# Systemic lupus erythematosus following human papillomavirus 9-valent vaccination

**Yuehua Wan, Jinshui Yang, Yurong Zhao, Jingyu Jin, Jian Zhu, Kunpeng Li, Jianglin Zhang**

Department of Rheumatology and Immunology, The First Medical Centre, Chinese PLA General Hospital, Beijing 100853, China.

*To the Editor:* Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown cause that can affect any organ of the body. Human papillomavirus (HPV) infection is associated with the development of cervical dysplasia and cancer in SLE patients. HPV vaccines can effectively prevent HPV infection and subsequent HPV-related diseases. HPV vaccination is effective, immunogenic, and safe for SLE patients.[1] However, concerns about the safety of HPV vaccine have been raised by case reports of the onset of SLE following HPV vaccination.[1-3]

We present two cases of SLE patients diagnosed after the HPV 9-valent (HPV9) vaccination and review the literature to explore the clinical characteristics of patients and the safety of HPV vaccine, especially HPV9.

Case 1: Five days after first immunization with the HPV9 vaccine, a 21-year-old women suffered from dizziness, fatigue, nausea, and vomiting. During the next 4 days, the patient developed cough, yellow phlegm, and chest tightness. Eighteen days later, she was admitted to this hospital with a fever. Her medical and family histories were unremarkable. She had no history of contact with cattle, sheep, or other relevant animals.

Laboratory tests demonstrated anemia, leukopenia, thrombocytopenia, hypocomplementemia, low serum albumin, elevated erythrocyte sedimentation rate (ESR), positive direct Coombs test, and proteinuria of 1.64 g/day. Her serum creatinine and C-reactive protein (CRP) levels were normal. Autoantibody screening showed high titers of antinuclear antibodies (ANA: 1:1000) and anti-double stranded DNA antibodies (anti-dsDNA: 1:5), and was positive for anti-nucleosome antibodies, anti-histone antibodies, and lupus anticoagulant. Antiphospholipid antibody testing was negative. Infection serology tests were positive for human Brucella IgG, herpes simplex virus IgG and IgM, rubella virus IgG, toxoplasma IgG, cytomegalovirus (CMV) IgG and IgM, and Epstein-Barr virus (EBV) IgG, and negative for EBV IgM, EBV-DNA, and CMV-DNA. Sputum culture showed gram-positive cocci. A chest computed tomography after admission showed that patch shadows and nodules in both lungs had increased in size and number compared with a scan carried out 6 days previously. A small amount of pleural effusion was found on both sides, with a slight increase on the right side. A small pericardial effusion was also noted.

After being diagnosed with SLE and pulmonary infection, the patient was treated with methylprednisolone, intravenous immunoglobulin (IV Ig), antiviral drugs, and antibiotics. Fever, cough, and yellow phlegm were gone after treatment, while anemia and thrombocytopenia continued to worsen and erythrocyte fragmentation, elevated D-dimer, and increased serum creatinine occurred. She was diagnosed with thrombotic microangiopathy and treated with plasma exchange. Unfortunately, she suffered epilepsy and mental abnormality during treatment. Magnetic resonance imaging and cerebrospinal fluid tests showed that she had neuropsychiatric SLE. As her infection was controlled, intravenous pulse methylprednisolone was administered. However, the therapeutic effect was unsatisfactory. She developed secondary left heart failure and a new infection, and eventually died of multiple organ failure.

Case 2: A 21-year-old women was admitted to hospital because of intermittent fever that began 6 days after her first dose of HPV9 vaccine. Her medical history included Raynaud phenomenon and a thyroid nodule, while her mother had been diagnosed with thyroid papillary carcinoma. The patient had no history of contact with cattle, sheep, or other animals.

Laboratory tests demonstrated anemia, leukopenia, low serum albumin, low complement (C3) levels, elevated ESR, a positive direct Coombs test, proteinuria of 0.94 g/d, and normal CRP level. Microscopic examination of urine

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001897

**Correspondence to:** Jian Zhu, Department of Rheumatology and Immunology, The First Medical Centre, Chinese PLA General Hospital, 28 Fuxing Road, Haidian District, Beijing 100853, China
E-Mail: jian_jzhu@126.com



Chinese Medical Journal 2022;135(15)

**Received:** 19-04-2021; **Online:** 15-12-2021 **Edited by:** Lishao Guo

erythrocytes found 25 to 30/HPF. Polymorphisms of urinary erythrocytes morphology accounted for 80%. Autoantibody screening showed high titers of ANA (1:1000) and anti-dsDNA (1:5) antibodies; was positive for anti-RNP, anti-SSA, anti-SSB, anti-centromere, anti-nucleosome, anti-histone, anti-β2 glycoprotein I, and anticardiolipin antibodies; and was negative for the anti-Smith antibody. Infection serology tests were positive for human Brucella IgG, herpes simplex virus IgG and IgM, rubella virus IgG, toxoplasma IgG and IgM, CMV IgM, EBV IgM and were negative for EBV-DNA, CMV-pp65, and influenza virus RNA. A kidney biopsy showed Class IV lupus nephritis with activity and chronicity indices of four and zero, respectively. A thyroid biopsy revealed papillary thyroid carcinoma with BRAF (V600E) gene mutation.

The patient was diagnosed as having SLE and papillary thyroid carcinoma, and was treated with high-dose prednisone, IV Ig, hydroxychloroquine, and radiofrequency ablation. After initiation of treatment, her temperature normalized and gradual remission of the SLE occurred. One month later, the human brucella IgG, herpes simplex virus IgM, toxoplasma IgM, CMV IgM, and EBV IgM turned negative without antiviral/antibiotic therapy.

After review, four peer-reviewed articles were included for data collection.[1-3] A total of 12 female patients were vaccinated with bivalent HPV vaccine (HPV2) (1 patient), quadrivalent human papillomavirus vaccine (HPV4) (6 patients), and HPV9 vaccine (2 patients); in three patients, vaccine type was not recorded. Five patients had symptoms after the first vaccination. A 32-year-old patient was diagnosed with SLE after her third vaccination and a 19-year-old patient was diagnosed with an SLE flare after her second injection, but noted that both had symptoms after their first immunization.[2] The time from vaccination to the onset of symptoms ranged from 5 days to 4 months. The median onset of symptoms after HPV9 immunization was 5.5 days, which was shorter than that of patients receiving the HPV2 or HPV4 vaccine. Nine patients had a medical or family history of autoimmune disease. Ten patients achieved remission after treatment, whereas the remaining two patients eventually died [Supplementary Table 1, http://links.lww.com/CM9/A850].

Of the 12 patients reviewed, eight presented with a rash (of which seven had malar rash) and arthralgia/arthritis, seven with fever, fatigue/weakness, alopecia, and renal lesion, four with neurological symptoms, three with oral ulcers and photosensitivity, two with serositis, and one with intestinal pseudo-obstruction. Other symptoms included livedo reticularis, lymphadenopathy, myalgia, weight loss, and so on.

Laboratory studies of the 12 recorded cases showed 11 had positive ANA, nine had positive anti-dsDNA antibodies, three had positive antiphospholipid antibodies, three had positive anti-Smith antibodies, 10 had hypocomplemente-mia, nine had elevated ESR, seven had leukopenia /lymphopenia, six had anemia, four had elevated CRP, three had thrombocytopenia, and two had a positive direct Coombs test.

SLE is a chronic autoimmune disease that appears to be triggered by genetic, hormonal, immunologic, and/or environmental agents. Evidence indicates that HPV plays a role in the induction and propagation of such diseases. HPV infection may induce or accelerate SLE via a mechanism of immune cross-reaction due to molecular homology. Bragazzi et al[4] found overlapping peptides between HPV vaccine and human protein. Aluminum oxyhydroxide (alum) is a common vaccine adjuvant for the preparation of HPV vaccine and is related to a variety of autoimmune phenomena. We found 75% of patients had a medical or family history of autoimmune disease, which hints at a genetic predisposition for autoimmune disease.

The patients we reported on here had a shorter median time from vaccination to the onset of symptoms than previously studied patients. This may be due to the different types of HPV or the higher amounts of virus-like particles and adjuvants in HPV9, activating the immune system in a shorter time. Various bacterial and viral antibodies were found in these two patients. One month later, in a patient who achieved remission, IgG and IgM antibodies tests were negative despite that fact that no antiviral or antibiotic therapy were given. We hypothesize that the HPV vaccine triggers the immune system of patients with certain genetic backgrounds, resulting in overactivation of B lymphocytes, which produce a variety of antibodies. Some of these antibodies are cross-reactive with certain bacteria or viruses, leading to false positive tests. Without stimulation from real bacterial or viral antigens, these B lymphocytes gradually deactivate when the dysfunctional immune system stabilizes. In contrast, autoantibodies do not disappear since such antigens are abundant and some B lymphocytes transform to long life plasmacytes.

Studies indicate that the HPV vaccine has high immunogenicity and safety in SLE patients. Nevertheless, literature also indicates autoimmune phenomena can occur after vaccination.[1] Miranda *et al*[5] found that the incidence rate of SLE among unvaccinated and vaccinated girls was 3.42 and 3.23 per 100,000 person-years. We hypothesize that the HPV vaccine may cause earlier onset of SLE in the susceptible population, but not in the general population. We cannot ignore SLE induced by HPV vaccination, especially in those with a medical or family history of autoimmune disease. It is important to evaluate the medical or family history of autoimmune disease and detect the autoantibodies of an individual before vaccination to avoid such serious adverse event.

HPV9 is the latest vaccine and has the potential to offer protection against almost 90% of cervical cancers. However, it may stimulate the immune system more strongly than the other two vaccines. Recipients of the 9-valent vaccine were more likely to experience adverse events. More research is needed to evaluate its safety.

### Declaration of patient consent

The authors certify that they obtained the patient or her family consent for inclusion of the patient clinical information in the study. They were assured that the patient name and initials would not be published, and due efforts would be made to conceal the identity of the patient, although anonymity could not be guaranteed.

### Acknowledgements

The authors thank the patient and her family for their cooperation.

### Conflicts of interest

None.

## References

1. Furer V, Rondaan C, Heijstek MW, Agmon-Levin N, van Assen S, Bijl M, *et al*. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2020;79:39–52. doi: 10.1136/annrheumdis-2019-215882.
2. Ito H, Noda K, Hirai K, Ukichi T, Furuya K, Kurosaka D. A case of systemic lupus erythematosus (SLE) following Human papillomavirus (HPV) vaccination. Nihon Rinsho Meneki Gakkai Kaishi 2016;39:145–149. doi: 10.2177/jsci.39.145.
3. Anaya JM, Reyes B, Perdomo-Arciniegas AM, Camacho-Rodriguez B, Rojas-Villarraga A. Autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA) after quadrivalent human papillomavirus vaccination in Colombians: a call for personalised medicine. Clin Exp Rheumatol 2015;33:545–548.
4. Bragazzi NL, Bridgewood C, Sharif K, Kamal M, Amital H, Watad A, *et al*. HPV vaccines and lupus: current approaches towards preventing adverse immune cross-reactivity. Expert Rev Vaccines 2019;18:31–42. doi: 10.1080/14760584.2019.1557519.
5. Miranda S, Chaignot C, Collin C, Dray-Spira R, Weill A, Zureik M. Human papillomavirus vaccination and risk of autoimmune diseases: a large cohort study of over 2 million young girls in France. Vaccine 2017;35:4761–4768. doi: 10.1016/j.vaccine.2017.06.030.

**How to cite this article:** Wan Y, Yang J, Zhao Y, Jin J, Zhu J, Li K, Zhang J. Systemic lupus erythematosus following human papillomavirus 9-valent vaccination. Chin Med J 2022;135:1864–1866. doi: 10.1097/CM9.0000000000001897