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Adverse events after mRNA vaccine administration from a busy orthopedic practice: a series of four cases

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MRNA technology is not new, but with the COVID-19 pandemic, it is the first time it has been used on a large-scale basis in humans. The mRNA vaccines, BNT162b2 and mRNA-1273, have both demonstrated a high efficacy rate and acceptable safety profile which led to emergency approval. Nevertheless, there have been several news reports and some publications documenting the side effects of COVID-19 vaccination. Many of these side effects are known effects of other types of vaccinations and were documented in the vaccine trials.[2,10] However, there have been some novel side effects related to the modulation of the immune system. These include facial swelling in patients with a history of facial cosmetic dermal filler injections[4] and herpes zoster in patients with autoimmune inflammatory rheumatic diseases.[5]

To date, there have been no publications describing musculoskeletal side effects. In this article, we present 4 shoulder cases that may have been impacted by mRNA vaccine administration. Of the 4 cases, 2 patients incurred a postoperative infection possibly related to vaccine administration, whereas the other two patients experienced functional loss related to vaccine administration.

Case #1

The first patient was a 58-year-old right-hand-dominant man who initially presented to our clinic 4.5 years before with a left shoulder rotator cuff tear. This injury was treated conservatively for 3.5 years until he underwent arthroscopic rotator cuff repair by the primary surgeon in March 2020, just before the COVID-19 pandemic. A double-row transosseous equivalent technique was used with 4.5-mm PEEK anchors in the medial row and 4.75-mm PEEK anchors in the lateral row. His postoperative course was unremarkable, and he had an excellent functional recovery.

The patient presented with right shoulder pain in February 2021, which had worsened after a recent fall. A full-thickness supraspinatus tear was confirmed on magnetic resonance imaging (MRI) (Fig. 1). He underwent arthroscopic right shoulder rotator cuff repair in March 2021. An identical technique with the same anchor pattern as the prior surgery was used for the contralateral shoulder. At his first postoperative visit for the right shoulder on postoperative day (POD) 10, he commented that the postoperative pain in the right shoulder was much less than the postoperative pain experienced in the left shoulder the prior year.

On POD 46, the patient contacted the office stating that he had been doing well until he received his second vaccination of the BNT162b2 mRNA vaccine on POD 38 in his left, not recently operated shoulder. He stated that soon after the vaccination, he started feeling fatigued and malaise with fever. He also noticed a significant increase of pain in the right arm, with redness and streaking distal to his right shoulder within two days of the vaccination. The malaise subsided after a few days, but the shoulder pain and discoloration symptoms worsened during this time.

The patient returned to the clinic on POD 47. Peripheral laboratory values were drawn to assess for infection (Table I). He was sent for both MRI and a fluoroscopically guided aspiration of the shoulder

The Texas Orthopedic Hospital Institutional Review Board approved this study (TOH192).

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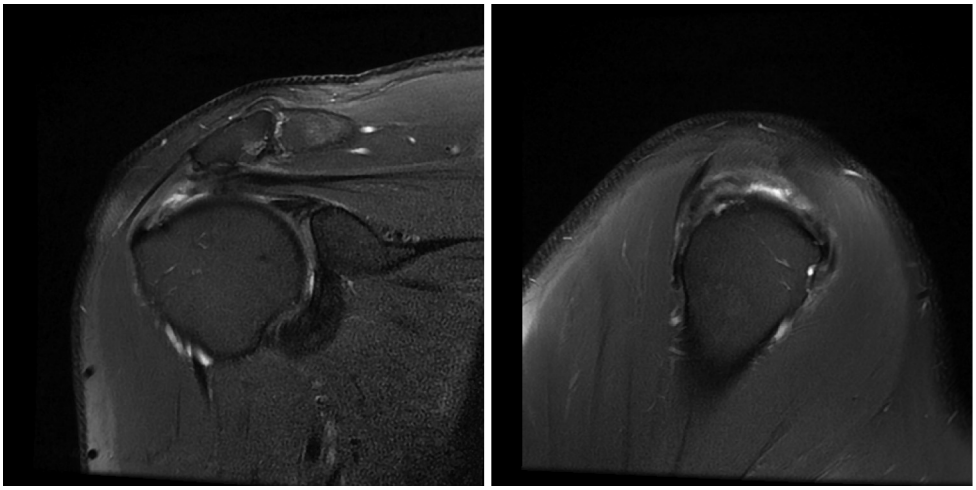

Figure 1 Preoperative MRI images confirming a full-thickness supraspinatus tear. *MRI*, magnetic resonance imaging.

joint. The aspirate yielded little fluid, mainly blood, but was still sent for analysis. The MRI demonstrated a large loculated fluid collection in the subacromial space with disruption of the rotator cuff repair and lucency around the previously placed anchors (Fig. 2).

On POD 49, he underwent arthroscopic débridement with hardware removal. Operative findings included a failure of the rotator cuff repair. The anchors were loose because of the surrounding destruction of bone but were not displaced. There was moderate reactive bursitis, and the arthroscopy fluid was initially cloudy, but there was no gross purulence or efflux of fluid with placement of the trochar and cannula or with the initial visual assessment. During the procedure, cultures were obtained from the reactive bursitis. The sutures and anchors were removed and sent along with the cultures. Antibiotic treatment was not initiated until all cultures were obtained.

A repeat arthroscopy and débridement were performed 2 days later. A peripherally inserted central catheter line was placed, and the patient was started on empiric antibiotics. The final Gram stain was negative. The cultures were held for 21 days and also remained negative. The patient was treated with 8 weeks of intravenous antibiotics for presumed *Cutibacterium acnes*. At 4 months after débridement and 8 weeks after conclusion of IV antibiotics, the patient underwent a revision rotator cuff repair, and postoperative recovery was unremarkable. The patient currently has little to no pain at 160 degrees of active elevation.

Case #2

The second case was a 68-year-old right-hand-dominant man with controlled type II diabetes. He has been followed by the primary surgeon for over 10 years for bilateral shoulder osteoarthritis. He underwent a right shoulder arthroscopic débridement with biceps surgery after 6 years of conservative treatment. He continued to have pain and presented for definitive shoulder arthroplasty 4 years later. He had not received any prior cortisone injections or invasive treatment to the shoulder since the arthroscopic procedure. A preoperative computed tomography scan was obtained to confirm the diagnosis and allow for templating for shoulder arthroplasty.

He underwent routine right shoulder anatomic total shoulder arthroplasty in early March of 2021. His postoperative course initially was unremarkable. Prophylactic clindamycin had been given. He was also given 2 more doses while in the hospital. His serum glucose levels were well controlled while in the hospital. He was discharged home on POD 1.

Table I
Peripheral laboratory values for case #1 on POD 47.

Test	Value	Normal
White blood cell count (WBC)	7.2	5.7-10.5
Erythrocyte sedimentation rate (ESR)	45*	0-15
C reactive protein (CRP)	2.2*	<.9

POD, postoperative day.
*Outside of normal range.

At his first postoperative visit on POD 14, he commented that his pain was surprisingly better than he thought it would be. He had some initial issues with constipation that had resolved, but otherwise unremarkable.

The patient then called on POD 50, stating that he had developed some redness surrounding his incision. He explained that he was doing well until POD 25 when he received his second mRNA-1273 injection in his left (nonoperative) shoulder. He stated that he felt significant malaise after the injection for several days. He also noticed an almost immediate increase in his right shoulder pain at that time which had persisted. He had not been taking narcotics for several weeks, but he now needed narcotics to manage the pain.

Examination of his wound demonstrated an apparent central abscess. A computed tomography scan was obtained looking for a deep abscess which was not identified. A fluoroscopically guided aspiration was also performed. Only 1 mL of bloody fluid was aspirated and was sent for culture and Gram stain. The peripheral laboratory values are in Table II.

The patient was then immediately taken to the operating room on POD 51 for open irrigation and débridement. It was noted to be superficial purulence which did track down to disrupt 30% of the subscapularis repair. There was no evidence of intra-articular purulence. More cultures were taken before antibiotic administration. The implants were well fixed and retained. A second open irrigation and débridement were performed on POD 53. The aspirate from POD 50 included testing for alpha defensin, which was positive. The cultures grew *C acnes* at 2 weeks after surgery, and oral antibiotics were prescribed.

The patient completed the course of oral antibiotics at 6 months after surgery. At clinical follow-up, the patient had regained 130 degrees of active elevation and reported less pain in the surgical

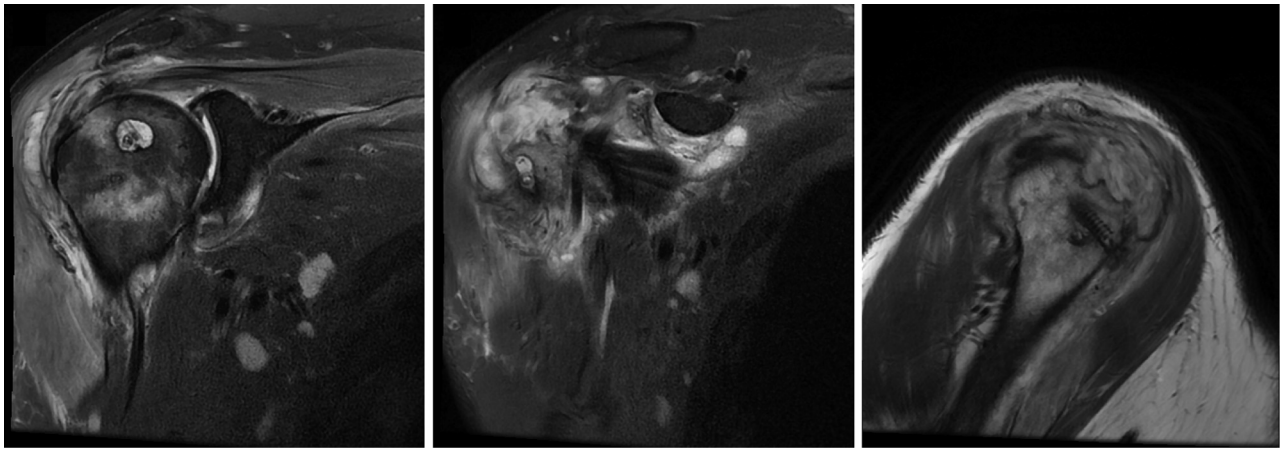

Figure 2 Postoperative MRI images on POD 47 showing a large loculated fluid collection in the subacromial space with disruption of the rotator cuff repair and lucency around the previously placed anchors. *MRI*, magnetic resonance imaging; *POD*, postoperative day.

Table II
Peripheral laboratory values for case #2 on POD 50.

Test	Value	Normal
White blood cell count (WBC)	8.2	5.7-10.5
Erythrocyte sedimentation rate (ESR)	50*	0-15
C reactive protein (CRP)	1.4*	<.9

POD, postoperative day.
*Outside of normal range.

shoulder than the contralateral shoulder which also has known glenohumeral osteoarthritis.

Case #3

The third case was an 80-year-old right-hand-dominant man with a history of right anatomic shoulder arthroplasty in September 2018. At the time of surgery, a soft tissue mass was identified over his bicipital groove. It was completely removed and sent for pathology. He was diagnosed with lymphoma and underwent postoperative chemotherapy. Because of his treatment for the lymphoma, his last visit was in December 2018. At that time, he had 90 to 100 degrees of active forward elevation, and his pain was well controlled.

He was not seen again until May of 2021. He stated that his shoulder was doing well until 6 weeks before, when he received the second dose of the BNT162b2 vaccination in his left, nonoperative arm. He subsequently developed shingles in his right upper extremity and face. In addition, he noticed that he lost the ability to raise his right arm. The shingles lesions had now resolved, but he was still unable to raise the arm, and he had significant pain in the shoulder. Active forward flexion was 0 with passive forward flexion to 120 degrees. He had significant deltoid atrophy on examination. An electromyography (EMG) had been ordered by another physician and was performed 3 days before his clinic visit, within 6 weeks of the onset of his symptoms. The results showed mild median, ulnar, and radial nerve neuropathy, whereas the axillary nerve showed normal function. An MRI ordered by an outside physician showed mild atrophy and fatty infiltration of the subscapularis and supraspinatus. The deltoid was difficult to assess because of signal artifact from the prosthesis.

As of June 2021, he is being managed with physical therapy and will have a repeat EMG 3 months from the onset of his symptoms. He has been improving slowly from physical therapy and is gradually regaining active shoulder function.

Case #4

A 58-year-old right-hand-dominant woman presented with left shoulder pain in mid-May 2021. She received the first dose of the mRNA-1273 vaccine 33 days before her clinic visit, after which she developed immediate pain that worsened over time. She could no longer raise her shoulder, and she subsequently developed patches of numbness over her forearm. She does have a history of type II diabetes that is not well controlled. Her hemoglobin A1c was 13.0 two months before (normal <6.0).

An MRI of the left shoulder performed 17 days after vaccination demonstrated a 30-mm paralabral cyst associated with the anterior glenoid labrum.

She had no atrophy on physical examination but was hypersensitive to light touch over the arm and forearm. Active forward elevation was to 60 degrees. An EMG was performed which was consistent with left neuralgic amyotrophy (brachial plexitis or Parsonage-Turner syndrome). She is being treated currently with physical therapy.

Discussion

All surgeries have a risk of infection and other complications; however, the risk of infection for orthopedic cases is low. Specifically, infection after rotator cuff repair is very rare, with a reported prevalence of 0.006% to 3.4%.[1,11] Systemic factors can influence the infection rate and include malnutrition, renal failure, liver failure, diabetes mellitus, chronic hypoxia, malignancy, immunodeficiency, immunosuppression, advanced age, tobacco use, and IV drug use.[11]

Comorbidities for case #1 are hypercholesterolemia and hypertension, but otherwise, the patient is healthy. He had undergone a prior rotator cuff repair of his left shoulder 1 year before with no complications. On the day of his right shoulder surgery, another patient with more comorbidities including diabetes also had a rotator cuff repair and has had no complications. The primary surgeon has had one prior rotator cuff repair infection in 18.5 years. This infection can certainly be explained statistically based on an expected infection rate of rotator cuff repair. However, the temporal association with the second vaccination is difficult to ignore.

The risk of infection in primary shoulder arthroplasty is approximately 1%.[12] The most common organism causing infection in total shoulder arthroplasty is *C acnes*, which accounts for approximately 39% of infections in shoulder arthroplasty.[9] The risk

factors of shoulder prosthetic joint infections include male sex, higher body mass index, and younger age at the time of the index procedure.[9]

Our case #2 has a history of well-controlled type II diabetes and no other risk factors. He had not received prior injections in the shoulder. Similar to the patient in case #1, he had little to no pain initially, but the pain significantly increased after a second mRNA injection for COVID-19. Another patient had a reverse shoulder arthroplasty on the same day as the index surgery and has had no complications. In addition, the primary surgeon has only had two primary arthroplasty infections in 18.5 years, which were both reverse arthroplasty for fracture cases. This is the first primary anatomic shoulder arthroplasty to present with infection. Similar to case #1, the temporal association with the second vaccination is difficult to ignore when evaluating case #2.

The third case in this series developed shingles after mRNA vaccination. This adverse event has been reported by Furer et al in patients with autoimmune inflammatory rheumatic disease.[5] Case #3 is unique in that shingles resulted in profound loss of function in the shoulder that underwent arthroplasty over 2.5 years before. The patient has known severe glenohumeral osteoarthritis on the contralateral shoulder which received the vaccination but did not have any adverse events on that side. In addition, this patient has other comorbidities and has undergone prior chemotherapy and radiation therapy on the surgical shoulder, possibly adding to the increased risk for right-side involvement. In this case, the shingles occurred on the extremity that had prior radiation therapy. Nevertheless, this case illustrates that the mRNA vaccine may cause some type of modulation of the immune system that allows previously suppressed pathology to manifest itself.

Patient #4 was diagnosed with neuralgic amyotrophy and had significant comorbidity with uncontrolled insulin-dependent diabetes mellitus. It is not clear if this played a role in her reaction to the vaccine, as uncontrolled diabetes is well known to adversely impact several other organ systems including the kidney, eyes, vascular system, and peripheral nervous system.[6] In addition, this type of nervous system reaction is not necessarily specific to mRNA vaccines, but her presentation illustrates the concept that an mRNA vaccine can have an impact on the immune system, leading to complications.

The 4 cases presented here represent possible musculoskeletal adverse events that will be evaluated in orthopedic clinics. These types of reactions are not unique to orthopedics, and anecdotal reports are beginning to be found in the literature. In a review of dermatologic reactions, McMahon et al reported 10 cases of shingles after the first or second dose of the mRNA vaccine.[7] Shingles was considered a less common adverse event in the report of 414 adverse reactions which primarily included local cutaneous reactions. In a cohort of patients after cardiothoracic surgery, Merritt-Genore et al recommended that patients recover from surgery and postoperative complications before vaccination. The rationales were to allow a robust immune response to the vaccination and to avoid possible diagnostic confusion as to whether a symptom was a surgical complication or vaccine adverse event.[8] Overall, there have been millions of mRNA vaccinations administered, and these types of adverse events are rare. However, orthopedic surgeons need to be aware of the possibility to better treat their patients.

Conclusions

In the United States, approximately 300 million doses of the mRNA vaccines, BNT162b2 and mRNA-1273, have been administered as of June 2021.[3,13] Most of the individuals receiving the mRNA vaccines experience only minor and/or well-documented side effects. The cases presented here represent possible musculoskeletal adverse events that will be evaluated in orthopedic clinics. Fortunately, these cases are rare, but orthopedic surgeons need to be aware of this possibility to better treat their patients.

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