of a high number of MSCs combined with PRP in the same syringe for synergistic effect and injected in multiple areas including various depths of the subacromial bursa, SST tendon insertion and the tendon substance itself. The positive result was a significant reduction in DASH score.[18] Additionally both USS and MRI showed evidence of regenerative healing of the full-thickness tear, this has also been demonstrated in the previous studies of intratendinous MSCs injections for partial thickness tears.[19]

We have followed the New Zealand guidelines and regulations for the use an alternative therapy of both MSCs and PRP, in addition we have provided a majority of the data included in the international Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO) for both MSCs and PRP therapies.[20]

Our case report has several weaknesses, the most obvious is that it is the report on a single case, so the generalizability of the findings of this presentation would not be prudent. Additionally, full characterization of one the PRP was not completed, and therefore its impact on treatment is difficult to quantify. Many different international regulatory bodies prohibit mixing of medications extracorporeally prior to injection, for the impact of effects of this action is generally not studied or known, so the effects of these actions are unknown.

In conclusion, our case of SST tear and subacromial bursitis has demonstrated a significant clinical and radiological response to autologous expanded MSCs combined with PRP. As the cells are autologous, rejection was not demonstrated and combining the stem cells with PRP may allow for a better outcome due to the presence of numerous growth factors in PRP. This therapy has potential for the non-surgical treatment of RCT.

Our recommendation that prospective comparative studies be carried out to ascertain whether consistent results of RC regeneration is indeed possible.

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