Autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA) after quadrivalent human papillomavirus vaccination in Colombians: a call for personalised medicine

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ABSTRACT

This was a case study in which 3 patients with autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA) after quadrivalent human papillomavirus vaccination (HPV) were evaluated and described. All the patients were women. Diagnosis consisted of HLA-B27 enthesitis related arthritis, rheumatoid arthritis and systemic lupus erythematous, respectively. Our results highlight the risk of developing ASIA after HPV vaccination and may serve to increase the awareness of such a complication. Factors that are predictive of developing autoimmune diseases should be examined at the population level in order to establish preventive measures in at-risk individuals for whom healthcare should be personalised and participatory.

Introduction

Vaccines have been safely and effectively administered to humans and animals worldwide for over 200 years, thus allowing the elimination of many serious and life-threatening infectious diseases. Nevertheless, the World Health Organization has defined four causal adverse event following immunisations: those directly related to the vaccine (A1), those related to vaccine quality (A2), those due to immunisation error (A3) and immunisation anxiety-related reactions (A4) (1). Autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA) entails autoimmune or autoinflammatory conditions appearing after the exposure to an external stimuli of an adjuvant including vaccines (2). Herein, we report three patients who developed ASIA after quadrivalent human papillomavirus vaccination (HPV4) in Colombians.

Patients

Patient 1

A 16-year-old Mestizo female presented to our hospital with a history of joint swelling of left knee lasting for a month and preceded by an episode of diarrhea some days before. However, her past medical history was remarkable for inflammatory back pain appearing 14 months ago after a month of having received an initial HPV4 dose. The second dose was administered with a six-month interval. Low back pain persisted and was associated with chest wall pain (*i.e.* costochondritis) and alternating buttock pain. There was no notable family or medical past history. The initial examination in the emergency department revealed tenderness at right buttock, right trochanteritis, Achilles enthesitis in right foot, and pain on motion and joint effusion in the left knee. Synovial fluid obtained from arthrocentesis disclosed a leukocyte count of 3 800/μL (predominantly neutrophils), while the examination for microorganisms and for crystals was negative. Additional laboratory findings revealed a white blood cell count of 10.920/μL, C-reactive protein (CRP) of 9.2 mg/dL, and erythrocyte sedimentation rate (ESR) of 50 mm/hour. Thyroid function tests (TFTs) results were within the reference ranges. Antinuclear antibodies (ANAs), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibodies were negative as were serological tests for Epstein-Barr virus (EBV), cytomegalovirus (CMV) and Parvovirus B19 (PB19). Human leukocyte antigen B27 (HLA-B27) was positive (Table I).

The diagnosis of enthesitis related arthritis (ERA) was established. Non-steroidal anti-inflammatory drug (NSAID) and paracetamol administration was initiated, together with physical therapy. An improvement was evident in the following days persisting during follow-up, with no additional symptoms (Table I).

Patient 2

A 20-year-old female with Mestizo ancestry presented to our consultation with a history of myalgias and arthralgias lasting for almost 8 months, having appeared a month after the second dose of HPV4 vaccine. After 6 months of the beginning of symptoms, she developed livedo reticularis followed by the appearance of Raynaud's phenomenon. In the last month, she developed headache and tinnitus with no other neurological symptoms. The patient denied previous history of spontaneous abortions or any previous thrombosis, but reported migraine and genital warts as personal medical history, with no notable family

history. The physical examination was remarkable for bilateral pain and swelling around the second and third metacarpophalangeal joints, right elbow and knees. The rest of the physical exam including neurological and vascular examinations was normal. Laboratory investigations revealed ANA 1:160 with a speckled and homogeneous pattern, prolonged partial thromboplastin time together with a positive lupus anticoagulant (LAC) test and anti-CCP antibodies at a moderate titre (44 U/ml). Complete blood count, liver and renal function tests, TFTs, ESR and PCR were within the normal ranges. Anti-double-stranded deoxyribonucleic acid (dsDNA) and extractable nuclear antigen antibodies were negative as were anti-cardiolipin and anti-beta 2-glycoprotein I antibodies. Serological tests for EBV and CMV were negative but IgG PB19 was positive. A diagnosis of rheumatoid arthritis (RA) was considered, although the possibility of polyautoimmunity due to systemic lupus erythematosus (SLE) was not completely ruled out (*i.e.* rhupus). Low dose prednisolone and hydroxychloroquine (HCQ) were initiated. HLA genotyping disclosed non-classical alleles associated with RA (Table I). The patient has been followed-up for four months with clinical improvement (*i.e.* articular index = 0), and no additional symptoms.

Patient 3

A 19-year-old female with Hispanic-Asian ancestry was seen in August 2014 for a second opinion consultation. Her family history was remarkable for autoimmune type 1 diabetes in her father. She had been diagnosed with SLE elsewhere in January 2014. Her clinical picture began in June 2013 a month after having received the first dose of HPV4 vaccine, and was characterised by cervical adenopathy, odynophagia, and dysphonia, treated with NSAID. During the next month, the patient developed myalgia, arthralgia and arthritis. Two months later, she presented with generalised weakness, oral ulcers, Raynaud's phenomenon, and alopecia. A month later, a first episode of fever was registered. At the end of December 2013, the patient was admitted to the emergency department because of fever, dyspnea at rest, headache, acute confusional state, and agraphia, lasting for two weeks. On admission, she presented with arterial hypotension, tachycardia, and gallop rhythm. She was admitted to the intensive care unit (ICU) where a pericardial effusion was confirmed by transthoracic echocardiogram. A pericardiocentesis was performed. She had a normal cranial computed tomography scan, but cerebrospinal fluid analysis revealed aseptic meningitis. No abnormalities were observed on brain magnetic resonance imaging. Immunology laboratory tests disclosed the presence of ANA (1:5120), anti-Sm, Anti-Ro, anti-RNP, anti-dsDNA, leukopenia, and complement consumption.

During ICU hospitalisation a urinary tract infection due to *Kluyvera ascorbata* was treated with ertapenem. Otherwise, liver and renal function tests were within the normal ranges. Intravenous cyclophosphamide and corticosteroid initially with three pulses of methylprednisolone 1g daily for 3 consecutive days and then steroids in the form of oral prednisolone 1mg/kg/day were administered. Within days of treatment, dramatic improvement was observed. The patient was subsequently placed on a disease-modifying therapy regimen, including HCQ and azathioprine. The prednisone was tapered. During follow-up the patient did not present any other SLE flare-up. On December 2014, when the patient consulted our centre, she was found in remission with normalisation of complement serum levels and negative anti-dsDNA antibodies. Although TFTs and antithyroglobulin antibodies were normal and negative, respectively, anti-thyroid peroxidase antibodies were positive (46.65 UI/mL, reference value <26 UI/mL). Infection serology tests revealed a positive IgG for EBV and negative results for PBB19, hepatitis C virus, human immunodeficiency virus, Herpes virus type II and CMV. HLA genotyping disclosed DRB1*15:02:01 (Table I).

Discussion

Three cases of HPV4-related reaction are reported (*i.e.* A1) (1). The development of ADs is a very important issue related to vaccines because of the risk that vaccines might promote autoimmune phenomena in susceptible individuals. The causality assessment of vaccination in ADs involves the demonstration of a significantly increased risk of these diseases in women who are vaccinated as compared with those who are not. The incidence of ADs ranges from one to 20 cases per 100,000 person-years (3), and varies from one region to another. These diseases are multifactorial and occur through the interaction of multiple hereditary and environmental factors over time.

An observational safety study for HPV4 in Californian women who received at least one dose of the vaccine reported a higher incidence rate for Hashimoto's disease in vaccinated females when compared to unvaccinated ones (4). Many confirmed "new-onset" events were likely pre-existing cases (4). Moreover, a Swedish and Danish study disclosed a significant association between exposure to HPV4 vaccine and Behçet's syndrome, Raynaud's disease, and T1D (5). Peculiarly, an "independent review committee" in the Californian study (4) as well as the introduction of "strengthening indicators" in the Nordic study (5) made the associations disappear. In France, a study (6) reported an association between a personal and family history of autoimmunity and the development of ADs post vaccination with HPV4, thus confirming the familial clustering of ADs (7). It also confirmed that exposure to the vaccine might spark the overt expression of an autoimmune clinical condition. However, when data were adjusted for the personal and familial history of autoimmunity, the association was no longer confirmed (6). The authors, nevertheless, acknowledged that statistical power was insufficient to allow conclusions to be drawn regarding individual ADs (6). More recently, a small although non-significant increase in the risk of multiple sclerosis was observed after HPV4 vaccination (8). The authors argued that "the short-term increase in risk suggests that vaccines may accelerate the transition from subclinical to overt autoimmunity in patients with existing disease." At the

Table I. General characteristics of patients with ASIA.

Characteristic	Patient 1	Patient 2	Patient 3
Gender	Female	Female	Female
Age at vaccination (years)	15	20	18
Type of vaccine	HPV4	HPV4	HPV4
Vaccination scheme	Two doses	Two doses	One dose
First symptom	Low back pain	Arthralgia	Cervical adenopathy
Delay of first symptom after first vaccine application (months)	1	7	1
Diagnosis delay (months)	14	8	8
Personal history of autoimmunity	No	No	No
Familial autoimmunity	No	No	T1D (Father)
Final diagnosis	Juvenile SpA (enthesitis related arthritis)	RA	SLE
Response to therapy	Good	Good	Good
Follow-up time after diagnosis (months)	4	4	12
HLA-A	*02:22:01/*02:01:01	*03:01:01/*29:02:01	*24:02:01/*68:01:02
HLA-B	*27:05:02/*35:49	*15:16:01/*44:03:01	*39:05:01/*52:01:01
HLA-C	*01:02:01/*04:01:01	*14:02:03/*16:01:01	*07:02:01/*12:02:01
HLA-DRB1	*03:01:01/*08:02:01	*07:01:01/*09:01:02	*15:02:01/*08:02:01
HLA-DQB1	*02:01:01/*04:02:01	*02:01:01/*02:01:01	*04:02:01/*06:01:01

HPV4: quadrivalent human papillomavirus vaccine; SpA: spondyloarthropathy; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus.

time, they recognised that larger studies are needed to completely rule out an effect (8). All together, these studies indicate that a personal or family history of autoimmune disease may indicate a risk of post-vaccination autoimmunity.

On the other hand, there are two studies suggesting that vaccination against both bivalent HPV (HPV2) and HPV4 is not contraindicated in patients with SLE (9, 10) and two studies showing safety and absence of relapses in patients with juvenile RA after HPV2 vaccination (11, 12). However, these studies preclude definitive conclusions, as they lacked genetic analysis and appeared underpowered.

The European League Against Rheumatism (EULAR) recommends following the HPV vaccination guidelines for each country while stressing the fact that there is an increased risk of HPV infection in female patients with SLE (13). These 2011 EULAR guidelines also indicate that physicians should be aware of possible thromboembolic events although these events cannot be unequivocally attributed to HPV vaccination (13).

In two of our patients, a previous viral exposure was evidenced (*i.e.* EBV and PB19) which did not preclude the diagnosis of ASIA or the involvement of HPV vaccination in triggering the AD. In fact, it has been suggested that for a clinically overt adjuvant disease, additional risk factors are required such as genetic susceptibility or co-exposure to other environmental factors (2). Furthermore, cases similar to ours have been reported previously (14-16). Recently, the epidemiological characteristic of ASIA among patients who developed it after vaccination with the HPV vaccine was evaluated based on the Vaccine Adverse Event Reporting System (VAERS) (17, 18). The estimated reporting rate was 3.6 cases per 100,000 doses of HPV vaccine distributed with a 95% confidence interval (CI) of 3.4–3.7 (17). In particular, the significant odds ratio (95% CI) of developing SLE, vasculitis, arthritis, and central nervous system conditions after HPV4 vaccine administration were 5.3 (1.5–20.5), 4 (1.01–16.4), 2.5 (1.4-4.3) and 1.8 (1.04–2.9) respectively (18). The median onset of symptoms revealed that vasculitis was associated with the closest median onset of symptoms following HPV4 vaccination (6 days), and arthritis was associated with the longest median onset of symptoms following HPV4 vaccination (55 days) (18).

The main known factors influencing the observed heterogeneity for immune responses induced by vaccines are gender, age, co-morbidity, immune system, and genetic background (19). Epidemiological and family vaccine studies showing familial aggregation of vaccine responses together with many association studies identifying both HLA and non-HLA gene markers that influence the heterogenic response to vaccine support genetics as a main factor in vaccinomics (19). The involvement of genetic factors in the development of ASIA has also been suggested (20, 21).

Our first case carried the HLA-B*27:05-C*01:02 haplotype, which is associated with Juvenile SpA (22) and enthesitis (23). HLA-B*27:05 has also been associated with reactive arthritis and ERA (24, 25). In addition, HLA-DRB1*08 also influences the development of Juvenile SpA (Table I) (25). The second patient, who developed RA and in whom rhupus was suspected (26), carried the HLA-DRB1*07:01:01 and *09:01:01 alleles which are thought to confer protection or have no influence on the risk of developing RA (27). She also carried the HLA-DQB1*02:01:01 allele which has been associated with SLE in Caucasians but not in Latin Americans, except when it is part of the DR3-DQ2 haplotype (28). Thus, this case highlights the fact that HLA is neither sufficient for nor indispensable to the development of RA. In fact, ADs like RA are polygenic conditions. The third patient carried DRB1*1502, which is a frequent allele in Asians and has been associated with SLE (29). Although evident genetic commonalities were not observed in our three cases, the first and third patients carried susceptibility alleles for the respective disease they developed. Genetic analyses

have not been done on all the reported cases of ASIA. Thus, further and larger studies are needed to elucidate the potential role of genetics in this syndrome. In conclusion, the benefit-risk ratio of developing ADs after HPV vaccination has not yet been resolved. Therefore, permanent pharmacovigilance of this vaccine is of paramount importance. Translational and personalised medicine still need better attention from not only the scientific but also the political and economic viewpoint (30). No matter how the scientific and political postures and economic monopolies are defined, it should be clear that, from any point of view, human protection should be safeguarded and prioritised. A personalised analysis of each individual, which includes an evaluation of personal and familial autoimmunity as well as a genetic test, is suggested in order to calculate the risk of developing AD after HPV vaccination. Then, individuals should be informed about their results and asked to participate in their own healthcare decisions.

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