Chapter 16
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Rotator Cuff Regeneration Post Expanded Stem Cell Therapy: Clinical Approach

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ABSTRACT

This study aims to investigate if biological therapy can repair rotator cuff tears (RCTs) without surgery. RCT is primarily a disease of middle-aged and older patients. Observational data estimated a linear increment in RCTs frequency over time due to the degenerative process. Sport and non-sport Injuries can contribute to RCTs; however, asymptomatic tears do not require any intervention. Tears can be treated conservatively with anti-inflammatory medication, physical therapy, and steroid injections for symptomatic relief and restore shoulder strength and function. RCTs have limited ability to heal independently, and most often, surgical repair is the last resort when non-operative therapy fails. The recovery period following surgery can be lengthy, in addition to possible complications of surgery and general anaesthesia. There are no conclusive data to support the routine use of biological therapy of mesenchymal stem cells (MSCs) or platelet-rich plasma (PRP) in treating symptomatic RCTs. We report a case of a full-thickness supraspinatus (SST) tear in an older woman. The tear happened after frequent injuries; an ultrasound (USS) and MRI scan showed a tear in SST of 9 mm in length and 13 mm in width with 7mm retraction, unresponsive to anti-inflammatory medicines, rehabilitation, and steroid injections. She has had a significant clinical and radiological response to implantation with fat-derived autologous expanded MSCs combined with PRP. We performed USS-guided injections into the subacromial bursa, supraspinatus tendon substance and tendon insertion. After five months, USS revealed that the SST had healed. Eight months post-MSC therapy, she improved dramatically in symptoms. She significantly dropped the Disability of the Arm, Shoulder, and Hand (DASH) score from a baseline of 88.3 before the therapy to 16.3 at the final visit. A Follow-up MRI scan revealed complete healing and regeneration of the SST, with reattachment of the retracted tendon to the greater tuberosity of the humerus, indicating a successful outcome of MSC therapy as an alternative non-surgical treatment. We reviewed the relevant literature and found that no other non-surgical medical therapy produces world record full-thickness tendon repair.

Keywords: Rotator cuff tear (RCT); regeneration; mesenchymal stem cells (MSCs); Platelet- Rich Plasma (PRP); stem cell therapy.

1. INTRODUCTION

Rotator cuff tears (RCTs) are relatively common pathologies; they are prevalent with ageing due to the degenerative process [1]. They can occur by trauma or get aggravated by it. The main problem with failure in rotator cuff repair is probably biological. It is well known that the delicate and highly specialized fibro-cartilaginous transition zone between the rotator cuff and the bone does not regenerate after repair [2-4]. Many tears are asymptomatic discovered incidentally and do not require any intervention. Still, when they cause symptoms such as significant pain and functional impairment, medical and physical therapies are suitable to try first. RCTs are unlikely to heal naturally; thus, surgical repair is the next cost-effective approach when needed [5]. A subacromial steroid injection can potentially help the symptoms, but that is often short-lived [6,7]. Recently, there has been a growing interest in animal and human trials in regenerative medicine, including MSCs and PRP as an alternative to surgical intervention for RCT treatment [8-14].

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2. CASE REPORT

A 70-year-old female presented with a painful shoulder following an injury suffered on a flight in June 2018 when a bag fell out of the baggage rack, landing on her right shoulder. She had conservative treatment with analgesia and physiotherapy. USS revealed a small partial tear of SST with subacromial bursa thickened to 2.8 mm. The radiologist administered an USS-guided subacromial steroid injection 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 subacromial bursitis. She had another USS-guided subacromial steroid injection.

Her condition was stable until she developed the third shoulder injury in April 2019 when a four-year-old child accidentally 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 doctor, she was referred to an orthopaedic surgeon for surgical management. In the meantime, she continued conservative treatment with oral anti-inflammatory medicine and rehabilitation. Despite that, her injury deteriorated.

A repeat USS was performed in 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. MRI confirmed this, which showed a full-thickness tear of STT anterior, middle, and posterior fibres with 7mm retraction and 13mm AP width from the footprint. A small glenohumeral joint effusion extends through the cuff tear into the subacromial space. There was no labral tear or MRI features of capsulitis (Fig. 1).

Fig. 1. Pre-treatment MRI demonstrating full-thickness supraspinatus tear

The orthopaedic surgeon advised her to undergo a surgical repair of the SST. However, the patient was not keen on surgical intervention and wanted to avoid general anaesthesia and lengthy post-operative rehabilitation.

In her research, she tried to explore the option of 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 anterolateral

deep sharp pain with loss of arm function. DASH score, a 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 symptoms and functional status for the last week. Symptoms include pain, weakness, tingling, and stiffness. Functional status addresses multiple physical tasks of daily living like preparing meals, opening jars, carrying a heavy object, and gardening.

Physical examination revealed right arm in an adducted posture to lessen the constant discomfort: tender subacromial area and SST insertion with positive Hawkins-Kennedy and Neer's tests. The dynamic range of movements of the right glenohumeral joint was reduced to flexion 0–80º, abduction 0–60º, and external and internal rotation was 0–20º. The clinical picture was consistent with symptomatic full-thickness SST tear with associated shoulder stiffness without MRI evidence of frozen shoulder.

After discussing the option of cellular-based therapy utilizing culture-expanded MSCs and PRP, she was happy to proceed with adipose tissue harvesting. She was offered PRP for symptom control while waiting for the fat tissue harvest and cell expansion. We performed the PRP procedure; the patient gave informed consent before undergoing a blood draw for PRP. We took 40 MLS of blood, placed it in anticoagulant ACD-A tubes, then centrifuged in 1500 RCF for 8 minutes producing good plasma separation with a total volume of 7.5 ML PRP.

We did a virtual follow-up by email and phone two weeks after the PRP, and she reported mild improvement of the symptoms, but this was not persistent beyond a month. There were no complications of the PRP. In September 2019, after informed consent, a qualified general surgeon harvested the abdominal adipose tissue. According to the approved protocol, the MSCs were extracted and expanded according to cGLP by licensed and registered providers. Lipo-aspirate was washed, then digested with 0.2 U/mL collagenases, and 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 six weeks and then cryopreserved until injection time. 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 hemocytometer, and the lab did the viability test using trypan blue exclusion dye (Table 1).

We characterize the MSCs using Flow Cytometry for CD surface markers analysis, and the results were consistent with MSCs per the International Society of Cellular Therapy guidelines (Table 2).

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. Shows flow cytometry - CD surface marker analysis

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

On 23 October 2019, we performed the stem cell injections; after informed consent and under the aseptic technique, we used 100×10^6 of MSCs (1.5 mL) combined with PRP (prepared on the day of the procedure, 10 MLS) in the same syringe. We injected 5 MLS in the subacromial bursa, 4 MLS in the SST substance, and 2.5 MLS at the SST insertion at the greater tuberosity. We also recommended shoulder immobilization for two weeks to prevent a post-injection flare-up. The physical

therapy rehab program commenced with gentle massage and graduated shoulder passive and active exercises.

The patient was followed up virtually by phone and email every 4–6 weeks. There was no adverse effect of the therapy. A follow-up five months post-injection in March 2020 showed "some healing of the tear occurring with some internal echoes present and bursitis has resolved". Seven months post-injection, the patient reported stopping all pain medications and experiencing no pain. She swam again, had a pain-free sleep, and carried 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 showed complete healing of the full-thickness STT tear demonstrated on the last scan had healed. Mild thickening of the inferior glenohumeral ligament suggests low-grade adhesive capsulitis (Fig. 2).

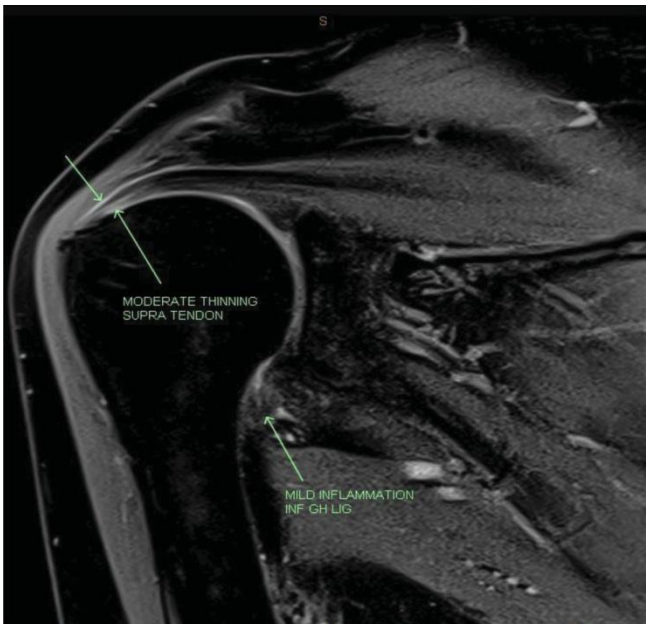

Fig. 2. post-treatment MRI demonstrating complete healing of the supraspinatus tear

3. DISCUSSION

Tendons are subject to degenerative changes due to a diminished regenerative capacity from the 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 fascinating and promising science as they can offer appropriate cellular signals to encourage new tendon formation (neotendon) during repair rather than scar tissue. This is currently being studied in various research facilities and clinical practices to determine efficacy and safety [15,16].

Cellular-based therapy is an evolving science with huge promises in managing musculoskeletal conditions. It is still considered investigational [17,18]. It has been shown in a meta-analysis that stem cells improved the rehabilitation of rotator cuff pathologies [19]. Some studies have shown the biological therapy of MSCs to help the outcome of orthopaedic surgical procedures [20].

Our case represents the world-first for healing a full-thickness tear of rotator cuff 9 x13 mm and resolution of 7mm tendon retraction by reattachment of the tendon to the greater tuberosity of the humerus. The process was equivalent to surgical repair, according to the radiology report. We believe our therapy's success is due to the implantation of the 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 and SST tendon insertion the tendon substance itself. The positive result was a significant drop in the DASH score [21]. Additionally, both USS and MRI showed regenerative healing of the full-thickness tear; we found literature suggesting healing response with intra-tendinous MSCs injections for partial-thickness tears [22].

We have followed the New Zealand guidelines and regulations for using an alternative therapy of MSCs and PRP. In addition, we have provided most of the data included in the international Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO) for both MSCs and PRP therapies [23]. We hope, with more experience, we can reproduce those results to make biologics therapy replace surgical repair without the complications of invasive procedures and the associated long recovery periods.

4. CONCLUSION

Our case of full-thickness rotator cuff tear demonstrated a significant clinical and radiological response to autologous expanded MSCs combined with PRP. There were no adverse reactions.

We recommend that prospective comparative studies ascertain whether consistent RC regeneration results are possible.

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COMPETING INTERESTS

The author has declared that no competing interests exist.

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