

# Antiphospholipid Syndrome Following a Diphtheria-Tetanus Vaccination: Coincidence vs. Causality

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The association between autoimmune disease and vaccines has been proposed in numerous reports in the past. We present here a case of a healthy young male who received a diphtheria-tetanus vaccination and was diagnosed with antiphospholipid syndrome a few months later.

## PATIENT DESCRIPTION

The patient was a previously healthy 28 year old student. Six months before his admission to our ward, he received a diphtheria-tetanus toxoid vaccination because of a laceration. Two weeks prior to the current admission, he was referred to the emergency department because of pleuritic chest pain. His blood tests and chest X-ray were normal and he was discharged. He returned to the ED 2 days later with a fever of 38.2°C. A chest X-ray revealed an infiltration in the right lower lobe. The patient was given amoxicillin/clavulanate and discharged. Three days later, he returned to our ED with complaints of hemoptysis, cough and persistent fever. Chest X-ray showed an infiltration on the

right lower lobe, with a small amount of pleural effusion and atelectasis. He was admitted to the pulmonary department. Antibiotic treatment was changed to moxifloxacin after consultation with the infectious diseases department. The patient's condition improved under this treatment and he was discharged after 5 days of therapy, afebrile with amelioration of his respiratory symptoms. Two days after discharge he began to experience leg pain that worsened gradually, followed by swelling of the left calf. Five days after the last discharge he returned to the ED, this time with a suspected deep vein thrombosis. Doppler ultrasonography was performed, demonstrating a thrombus in the popliteal and saphenous veins. He was admitted to our ward, and subcutaneous injections of enoxaparin and oral warfarin were given.

The patient had no history of prior venous or arterial thromboembolism and denied smoking. There was no known family history of thromboembolism. He denied weight loss, night sweats, pruritus, or change in bowel habits. A chest computed tomography was performed, which revealed a pulmonary embolism that probably explains the earlier clinical picture of non-resolving pneumonia.

We performed a workup for thrombophilic states, which showed a high lupus anticoagulant titer and low activated protein C resistance. Three months after discharge, a second test for lupus anticoagulant was positive and the diagnosis of antiphospholipid syndrome was made. The patient was also heterozygous to factor 5 Leiden.

## COMMENT

Numerous reports have discussed a possible association between vaccines and autoimmune diseases. One of the suggested mechanisms is the "molecular mimicry" theory, according to which an antigen of the vaccine resembles a host antigen, leading to an autoimmune process. Another theory is that immunization may cause the appearance of, or an increase in immune complexes, which may induce vasculitis or exacerbate a preexisting autoimmune disease [1]. Patients with a genetic predisposition for an autoimmune disease may be at higher risk for developing one after a vaccination. Nevertheless, most epidemiologic studies have not found a direct causal link between vaccinations and the onset of an autoimmune disease [2].

Autoantibodies to various phospholipids have been identified in patients with antiphospholipid syndrome, resulting in a wide spectrum of clinical phenomena such as arterial and venous thrombosis, microvascular thrombosis, placental insufficiency, and a variety of other manifestations. Despite the well-established clinical picture, certain pathogenetic issues remain unanswered, especially regarding the initial triggering events leading to a thrombosis.

There is little information on the connection between immunization and antiphospholipid antibodies. In one study, 85 healthy students were vaccinated with a recombinant hepatitis B virus vaccine. One month later, a minor, statistically insignificant rise in antiphospholipid antibodies was detected [3]. Recently, Inic-Kanada et al. [4] showed that mice

ED = emergency department

monoclonal antibodies against diphtheria-tetanus toxoid cross-react with  $\beta 2$  glycoprotein and cause adverse pregnancy outcomes when injected in BALB/c mice. These outcomes can mimic the pathogenesis of antiphospholipid syndrome in humans.

Agmon-Levin et al. [5] recently proposed that each component of the vaccine can induce autoimmunity via several mechanisms. Yet, large epidemiologic studies have failed to demonstrate post-vaccination autoimmunity.

Possible causal relationships between vaccinations and autoimmunity have long

been discussed, but have not been proven. We present here a patient with clinically and serologically proven antiphospholipid syndrome that manifested a few months after a diphtheria-tetanus vaccine. A possible pathogenic role of the vaccine in the appearance of antiphospholipid syndrome cannot be excluded.

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