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The onset of rheumatoid arthritis and systemic lupus erythematosus following influenza vaccination: Report of three cases

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Abstract

Standard dose, inactivated, trivalent influenza vaccine was administered in 2009 to two healthy women age 46 and 56. Another woman, age 29, received an unspecified influenza vaccine in 2013. The first two developed rheumatoid arthritis, and the third developed systemic lupus erythematosus, all in close proximity to their immunizations. All three disease processes remained chronic, requiring continuous standard treatment.

Introduction

A variety of environmental risk factors are capable of triggering the onset of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). These include (but are not limited to) infections, physical trauma, severe emotional upset, drugs, insecticides, pesticides, smoking, periodontitits, hypoxia, hormonal imbalances, foods, ultraviolet light, prolonged exposure to unusual temperature changes, chemical pollution, poor nutrition, microbiota imbalances, and vaccinations [1-5]. With regard to vaccinations, numerous immunizations against a wide variety of infectious agents have been reported to be the initiating triggers associated with the onset of many autoimmune diseases, including inflammatory systemic connective tissue diseases, the latter of which encompass RA, SLE, polymyositis (PM), dermatomyositis (DM), ANCA associated vasculitis (AAV), polymyalgia rheumatica (PMR), giant-cell arteritis (GCA), and reactive arthritis [4-17]. The following three case reports, although clearly not novel first-time observations, add to a growing list of published adverse autoimmune rheumatologic phenomena following influenza vaccination and reinforce prior alerts for physician awareness of these occurrences.

Case report 1

A 46-year-old female physical therapist, on no medications and not suffering from any definable chronic medical or rheumatic ailments, received a standard inactivated trivalent influenza vaccine in the fall of 2009. Within 24 hours she began to complain of pain and stiffness in multiple small and large joints symmetrically, which continued on a daily basis. Six weeks later physical examination revealed swelling, limited motion, and pain on motion in both wrists, similar observations in the MCP's and PIP's of her hands, and ankle swelling, accompanied by pain on motion in her shoulders and hips and two hours of morning stiffness. Rheumatoid factor via SCAT (sheep cell agglutination test) was positive, and a diagnosis of rheumatoid arthritis was made. Over the next four years her RA proved refractory to NSAID's, hydroxychloroquine, methotrexate, leflunamide, and corticosteroids. Subsequently treatment with etanercept was instituted, resulting in substantial and sustained improvement (but by no means resolution) of her systemic inflammation. Any attempt over the next five years to discontinue this remitting therapy resulted in a prompt exacerbation of her RA.

Case report 2

A 56-year-old female with a history of penicillin allergy and osteoarthritis in her knees received a standard inactivated trivalent influenza vaccine in the fall of 2009. Eight hours later she developed progressively intense left shoulder pain, accompanied three days later by pain and swelling in her left hand. Five days after her vaccination she noted pain and swelling in both wrists and her right hand, followed four days later by pain in both ankles and feet. Her acute arthritis remained unremitting, and within one month of her influenza vaccination pain and stiffness and limited motion developed in her right shoulder. Two months later blood tests revealed a positive rheumatoid factor and and elevated sedimentation rate of 62. Rheumatology consultation five months after her vaccination verified a definitive diagnosis of rheumatoid arthritis, whereupon prednisone, methotrexate and hydroxychloroquine were prescribed. Despite significant improvement her polyarthritis has continued unabated.

Case report 3

A 29-year-old female, in excellent health and on no medications, received an unspecified influenza vaccine in the fall of 2013. Within 24 hours she developed fatigue which persisted unabated. Two weeks later she developed a chronic headache, myalgias in her calves and upper arms, arthralgias in multiple small and large joints, and

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classical fortification spectra, the latter characterized by overlapping irregular and jagged "rings" permeated by a diversity of different colors. Shortly thereafter tingling and numbness developed in her toes, accompanied by weakness in her extremities. A neurologist performed an examination of spinal fluid, revealing a mild pleocytosis. Further testing revealed a five-fold elevation of CPK, hemolytic anemia with a positive direct Coombs, thrombocytopenia, and a positive ANA (antinuclear antibody) test in a titer of 1:160. Urinalysis and other serologic tests were normal or negative. She was diagnosed with systemic lupus erythematosus and was treated with chronic oral corticosteroids and six weeks of intravenous gammaglobulin, resulting in substantial improvement (but by no means resolution) of all clinical phenomena. One year later she developed malar erythema, and shortly thereafter a pregnancy ended with death in utero at ten weeks gestation despite concomitant progesterone supplementation. Testing for anti-phospholipid antibodies was negative. Over the next four years there has been no evidence for Raynaud's, Sjogren's, photosensitivity, hair loss, renal disease, or seizures. Present treatment consists of low dose prednisone and hydroxychloroquine.

In all three patients there is no family history of inflammatory systemic connective tissue diseases, nor had anyone previously received any type of influenza vaccination. Historical data on other prior vaccinations (tetanus, pertussis, hepatitis, etc.) were not recorded. Generalized allergic diatheses were not manifested by any of the three patients. Previous serologic testing for autoantibodies (prior to influenza vaccination) had not been performed on anyone.

Discussion

On March 23, 2011, in the United States Court of Federal Claims, Special Master Patricia E. Campbell-Smith issued a ruling (unrelated to these three cases), asserting that Hepatitis B vaccine was the cause of systemic lupus erythematosus [18]. Five years later, in case 1 of this report, a final verdict was rendered by a different special master stating that influenza vaccine caused rheumatoid arthritis (verdicts in cases 2 and 3 are still pending). The venue for these decisions was created in 1986 and is known as the National Vaccine Injury Compensation Program, a no-fault alternative to the traditional legal system for resolving vaccine injuries. Special Masters are not judges, but rather federal employees, and the standard of proof in "vaccine court" is vastly different than in a routine court of law. We acknowledge that judicial rulings are not the equivalent of scientific investigations, and we also acknowledge publications supporting the efficacy and safety of various influenza vaccines [19-21]. In addition, a temporal association of autoimmunity following vaccination is not synonymous with causation, the latter of which requires careful epidemiologic studies. Nonetheless, these three case reports, when coupled with the references cited in the introduction section of this manuscript, are a testimony to the existence of adverse autoimmune reactions initiated by influenza immunization. Over the past thirty years researchers have proposed a variety of medical theories to explain this reality, and current immunologic observations are proving insightful [5,22-24]. With these advances it is becoming obvious that immunologic mechanisms in the first few days and weeks of vaccine-induced autoimmunity are quite different from definable immunologic events transpiring in patients with spontaneous autoimmune disease onset [23,24]. These scientific publications enhance our understanding of how vaccinations produce injury and lend evidence to cause and effect. One such mechanism, however, is drawing intense criticism lately from the medical community, namely ASIA (autoinflammatory syndrome induced by adjuvants, or Shoenfeld's syndrome) [25-28]. As a result, since 2015 the special masters in vaccine court in Washington, D.C. will no longer allow ASIA to be referenced by any experts testifying on behalf of vaccine injury claimants [28].

The incidence of autoimmune reactions to influenza vaccines is currently unknown, but it can no longer be assumed that a coincidental (i.e., unrelated) association exists between immunization and the onset of RA and SLE. It would be ideal if researchers could eventually determine which individuals are at risk for such phenomena, including delineation of an acceptable definitive time span between vaccination and disease onset. Until then, physicians will need to do the next best thing, namely become aware of vaccine-induced rheumatologic autoimmunity and its potential to persist indefinitely.

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