

**RESEARCH ARTICLE****A Case of Myopericarditis and the HPV vaccine****Author**

\*\*Angela H Pegram, PharmD, BCPS, CDCES  
Cabarrus Family Medicine  
Inpatient Residency Service  
Atrium Health Cabarrus  
Concord, NC  
Email: [a.pegram@wingate.edu](mailto:a.pegram@wingate.edu)

Tara V Bush, PA-C  
Cabarrus Family Medicine  
Inpatient Residency Service  
Atrium Health Cabarrus  
Concord, NC

**Abstract****Introduction:**

Human Papillomavirus (HPV) is the underlying etiology of numerous cancers and genital warts in both males and females. Vaccines were developed against HPV to prevent transmission and arrest development of cancers caused by the virus. Gardasil 9® is the newest vaccine, covering 9 serotypes of HPV and is recommended by the CDC for both males and females over 9 years of age in a series of vaccinations. Myopericarditis (including myocarditis and pericarditis) is not reported as an adverse reaction in the Gardasil 9® package insert.

**Case Report**

A healthy 18-year-old male with no significant past medical or social history received dose number 3 of HPV vaccine at his physician's office. Within 24 hours, he developed chills and a fever (normal HPV reactions) and then recovered without sequelae within 48 hours. Three days later, he developed crushing chest pain, with arm tingling and jaw pain. He was triaged directly to the emergency room where he had troponins of greater than 11000 and T wave inversions on his EKG. Other diagnostic tests and labs showed normal heart anatomy and no early coronary artery disease. He was diagnosed with myopericarditis by cardiology. He was treated and recovered fully within 3 months.

**Discussion**

Using the WHO tool for adverse vaccine reactions, this case has a consistent causal relationship with vaccination. This is the eleventh case of myopericarditis reported to the Vaccine Adverse Effects Reporting system for the HPV vaccine.

**Conclusion**

Although rare, myopericarditis should be considered as a possible adverse effect from the human papillomavirus vaccine.

### **Introduction:**

Human Papillomavirus (HPV) is a common cause of oropharyngeal or anal cancers and genital warts in both males and females. Additionally, it is a leading etiology of vaginal, vulvar, and cervical cancer in women. Most HPV infection is asymptomatic in both males and females; however, the incidence of HPV infection is increasing in males in the US.<sup>1</sup> Population-based studies show the incidence of new HPV infections over 12 months as low as 29.2% in males 18-45 years of age<sup>2</sup> and as high as 62.4% in university males<sup>3</sup>. Thus, vaccines against HPV have been developed and approved in the past 15 years in both females and males to decrease transmission and prevention of the above diseases caused by HPV.

Preclinical studies and male-only trials show a consistent 85% or greater efficacy in prevention of genital lesions, condyloma and intraepithelial neoplasms in young men 16-26 years of age using the 4 valent HPV vaccine.<sup>4</sup> Gardasil 9® is the newest HPV vaccine, covering 9 HPV serotypes 16, 18, 31, 33, 45, 52, and 58. The CDC recommends the 9 valent vaccine over the older 4 valent vaccine due to increased coverage of common serotypes of HPV in both females and males. Patients who complete the vaccination series between 9-14 years of age can complete a 2 or 3 dose regimen. Patients 15-45 years old should complete a 3-dose series.<sup>5</sup>

Safety with Gardasil 9® was extensively studied in seven clinical trials in over 15 thousand patients prior to public vaccine availability. Injection site reactions including pain, erythema, swelling and an oral temperature following vaccination were commonly solicited adverse reactions (seen in 89.9% vaccinations) with each successive dose of HPV vaccine. Serious adverse events that were determined to be vaccine related in clinical trials were reported in 2.3% (354 out

of 15705) of the population and included fever, allergy to vaccine, asthmatic crisis, and headache. Post marketing adverse events reported include vomiting, urticaria, myalgias and immune system disorders. However, myocarditis nor pericarditis do not appear in the Gardasil 9® package insert as a reported adverse event.<sup>5</sup>

### **Case Report:**

A healthy 18-year-old male visited his primary care physician (PCP) office for his last official well child check. He had no pertinent past medical history except seasonal allergies. He graduated 6 months early from high school and was working a part time job to save money for college. His social history was negative for alcohol, tobacco, or illicit drugs. He was administered dose # 3 of Gardasil 9® at this visit, completing his HPV series. He has had no adverse reactions to any of his vaccinations prior to this time. He has not yet been vaccinated for COVID-19 but plans to get the vaccinations soon as he prepares for college admission requirements.

Approximately 12 hours after his HPV vaccination, his mother called the PCP office informing them that the patient has chills and a low-grade fever and vomited once during the night. He also had a frontal headache since the injection was given. These were recorded as typical HPV vaccine reactions and the mother was instructed to give acetaminophen for fever and asked to encourage fluid intake by the office nurse. Within the next 24 hours, all these symptoms subsided, and the patient was back to normal per his report.

Three days later, the mother again contacted the PCP office reporting the patient had left arm tingling, crushing pain with a tight sensation across his chest and lower jaw pain. He was immediately sent to the emergency

room by nurse triage for these symptoms, as they were not typical vaccination reactions. In the emergency room, the patient had a BP of 143/73. Heart rate, respiratory rate, temperature and O<sub>2</sub> saturation were all normal. His EKG showed T wave inversion and troponin was reported as 11309. Patient was questioned about history and again adamantly denied any cocaine or other illicit drug, alcohol, or tobacco use. The urine drug screen and alcohol levels were both negative, confirming his reported social history. He did report a recent car trip over the past weekend of 6 hours each way with no stopping. D-dimer was 0.65 and a CT angiogram (CTA) of the chest was ordered. The CTA revealed no pulmonary embolism, no pericardial effusion or aortic dissection. A COVID-19 test was also ordered, which returned as negative for COVID antibodies or antigen. A second and third troponin were reported at 11067 and 12151, respectively. Cardiology was consulted and started the patient on IV heparin as his differential diagnosis was narrowed over the next 36 hours.

The following morning, the patient received an echocardiogram which showed an ejection fraction of 60-65% and normal left ventricle and right ventricle size and function. A coronary angiogram was completed the following day which showed normal coronary arteries, ruling out abnormal coronary anatomy and premature CAD as the etiology of the chest pain. Cardiology surmised the cause of the pain as myopericarditis, likely related to the recent HPV injection. Additionally, CRP was reported at 2.4, validating an underlying inflammatory process. The patient was started on ibuprofen and omeprazole until the pain was gone and colchicine x 3 months. He was then discharged pain free from the hospital, 3 days after his chest pain had appeared.

The patient was seen at the PCP office for follow up in 1 week. He reported doing well with meds and no more chest pain. He was given instructions for weaning off ibuprofen and omeprazole to prevent rebound pain and reflux. He was to continue the colchicine for 3 months. He was seen 4 months later by cardiology and reported feeling great. Colchicine was stopped at that time and no further cardiology recommendations were made.

### **Discussion:**

Myopericarditis (MP) is an overlapping disease in which the patient has both myocarditis and pericarditis simultaneously. Many causes exist such as infections, drugs, toxins, and vaccines, but their underlying etiology is not always identified in clinical practice.<sup>6</sup> The actual etiology of myocarditis is not well understood, but Interferon (INF) gamma and tumor necrosis factor (TNF) alpha seem to play a key role as a signaling molecules that turn on cardiac inflammation pathways. These inflammatory cytokine mediators have been proposed by several studies to mediate post vaccine allergy reactions.<sup>7-9</sup> B cell activation and the initiation of T helper cell production by these mediators produce memory cells for the vaccine from the original vaccination. These activated memory cells produce the local post vaccine side effects such as injection pain, fever, headache, and joint/muscle pain due to inflammatory activation. Thus, second and third injections of the identical vaccine cause amplified release of these cytokines and are likely responsible for a profound immune response that sets off the cardiac inflammation cascade leading to myocarditis or pericarditis.<sup>8-11</sup>

Review of the literature reveals a small number of cases of MP with vaccines, most notably with the smallpox vaccine in the early 2000.<sup>12</sup> There are a handful of other reports with influenza, tetanus, hepatitis B

and the HPV vaccine.<sup>13-16</sup> Only one single case report of myocarditis after the HPV vaccine was located after an extensive review of the PubMed, Google scholar and OVID databases. This report details a fatal case of fulminant myocarditis for a young healthy 17-year-old female. She presented after 1 week of symptoms in cardiogenic shock. Intense myocardial inflammation and necrosis was found on autopsy.<sup>13</sup>

Due to the lack of additional case reports, the vaccine adverse events reporting system (VAERS) was reviewed to provide a broader view of adverse events following HPV administration. Ten cases of pericarditis from the HPV vaccine have been reported to the VAERS system from 1990 through September 2021.<sup>8</sup> Using the universal WHO tool for vaccine adverse effects, this case produces a consistent causal association to immunization.<sup>17</sup> Thus, it is very likely that the HPV vaccine was the causative factor of this patient's myopericarditis event, making it case # 11. This written case report is an important addition to the medical literature, as MP has been reported with the HPV vaccine in several patients only in the VAERS database, not formally written as a case report.

Myocarditis in children and young adults is difficult to diagnose. Early intervention seems to be the key to good outcomes, as the guidelines suggest rapid progression to heart failure and cardiogenic shock with untreated cases.<sup>18</sup> The patient case presented in this article received early intervention by seeking treatment for his chest pain right away. Although his troponin levels were elevated, they remained relatively flat throughout the stay. His echocardiogram and coronary angiogram were also reassuring for normal cardiac function with no damage reported. He also had close follow up with his primary care physician and cardiology practice, allowing him to recover fully with treatment.

#### **Conclusion:**

Although rare, myopericarditis (including pericarditis and myocarditis) should be considered as a possible adverse effect from the human papillomavirus vaccine. Diagnosis of this adverse effect may be difficult to determine, and early intervention is needed for successful treatment, even in young healthy patients.

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