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CASE REPORT

Combined Reduced-Antigen Content Tetanus, Diphtheria, and Acellular Pertussis (Tdap) Vaccine-Related Erythema Nodosum: Case Report and Review of Vaccine-Associated Erythema Nodosum

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ABSTRACT

Background: Vaccination programs reduce the morbidity and mortality of diphtheria, pertussis, and tetanus. Erythema nodosum is a reactive erythema that can be associated with infections, drugs, and many conditions. The new onset of erythema nodosum after receiving vaccination is uncommon.

Purpose: Combined reduced-antigen content tetanus, diphtheria, and acellular pertussis (Tdap) vaccine-associated erythema nodosum is described and the reports of vaccine-related erythema nodosum are summarized.

Methods: The clinical features of a 39-year-old woman who developed erythema nodosum after receiving Tdap vaccine are reported. Using the PubMed database, an extensive literature search was performed on erythema nodosum, vaccine, and vaccination.

Results: Tdap, the most commonly used booster vaccine against tetanus, diphtheria, and pertussis, is well tolerated in all age groups. Local injection-site reactions are the most common adverse events, whereas headache, fatigue, gastrointestinal symptoms, and fever are the most frequent systemic events. Erythema nodosum has not previously been reported in patients who have received Tdap vaccine. The patient developed erythema nodosum within 48 h after receiving Tdap vaccine; her symptoms cleared and nearly all skin lesions resolved within 2 weeks after initiating oral treatment with ibuprofen, fexofenadine, and prednisone. Vaccine-associated erythema nodosum has previously been reported following vaccination for cholera, hepatitis B, human papillomavirus, malaria, rabies, small pox, tuberculosis, and typhoid.

Conclusion: Vaccine-associated erythema nodosum is uncommon. Erythema nodosum occurring after Tdap vaccination is a rare, yet potential, adverse effect.

Keywords: Acellular pertussis; Dermatology; Diphtheria; Erythema nodosum; Tdap;

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Tetanus; Vaccine; Vaccine-associated; Vaccine-related; Vaccination

INTRODUCTION

The combined reduced-antigen content tetanus, diphtheria, and acellular pertussis (Tdap) vaccine is a single-dose booster vaccine that not only maintains the standard of care for tetanus and diphtheria protection but also reduces pertussis morbidity [1–7]. Erythema nodosum is a reactive erythema that can be associated with infections, drugs, and many conditions [8–12]; however, the new onset of erythema nodosum after receiving a vaccine is rare. A young woman who developed erythema nodosum after receiving Tdap vaccine is reported and vaccinations that have been associated with erythema nodosum have been summarized.

CASE REPORT

A healthy 39-year-old Japanese woman visited her primary care physician for an annual examination. She had received all of her childhood vaccinations without any complications. She did not have any history of preceding infections, sore throat or diarrhea. She also had no prior or current skin or systemic diseases and her laboratory studies were normal. There was no personal or family history of tuberculosis. Her physician recommended prophylactic vaccination with combined tetanus-diphtheria-pertussis (Tdap) vaccine since her booster immunization was due. Informed consent was obtained from the patient for being included in the study and for the publishing of photographs. This article does not contain any studies with human subjects performed by the author.

Within 24 h of receiving Tdap vaccine, she noted several areas of pruritus and swelling on her distal lower extremities. During the next 24 h these areas enlarged and developed into tender red nodules. The painful nodules persisted and she sought dermatologic medical attention.

Cutaneous examination, 7 days after receiving Tdap vaccine, revealed tender erythematous nodules on her legs (Fig. 1). There was a large, 12 by 8 cm, erythematous nodule on distal pretibial left leg (Fig. 1). Multiple, individual and grouped, nodules were present on her right leg; they were located on the distal lateral thigh (4.0 by 2.5 cm), the proximal lateral calf (6.0 by 3.5 cm), the distal lateral calf (2.0 by 2.0 cm), and the distal lateral leg proximal to the ankle (each of 3 lesions measuring 2.5 by 2.5 cm) (Fig. 2).

Correlation of her medical history, clinical symptoms, and lesion morphology were compatible with a diagnosis of Tdap vaccine-

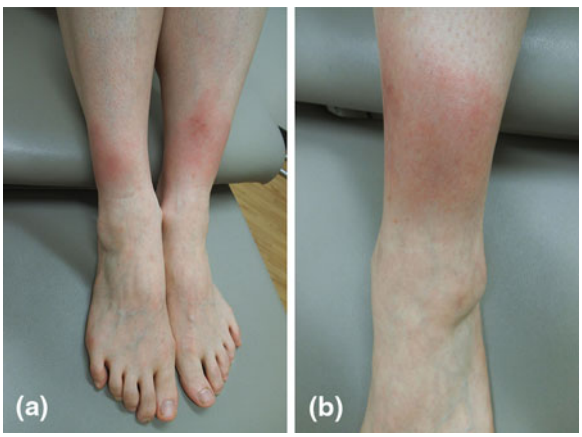

Fig. 1 Distant (**a**) and closer (**b**) frontal views of the anterior lower extremities of a 39-year-old Japanese woman with erythema nodosum developing after she received vaccination with Tdap vaccine. Tender, erythematous, individual (left leg) and grouped (right leg), nodules are present on the distal pretibial legs (**a**). Erythema nodosum appears as a large, 12 by 8 cm, nodule on the distal pretibial left leg (**b**)

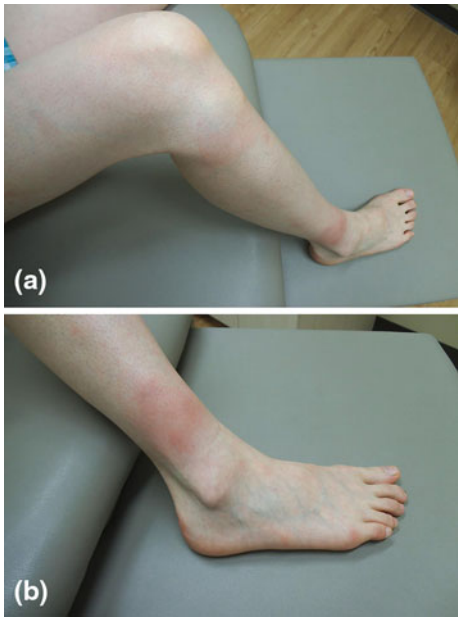

Fig. 2 Distant (**a**) and closer (**b**) view of the woman's right leg show multiple individual and grouped nodules of Tdap vaccination-associated erythema nodosum. Lesions of erythema nodosum on the right leg are located on the distal lateral thigh, the proximal lateral calf, the distal lateral calf, and the distal lateral leg proximal to the ankle (**a**). A group of 3 nodules of erythema nodosum are noted on the distal right leg (**b**)

related erythema nodosum; however, the differential diagnosis also included an Arthus-like phenomenon induced by immunization and erythema nodosum secondary to another etiology with immunization being associated by chance. Several circumstances favored Tdap vaccine-related erythema nodosum. Specifically, she had not receiving any topical or systemic medications. Also, she had no recent streptococcal pharyngitis or systemic conditions such as Crohn's disease, sarcoidosis, or tuberculosis. Therefore, the temporal association between her recent Tdap vaccination and the development of the skin lesion suggested that the development of her erythema nodosum was related to her receiving Tdap vaccine.

Symptomatic treatment was initiated: oral ibuprofen 600 mg four times daily. Since a drug-induced etiology was suspected, daily oral systemic therapy with an antihistamine and a corticosteroid was started: 180 mg of fexofenadine and prednisone (60 mg for 4 days, followed by 40 mg for 3 days, and followed by 20 mg for 2 days). Her symptoms began to improve and the nodules started to flatten within 3 days.

Follow-up examination occurred 2 weeks after her initial visit. Her symptoms had completely resolved. One of the nodules proximal to her right ankle was smaller, yet palpable with mild erythema of the skin. All of her other nodules had completely flattened and there was macular hyperpigmentation at the sites.

DISCUSSION

The morbidity and mortality from the bacterial diseases diphtheria, pertussis and, tetanus have been dramatically reduced secondary to vaccination programs beginning in infancy [1–7]. The originally developed infant combined diphtheria-tetanus-whole-cell pertussis (DTwP) vaccine was subsequently supplanted by the infant combined diphtheria-tetanus-acellular pertussis (DTaP) vaccine that is less reactogenic [1, 2]. Booster vaccination of adolescents and adults is still necessary since immunity—either vaccine induced or naturally acquired—to pertussis is not lifelong. However, because of the risk of increased reactogenicity with successive doses, the infant DTaP vaccine is not suitable for use as a booster vaccine in adolescents and adults [1, 2].

The most commonly used booster vaccine against tetanus, diphtheria, and pertussis in adolescents and adults is the three-component pertussis Tdap (Boostrix^{TM}, GlaxoSmithKline, Research Triangle Park, NC, USA) vaccine that contains an aluminum adjuvant [1, 2]. The

quantities of antigens (toxoids) in Tdap vaccine are reduced by 10–50 percent of those in the infantile DTaP vaccine. The three pertussis antigen components are filamentous haemagglutinin, pertactin, and pertussis toxin [1, 2].

Combined reduced-antigen content tetanus, diphtheria, and acellular pertussis vaccine is well tolerated in all age groups [1–7]. The most common adverse events associated with Tdap vaccine administration are local injection-site reactions such as pain, redness, swelling, and increased upper-arm circumference [1–7]. Headache, fatigue, gastrointestinal symptoms and fever are the most frequent systemic events [1–7]. These adverse events occur in up to approximately 20 percent of individuals, are only mild or moderate in intensity, and are typically transient [1–7].

Serious adverse events following Tdap immunization are rare [5]. They include allergic reactions (such as anaphylaxis), cardiac conditions (pericarditis, myocardial infarction, and arrhythmia), exacerbation of pre-existing illnesses, general systemic symptoms, infections, injection site cellulitis, neurologic conditions (Guillain–Barre syndrome, Bell's palsy, seizure, demyelinating diseases, and encephalopathy), syncope, and thrombocytopenia [5]. However, to the best of my knowledge, erythema nodosum has not previously been described following vaccination with Tdap.

Erythema nodosum is clinically characterized by acute onset of painful, warm, red subcutaneous nodules—of 1 to 5 cm in diameter–appearing bilaterally on the pretibial legs. Associated systemic symptoms may include fever, fatigue, malaise, and arthralgias. Microscopic examination of a lesion typically demonstrates a septal panniculitis, with a neutrophilic infiltrate; vasculitis is absent. Within a few days to 2 weeks, the erythematous nodules begin to slowly involute by flattening and developing purple color that subsequently evolves into a bruise-like macular hyperpigmentation that has been referred to as erythema contusiformis [8–12].

Erythema nodosum is most commonly observed in young women—particularly those between 20 and 50 years of age [8–12]. Indeed, erythema nodosum occurs 4–6 times as often in women as compared to men [8–12]. Although the extensor leg below the knee is the most frequent location, lesions may also appear on other sites such as the thighs and extensor arms [8–12].

Erythema nodosum can present as an idiopathic reactive erythema. However, there is an extensive list of infections (such as bacterial, viral, fungal, mycobacterial, and protozoan), drugs (such as antibiotics and oral contraceptives), and conditions (such as inflammatory bowel disease, pregnancy, and sarcoidosis) that have been described in patients with developed erythema nodosum. Some of the erythema nodosum-associated etiologies (such as streptococcal throat infection, oral contraceptives and pregnancy, sulfonamides, Crohn's disease, and sarcoidosis) are more commonly observed whereas other erythema nodosum-related causes have only been noted in a small number of patients or single individuals [8–12].

Erythema nodosum has occurred following vaccination; however, vaccines are an uncommon etiology for this reactive erythema (Table 1) [13–24]. To the best of my knowledge, the currently described woman is the first individual in whom erythema nodosum has been reported following vaccination with Tdap. Her symptoms and lesions began within 48 h after she was vaccinated; she had no conditions that have previously been noted to cause

Table 1 Vaccinations associated with the subsequent development of erythema nodosum

Vaccine	References
Bacille–Calmette–Guerin[a]	[13–15]
Hepatitis B[b]	[16–18]
Human papillomavirus[c]	[19]
Malaria[d]	[20]
Rabies[e]	[21, 22]
Smallpox[f]	[23]
Tetanus, diphtheria, and pertussis[g]	Current report
Typhoid and cholera[h]	[24]

[a] Bacille–Calmette–Guerin (BCG) vaccine, a live attenuated vaccine derived from attenuated strains of Mycobacterium bovis, is used to prevent tuberculosis [13]. A retrospective study of etiologic factors associated with erythema nodosum in children was performed; BCG vaccination was the related etiology in 1 of 45 patients [14]. Another patient developed erythema nodosum 30 days after BCG vaccination; the local inflammatory reaction caused by the vaccine was normal [15]

[b] Erythema nodosum has been associated with administration of hepatitis B vaccine prepared either from human serum (Heptavax B®, Merck & Co., Inc., Whitehouse Station, NJ, USA) [18] or by recombinant-DNA techniques (Engerix B, GlaxoSmithKline, Research Triangle Park, NC, USA [16] and Recombivax HB®, Merck & Co., Inc., Whitehouse Station, NJ, USA [17])

[c] A 16-year-old girl developed erythema nodosum after administration of vaccine against human papillomavirus types 6, 11, 16, and 18 (Gardasil®, Merck & Co., Inc., Whitehouse Station, NJ, USA) [19]

[d] Two of 10 volunteers (a 25-year-old Asian woman and a 26-year-old Caucasian woman—both taking oral contraceptives) developed dermatology consultant-confirmed erythema nodosum after receiving 1 dose of 20 μg Pvs25/ISA 51 vaccine [a vaccine consisting of recombinant Pvs25 (a surface protein of mosquito stage of the malaria parasite Plasmodium vivax) which is formulated with Montanide ISA 51 (a water-in-oil emulsion)] [20]

[e] An 11-year-old girl developed erythema nodosum at the site of a dog bite after receiving a vaccination against rabies [22]. Another patient, 35-year-old woman developed biopsy-confirmed erythema nodosum a few days after receiving the second dose of a rabies vaccine treatment: Rabipur® (Novartis Vaccines and Diagnostics, Cambridge, MA, USA), a purified chick embryo/second generation tissue culture vaccine [21]

[f] Three patients are reported who developed cutaneous eruptions that were essentially varioliform, but ranged from erythema multiforme and erythema nodosum to severe hemorrhagic exanthems, on the 14th, 20th, and 22nd day after primary vaccination [23]

[g] A 39-year-old woman developed erythema nodosum within 48 h after receiving a dose of the combined reduced-antigen content tetanus, diphtheria, and acellular pertussis (Tdap) vaccine [current report]

[h] A 56-year-old woman developed pain and stiffness in both ankles, knees and lower back 24 h after receiving 0.5 ml of typhoid vaccine (to prevent salmonella infection) and 1.0 ml of cholera vaccine (to prevent cholera infection) intramuscularly; the symptoms were followed by the development of classical erythema nodosum on the anterior aspects of both lower legs [24]

erythema nodosum and she was not taking any medication that has previously been associated with the development of erythema nodosum. The lesion-associated tenderness and the nodules both began to resolved within 3 days after initiating oral treatment with a corticosteroid and a long-acting antihistamine daily, and a nonsteroidal anti-inflammatory agent four times each day. During the next 1½ weeks, her symptoms resolved and all but one of the nodules had completely cleared.

The onset of clinical symptoms and skin lesions is variable in patients with vaccine-associated erythema nodosum. Similar to the

rapid onset of Tdap-related erythema nodosum within 48 h, symptoms and skin lesions of erythema nodosum associated with hepatitis B vaccine (prepared by recombinant-DNA techniques) appeared within less than 24 h [16] or after only 4 days [7], in the patients who received either Engerix B (GlaxoSmithKline, Research Triangle Park, NC, USA) [16] or Recombivax® (Merck & Co., Inc., Whitehouse Station, NJ, USA) [17]. In addition, the woman who had previously received a course of typhoid and cholera vaccine more than 5 years earlier, developed symptoms 24 h after her booster vaccination followed by classic appearing erythema nodosum lesions on her anterior lower legs [24]; similar to this patient, erythema nodosum developed within a few days after the second dose of rabies vaccine [21] and 15 days after the second injection of human papillomavirus vaccine (and subsequently 10 days after the third injection of Gardiasil 4 months later) [19]. In contrast, vaccine-related erythema nodosum appeared 18, 14–22, and 30 days after vaccination with malaria [20], small pox [23], or Bacille–Calmette–Guerin [15], respectively.

The pathogenesis of vaccine-related erythema nodosum remains to be established. Many of the investigators favor the development of erythema nodosum being secondary to the antigen of the infectious disease. However, it is impossible to absolutely exclude the possibility of a hypersensitivity reaction to one or more of the adjuvant components used to prepare the vaccine.

CONCLUSION

The new onset of erythema nodosum after receiving vaccination is uncommon, but has been reported following vaccination for cholera, hepatitis B, human papillomavirus, malaria, rabies, small pox, tuberculosis, and typhoid [13–24]. This is the first report of erythema nodosum occurring after Tdap vaccination for the prevention of tetanus, diphtheria, and pertussis. It is important for clinicians to be aware of this rare, yet potential, adverse effect to Tdap vaccine.

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Compliance with ethical guidelines. Informed consent was obtained from the patient for being included in the study and for the publishing of photographs. This article does not contain any studies with human subjects performed by the author.

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