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ORIGINAL ARTICLE

Human papillomavirus vaccine and systemic lupus erythematosus

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Abstract To investigate the association between human papillomavirus (HPV) vaccination and autoimmune manifestations compatible with systemic lupus erythematosus (SLE) or SLE-like disease, the medical history of six women who presented with SLE or SLE-like disease following HPV immunization was collected. Data regarding type of vaccine, number of immunization, family and personal, clinical and serological features, as well as response to treatments were analyzed. In the reported cases, several common features were observed, such as personal or familial susceptibility to autoimmunity or adverse response to a prior dose of the vaccine, both of which may be associated with a higher risk of post-vaccination autoimmunity. Favorable response to immunosuppressant was observed in all patients. In the current study, a temporal association between immunization with HPV vaccine and the appearance of a spectrum of SLE-like conditions is reported. Additionally, among the patients described, several common features were observed that may enable better identification of subjects at risk. Further studies are required to assess the safety of immunization with the HPV vaccine in patients with autoimmune-rheumatic diseases or in subject at risk of autoimmunity as well as the potential beneficial effect of preventive immunosuppressants.

Keywords Anti-phospholipids antibodies · ASIA · Autoimmunity · Human papillomavirus · Systemic lupus erythematosus · Vaccine

Introduction

Human papillomavirus (HPV) infection is widespread worldwide, affecting women of any age, with the highest risk of infection being reported among young women aged 15–19 years [1]. Nearly 80 % of women are predicted to encounter the infection within the first 5 decades of their lives, mostly through heterosexual activity [2].

HPV infects squamous epithelial cells (e.g., uterine cervix), which can be eventually pushed to neoplastic transformation. Nowadays, more than 100 HPV serotypes are known, among them, 40 have been shown to infect the human genital or oropharyngeal tracts [1]. HPV serotypes 16 and 18 are considered to be the most hazardous, being related to the majority (~80 %) of cervical cancer. Notably, cervical cancer is the third most frequent gynecological malignancy and is the fourth leading cause for cancer death in women worldwide [3], of which, the great majority of deaths occurring in developing countries.

In the last decade, two vaccines (Gardasil™ and Cervarix™) were developed for preventing HPV infection and its associated morbidity. Both vaccines (CervarixTM and Gardasil™) are composed of HPV-like proteins, such

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as the L1 viral proteins. The vaccines differ in a way that Cervarix™ is a bivalent vaccine (directed at HPV serotypes 16 and 18) while Gardasil™ is quadrivalent (directed at HPV serotypes 16, 18, 6, 11). Different adjuvants were added to these vaccines, the Gardasil™ utilizes the hydroxyphosphate sulphate adjuvant whereas the Cervarix™ exploits a double-adjuvant system, ASO4 composed of 3-O-desacyl-4′ monophosphoryl lipid A and aluminum hydroxide [4]. Cervarix™ and Gardasil™ are administered through three boost intramuscular injections given within a period of 6 months (at 0, 1, and 6 months, and 0, 2, and 6 months respectively). Both HPV vaccines have been studied in terms of efficacy and safety [5–7]. They were found to be effective, providing a long-lasting protection against HPV infection and premalignant lesions (90–100 % of cases prevented) [6, 7]. Moreover, they may elicit a cross-protective antibody response against other HPV serotypes which are antigenically related to the vaccine-included ones [8, 9]. Both HPV vaccines are well tolerated, and in the general population, only mild local-site reactions and general symptoms such as fatigue, headache, and myalgia were reported following immunization [10, 11]. Nevertheless, it should be noted that a few serious adverse effects were also reported, including venous thrombosis, hypersensitivity reactions, anaphylaxis, motor neuron disease, and even deaths mainly in patients immunized with Gardasil™ [10, 12] of which, only the rate of venous thrombosis was significantly higher than that expected in the general population. Furthermore, an association between Gardasil™ and autoimmunity was suggested following reports of diverse post-vaccination autoimmune conditions [10, 13]. While considering Cervarix™, a large study of more than 60,000 subjects immunized with different ASO4 adjuvanted vaccines was conducted by GlaxoSmithKline Biologicals. In this study, the control groups received vaccines that were ASO4 free, non-adjuvanted, or adjuvanted with aluminum. The overall relative risk for developing an autoimmune disease was found to be 0.98, hence no direct statistically significant difference could be attributed to the ASO4 adjuvant. However, in the entire database, which included data for HPV as well as Hepatitis B and Herpes vaccines, the highest relative risk for an individual autoimmune event was for systemic lupus erythematosus (SLE) (RR-2.39) [14].

Methods

In the current study, we describe six patients who developed SLE or SLE-like disease after administration of the quadrivalent HPV vaccine. Data including demographics, disease manifestations, number of immunizations, family and personal medical history, serological features, as well as response to treatments were collected and analyzed.

Patients' descriptions

Five patients presented with naïve autoimmune disease and one patient with SLE flare.

Patient n° 1

A 32-year-old woman was admitted to the hospital 5 days following the third immunization with Gardasil™. On admission, she suffered from general weakness, severe myalgia, polyarthralgia, anorexia, severe skin rash (urticaria-like), malar rash, aphtous stomatitis, pharyngodynia, cervical lymphadenopathy (more than 3.5 cm), and hair loss. In addition, in the 4 weeks prior to her hospitalization she lost 10 kg of body weight. Laboratory tests demonstrated elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), anemia (without evidence of hemolysis), leucopenia, and lymphopenia. Autoantibodies screening showed positive antinuclear antibodies (ANA) with very high titers of anti-Ro (SSA) and anti-La (SSB) antibodies and high positive anti-dsDNA antibodies. Antiphospholipid antibodies were undetectable. Complement (C3) levels were very low. Urine analysis showed no active sediment and no evidence of infections was documented (i.e., normal blood and urine culture, negative serology for hepatitis, Epstein–Barr virus, cytomegalovirus, parvovirus). CPK and TSH levels were normal, as well as chest radiography and endoscopy. Of note, her medical history was unremarkable prior to immunization. However, mild weakness, facial malar rash, and hair loss were observed following the first immunization (6 months prior to hospitalization). Local reaction to vaccination, fever, fatigue, mild rash, and arthralgia were documented following the second dose but were interpreted as a "common cold." Her family history was remarkable for autoimmune thyroid diseases.

The patient was diagnosed as having SLE and treatment with high-dose prednisone (PDN) and hydroxychloroquine (HCQ) was commenced with gradual clinical improvement. PDN therapy was tapered slowly up to 5 mg/day, HCQ was continued at 400 mg/day along with supplementation of calcium and vitamin D. Eight months afterwards, the patient was in remission, with normalization of inflammatory laboratory parameters (CRP, ESR), as well as blood counts and complement levels.

Patient n° 2

A 29-year-old woman was admitted to the hospital 3 weeks following the second dose of Gardasil™ due to severe weakness, diarrhea, and elevated markers of inflammation. On admission, her physical examination revealed malar rash, photosensitivity, arthritis, and alopecia. In the next couple of months, she lost 30 % of her body weight and

remained hospitalized. Laboratory tests demonstrated elevated ESR, high titers of ANA, and anti-dsDNA antibodies, low levels of complement, and proteinuria of 1 g/day. The patient was diagnosed with SLE and severe protein-losing enteropathy.

Her medical history included immune thrombocytopenia diagnosed several years before immunization. At that time, she had normal bone marrow biopsies and no detectable serum autoantibodies, including ANA. She was treated with PDN and intravenous immunoglobulins. Two years prior to the administration of HPV vaccine, she underwent splenectomy with normalization of her platelet counts, and abortion of additional therapies. Of note, the patient was immunized with pneumococcal vaccine, as required, before splenectomy with no adverse events. In addition, the patient was diagnosed with early cervical intraepithelial neoplasia related to HPV months before immunization with Gardasil™. Her family medical history was unremarkable for autoimmune disorders.

Following immunization and diagnosis of SLE, she was treated with high-dose corticosteroids, azathioprine (AZA) and HCQ with gradual remission of her symptoms which were followed by slow down-tapering of PDN and AZA doses. Two years following the diagnosis of SLE, the patient achieved clinical and serological remission excluding ANA seropositivity and traces of protein in her urine. Her present therapy comprises of HCQ and calcium/vitamin D supplementation.

Patient n° 3

A 16-year-old high school girl was admitted to the Infectious Diseases Department because of high-grade fever (39.5 °C), generalized asthenia, diffuse polyarthralgia, and multiple erythematous annular cutaneous lesions on the face, trunk, and lower limbs which occurred 8 days after the first dose of Gardasil™ (Fig 1a–b). While she received the vaccine, she developed low-grade fever, which was interpreted as viral flu syndrome. Laboratory examinations revealed normochromic normocytic anemia with elevated CRP and ESR, an extensive bacterial and viral screening was negative, and her urine sediment was normal. Autoantibodies profile revealed seropositivity for ANA and lupus anticoagulant (LAC). Her medical and family histories were remarkable for Raynaud's phenomenon while her maternal aunt was diagnosed with systemic sclerosis.

A diagnosis of "lupus-like" syndrome was determined and the patient was treated with intravenous high-dose methylprednisolone followed by oral PDN. Following initiation of treatment, her blood temperature normalized and her skin lesions significantly improved (Fig 1c–d), with almost complete resolution in a month, while receiving 50 mg of PDN (Fig 1e–f). The latter was tapered down within 6 months, and at 1 year following immunization, the patient was in good health.

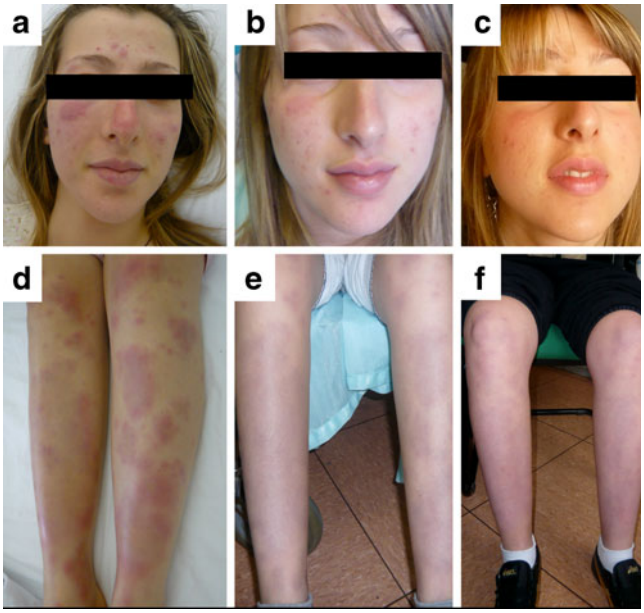

Fig. 1 Multiple erythematous cutaneous lesions of the face and lower limbs of patient number 3, occurring 8 days after the first dose of Gardasil™ (**a**–**b**), 1 week later in course of steroid therapy (**c**–**d**) and 1 month later (**e**–**f**)

Patient n°4

A 16-year-old high school girl was admitted to the hospital with a preliminary diagnosis of FUO (fever of unknown origin), which appeared for the first time 3 weeks after the second dose of Gardasil™. Fever was prolonged, mainly present in the morning, and rose up to 39 °C. In addition, pharyngodynia, erythematous skin lesions of elbows and knees, generalized asthenia, anorexia, polyarthralgia, and headaches were present. Pharyngeal culture as well as the urine and blood cultures excluded active infections. Laboratory workup revealed normochromic normocytic anemia, slight increase of serum amyloid A (SAA) levels of 9 mg/l (normal less than 6 mg/l). Proteinuria was absent. Autoantibodies profile demonstrated persistent positivity of anti-cardiolipin IgM and LAC. Magnetic resonance imaging of the brain excluded the *presence of brain abnormalities* consistent with antiphospholipid syndrome.

Her medical history was remarkable for recurrent tonsillitis during childhood and a streptococcus group B infection 1 year before admission, treated with penicillin. In addition, the patient suffered from Raynaud's phenomenon grade II, defined by nailfold capillaroscopy. Her family history was also remarkable for Raynaud disease of patient's mother.

The patient was diagnosed with fever in a patient with antiphospholipid antibodies, possibly related to Gardasil™

vaccination, compatible with the autoimmune/auto inflammatory syndrome induced by adjuvants (ASIA). She was treated with naproxen 500 mg/day for 2 months and omega-3 polyunsaturated fatty acids 2,000 mg/day for 4 months; the doses were very gradually tapered down. She was discharged with instructions to avoid sun exposure and to avoid further vaccination. At follow-up visit, the patient was in remission and in good health.

Patient n° 5

A 19-year-old SLE patient was diagnosed with SLE flare 10 days following the second dose of Gardasil™, while in retrospect minor symptoms were already acknowledged following the first immunization. The patient was diagnosed with SLE 4 years prior due to the appearance of malar rash, typical SLE skin rash, arthritis, positive serology for ANA and anti-dsDNA antibodies, as well as very low C4 complement levels. She was treated with corticosteroid and HCQ and achieved a full clinical remission with normalization of complement and anti-dsDNA antibodies levels. Her maintenance therapy included low-dose HCQ and vitamin D. Following the first dose of HPV immunization, she experienced mild arthralgia, dyspnea (with no abnormalities on her chest x-ray), cervical lymphadenopathy, and skin rash. Treatment with PDN 40 mg/day was commenced with good response and the dose was slowly tapered down. Although otherwise advised, the patient decided to receive the second boost of the vaccine. This time SLE-symptoms were more pronounced with very notable malar rash, severe skin rash, cervical lymphadenopathy of more than 3 cm, alopecia, leucopenia, elevated ESR, and decreased complement levels. Corticosteroids dose was increased, and following discussions with the patient, therapy with belimumab (anti-BLyS) was commenced, which induced an improvement.

Patient n° 6

A 13-year-old African-American female approached her general physician 3 weeks following immunization with the second dose of Gardasil™ due to swelling of her index finger and a rash. During the following couple of months, she developed erythematous rash on her face, fever, periorbital edema, weight loss, malaise, fatigue, cervical, axillary and inguinal lymphadenopathy, as well as mild anemia. At this stage, she was referred to a rheumatologist who noted that she had a petechial rash, alopecia, leucopenia of *2,100 cells/mm*^{3}, and mild thrombocytopenia.

Further evaluation documented seropositivity for ANA, anti-RNP, anti-Smith and anti-RO/SSA antibodies as well as low C3 and C4, elevated ESR. The CRP level was normal. The patient was diagnosed with SLE. Hydroxychloroquine and prednisone treatment was started. Despite therapy, disease progression was documented with the appearance of CNS (i.e., seizures) and kidney involvement. Renal biopsy was compatible with mesangial proliferative glomerulonephritis, class II lupus nephritis. Thus, therapy was enhanced with high-dose steroids, cyclophosphamide, as well as antiepileptic medications. Under this therapy, there was gradual remission of the SLE. Notably, her personal medical history was remarkable only for common infections and a rash due to pityriasis rosea treated and resolved several months before immunization. Her family history revealed several members of the family with autoimmune diseases including SLE.

Discussion

The above reported cases reveal a temporal association between immunization with Gardasil™ and the appearance of a spectrum of SLE-like conditions. Lately, other cases of SLE onset or relapse following HPV vaccinations were reported [15]. Moreover, several features were common among patients (Table 1), and may shed some light on the link between HPV immunization and SLE.

In this study, all patients had a personal or family history of autoimmune-rheumatic conditions suggesting genetic or epigenetic contributing components. Genetic factors are key players in the mosaic of autoimmunity and complex genetic and epigenetic predisposition was defined in patients with SLE [16–19]. It has been noted that some vaccines may trigger autoimmunity in a predisposed recipient, since they widely stimulate the immune system [20, 21]. Specifically, SLE onset was reported after diverse vaccinations [22–24], while narcolepsy, another autoimmune disorder, was recently reported as having a strong link with genetic markers as well as the adjuvanted H1N1 vaccine [25]. In this context, it is important to mention that there are clinical data regarding using non-adjuvanted influenza A/H1N1 vaccine in a large cohort of autoimmune-rheumatic diseases, where the response to the vaccination was reduced, although adequate [26]. Intriguingly, adjuvants contained in many vaccines may per se tantalize both the innate and the adaptive immune response resulting in aberrant autoreactivity [27, 28]. Thus, one may suggest that a common denominator to post-vaccination autoimmunity is genetic or epigenetic vulnerability, and that personal or familial medical history of autoimmunity should be considered a risk factor for such adverse events. On the other hand, although vaccines related perturbations of the immune state may rarely unveil autoimmunity [21], patients affected with autoimmune-rheumatic diseases are at risk of infectious diseases owing both to impairment in their immune system and/or to the immunosuppressive therapy they often

Table 1 Summary of six patients with SLE and/or SLE-like manifestations following HPV immunization

Patient number	Age of patient (years)	First manifestations (following HPV immunization)	Diagnosis of SLE/SLE-like disease (following HPV immunization)	Personal history of autoimmunity	Family history of autoimmunity	Diagnosis (following HPV immunization)	Response to therapy
1	32	1st dose	3rd dose	negative	positive	SLE	Good
2	29	2nd dose	2nd dose	positive	negative	SLE	Good
3	16	1st dose	1st dose	positive	positive	SLE-like	Good
4	16	2nd dose	2nd dose	positive	positive	Fever-APLA	Good
5	19	1st dose	2nd dose	positive	negative	SLE flare	Good
6	13	2nd dose	2nd dose	negative	positive	SLE	Good

undergo [29]. Particularly, women affected with SLE display a higher prevalence of HPV infection as compared to the general population [30, 31]. As such, they should be carefully followed for HPV-related diseases (e.g., performing PAP smears regularly), as well as assessed for vaccination directed at HPV and others infectious agents. In summary, it seems that a careful individualized risk assessment is required regarding both the patient medical history of autoimmune and infectious diseases as well as history of adverse reactions to past vaccination is needed [20].

Another point for consideration was reported in four of the patients described. These patients received boost immunization (second or third vaccination) although mild adverse events were observed following a previous dose of Gardasil™ (Table 1). Notably, in most healthy subjects, mild adverse events following immunization are transient and can be disregarded. Alas, in a high-risk population, these mild events may be of significance, and although further studies are required, it seems that assessment following each boost of vaccination may be beneficial [23].

In this study, all patients responded favorably to therapy with corticosteroids, antimalarial drugs, and immunosuppressants, further supporting the notion that immune-mediated mechanisms underline these post-vaccination events. In addition, at the time of immunization, only one patient was treated with low-dose HCQ. The latter was found to be beneficial both for active therapy as well as for prevention of SLE exacerbations [32]. Thus, we could speculate that immunomodulatory therapy taken appropriately at the time of immunization may have a protective effect for patients at high risk for post-immunization adverse responses [33].

Notably, patients with autoimmune-rheumatic diseases are likely to achieve a less striking seroconversion (fourfold antibody increase after injection) as compared to healthy controls, especially while receiving immunosuppressants such as mycophenolate or azathioprine [34, 35]. Nonetheless, in most studies anti-infectious immunity following vaccination was achieved regardless of immunosuppressant use [20].

As pointed above, in addition to our series, another case series of three patients from the Philippines with SLE flares was reported recently [15]. Moreover, other autoimmune and neurological immune-mediated conditions have been related to HPV vaccination [10, 36, 37, 38]. With regard to HPV vaccines, and particularly Gardasil™, no large studies have ever outlined a significant incidence of autoimmune disorders in immunized populations [39, 40]. However, limitations to these large studies, especially in assessing rare events, have been underlined before. Extremely large cohort studies are required for investigation of rare events, a longer follow-up duration may be needed for assessment of post-immunization effects and the lack of data regarding immune modulatory therapy taken at the time of immunization may be of importance. Performing such studies may be difficult, if not, impossible [40, 41]. Recently, official recommendations for vaccinations of patients affected with autoimmune-rheumatic disorders were drawn by a task force of the European League against Rheumatism [20, 42, 43]. By which, vaccination is recommended to these patients depending on the prevalence of the infective disease, the safety of the individual vaccine, and the ongoing activity of their autoimmune-rheumatic condition while hazardousness of some vaccines/ adjuvants is still being explored [20, 21, 27, 28]. In our study, as well as in the study from the Philippines mentioned above, HPV vaccine, which is indicated mainly to young women, was recommended to relatively older patients at the age of 32, 45, and 58 years. Furthermore, in our cohort, one of the patients was immunized following a documented HPV-related cervical carcinoma in situ.

In summary, based on the current data, a causal link between HPV vaccination and onset or relapse of SLE is plausible. Therefore, although for most patients, the benefits of immunization outweigh its risks, clinicians must be aware of the odds for an autoimmune disease onset or exacerbation following HPV vaccination. A meticulous pre-vaccination risk-benefits assessment, close follow-up during and after each boost of vaccination, as well as assessment of concomitant therapy with immune-modulating agents such as HCQ,

seems reasonable for patients with an autoimmune disease. Last but not least, a growing need to define risk factors (i.e., genetic susceptibility markers) and methods of intervention to decrease post-vaccination autoimmunity in healthy and diseased populations is yet unmet. Encouraging physicians to report similar cases and establishing active vaccines surveillance registries [44] may improve our knowledge and decision making regarding vaccinations in the future.

Disclosure YS appears in court defending subjects afflicted by immunization. All other authors: disclosure: none.

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