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Clinical and Radiological Outcomes of Transarterial Embolization for Adhesive Capsulitis

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Objective: To assess the effect of transarterial embolization (TAE) for adhesive capsulitis (AC) by evaluating clinical outcomes and changes in inflammation using magnetic resonance imaging (MRI).

Materials and Methods: Patients who had undergone TAE between August 2020 and August 2023 for AC refractory to conservative treatments without any invasive procedures for more than 3 months, and had undergone baseline and 3-month post-AC follow-up contrast-enhanced MRI evaluations, were included. A suspension mixture of 500 mg imipenem/cilastatin in 10 mL of iodinated contrast agent was used for TAE. MRI results were analyzed to assess periarticular capsule/ligament inflammation. Clinical assessments included pain scores using the numeric rating scale (NRS) and functional scores using the quick disabilities of the arm, shoulder, and hand (Quick DASH) questionnaire.

Results: Twenty-five patients (female:male, 14:11; age, 54.9 ± 7.1 years) were included. Significant reductions in average NRS pain scores as well as improvements in Quick DASH scores and range of motion, including anterior flexion and abduction, were observed at 1, 3, and 6 months after TAE (all $P < 0.001$). MRI analyses revealed that TAE significantly decreased the grades of axillary recess capsule enhancement, rotator interval (RI) capsule T2 signal intensity, and RI capsule enhancement (all $P \leq 0.004$).

Conclusion: TAE may be an effective and safe therapeutic approach for AC refractory to conservative treatments, alleviating pain and supporting functional recovery. The observed MRI findings suggest that the effectiveness of TAE for AC may be attributed to the reduction of inflammation and the elimination of angiogenesis.

Keywords: Adhesive capsulitis; Angiogenesis; MRI; Pain; Transarterial embolization

INTRODUCTION

Adhesive capsulitis (AC) of the shoulder, also known as frozen shoulder, is characterized by painful, gradual loss of both active and passive glenohumeral motion [1]. The underlying pathology of AC is the combination of synovial inflammation and capsular fibrosis [1]. The prevalence of AC is 2%–5% and most patients are over 40 years old, with a slight female predominance [2]. Although existing therapeutic modalities for AC such as rehabilitation exercises, manipulation under anesthesia, steroid injections, shoulder hydro-dilatation, and suprascapular nerve block, offer partial pain relief, they frequently require extended treatment duration to yield substantial improvement [3].

Transarterial embolization (TAE) has emerged as a promising alternative treatment for AC, resulting in

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significant pain reduction and minimal adverse effects, and its effectiveness has been demonstrated by multiple institutions [1,4-12]. Chronic inflammation in AC decreases after TAE, as shown in recent imaging studies using fluorine-18 fluorodeoxyglucose positron-emission tomography/computed tomography (FDG-PET/CT) [13,14]. Thus, TAE is likely to exert its effects in AC by suppressing chronic inflammation.

Magnetic resonance imaging (MRI) is a valuable tool for assessing soft tissue structure and inflammatory conditions in AC. MRI features associated with the AC diagnosis exhibit a high degree of specificity and sensitivity [15-18]. However, alterations in shoulder joint structures of AC after TAE have been rarely explored using MRI [19]. Consequently, this retrospective study aimed to evaluate clinical and radiological outcomes of TAE in patients with AC, including MRI evaluation. This information may provide insights into the radiological changes associated with soft tissue structure and inflammatory conditions in patients with AC who undergo TAE.

MATERIALS AND METHODS

Patient Selection

The Institutional Review Board of our hospitals approved this retrospective study (IRB No. B-ER-113-038 and CS1-21152) and waived the requirement for informed consent. The procedures used in the study adhered to the tenets of the Declaration of Helsinki.

Patients with AC refractory to conservative treatments for more than 3 months, and undergoing shoulder TAE between August 2020 and August 2023, were initially selected. The diagnostic criteria for AC included 1) refractory shoulder pain with a numeric rating scale (NRS) ≥4, 2) limited range of motion (ROM) with a forward elevation <100 degrees and abduction <100 degrees, and 3) baseline MRI features of AC, including rotator interval (RI) enhancement, axillary capsule enhancement, inferior glenohumeral ligament (IGHL), hyperintensity on T2-weighted images (T2WIs), IGHL thickening, fat obliteration of the RI, or coracohumeral ligament thickening [17]. Patients were included if they: 1) were followed-up at 1, 3, and 6 months after TAE, and 2) underwent an MRI scan 3 months after TAE. Patients were excluded if they: 1) had MRI confirmation of other etiologies for shoulder pain, such as tendon injury or labrum tear, or 2) received additional invasive procedures, including arthroscopic capsulotomy, manipulation under anesthesia, and steroid injection, during the follow-up period.

TAE Procedure

All TAE procedures were performed by three interventional radiologists (B.W, K-W. L, and H-Y. L) with over 5 years of experience. TAE was performed under local anesthesia, and percutaneous arterial access was obtained using a 4 Fr or 5 Fr introducer sheath via the ipsilateral radial or distal brachial arteries. Subclavian and axillary digital subtraction angiography (DSA) was then performed using a 4 Fr or 5 Fr guiding catheter (J curve small tip, 4 Fr 65 cm, and Judkins Right 4 Fr 100 cm, Terumo Vietnam CO, Ho Chi Minh, Vietnam; RIM 5 Fr 100 cm, Cook Medical, Bloomington, IN, USA) and manual injection of 3–5 mL of contrast medium to locate the arteries feeding the shoulder joint.

Six major feeding arteries to the shoulder joint were identified on DSA. Selective catheterization of these branches was achieved with the guiding catheter to engage the orifice. A 1.98 Fr (ASAHI Masters PARKWAY SOFT, Asahi INTECC, Chonburi, Thailand), or 1.7 Fr microcatheter (Lambda microcatheter, Terumo Corporation, Tokyo, Japan, or Veloute microcatheter, Asahi INTECC, Irvine, CA, USA) was then advanced into a relatively distal segment. Super-selective angiography was performed with a manual, slow injection of 1–2 mL of contrast agent. If abnormal staining was observed or the patient reported typical shoulder pain during selective angiography, embolization was executed.

Embolization was performed using a suspension mixture of 500 mg imipenem/cilastatin (IPM/CS) in 10 mL of iodinated contrast agent, Iopromide (Ultravist 370, Bayer AG, Leverkusen, Germany) [6,20,21], until abnormal staining resolved on follow-up DSA. For transradial artery access, the radial artery was manually compressed with a compressive dressing (STEPTY™ P, Nichiban, Tokyo, Japan) for 10 minutes to establish hemostasis, followed by local compression using a compression device (TR band, Terumo, Tokyo, Japan). For transbrachial artery access, the arterial sheath was removed after the procedure, and the brachial artery was then manually compressed with a compressive dressing (STEPTY™ P) for 10 minutes to establish hemostasis. Subsequently, local compression using an elastic bandage and a 2 kg sandbag was applied to the brachial artery, and the elbow was immobilized in a straight position for 4 hours. Patients were discharged after a 4-hours observation period. Patients were allowed to maintain their existing conservative treatment regimens, including oral medication and physical therapy [10], but no new interventions were allowed for 6 months after TAE.

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Clinical Efficacy and Safety Outcomes

Technical success was defined as achieving selective angiography of all six arteries and delivering IPM/CS to at least one artery supplying the neovascularity. Pain severity was evaluated using the NRS, a self-report pain scale [22], at baseline, 1, 3, and 6 months after TAE. Functional changes were assessed using the quick disabilities of the arm, shoulder, and hand (Quick DASH) questionnaire at baseline, 1, 3, and 6 months after TAE. Quick DASH is a self-reported 11-item questionnaire validated for upper limb musculoskeletal (MSK) disorders [23]. Shoulder ROM, including anterior elevation and abduction, was also measured at baseline, 1, 3, and 6 months.

Clinical success was defined as a minimum 50% reduction in baseline NRS pain score at 3 months [6]. Adverse events (AEs) were classified according to the Society of Interventional Radiology guidelines [24].

MRI Scans

Shoulder MRI was performed using a standardized protocol on a 1.5T or 3T scanner (Magnetom Aera or Skyra, Siemens, Malvern, PA, USA; SIGNA Artist GE, GE Healthcare, Troy, NY, USA; or Ingenia, Philips, Amsterdam, Netherlands) with a dedicated shoulder coil. Images were acquired with a slice thickness of 3–4 mm and a 0.5 mm gap. All included patients underwent baseline MRI within two weeks prior to TAE and 3 months after TAE. A standard multiplanar multisequence MRI of the shoulder was independently reviewed by two MSK radiologists (C-Y. G and C-K. W) with more than 10 years of experience in analyzing MSK MR images, using a picture archiving and communication system (PACS; INFINITT Healthcare, Seoul, Korea). The MRI findings of AC were evaluated as previously described [15-18,25].

Qualitative MRI Measurements

Qualitative evaluation was independently conducted by two MSK radiologists as previously described [15]. Two radiologists reached a consensus on the final grade. Four qualitative measurements were rated as 0 (none), 1 (moderate), or 2 (intense). First, the signal intensity of the joint capsule in axillary recess (AR) on T2-weighted fat-saturated images was evaluated on oblique coronal images and compared with that of the same vertical portion of the long head of the biceps tendon. Second, the intensity of enhancement of the joint capsule in AR on T1-weighted fat-saturated contrast-enhanced images was evaluated on oblique coronal images and compared with the same vertical portion of the long head of the biceps tendon. Third, the signal intensity of the joint capsule in the RI on T2-weighted fat-saturated images was evaluated on sagittal images and compared to subcutaneous fat. Fourth, the intensity of enhancement of the joint capsule in the RI on T1-weighted fat-saturated contrast-enhanced images was evaluated on sagittal images.

Quantitative MRI Measurements

The two MSK radiologists independently performed quantitative measurements using a millimeter caliper on the PACS system. The final quantitative values were obtained by averaging the measurements. Joint capsule thickness in the AR was measured on coronal T2-weighted MRI at the mid-axillary pouch, humeral, or glenoid insertion. The joint capsule thickness in the RI between the subscapularis tendon and the long head of the biceps tendon was measured on sagittal T2-weighted MRI. The coracohumeral ligament at the level of the RI was measured on a sagittal T1-weighted MRI.

Statistical Analysis

Continuous variables are presented as mean and standard deviation, whereas categorical variables are presented as count and percentages. Comparisons between pre- and post-treatments were carried out by repeated measure ANOVA or paired *t*-test for quantitative data, or by McNemar–Bowker test for qualitative data. The Bonferroni post hoc test was applied when the result was statistically significant. The significance level was set as two-sided $P < 0.05$. All statistical analyses were performed using SPSS Statistics V22.0 (IBM Corp., Armonk, NY, USA). Inter-rater agreement for both qualitative and quantitative MRI measurements was assessed using the intraclass correlation coefficient (ICC) with a two-way random effect [26].

RESULTS

Patients

A total of 45 patients with AC who underwent shoulder TAE were initially screened. Among them, 20 patients were excluded because of shoulder pathologies other than AC, such as tendon injury or labrum tear (n = 5), receiving additional invasive procedures after TAE during the follow-up period (n = 5), or the lack of a 3-month MRI follow-up (n = 10). Consequently, 25 patients were included in the analysis. The flowchart illustrating patient selection is presented in Figure

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1. The baseline patient characteristics are summarized in Table 1.

Clinical Efficacy

Technical success was achieved in all patients (100%). Three patients required a second TAE procedure due to persistent pain on the 31st, 49th, and 61st days after the first TAE. Periarticular hypervascularity was identified in all procedures (100%). An average of 3.9 arterial branches were embolized, and an average of 375 mg of IPM/CS was used per TAE procedure. Clinical success was achieved in 22 of the 25 patients (88%).

The pain scores, functional scores, and use of conventional treatments before and after TAE are summarized in Table 2. The mean baseline NRS score significantly decreased from 7.0 ± 1.7 at baseline to 3.7 ± 1.5 at 1 month, 2.1 ± 1.2 at 3 months, and 1.2 ± 1.1 at 6 months (P < 0.001). The mean Quick DASH scores were 52.1 ± 20.3, 33.5 ± 13.9, 19.0 ± 11.7, and 11.5 ± 9.3 at baseline, 1-, 3-, and 6-months after TAE, respectively (P < 0.001). The degrees of anterior flexion were 98.0° ± 12,6°, 120.4° ± 15.7°, 140.0° ± 19.8°, and 152.4° ± 16.4° at baseline, 1-, 3-, and 6-months after TAE, respectively (P < 0.001). The degrees of abduction were 79.2° ± 11.9°, 105.6° ± 15.3°, 139.2° ± 21.0°, and 149.6° ± 16.2° at baseline, 1-, 3-, and 6-months after TAE, respectively (P < 0.001) (Table 2). Significant improvements in pain reduction, function, and ROM over time were observed in box-and-whisker diagrams (Supplementary Figs. 1, 2).

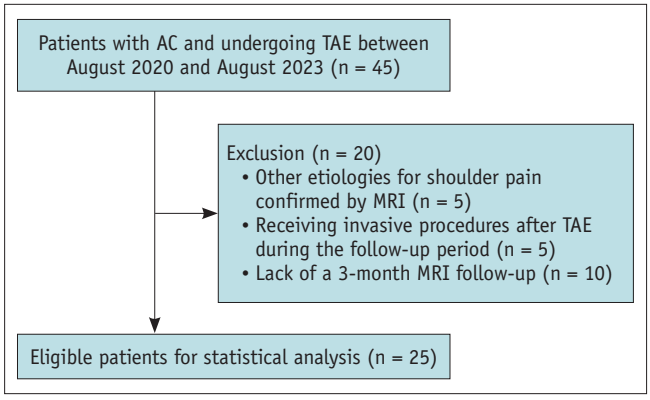

Fig. 1. Flowchart showing patient selection. AC = adhesive, TAE = transarterial embolization

Changes in MRI Parameters

The qualitative changes in shoulder MRI features before and 3 months after TAE are summarized in Table 3, and the quantitative changes in MRI features are summarized in Table 4. AR capsule enhancement, RI capsule signal intensity on T2-weighted imaging, and RI capsule enhancement were significantly different between pre-TAE and 3 months after TAE (all $P \leq 0.004$) based on the grading of qualitative MRI measurements. The AR capsule thickness of humeral (4.0 ± 1.3 mm vs. 3.3 ± 0.8 mm), AR capsule thickness of glenoid (4.8 ± 1.2 mm vs. 4.5 ± 1.3 mm), RI capsule thickness (4.8 ± 1.3 mm vs. 4.2 ± 0.8 mm),

Table 1. Patients characteristics for 25 patients analyzed

Patient characteristics	Data
Age, yrs	54.9 ± 7.1
Sex, female:male	14:11
Body mass index, kg/m^2	25.0 ± 4.4
Symptom duration, mos	12.0 ± 5.0
Nighttime pain	22 (88)
Smoke	5 (20)
Diabetes mellitus	7 (28)
Laterality, right:left	11:14
NRS score of pain in shoulder (0–10)	7.0 ± 1.7
Prior treatment (within 1 month)	
Rehabilitation	22 (88)
Oral NSAIDs	19 (76)
Local steroid injection	20 (80)

Data are presented as mean ± standard deviation or number of patients with the percentage in parentheses.
NRS = numerical rating scale, NSAIDs = nonsteroidal anti-inflammatory drugs

Table 2. The changes in pain scores, functional scores, and use of conventional treatments after transarterial embolization for 25 patients

	Baseline	1 month	3 months	6 months	P*
NRS score (0–10)	7.0 ± 1.7	3.7 ± 1.5	2.1 ± 1.2	1.2 ± 1.1	<0.001
Quick Dash score (0–100)	56.1 ± 20.3	33.5 ± 13.9	19.0 ± 11.7	11.5 ± 9.3	<0.001
Range of motion					
Anterior flexion (°)	98.0 ± 12.6	120.4 ± 15.7	140.0 ± 19.8	152.4 ± 16.4	<0.001
Abduction (°)	79.2 ± 11.9	105.6 ± 15.3	139.2 ± 21.0	149.6 ± 16.2	<0.001

Data are presented as mean ± standard deviation.
*Repeated measures ANOVA. Bonferroni post hoc test has been applied between each time-point and the result remained statistically significant.
NRS = numerical rating scale

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and CHL thickness (3.8 ± 1.4 mm vs. 3.5 ± 1.3 mm) were significantly decreased after TAE (all $P \leq 0.012$), based on quantitative MRI measurements. Two representative cases demonstrating MRI changes before and after TAE are presented in Figure 2 and Supplementary Figure 3.

Safety

We identified no severe AEs. Mild AEs included puncture-site hematoma (n = 5, 20%), cutaneous erythema (n = 6, 24%), and post-embolization ischemic pain (n = 9, 36%), which resolved within 2 weeks after taking painkillers [27].

Inter-Rater Reliability

The calculated ICC values for qualitative MRI measurements ranged from 0.77 to 0.93, and the ICC values for quantitative MRI measurements ranged from 0.84 to 0.97, indicating strong consistency in inter-observer measurements.

Table 3. Qualitative changes in shoulder magnetic resonance image features 3 months after TAE for adhesive capsulitis for 25 patients

	Before TAE	Post TAE	*P**
AR capsule T2 signal intensity			0.070
Grade 0	10 (40)	15 (60)	
Grade 1	10 (40)	9 (36)	
Grade 2	5 (20)	1 (4)	
AR capsule enhancement			<0.001
Grade 0	1 (4)	12 (48)	
Grade 1	8 (32)	7 (28)	
Grade 2	16 (64)	6 (24)	
RI capsule T2 signal intensity			0.002
Grade 0	1 (4)	5 (20)	
Grade 1	13 (52)	20 (80)	
Grade 2	11 (44)	0 (0)	
RI capsule enhancement			0.004
Grade 0	0 (0)	4 (16)	
Grade 1	10 (40)	17 (68)	
Grade 2	15 (60)	4 (16)	

Data are number of patients, with the column percentage in parentheses.
*McNemar–Bowker test.
TAE = transarterial embolization, AR = axillary recess, RI = rotator interval

Table 4. Quantitative changes in shoulder magnetic resonance image features 3 months after TAE for adhesive capsulitis for 25 patients

	Before TAE	Post TAE	*P**
AR capsule thickness, humeral, mm	4.0 ± 1.3	3.3 ± 0.8	<0.001
AR capsule thickness, glenoid, mm	4.8 ± 1.2	4.5 ± 1.3	0.012
RI capsule thickness, mm	4.8 ± 1.3	4.2 ± 0.8	<0.001
CHL thickness, mm	3.8 ± 1.4	3.5 ± 1.3	<0.001

Data are presented as mean ± standard deviation.
*Paired *t*-test.
TAE = transarterial embolization, AR = axillary recess, RI = rotator interval, CHL = coracohumeral ligament

DISCUSSION

This study investigated the effectiveness of TAE for AC. We observed improvements in pain reduction, functional scores, and ROM. Technical success was achieved in all patients. No major AEs were reported, indicating the safety of shoulder TAE. Clinical success, defined as >50% pain reduction at 3 months after TAE compared to baseline, was achieved in 88% of the patients. In the pathogenesis of AC, inflammation is involved in synovial hyperplasia and hypervascularity [28]. Although TAE can reduce angiogenesis and exert anti-inflammatory effects, fibrosis is still present in the pathophysiology of capsular contracture, which might be responsible for the poor response to TAE in 12% patients. To sum up, these findings align with previous studies on treating chronic shoulder pain with TAE [6,12,29-31].

AC is often characterized by three phases: the freezing phase (pain and loss of motion of the glenohumeral joint in all directions), the frozen phase (maximum stiffness), and the thawing phase (ROM returns to normal) [32]. Night pain and stiffness are common clinical presentations of AC in the freezing and frozen phases, respectively [32,33]. Spontaneous resolution of frozen shoulders typically occurs, but takes time. Joint mobility returns to normal in 18–54 months in most patients, but 10%–50% of patients only have a partial recovery over this time period [2]. In this study, patients with AC refractory to conservative treatment for more than 3 months underwent shoulder TAE due to chronic shoulder pain. These patients were unlikely to have a spontaneous functional full recovery.

AC is characterized by a multidirectional limitation of both active and passive shoulder movement. MRI is a valuable tool for evaluating soft tissue edema and has been used to confirm the diagnosis of AC [17]. Six informative MRI features were found to be useful for diagnosing AC, all of which have a diagnostic odds ratio greater than 1 [17]. Enhancement of the RI and axillary joint capsule, as well as hyperintensity of the IGHL on T2WI, have high sensitivities and specificities (over 80%) [17].

Several studies have demonstrated correlations between MRI findings (such as periarticular capsule/ligament edema, enhancement, or thickness) and clinical features in patients

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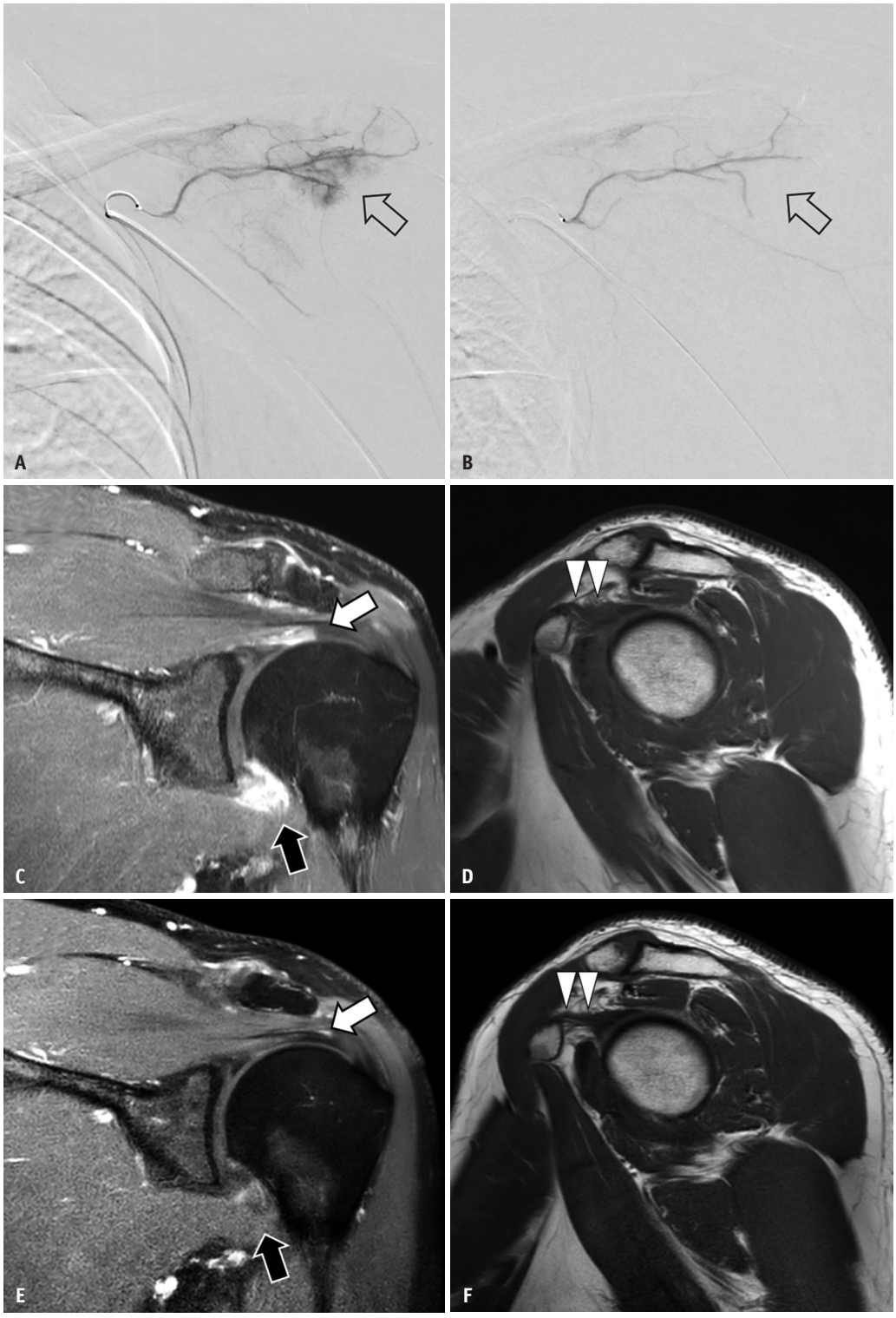

Fig. 2. Selective angiography demonstrating successful transarterial TAE with imipenem/cilastatin for abnormal angiogenesis in a 57-year-old male patient with adhesive capsulitis in the left shoulder. **A:** DSA via the right thoracoacromial artery shows blush-like abnormal neo-vessel formation at the rotator interval before TAE (arrow). **B:** DSA via the right thoracoacromial artery demonstrates elimination of the neo-vessels after TAE (arrow). **C, D:** Pre-TAE MRI scans show vivid capsule enhancement (arrows, **C**) on oblique coronal T1-weighted fat-saturated contrast-enhanced image and fat infiltration within the rotator interval on oblique sagittal T1-weighted fat-saturated (arrowheads, **D**), indicative capsulitis and synovitis with inflammation and edema. **E, F:** Post-TAE MRI scans demonstrate significant decrease in the enhancement (arrows, **E**) and decrease in fat infiltrates within the rotator interval (arrowheads, **F**), indicating reduced infiltrates/edema. Additionally, a decrease in capsule thickness is observed in both areas. TAE = transarterial embolization, DSA = digital subtraction angiography

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with AC [34-37]. In the present study, all patients exhibited abnormal blood vessel growth in the axilla and/or the RI region on angiography. Additionally, pre-treatment MRI showed edema, enhancement, or increased thickness in the periarticular capsule and ligaments. After TAE treatment, qualitative measurements indicated a decrease in edema and/or enhancement, and quantitative measurements demonstrated decreased thickness of the capsule on both the humeral and glenoid sides at the AR, the capsule at the RI, and the coracohumeral ligament. The remaining MR T2 signal/enhancement may indicate ongoing inflammation or edema in the early stage of AC, rather than fibrosis or scarring in the late stage [34,35]. Anti-inflammatory treatments, such as a second embolization or intra-articular steroid injection, may be applied for further clinical improvement.

These changes in MRI, along with clinical improvement, suggest that TAE may reduce inflammation in the affected shoulder joints of patients with AC. Supporting this notion, a study using a rat model of frozen shoulder demonstrated that abnormal blood vessel growth and inflammatory cell accumulation in the affected shoulder were decreased after TAE [14]. In addition, a recent study reported that TAE may reduce inflammation by decreasing FDG uptake and MR contrast enhancement in patients with AC [13]. Additionally, the decrease in FDG uptake is significantly correlated with pain score reduction [13].

Two previous studies investigated MRI changes after TAE in patients with chronic shoulder pain [13,30]. Although both studies reported a decrease in synovial inflammation or joint effusion in some patients, their methods of interpreting the MRI findings were unclear and their observations were not supported by statistical analyses [13,30]. In contrast, our study employed a well-established qualitative grading system for shoulder inflammation and included quantitative measurements of capsule/ligament thickness on MRI. This more rigorous approach allowed us to demonstrate clear associations between specific MRI changes and improvements in patients' clinical symptoms. These findings may facilitate the development of a more objective assessment of the inflammatory state in patients with AC, thereby improving post-TAE management.

This retrospective study had several limitations. First, it was a single-arm study without a control group; therefore, the placebo effect on clinical outcomes, such as pain and functional scores, could not be evaluated. Second, the present retrospective study involved a small number of patients, and the possibility of reporting incomplete data cannot be ruled out. Third, the classification of hypersignality and enhancement intensity is arbitrary. Finally, different MRI machines with varying magnetic field strengths (1.5T and 3T) were used across patient examinations, introducing potential discrepancies in image interpretation. Hence, large-scale prospective studies using the same MRI machine and data integrity are warranted to confirm the findings of this retrospective study.

In conclusion, this study shows that shoulder TAE may be a viable treatment option for AC refractory to conservative treatments, exhibiting a favorable safety profile and promising effectiveness. The reduction in periarticular edema, enhancement, and thickness observed on follow-up MRI indicates that TAE may help alleviate chronic inflammation in the affected shoulder joint, potentially benefiting patients with AC.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2024.0883.

Availability of Data and Material

All relevant data are within the manuscript and its supporting information files.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Keng-Wei Liang, Bow Wang. Data curation: Keng-Wei Liang, Bow Wang. Formal analysis: Keng-Wei Liang, Bow Wang. Funding acquisition: Chien-Kuo Wang, Wei-Ren Su. Investigation: Keng-Wei Liang, Hsuan Yin Lin, Bow Wang. Methodology: Keng-Wei Liang, Bow Wang. Project administration: Keng-Wei Liang, Chien-Kuo Wang, Wei-Ren Su, Bow Wang. Resources: Keng-Wei Liang, Hsuan Yin Lin, Kai-Lan Hsu, Fa-Chuan Kuan, Bow Wang. Software: Keng-Wei Liang, Bow Wang. Supervision: Keng-Wei Liang, Chien-Kuo Wang, Wei-Ren Su, Bow Wang. Validation: Keng-Wei Liang, Chia-Yu Gean, Chien-Kuo Wang, Bow Wang. Visualization: Keng-Wei Liang, Bow Wang. Writing—original draft: Keng-Wei Liang, Bow Wang. Writing—review & editing: all authors.

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