

# COVID-19 Vaccination Delayed Hypersensitivity Reaction Pseudo-tumor

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**INTRODUCTION:** Delayed hypersensitivity reactions (DHR) have been associated with COVID-19 vaccines, especially with the mRNA-1273 (Moderna) vaccine. The initial Moderna trials reported DHR in 0.8% of patients after the first dose and 0.2% after the second dose. DHR, also known as adverse cutaneous events, present > four hours post-vaccination. DHR from COVID-19 mRNA-based vaccines may vary from localized injection-site skin reactions to generalized symptoms that include rash, urticaria, or bullous pemphigoid with onset of eight days. Typical morphology ranges from erythematous patches to large plaques, and lesion diameters typically range from 5 to 20 centimeters (cm). However, the appearance of benign soft-tissue masses (pseudo-tumor) at the injection-site is a rarely reported adverse event. We present clinical, imaging and available pathology for three pseudo-tumors in two patients secondary to DHR to the Moderna vaccine, each of which caused concern regarding neoplastic etiology.

**METHODS:** Retrospective chart review on two patients, one observed and the other who contacted our orthopedic department, was accomplished to collect demographic, clinical presentations, imaging, labs, treatment, and follow-up data. Consent was obtained from each patient.

**RESULTS SECTION:** Demographics and clinical presentations of each patient can be seen in Table 1. The first patient, a 53-year-old female, presented with an eight-month history of firm, posterior-lateral, bilateral upper-arm pseudo-tumor. Right shoulder magnetic resonance imaging (MRI) showed subcutaneous edematous tissue from the humeral surgical neck to the distal diaphysis (Figure 1A). MRI of the left shoulder was obtained due to persistent swelling and showed similar edema but in an intramuscular rather than subcutaneous location (Figure 1B). The second patient, a 49-year-old male, presented with a two-month history of a firm pseudo-tumor in the right biceps muscle region. MRI of the right arm showed a mass in the short head of the biceps with mild hemorrhagic fluid (Figure 1C). A needle biopsy obtained for an indeterminate neoplasm showed fibromuscular tissue with chronic lymphohistiocytic inflammatory infiltrate with mixed T and B cell population.

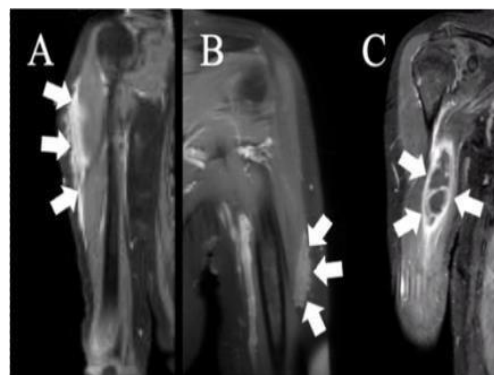
**DISCUSSION:** The incidence of COVID-19 vaccination DHR cutaneous involvement is estimated at 1%-2%. To date, there has been only one other case of the Moderna vaccine inducing a pseudo-tumor. Etiology of COVID-19 vaccine-related DHR has been attributed to key vaccine ingredients but without a specific component identified. Inoculation of PEG, an ingredient in the Moderna vaccine, in a rabbit aorta model resulted in intense granulomatous reactions. Existing literature on PEG-related allergy from its use in cosmetics and drugs suggest it as a possible culprit of COVID-19 vaccine DHR. However, patients with existing allergies to PEG have been safely administered with the mRNA-based Pfizer vaccine. The lipid components of the mRNA vaccine have also been proposed as a contributing agent due to their role in complement-mediated activation of the acute phase response. Histologic examinations from the first reported case of a pseudo-tumor and from our second case found local perivascular mixed infiltrate of predominantly CD3+ T cells and eosinophils. DHR are delayed T-cell mediated reactions. Sensitized T lymphocytes release cytokines to activate macrophages into epithelioid histiocytes that form granulomas, nodular collections of epithelioid histiocytes, lymphocytes, and giant cells. Eosinophils facilitate this reaction to foreign antigens by releasing histamine to increase vascular post-capillary venule permeability to granulocytes and monocytes. It is this secondary edematous response to DHR that is hypothesized to have led to the palpable pseudo-tumors in these patients. The consistent finding of edema on MRI, whether in the subcutaneous tissue or the muscle, reflects that edematous tissue response. In the correct clinical context, this MRI appearance may be sufficient to allow observation rather than invasive procedures to establish diagnosis. However, when any doubt remains, biopsy will show absence of neoplasm and presence of an inflammatory response, as it did in patient 2. DHR from COVID-19 vaccines have been mostly associated with the Moderna vaccine, and the appearance of pseudo-tumor is a very rare complication that has been only associated with the Moderna vaccine.

**SIGNIFICANCE/CLINICAL RELEVANCE:** Pseudo-tumors due to DHR are rare manifestations of COVID-19 vaccination for which the key vaccine components linked to the granulomatous reactions remain unknown. Clinicians should be aware of the pseudo-tumorous appearance in the context of history of COVID-19 vaccination in the region of a soft tissue mass.

## IMAGES AND TABLES:

**Table 1.** Patient demographics and clinical presentations.

	Age	Sex	Past Medical History	Injection Site	Type of Vaccine and Attributed Dose to DHR	Constitutional Symptoms
Patient 1	53	Female	None	Right Shoulder Left Shoulder	Moderna, 1 <sup>st</sup> dose Moderna, 2 <sup>nd</sup> dose	None
Patient 2	49	Male	Lipoma x2	Right Biceps	Moderna, Booster	Fatigue Malaise Hyperpnea
	Pseudo-Tumor Onset (months)	Pseudo-Tumor Characteristics		Size of Pseudo-Tumors (centimeters)	Treatment	Time of Resolution (months)
Right Shoulder	3	Painful, Pruritic, Indurated, Tender		14.9 x 8.2 x 1.8	Tylenol	8
Left Shoulder	2			5.6 anterior-posterior x 1.0 medial-lateral	Observation	
Right Biceps	6	Painless, Heavy, Solid, Non-pruritic		7.4 x 3.7 x 2.6	Advil Tylenol Needle Biopsy	2



**Figure 1.** MRIs taken postvaccination. Case 1: A (right)-B (left). (A) Coronal T2 image shows subcutaneous edema (arrows). (B) Coronal T1W FS image shows intramuscular edema within the lateral deltoid muscle (arrows). Case 2: (C) Coronal T1W FS postcontrast image shows intramuscular edema within the short head right biceps (arrows).