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Case Reports

Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA) Following SARS-CoV2 Vaccination

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A 67-year-old man presented with joint swelling, muscular weakness, pain and anemia after the second dose of BNT162b2 (Pfizer-Biontech) mRNA COVID-19 vaccination. The signs and symptoms in the case met criteria for post-vaccination polymyalgia rheumatica (PMR) and Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA) demonstrating the close association between these two conditions. The patient underwent a broad workup to rule out other causes and improved with corticosteroid therapy. Vaccine-associated autoimmune syndromes likely have heterogenous presentations and require a high index of suspicion to expedite recognition and treatment.

INTRODUCTION

Inflammatory symptoms following vaccinations are commonly encountered and include fever, myalgia, and arthralgia and injection site reactions. The widespread use of COVID-19 vaccination has raised awareness of specific post-vaccination inflammatory syndromes including Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA), multisystem inflammatory in adults and children (MIS-A/C), myocarditis and pericarditis, Guillain-Barre syndrome, polyarthritis, rheumatoid arthritis, systemic lupus erythematosus, giant cell arteritis and polymyalgia rheumatica (PMR).[1–5]

CASE PRESENTATION

A 67-year-old man with past medical history of cervical stenosis, bilateral knee arthritis and hypertension presented to his primary care physician's office with four weeks of progressive left ankle swelling without pain, rash, or erythema. He also reported mild right ankle swelling, not as prominent as on the left. His physical examination confirmed these complaints and was otherwise unremarkable. He was up to date on preventative screening and immunizations, completing the second dose of BNT162b2 (Pfizer-Biontech) mRNA COVID-19 vaccination two months prior. His home medications included atorvastatin, benazepril/amlodipine, and diclofenac gel as needed. He denied fevers, chills, chest pain, shortness of breath, abdominal pain, nausea, vomiting, diarrhea, constipation, melena, hematochezia, or rash. Ultrasound of the lower extremities was negative for deep venous thrombosis.

Six weeks later, he reported increased ankle swelling bilaterally, morning stiffness and an interval 10 lb (4.5kg) unintentional weight loss. His review of systems was otherwise unchanged from his previous admission. His exam was notable for 2+ pitting edema of the lower extremities up to mid shin bilaterally. Mucous membranes were moist and without lesions. There was no rash, conjunctival erythema, joint erythema, or joint tenderness. A small joint effusion was noted over the right knee. Laboratory studies (**Table 1**) obtained to evaluate ankle swelling and weight loss revealed significant anemia (serum hemoglobin 9.5g/dL). His hemoglobin and hematocrit one year previous were 14.8g/dL and 44%, respectively. Urinalysis in the past and during this presentation was normal.

A workup for gastrointestinal blood loss including esophagogastroduodenoscopy, colonoscopy, and video capsule endoscopy was unremarkable. A computed tomography (CT) scan of the abdomen and pelvis revealed no significant findings to explain his anemia or weight loss. There was no change in his lower extremity swelling. An echocardiogram revealed left ventricular ejection fraction of 60% with mild aortic stenosis.

The patient then noticed progressive proximal weakness of all extremities along with bilateral decreased grip strength. He started using a cane to walk and to stand from a seated position. He also reported aching sensations of his arms and hands. A rheumatologic work up and repeat iron studies after six weeks of oral iron therapy were done (**Table 1**). Further work-up, including a computed tomography (CT) scan of the chest with contrast, urine and serum protein electrophoresis, serum kappa/lambda free light chains were performed and were unremarkable. Positron emission tomography (PET) scan revealed mildly hypermetabolic/mildly enlarged right external iliac lymph nodes with benign morphology and diffuse increased uptake in the soft tissues surrounding bilateral shoulder and hip joints.

Table 1. Initial and subsequent laboratory testing

Variable	Value	Reference Range
Initial:		
Hemoglobin	9.5g/dL	13.7-17.5g/dL
Hematocrit	31%	40-51%
MCV	85fL	80-95 fL
CRP	169 mg/L	0-8mg/L
ESR	75 mm/hr	0-20mm/hr
Iron	16 ug/dL	45-170 ug/dL
Total iron binding capacity	220 ug/dL	250-450 ug/dL
Transferrin saturation	7 %	20-50%
Ferritin	1059 ng/mL	20-250ng/mL
Fecal Occult Blood test	Positive	Negative
After 6 weeks:		
Iron	8 ug/dL	45-170 ug/dL
TIBC	211 ug/dL	250-450 ug/dL
Transferrin saturation	4 %	20-50%
Ferritin	1119 ug/mL	20-250ng/mL
Reticulocyte Index	0.74	>2 – Adequate response <2 – Inadequate response
ANA	Negative	Negative
Anti-Double Stranded DNA	1 IU/mL	0-4 IU/mL
Rheumatoid Factor	<10 IU/mL	<10 IU/mL
Cyclic Citrullinated Peptide Antibody	< 0.5 U/mL	0.0-2.9 U/mL
Complement levels	C3: 142mg/dL C4: 24	C3: 90-180 mg/dL C4: 10-40mg/dL
Anti-Ro/SS-A	<0.2 AI	0.0-0.9 AI
Anti-LA-B	<0.2 AI	0.0-0.9 AI
Creatine Kinase (CK)	57	39-308 U/L

Prednisone taper was started at 60 mg daily for a presumptive diagnosis of ASIA versus polymyalgia rheumatica. Within a few days of starting prednisone, the patient noticed significant improvement in his proximal extremity and grip strength. He reported more energy and increased appetite. His repeat serum analysis revealed an undetectable C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) was within normal limits. Hemoglobin and hematocrit were 12.3g/dL and 39% respectively and serum iron studies also showed dramatic improvement. He was referred to rheumatology and remained asymptomatic while prednisone dosing was tapered to 10 mg daily.

Seven months after starting prednisone, currently 5 mg daily, the patient's hemoglobin and hematocrit returned to his baseline. The patient felt well enough to undergo previously planned knee replacement surgery. He returned to work and reports minimal symptoms and an overall significantly improved quality of life.

DISCUSSION

Autoimmune/inflammatory Syndrome Induced by Adjuvants (ASIA) constitutes a set of closely related immune mediated diseases that share a common clinical picture including exposure to an adjuvant agent or other stimulus within weeks to months of symptom onset.[6] Major and minor criteria for the diagnosis of ASIA syndrome have been proposed.[7] Major criteria include exposure to an external stimulus (infection, vaccine, or adjuvant) in addition to myalgia, myositis, muscle weakness, arthralgia and/or arthritis, chronic fatigue and cognitive impairment. Minor criteria include appearance of autoantibodies directed at suspected adjuvant, other clinical manifestations, or specific human leukocyte antigen (HLA) type and evolvement of an autoimmune disease (**Table 2**).[8]

The post vaccination phenomena in ASIA syndrome are postulated to be largely attributed to the immunological characteristic of adjuvants that are associated with vaccination.[9] Adjuvant formulations have been widely studied with the intention of finding preparations with high stability, strong immunogenicity, and sufficient bioavailability while still being well tolerated.[9,10] Aluminum salts, mostly aluminum phosphate or hydroxide, are one of the most frequently utilized adjuvants which were shown to enhance antigen presentation, complement activation, innate immune system stimulation and T-helper cells (TH1 and TH2) activation.[10] Vaccines with aluminum-based adjuvants are

Table 2. Diagnostic criteria for Autoimmune/inflammatory Syndrome Induced by Adjuvants.

Major criteria	Exposure to external stimuli (infection, vaccine, silicone, adjuvant) before clinical manifestations
	Typical clinical manifestations: • Myalgia, myositis, or muscle weakness • Arthralgia and/or arthritis • Chronic fatigue • Unrefreshing sleep, sleep disturbance • Neurological manifestations • Cognitive impairment, memory loss • Pyrexia, dry mouth
	Removal of inciting agent induces improvement
	Typical biopsy of involved organs
Minor criteria	The appearance of autoantibodies or antibodies directed at the suspected adjuvant
	Other clinical manifestations
	Specific human leukocyte antigens
	Progression of an autoimmune disease

known to be associated with ASIA-related symptoms.[10,11] In contrast, recent reports suggest that mRNA vaccines may be self-adjuvating, not mediated by aluminum adjuvants.[12]

Polymyalgia rheumatica (PMR), also in consideration in the differential diagnosis in this case, is an inflammatory disorder typically characterized by significant pain and stiffness affecting the shoulders, pelvic girdle and proximal aspects of the arms and thighs. PMR can also involve the neck.[13] The majority of patients report morning stiffness and non-specific symptoms such as fatigue and malaise.[13] The etiology of PMR is not well understood. Elevated inflammatory markers are one of the core features of the disease, with IL-6 appearing to have a central role in mediating the associated inflammation.[14,15]

Muscle pain and stiffness experienced by this patient are typical features of PMR, but proximal muscle weakness, loss of grip strength, lower extremity swelling, and anemia are atypical, more in keeping with the diagnosis of ASIA. Both ASIA and PMR present with laboratory studies indicating a pro-inflammatory response. However, unlike ASIA, which often improves with removal of or temporal distance from adjuvants (one of the major criteria for ASIA), PMR in the context of ASIA appears to require initiation of prednisone for symptom resolution.[16] This patient meets criteria for the diagnosis of both ASIA and PMR. PMR in this context may be a true autoimmune disease (a minor criterion for the diagnosis of ASIA) occurring in the context of ASIA. In other words, autoimmune signs and symptoms which develop in the context of ASIA may become established as independent autoimmune conditions.

Clinicians should be aware of post-vaccination complications including autoimmune conditions such as PMR and generalized inflammatory syndromes such as ASIA. The intersection of vaccination and immunologic reaction will require further evaluation as these newly described syndromes gain recognition in order to improve associated patient outcomes.

DISCLOSURES/CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTION

All Authors (JSB, JH, SM, RT) have reviewed the final manuscript prior to submission.

All the authors have contributed significantly to the manuscript, per the ICJME criteria of authorship.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
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- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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