Case and Review

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The Quadrivalent Human Papillomavirus Vaccine: Erythema Multiforme and Cutaneous Side Effects after Administration

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Key Words
Erythema multiforme · Human papillomavirus · Immunization

Abstract
The quadrivalent human papillomavirus (qHPV) vaccine, the first vaccine for use in the prevention of cervical cancer and condyloma acuminatum, was approved in June 2006. In 2008, the mass media reported suspected links between the qHPV vaccine and serious adverse events; however, several studies have found that the vaccine is safe and the main adverse events are mild local reactions. Erythema multiforme (EM) is an acute self-limited cutaneous or mucocutaneous syndrome characterized by the abrupt onset of symmetric target lesions. The clinical manifestations and histological features of EM, Stevens-Johnson syndrome and toxic epidermal necrolysis show considerable overlap, and they are classically considered to represent a spectrum of skin disorders. We present a case of EM following qHPV vaccination to review the cutaneous side effects of this vaccine and the possibility of more serious side effects with the administration of booster doses.

Case Report

A healthy 15-year-old female presented with a 2-day history of symmetric multiple erythematous-oedematous papules on the extremities that enlarged gradually into target lesions (fig. 1). There was no evidence of mucosal involvement, fever or respiratory symptoms, although mild arthralgias were present. The patient had been vaccinated 7 days earlier with her third dose of quadrivalent human papillomavirus vaccine (qHPV). She had received no medication before the onset of her cutaneous eruption, and she had no history of herpes simplex virus (HSV) infection. Due to clinical suspicion of erythema multiforme (EM), a punch biopsy was taken from the elbow. The histology showed dermal oedema, perivascular mononuclear cell infiltrate and interface dermatitis, with vacuolar damage and necrotic keratinocytes. The histopathological features were consistent with a lesion of EM. Complete analyses were within normal limits. Viral serological tests (HSV-1 and -2, cytomegalovirus, Epstein-Barr virus, enterovirus) and a serological test for *Mycoplasma pneumoniae* were all negative.

A diagnosis of EM was made on the basis of the clinical presentation and histology. The absence of a history of herpesvirus infection or any other cause of EM and the temporal relationship with qHPV vaccination suggest that the cause of EM was the qHPV vaccine. The patient was treated with a low dose of oral corticosteroids and oral antihistamines, and all of her lesions resolved completely and without scarring in a few days.

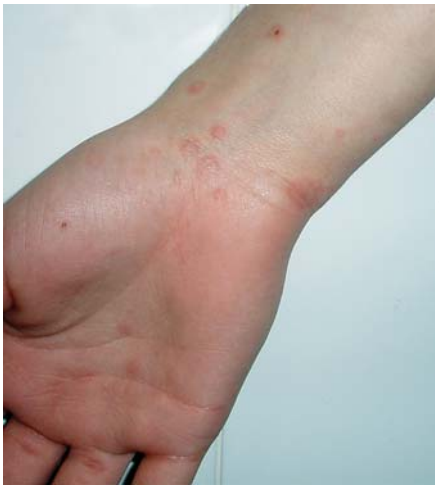

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Fig. 1. Erythematous papules on the wrist that evolved into target lesions.

Discussion

EM is an acute, self-limited but frequently recurring cutaneous or mucocutaneous syndrome characterized by the abrupt onset of symmetric red papules that may evolve into target lesions, typically involving the extremities [1, 2]. The pathophysiology of EM is not certain but is believed to be immune-mediated. EM is most commonly caused by infections, especially by HSV and by *M. pneumoniae* [1]. Other causes of EM include drugs (barbiturates, hydantoins, sulphonamides, pheno-

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thiazines, penicillins and non-steroidal anti-inflammatory drugs), haematological disorders and other viruses [1–3]. In addition, there have been reports of EM and Stevens-Johnson Syndrome (SJS) associated with vaccination (diphtheria-tetanus, hepatitis B, smallpox, meningitis and others), supporting the hypothesis that EM and SJS are a host-specific response to a wide variety of infectious antigenic stimuli [1–6]. Our patient is the second case of EM following HPV vaccination reported in the literature.

The clinical manifestations and histological features of EM, SJS and toxic epidermal necrolysis (TEN) show considerable overlap. These entities are classically considered to be a part of a spectrum of skin disorders characterized by polymorphous lesions affecting the skin and/or mucosa, with variable amounts of necrosis among basal keratinocytes and/or mucosal epithelial cells [1, 7].

It has been proposed that EM and SJS/TEN could represent 2 distinct nosological entities with specific clinicopathological and immunological features [7–9]. However, many authors still consider EM, SJS and TEN to be a single disease group with different degrees of clinical severity. Although the causes of EM and SJS/TEN are usually different [8], several agents have been reported as precipitating factors for both EM and SJS/TEN [10–13]. The clinical manifestations of EM and SJS often differ [8], but sometimes there is clinical overlap [13]. In these cases, it is difficult to decide whether a patient has EM or SJS. Leaute-Labreze et al. [13] suggested that an aetiological classification would be more satisfactory than a clinical classification based solely on skin eruptions.

Quaglino et al. [14] performed several studies investigating the pathophysiology of both EM and SJS/TEN. These authors found differences in the expression of interleukin 13, Fas, cytokines and chemokine receptors in the cutaneous lesions of patients with EM compared to those with SJS/TEN [15]. However, the serum levels of interleukin 12 and the chemokine TARC [9] as well as the expression of matrix metalloproteinases 2, 9 and 11 [16] were increased in both EM and SJS/TEN; no statistically significant differences existed between the two groups. The immunological background that characterizes EM and SJS/TEN is still poorly defined, and further studies are needed to clarify if EM and SJS/TEN are different diseases or are part of a single spectrum of skin disorders.

Recurrent EM is usually associated with HSV recurrences [13]. Chang et al. [17] reviewed the medical records of 207 patients hospitalized with a diagnosis of EM, SJS or TEN. In this study, recurrences occurred in 5 (2.4%) of the patients, and all were attributed to drugs. Two patients with SJS had severer mucocutaneous manifestations at the second attack. The other 3 patients (1 with EM and 2 with TEN) had attacks of similar severity when compared with the first episode [17]. Huang et al. [18] reported a case of TEN induced by carbamazepine in a patient who previously experienced SJS induced by the same drug. However, there is no evidence that EM may recur as SJS/TEN.

EM, SJS and TEN have been reported after vaccination in some cases [2–6, 19]. As mentioned above, it is unclear whether EM and SJS/TEN are different entities. Therefore, there is controversy over whether booster doses of the vaccine could trigger SJS or TEN in patients who have previously suffered EM following vaccination. Although there are a few case reports of EM following vaccination in the literature, the exact incidence of such cutaneous reactions has not been determined [3].

There is a paucity of information regarding the administration of booster doses following an adverse reaction. Gold et al. [20], after studying 970 children revaccinated with booster doses, concluded that only anaphylaxis and encephalopathy are absolute contraindications for continuing the vaccination programme. Katoulis et al. [4] suggested that EM minor is a mild adverse reaction, and their studied patient completed the vaccination programme successfully. The administration of the third booster dose was followed by transient recurrence of EM [4]. However, Studdiford et al. [6] recommended that patients who develop EM following vaccination should not be given additional doses due to the potential for more serious dermatological reactions with repeated exposure. Therefore, although the occurrence of EM following vaccination is not an absolute contraindication for revaccination, we recommend that care be taken in the revaccination of these patients, with close monitoring due to the possibility of developing more serious side effects, such as EM major, SJS or TEN.

In June 2006, the Food and Drug Administration approved Gardasil® (qHPV vaccine for types 6, 11, 16 and 18), the first vaccine for use in the prevention of cervical cancer and condyloma acuminatum. The vaccine is composed of recombinant HPV capsid L_1 proteins derived from HPV-6, -11, -16 and -18, which cause 70% of cases of cervical cancer. In addition, the drug's formulation includes 225 μg of aluminium hydroxyphosphate sulphate as an adjuvant [21]. Other constituents include sodium chloride, L-histidine, polysorbate and sodium borate, plus residual yeast components from the expression vector, *Saccharomyces cerevisiae* [22]. In 2008, the mass media reported suspected links between the qHPV vaccine and serious adverse events; however, several studies have found that the vaccine is safe and that the risk associated with receipt of the qHPV vaccine appears to be minimal as compared with infection with the virus [23, 24]. The main adverse events of the vaccine are mild local reactions (pain, erythema and swelling) and some systemic responses (fever, nausea and dizziness) [23]. The proportion of subjects who reported an adverse experience tended to be higher after the first injection than after subsequent injections [25].

Cutaneous side effects of qHPV vaccine are frequent. Local injection site reactions are the most common cutaneous side effects of qHPV vaccine. The reaction usually begins on the day of vaccination [25]. According to studies, the frequency varies between 1 and 81.7% [25–30]. These reactions are usually mild, such as injection site pain, erythema and swelling. Other local reactions, such as cellulitis [25], lipo-atrophy [26], aluminium granuloma [21] or iatrogenic subcutaneous emphysema [27], are less frequent. In a study performed in 2007, Reisinger et al. [28] found a significantly higher proportion of subjects reporting injection site adverse experiences in a qHPV vaccine group as compared to a non-aluminium-containing placebo group. Other studies showed similar results [29–30]. In a study of a cohort of Latin American subjects, more adverse vaccine experiences were reported by patients who received qHPV vaccine as compared to those subjects who received aluminium-containing placebo [31]. This increase in the frequency of adverse experiences seen in subjects receiving qHPV was due to increased numbers of adverse events at the injection site [31]. Similarly, Muñoz et al. [32] reported that the injection site adverse events were mainly responsible for the slight increase in adverse events in the vaccine group as

compared with the aluminium-containing placebo group.

It appears that local reactions following qHPV vaccine are mainly related to the aluminium content in the vaccine. Aluminium has been suspected to play a role in the development of local reactions with other vaccines [33]. However, an error in injection technique [28] or involving components of the vaccine, including HPV-like particles of the major capsid (L_1), could be responsible for local reactions in other cases [31, 32].

Cutaneous hypersensitivity reactions have been reported after qHPV vaccination including urticaria, rash, pruritus, anaphylactic reaction, angio-oedema and dermographism. Slade et al. [25] summarized reports to the Vaccine Adverse Event Reporting System following receipt of qHPV vaccine. In that study, the rate of hypersensitivity reactions was 3.1/100,000 doses. Urticaria was the most frequent reaction, with a rate of 2.6/100,000 doses. The median time interval from immunization to onset of symptoms of urticaria was 17 days, and 96% of these cases were non-serious events. The rate of anaphylaxis was 0.1/100,000 doses. The majority of these cases occurred on the same day as vaccination [25]. Kang et al. [34] evaluated hypersensitivity reactions to qHPV vaccine in Australian schoolgirls. The authors suggested that true hypersensitivity to HPV vaccine is uncommon and that urticaria is often idiosyncratic and not usually a contraindication to further vaccinations. The rate of anaphylaxis was 0.5/100,000 doses in that study [34]. However, another study showed a higher rate of anaphylaxis, with 2.6/100,000 doses. This rate was only comparable to the rate following administration of bovine-gelatin-containing vaccines in Japan [24]. However, this rate of anaphylaxis was within the World Health Organization's categorization of 'very rare' [24].

The cause of anaphylaxis is unclear. HPV-like particles are highly immunogenic when injected, and some people may produce an IgE response to injected HPV antigens [24]. Polysorbate 80 is a stabilizer contained in qHPV vaccine that could be a potential trigger of non-allergic anaphylaxis. On the contrary, aluminium adjuvants contained in qHPV vaccine are not a documented cause of anaphylaxis [24].

Auto-immune disorders are infrequent after qHPV vaccine. Slade et al. [25] reported a rate of 0.2/100,000 doses of vaccine. The most common auto-immune disorders reported are systemic lupus erythematosus and rheumatoid arthritis, although there are also cases of other diseases, such as scleroderma, dermatomyositis, Sjögren's syndrome and mixed connective tissue disease [25]. Pugnet et al. [35] reported a case of immune thrombocytopenic purpura in a patient 3 months after receiving a second dose of the qHPV vaccine. However, no other cases of haematological disorders have been reported after qHPV vaccination.

Recently, EM has been described in a 19-year-old female after the second dose of qHPV vaccine [4]. EM has been triggered by HPV protein components that act like keratinocyte-expressed antigens. It may also occur due to other vaccine components initiating a T-cell-mediated immune response [4]. To our knowledge, this is the second case of EM following qHPV vaccine reported in the literature.

In conclusion, severe adverse reactions after qHPV vaccine are uncommon (<0.1%). Cutaneous side effects are frequent after qHPV vaccination, especially local injection site reactions. Other reactions involving the skin, such as cutaneous hypersensitivity reactions or autoimmune diseases, are rare. We present a new case of EM following qHPV vaccination. So far, it is unclear whether EM and SJS/TEN are part of a spectrum of skin diseases or, conversely, are different entities. We recommend care in the administration of further doses of vaccine in these reacting patients, due to the possibility of developing more serious side effects (SJS or TEN), at least until this issue is clarified.

Disclosure Statement

The authors have no conflict of interest to declare.

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