EXPERT REPORT

in the Matter of

Gomez v. United States Department of Health

By

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INTRODUCTION

The author of this report, Sin Hang Lee, MD, who has been retained as the expert by Roberts Law Firm, offers his evaluation of this case based on the information supplied by the above-referenced law firm in a document referred to as Adan Gomez and Raquel Ayon, petitioners vs. Secretary of Health and Human Services, Respondent, and based on his experience with the subject matter. According to the information available, the decedent suffered a sudden unexpected death in sleep. The relevant information is summarized as follows.

Joel Gomez, a 14-year old healthy boy who had regular visits to the pediatrician' office for periodic check-ups since birth showed no evidence of any pre-existing health issues, specifically no evidence of cardiac abnormalities, psychological disorders or substance abuse. The teenager had been training for the high school football team for the last two months before his death four to five hours a day without incident.

On June 19, 2013, the boy was given the first dose of the vaccine, Gardasil®, in his left arm in the doctor's office. No adverse reactions following this first vaccination were reported to the family or the physician. On August 19, 2013, the boy was given a second injection of Gardasil® as scheduled in the doctor's office. Then he went home and went to sleep. The boy was found to be unresponsive in bed the following morning on August 20, 2013 at 7:00 a.m. by his family.

Paramedics were called in and transported the boy to the hospital where he was pronounced dead at 9:07 a.m. on August 20, 2013.

An autopsy was performed on August 23, 2013 by James K. Ribe, MD, senior deputy medical examiner of Los Angeles, California.

Significant abnormal findings of the autopsy include "a long narrow band of dark reddish discoloration which is somewhat darker than the rest of the myocardium, extends over a length of 6 cm and has a width of 0.4 cm extending from the anterior base of the heart almost to the apex." "..this lesion is limited to the anterior free wall. Both lungs are extremely heavy. The lung parenchyma is dark-purple-red and completely soaked with edema fluid and blood."

The medical examiner analyzed 3 slides of the heart and made the following comments:

Slide 1: Left ventricle showing extensive patchy areas of acute & chronic inflammation with myocyte damage and fibrosis.

Slide 2: Papillary muscle unremarkable.

Slide 3: Right ventricle unremarkable.

The Opinion of the medical examiner is:

Decedent died of myocarditis, which apparently was completely asymptomatic. By histology, the disease had been present for at least several days or weeks. The cause is unknown.

MATERIALS EXAMINED BY AUTHOR

The author received 3 H&E stained slides for microscopic examination.

Slide 1, labeled 13-5839-1, H&E RECUT, 4/21/2015, LAC ME Coroner.

Microscopic description: This is a section of the left ventricle of the heart as described in the medical examiner's report, measuring about 12-13 mm thick from endocardium to epicardium. It shows a mid-zonal patchy granulation tissue formation composed of fibroblasts, newly formed capillaries, and regenerating cardiac myocytes with numerous macrophages, occasional eosinophils and scattered lymphocytes and plasmacytoid cells. The granulation tissue has replaced about 80% of the thickness of the ventricular muscle in this section. But there are irregular interlacing fascicles and isolated fragments of myocytes with well-preserved striations in the granulation tissue. The subendocardial and subepicardial myocytes for a thickness of 2-3 mm appear normal and well-preserved without granulation tissue, inflammatory cell infiltration or scarring. There is practically no infiltration by polymorphonuclear leukocytes in the entire section. No acute myocyte necrosis is recognized.

Slide 2, labeled 13-5839-2, H&E RECUT, 4/21/2015, LAC ME Coroner.

Microscopic description: This is consistent with a papillary muscle, histologically unremarkable.

Slide 3, labeled 13-5839-3, H&E RECUT, 4/21/2015, LAC ME Coroner.

Microscopic description: This slide shows two sections consistent with the wall of right ventricle of the heart, histologically unremarkable.

AUTHOR'S POSTMORTEM ANATOMIC DIAGNOSIS

Localized healing recent myocardial infarct of the left ventricle of the heart.

AUTHOR'S INTERPRETATION OF THE AUTOPSY FINDINGS

The postmortem findings of this case are most consistent with a healing myocardial infarct, not a case of myocarditis of unknown etiology based on the evidence and discussion presented as follows.

Myocarditis of unproven etiology is generally believed to be caused by virus infections. Viral myocarditis, defined clinically as an inflammation of the heart muscle, is a major cause of sudden unexpected death [1-6]. Diffuse lymphocytic infiltration of the heart muscle, especially in the subendocardial myocardium of the right ventricle, is the diagnostic hallmark of viral myocarditis [7, 8]. Patients with viral myocarditis typically have a recent history (≤1-2 wk) of flu-like symptoms of fevers, arthralgias, and malaise or pharyngitis, tonsillitis, or upper respiratory tract infection [9]. In the current case, the decedent did not have any flu-like symptoms before his sudden unexpected death, and histologically there is no lymphocytic infiltration in the myocardium. The localized lesion in the left ventricle represents a repair process and focal fibrosis with only scattered lymphocytes and plasmacytoid cells in the granulation tissue. A diagnosis of viral myocarditis is not supported by the decedent's clinical history and the autopsy findings.

On the other hand, the presence of a large number of fibroblasts, newly formed capillaries, macrophages and eosinophils and only occasional lymphocytes and plasmacytoid cells with regenerating myocytes confined to a localized mid zone for a 0.4 x 6 cm area in the left ventricle indicates a healing myocardial infarct of a few weeks duration [10]. As shown in slide 1, preservation of a thin layer of normal subendocardial and subepicardial myocardium in the section of the left ventricle is characteristic of a localized necrosis of the myocardium which might have resulted from a transient low perfusion of the heart [11] in a most vulnerable region, the left ventricle toward the apex. The subepicardial myocardium usually gets more blood supply from the coronary arteries than the muscle cells in the deep layer of the left ventricle, and the subendocardial myocardium gets more oxygen diffused from the ventricular blood when the circulating blood to the myocardium is cut off for a short period of time while the ventricular blood is still highly oxygenated [11]. Since there are many well-preserved myocytes in the healing area among the fibroblasts and capillaries with preservation of the sarcolemma framework, the infarction was probably induced by a transient myocardial ischemia and not the result of a complete blockage of a major branch of the coronary arteries as often observed in myocardial infarcts in occlusive coronary arterial disease of the old patients.

The conclusion based on the autopsy findings is that the decedent died of left heart failure with pulmonary edema and an asymptomatic healing myocardial infarct. Since the healing infarct was a few week old and since the patient was still able to play football 4-5 hours a day without complaining of shortness of breath or chest pain during this period, the healing myocardial

infarct must not be a primary cause of death while the patient was in sleep. The only plausible mechanism causing the sudden unexpected death of this teenager is the physiopathologic events induced by injection of the second dose of Gardasil®.

EVIDENCE IN SUPPORT OF SUDDEN UNEXPECTED DEATH CAUSED BY GARDASIL® VACCINATION IN THIS CASE

I. Gardasil® vaccination is known to cause hypotension (drop of blood pressure) which may be fatal in certain predisposed vaccinees.

The FDA Prescribing Information for Gardasil® (qHPV) contains the following Warnings and Precautions [12]:

"Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with GARDASIL®. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position."

According to a CDC report, syncope is the most common adverse reaction after Gardasil® injections and "*The reporting rates per100 000 qHPV doses distributed were 8.2 for syncope;…"* [13].

Syncope is defined as temporary loss of consciousness and posture, described as "fainting" or "passing out." It's usually related to temporary insufficient blood flow to the brain. It most often occurs when the blood pressure is too low (hypotension) and the heart doesn't pump a normal supply of oxygen to the brain [14].

Orthostatic hypotension and postural orthostatic tachycardia syndrome are well documented in some of the patients after HPV vaccination [15]. However, the pathogenesis of orthostatic hypotension and tachycardia after HPV vaccination has not received much attention of the medical community.

While hypotension is a common consequence of myocardial infarcts encountered in clinical practice, human myocardial infarction can also result from hypotension of non-cardiac origin, for example in patients under treatment with a cardiotoxic drug like liposomal amphotericin B [16].

A CDC study shows that among 12,424 reported adverse events following Gardasil® vaccination from June 1, 2006 through December 31, 2008, there were 32 deaths with a mean age of 18 years old, who died 2 to 405 days after the last Gardasil® injection. Medical records and autopsy reports on 20 of the 32 deaths were available for review and confirmed there were 4 unexplained deaths and 6 cardiac-related deaths [13].

Therefore, based on the medical and scientific information available in the public domain there is evidence that Gardasil® vaccinations may cause hypotension with reduced blood flow to the brain and heart which may lead to syncope and sudden unexpected death or asymptomatic myocardial infarction in certain genetically or physically predisposed persons although the mechanism leading to hypotension remains to be explored.

II. Molecular mechanism of Gardasil®-induced hypotension and sudden unexpected death

The active ingredients in the vaccine Gardasil® are purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18 [12]. The vaccine uses a highly effective adjuvant, amorphous aluminum hydroxyphosphate sulfate (AAHS), to boost the anti-HPV L1 VLP responses in the host [17]. However, recombinant HPV L1-specific DNA fragments are also present in the vaccine products, according to a document issued by the Food and Drug Administration [18].

Aluminum salts have been used as adjuvants in vaccination to boost immune responses of the host to the protein antigens for many decades. The mechanism of the adjuvant effects of aluminum salts has only been recently investigated at the molecular level. It is now generally agreed in the scientific community that aluminum salts are toxic and damage the cells of the host at the site of injection, causing a localized inflammation at the vaccination site. The free host DNA molecules released from the aluminum salt-damaged cells act as mediators to trigger augmented immune responses of the host. The free DNA molecules of the dying host cells, also referred to as damage-associated molecular patterns (DAMPs) [19] bind the aluminum salt adjuvant, and the resulting DNA/aluminum complexes are phagocytized by the antigen-presenting cells (APCs) and macrophages [20]; in vaccination with aluminum adjuvants, the transfected host DNA activates the pathways that would increase their ability to interact productively with antigen-specific CD4 T cells to boost host immune responses [22, 22]. ***In plain language, free DNA derived from the dying host cells is needed to be carried by aluminum adjuvants into the APCs or macrophages to function as mediators for boosting immune responses in vaccination.***

However, the presence of recombinant HPV L1-specific DNA fragments in the vaccine Gardasil® has disrupted this expected normal immunity response platform in vaccination. The HPV DNA molecules, being of a viral origin, are "non-self" microbial products, also referred to as pathogen-associated molecular patterns (PAMPs). The human body's defense system can distinguish the PAMPs from the DAMPs in order to mount an appropriate immune response to either the presence of a pathogen or a tissue damage [19].

The AAHS nanoparticles which are expected to bind the free host DNA at the site of vaccine injection can also bind the fragments of HPV L1 gene DNA present in the vaccine Gardasil® [23] through a ligand exchange process between the phosphate groups of the DNA molecule and the hydroxyl groups on the aluminum adjuvant surface, similar to a reaction between phospholipids and AAHS in the recombinant hepatitis B vaccine [24]. In other words, Gardasil®

has been furnished with a set of ready-made instant DNA immune "mediators" already in the adjuvant, in the form of a viral DNA/aluminum chemical compound, specifically an HPV L1 gene DNA/AAHS complex. The downstream events after transfection into the human macrophages of these viral DNA fragments which are rarely found in the human genome [25] are quite different from those after the DNA of the dying host cells is introduced into the macrophages. Despite similarities between DNA molecules, mammalian cells have the remarkable ability to distinguish viral DNA from their own DNA. The human macrophages are able to recognize the HPV L1 gene DNA as a 'stranger' and a 'danger' signal, and in response produce many antiviral immune molecules, collectively referred to as type I interferons and pro-inflammatory cytokines [26-28].

Massive systemic production of these type I interferons and pro-inflammatory cytokines induces an antiviral state and protects the host, but it also can contribute to endotoxin lethality and autoimmune diseases [27]. Many of these cytokines are myocardial depressants. The two cytokines that show the greatest cardiovascular effects in animals and humans are tumor necrosis factor (TNF)-α and IL-1β [29]. Administration of recombinant TNF-α in animal models is known to cause hemodynamic changes and even death [29].

Injection of Gardasil® into animals has been shown to induce unusually early strong innate immune responses with quick releases of a variety of cytokines from the macrophages [30]. Injection of HPV DNA/AAHS complexes into the host is also known to induce a strong immune reaction and a strong CD8 T cell response [17]. Based on experiments with other viral DNA molecules, the recombinant HPV L1 gene DNA fragments transfected into human macrophages would also be recognized as "stranger" and "danger" signal, and invariably activate the macrophages to release numerous antiviral cytokines. Many of these cytokines, including TNF-α and IL-1β, are recognized myocardial depressants [31-35]. Hypotensive shock induced by TNF-α has been well documented among animals [36, 37] and humans [38, 39].

According to information available in the public domain, the HPV L1 gene DNA fragments in the Gardasil® vaccine are firmly bound to the cationic AAHS nanoparticles, thus well protected from degradation by various DNA nuclease activities [23, 40-42]. After these particles have gained access into the macrophages at the site of injection, the macrophages can carry these HPV DNA/AAHS complexes in particulate form to the regional lymph nodes, the circulating blood and to various organs while these viral DNA molecules may function as a potent long-acting immune stimulator in the macrophages, leading to sustained production and release of cytokines, including TNF-α. HPV L1 gene DNA fragments have been detected in the postmortem blood and spleen collected at autopsy from the body of a young woman who died of a sudden unexpected death in sleep six months after the 3rd dose of Gardasil® vaccination [40].

This brief review of literature shows that there is a known molecular mechanism to explain why syncope occurs more often in people injected with Gardasil® than with other vaccines, and why certain predisposed vaccinees may suffer a sudden unexpected death as the result of Gardasil® vaccination.

III. Gardasil® vaccination was the most likely cause of the decedent's death

The decedent in this case was a healthy teenager, a member of his high school football team, and had training exercise for about 4-5 hours a day up to the last day of his life, the day when he received his second scheduled vaccination of Gardasil®. He had been regularly followed by his pediatrician since birth for health care. There was no evidence of any illnesses on or before the day of his second Gardasil® vaccination. Otherwise, the physician would have postponed the vaccination according to the Instructions given for administering Gardasil® vaccines. Since the decedent had not taken any medications or drugs and had not suffered any injuries, the only known factor which might cause his death on August 19, 2013 is the second Gardasil® injection given to him shortly before he went home and went to sleep. The autopsy findings did not find any abnormalities except a localized healing myocardial infarct of several weeks old with associated pulmonary edema, a consequence of left heart failure. The lesion of a healing infarction in the left ventricle of the heart was not the immediate cause of death. The patient with this lesion was able to continue his daily football training without difficulty although the healing infarct might have been a contributing factor to his heart failure.

IV. The timing of decedent's sudden death caused by Gardasil®

As discussed above, the link between sudden unexpected death and Gardasil® vaccination is mediated through myocardium-depressing cytokines, including TNF-α, released by activated macrophages. Since the activated macrophages are usually first brought to the regional lymph nodes by lymphatics from the site of vaccine injection, then to the circulating blood and further to various organs, it is not possible to predict the time when the myocardium-depressing cytokines would reach a local concentration high enough in the myocardium to cause the heart to stop pumping blood in a predisposed person. Sensitivity to the myocardium-depressing cytokines may vary from person to person due to different genetic makeups. Small quantities of HPV L1 gene DNA fragments were detected in the blood sample and spleen tissue collected at the time of autopsy from a deceased young woman who died of a sudden unexpected death in sleep 6 months after the third injection of Gardasil® [40]. The findings in the latter reported case indicate that the HPV L1 gene DNA fragments from the vaccine Gardasil® may be stabilized and protected in the form of DNA/aluminum complexes in the macrophages for several months or longer, functioning as a long-acting activator to the macrophages and causing these cells to release cytokines, including TNF-α, continuously in different organs. Since the activated macrophages can travel through the blood stream to any tissues, including the myocardium, it is unpredictable when these macrophages may aggregate in a focus of the myocardium, releasing a quantity of myocardium-depressing cytokines to reach a high enough concentration in the heart to cause a fatal arrhythmia or ischemia of the heart. In the current case, the records state "The night Joel received the second dose of Gardasil®, he went home and went to sleep." This brief clinical history indicates that this 14-year old teenager must not feel well and needed to go to bed to lie down after receiving the second dose of Gardasil® as soon as he came home. Such a history is most consistent with that of a healthy teenager suffering from hypotension with low blood perfusion of the brain. The most plausible cause of death for the decedent is myocardial

depression by a surge of cytokines, including tumor necrosis factor-α, from the activated macrophages following the second dose of Gardasil® which contained HPV L1 gene DNA bound to AAHS as adjuvant. Since Gardasil® does contain HPV L1 gene DNA, sub-lethal doses of myocardium-depressing cytokines are expected to be released from the activated macrophages after Gardasil® vaccinations. The small surges of cytokines generally cause no serious adverse side effects among the vaccinees. However, in the case of Joel Gomez there was a pre-existing silent healing myocardial infarction in the left ventricle which was induced by the first Gardasil® dose. An otherwise sub-lethal dose of cytokines newly brought to the already damaged heart finally caused the left ventricle to fail, and the decedent died of left ventricular failure of the heart in sleep shortly after the second vaccination.

V. Summary

After reviewing the case of Joel Gomez, the most plausible cause of death for the decedent is cardiac failure brought about by a surge of myocardium-depressing cytokines, including tumor necrosis factor-α, released from the macrophages activated by the HPV L1 gene DNA fragments present in the vaccine product after injection of the second dose of Gardasil® on August 19, 2013.

When the free HPV DNA molecules in Gardasil® are transfected with the AAHS adjuvant into the antigen-presenting cells or macrophages in the host, these latter immune cells recognize immediately the HPV DNA being pathogen DNA by nature of their DNA sequences, and react rapidly in an innate immunity response by releasing numerous cytokines, including TNF-α. Some of these cytokines are potent cardiac depressants capable of causing hypotension which may in turn reduce the blood flow to the brain and the heart. Since the HPV DNA in Gardasil® is bound to the AAHS adjuvant as nanoparticles, the viral DNA is protected from degradation by DNA nucleases and may function as a long-acting molecular stimulator. Most vaccinees tolerate these small cytokine surges well with no adverse reactions. But some of them develop syncope and orthostatic hypotension; most of them recover fully. After he was given the first dose of Gardasil® vaccine on June 19, 2013, Joel Gomez, a football player apparently developed a silent localized myocardial infarction during one of these cytokine surges probably when he was playing football at a time as the demand for blood perfusion to the heart muscle was high. A sudden reduction of blood perfusion apparently caused a transient ischemia and an infarction in the left ventricle where the demand of oxygen is most critical in competitive sports. But Joel did not have any significant clinical symptoms during and after the infarction. The lesion began to heal.

However, after the second Gardasil® vaccination a new surge of cytokines directed more myocardial depressants to the heart, causing an episode of hypotension when Joel went home in the evening of August 19, 2013. The heart with a damaged left ventricle now under the effects of a new wave of myocardial depressants could not pump enough blood into the arterial circulation to maintain the needed blood pressure. Joel came home and went to bed when his blood pressure was dropping. The patient eventually died of left heart failure due to insufficient blood perfusion to the heart muscle and brain.

In the opinion of this author, there is sufficient evidence based on which to conclude that the vaccine Gardasil® is capable of causing sudden unexpected death in certain predisposed vaccinees, that Gardasil® did cause or contributed to a myocardial infarction in the decedent, and that the second dose of Gardasil® finally caused a fatal hypotension in this case on the day of vaccination. There was no other plausible cause for the death of Joel Gomez at the night of August 19, 2013.

Signed Dated September 25, 2015

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