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CASE REPORT

Injection Site Lichenoid Dermatitis Following Pneumococcal Vaccination: Report and Review of Cutaneous Conditions Occurring at Vaccination Sites

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ABSTRACT

Background: Cutaneous dermatoses and malignancies have occurred at the sites of vaccines.

Purpose: To describe a man who developed a lichenoid dermatitis at the pneumococcal vaccine injection site and to review cutaneous dermatoses and malignancies occurring at vaccination sites.

Methods: PubMed was used to search the following terms, separately and in combination: adverse, condition, cutaneous, dermatosis, dermatitis, injection, PCV13, pneumococcal, pneumonia, prevnar, reaction, skin, site, vaccination, and vaccine. All papers were reviewed, and relevant manuscripts, along with their reference citations, were evaluated.

Results: Several vaccines—including bacillus Calmette-Guerin, hepatitis B, influenza, leishmaniasis, meningitis, pneumococcal, smallpox, tetanus (alone and in combination with diphtheria, pertussis, polio, *Haemophilus influenza* type B or plague and yellow fever), and varicella-zoster—have been associated with post-vaccination site reactions. A 70-year-old male developed a lichenoid dermatitis that occurred at the pneumococcal vaccine injection site within 2 weeks after PCV13 vaccination; the erythematous nodule resolved spontaneously within 9 weeks following immunization.

Conclusions: Dermatoses at the injection sites of vaccines can be granulomatous, immunity-related conditions, infections, lichenoid, neutrophilic, or pseudolymphomatous. Basal cell carcinoma and squamous cell carcinoma are the most common vaccination site-associated malignancies; however, melanoma and sarcomas (dermatofibrosarcoma protuberans, fibrosarcoma, and malignant fibrous histiocytoma) are also smallpox vaccine-related site neoplasms. A cutaneous immunocompromised district that is created by vaccine-induced local immunologic changes is hypothesized to be the pathogenesis of vaccination site reactions.

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INTRODUCTION

The pneumococcal polysaccharide conjugated vaccine (13-valent, adsorbed; PCV13, Prevnar 13) is approved in adults ≥50 years for the prevention of pneumonia in the USA [1–3]. Lichenoid dermatitis describes a skin condition that is microscopically characterized by band-like lymphocytic inflammation with alteration of the epidermal basal layer. The case of a man who developed a lichenoid dermatitis at the site of immunization within 2 weeks after receiving the PCV13 vaccine is described, and cutaneous conditions occurring at vaccinations sites are reviewed.

CASE REPORT

A 70-year-old male presented for evaluation of a new, asymptomatic, red and scaly lesion on his left arm. He had received a vaccination, pneumococcal polysaccharide conjugated vaccine (13-valent, adsorbed; PCV13, Prevnar 13) at the site 5 weeks earlier. Within 2 weeks after being immunized, he noticed the skin lesion. He had been vaccinated with the pneumococcal polysaccharide vaccine (PPSV23, Pneumovax) 6 years earlier.

Cutaneous examination showed a 12 × 5-mm linear, focally crusted, erythematous nodule on the deltoid area of his left arm (Fig. 1); the location corresponded to the PCV13 injection site.

Microscopic evaluation of a 3-mm punch biopsy showed orthokeratosis, acanthosis, and a prominent granular layer. Dyskeratotic keratinocytes were present in the epidermis,

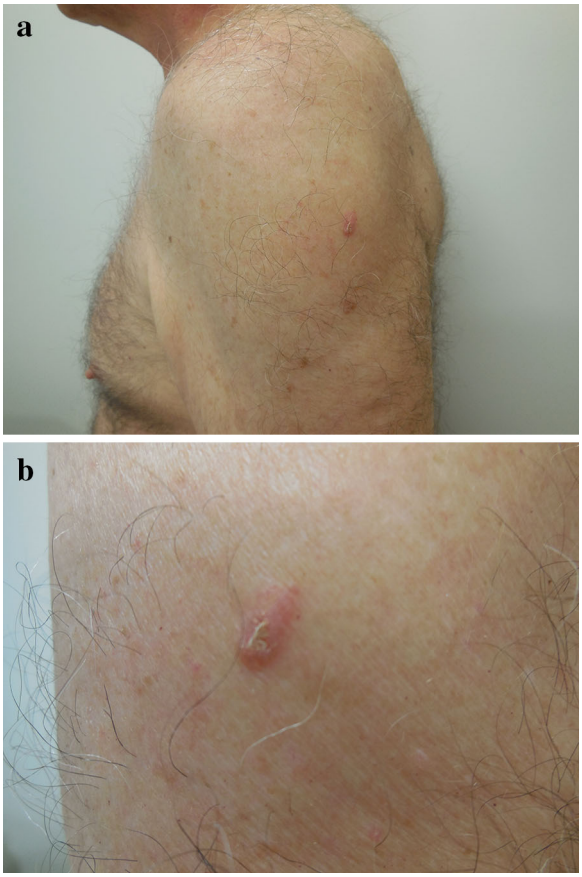

Fig. 1 Distant (**a**) and closer (**b**) views of the pneumococcal vaccination site on the left deltoid area show a 12 × 5 mm linear, focally crusted, erythematous nodule

and there was a vacuolar change of the basal cells at the dermoepidermal interface. In the upper dermis there was dense, band-like infiltration of lymphocytes with occasional exocytosis of the inflammatory cells into the overlying spongiotic epidermis (Fig. 2).

Correlation of the history, clinical morphology, and pathologic changes established the diagnosis of a lichenoid dermatitis occurring at the vaccination site of the PCV13 vaccine. The residual dermatosis resolved spontaneously within 4 weeks after the biopsy, corresponding to 9 weeks after immunization. Follow-up examination showed normal-appearing skin at the vaccination site.

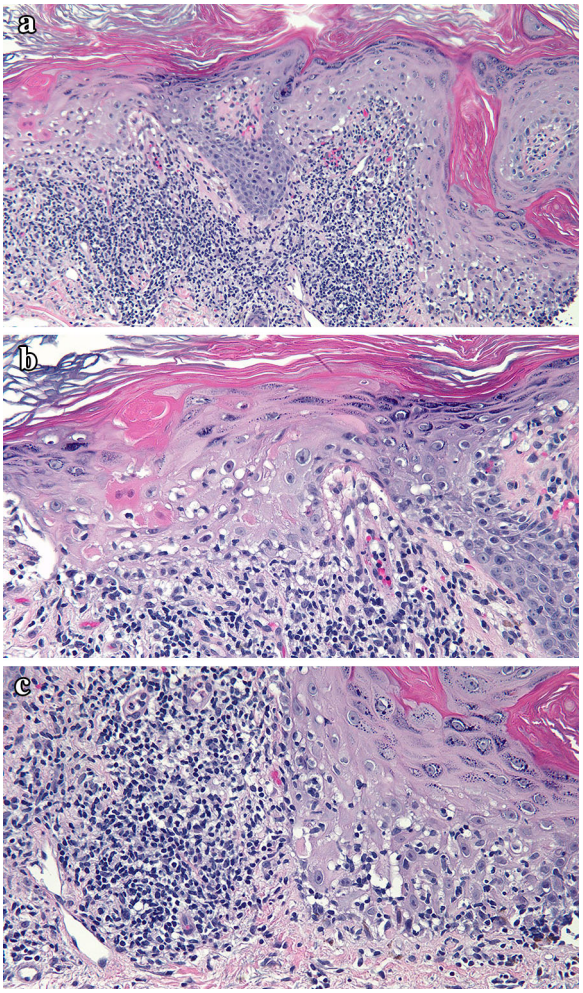

Fig. 2 Distant (**a**) and closer (**b**, **c**) views of the skin biopsy show orthokeratosis, acanthosis, and a prominent granular layer (**a**, **b**). There is mild spongiosis (**c**), dyskeratotic keratinocytes (**a**, **b**), and vacuolar change of the basal cells at the dermoepidermal interface (**a**–**c**). Lymphocytes are present in a dense, band-like infiltrate in the upper dermis (**a**, **b**), and there is exocytosis of the inflammatory cells into the overlying epidermis (**a**, **c**) (hematoxylin and eosin, **a** = ×10; **b** = ×20; **c** = ×20)

Informed consent was obtained from the patient for being included in the study.

DISCUSSION

The 7-valent pneumococcal conjugated vaccine (PCV, known by the trade name Prevnar) was licensed by the Food and Drug Administration (FDA) on 17 February 2000 [4]. Subsequently, vaccines toward 13 and 23 serotypes of *Streptococcus pneumonia* were developed. PCV13 consists of 13 serotype-specific polysaccharides of *S. pneumoniae* (1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F) conjugated individually to non-toxic diphtheria CRD_{197} carrier protein and adsorbed on aluminum phosphate. The US Advisory Committee on Immunization Practices (ACIP) has recommended PCV13 [in series with 23-valent pneumococcal polysaccharide vaccine (PPVS23, Pneumovax)] for all adults aged ≥65 years. A single 0.5-mm dose is given as an intramuscular injection in the deltoid muscle [3, 5–9].

PCV13 has been associated with not only systemic adverse events, but also local reactions of only mild or moderate severity; no vaccine-related serious events were reported [8]. Systemic adverse events associated with the vaccine include arm movement limitation, arthralgia, chills, decreased appetite, diarrhea, fatigue, fever, headache, myalgia, rash, and vomiting. In general, these reactions were less common in older persons than in younger individuals [1–3, 7].

Skin and subcutaneous tissue disorders accounted for 20% of total adverse events following immunization in a 10-year retrospective analysis of spontaneous reports following pediatric immunizations [10]. Cutaneous reactions to vaccinations can be nonspecific or related to the live attenuated virus; they can also be localized to the injection site or associated with generalized hypersensitivity reactions [11]. Investigators have proposed not only the case definition, but also the guidelines for collection, analysis, and presentation of immunization safety data for local reactions at or near vaccine injection sites [12].

Table 1 Pneumococcal vaccination site reactions

Injection site reactions:
Abscess or cellulitis[a] [4]
Erythema, pain, and swelling[a] [1–4]
Itching granuloma[b] [14]
Keratoacanthoma [15]
Lichenoid dermatitis [current report]
Sweet's syndrome[c] [16]

Delayed maturation of the antibody response to the pneumococcal vaccine was observed in children with atopic eczema who received Pneumovax II (Pasteur Merieux MSD Ltd., Maidenhead, UK). Specifically, in comparison to controls (of whom 57% responded to the vaccine), only 17% of children with atopic dermatitis aged 3–8 years responded to Pneumovax II [13]

[a] Injection site reactions following vaccination with the 7-valent pneumococcal conjugated vaccine (PCV, trade name Prevnar, Wyeth Pharmaceuticals, Philadelphia, PA) were described in 54% of 4154 reports of events after immunization; 8 serious reports described abscess or cellulitis [4]

[b] Itching granuloma occurred in 38 of 4758 children (0.83%) who received Infanrix or Pentavac alone or concomitant with pneumococcal conjugate (Prevnar). Accompanying clinical features at the injection site in some of the patients also included bluish discoloration, dermatitis, excoriations, hyperpigmentation, hypertrichosis, and scar. Contact allergy to aluminum was verified in 29 of the 34 children (85%) who were evaluated by epicutaneous testing with aluminum

[c] Sweet's syndrome was also triggered by pneumococcal vaccination that had taken place 15 days earlier; however, the patient did not have any lesions at the injection site [17]

Cutaneous reactions at the site of PCV13 are summarized in Table 1 [1–4, 13–17]. Local reactions such as erythema, pain and swelling at the injection site were common; they were more severe in younger aged patients than in older individuals [1–3]. The reported patient is the first individual with a lichenoid dermatitis that appeared at the vaccine injection site within 2 weeks and spontaneously resolved in 9 weeks.

Table 2 Bacillus Calmette-Guerin (BCG) vaccination site reactions

Abscess [18–20]
Basal cell carcinoma [21]
Blistering [18, 19, 22]
Epithelial cysts [18, 19, 22]
Erythema [18, 19, 22]
Erythematous nodule (necrotizing granulomatous reaction) [22]
Fixed drug eruption [23]
Foreign body granuloma (non-necrotizing) [24]
Granuloma annulare [25, 26]
Granuloma (delayed) [19]
Isotopic response to patch testing [27]
Keloid [7, 19, 22, 28]
Lupus vulgaris (cutaneous tuberculosis) [29–33]
Lymphadenopathy (suppurative) [18–20, 34]
Papular tuberculids [20]
Pilomatricoma [35]
Psoriasis [36]
Sarcoidosis (juvenile) [37]
Squamous cell carcinoma [33, 38]
Sweet's syndrome [39, 40]
Tufted angioma [41]
Ulceration [18, 19, 22]
Ulceration during Kawasaki disease [42, 43]
Vasculitis (ulcerating) [44]

Cutaneous dermatoses and malignancies have occurred at the sites of other vaccines, including Bacillus Calmette-Guerin (Table 2) [18–44], hepatitis B (Table 3) [28, 45–53], smallpox (Table 4) [28, 54–79], tetanus (Table 5) [14, 80–86], and others (Table 6) [36, 51, 55, 73, 87–97]. Granuloma annulare is one of the more common skin conditions to subsequently occur

Table 3 Hepatitis B vaccination site reactions

Churg–Strauss vasculitis [45]
Granuloma annulare [46]
Injection site reactions: edema, erythema, induration, and pain [47]
Keloid [28]
Mastocytoma [48]
Necrobiotic granuloma [49]
Nodules [50]
Papulonodular lichenoid[a] and pseudolymphomatous reaction [47]
Subcutaneous nodule (cutaneous B-cell pseudolymphoma) [51]

[a] Generalized lichenoid reactions and lichen planus have occurred following hepatitis B vaccination; however, the initial or individual lesion was not localized to the site of vaccination [52, 53]

at the site of an immunization [25, 26, 46, 98, 99]. The most frequently observed vaccination site-associated malignancy is basal cell carcinoma [33, 38, 55–57, 73], followed by squamous cell carcinoma [33, 38, 54, 55, 57, 73]. However, the prevalence of melanoma [55, 57, 73] and sarcomas (dermatofibrosarcoma protuberans, fibrosarcoma, and malignant fibrous histiocytoma) [55, 57, 60–62, 72] in smallpox vaccination scars—as compared to the scars of other vaccines—is greater than expected and may be secondary to a unique characteristic of the vaccine (Table 7) [15, 33, 38, 54–57, 60–62, 69, 72, 73, 86, 90, 94–96].

Vaccine-associated adverse effects at the site of injection may, in part, be secondary to the the polysaccharides and bases it contains. However, there are no predictors as to which individuals will develop these side effects. It remains to be determined why some patients experienced inflammatory dermatoses whereas others developed neoplasms at their vaccination sites.

Table 4 Smallpox vaccination site reactions

Allergic contact dermatitis [54]
Basal cell carcinoma [55–57]
Dermatitis, chronic [54]
Dermatofibroma [58, 59]
Dermatofibrosarcoma protuberans [55, 57, 60, 61]
Fibrosarcoma [62]
Herpes simplex virus infection [63]
Inflammatory reaction, localized[a] [64]
Keloid (exaggerated scarring) [28, 55, 64–68]
Keratoacanthoma [69]
Lupus erythematosus (discoid) [70, 71]
Malignant fibrohistiocytoma [55, 57, 72]
Melanoma [55, 57, 73]
Myxedematous infiltration, diffuse (Graves' disease) [74]
Nevus sebaceous [75]
Pigmentation [76, 77]
Post scab lesions[b] [54]
Progressive vaccinia[c] [78]
Pyogenic infections [78]
Robust take[d] [78]
Scar response (normal)[e] [57, 78]
Squamous cell carcinoma [54, 55, 57]
Sweet's syndrome [79]

[a] A localized inflammatory reaction at the vaccination site heals with a slightly depressed smooth scar that slowly fades and rarely requires treatment

[b] The morphology of the lesion includes (in order of frequency) erythema, papule, pustule, vesicle, induration, and scab; all except induration and scab may recur in some patients after the original lesions spontaneously resolve. Lesion biopsies (in 4 patients) showed allergic contact dermatitis (2), chronic dermatitis (1), and squamous cell carcinoma (1)

[c] Progressive vaccinia is also referred to as disseminated vaccinia, prolonged vaccinia, vaccinia gangrenosum, and vaccinia necrosum. The vaccination site does not heal; there is painless progressive necrosis that develops into an ulcerative lesion. Additional lesions may or may not appear at distant sites, such as skin, bone, and viscera

[d] Robust take is a non-progressive cutaneous reaction at the vaccination site of >7.5 cm with swelling, warmth, and joint pain; the symptoms peak at 8–10 days post vaccination, and there is improvement within 24–72 h

[e] The normal scar response at the site of vaccination is the following sequence: papule at day 4 post vaccination, pustule at day 7–14, and scab at day 21

Table 5 Tetanus vaccination site reactions

Tetanus vaccine
Angiolymphoid hyperplasia with eosinophils [80]
Indurated erythematous plaque (cutaneous B-cell pseudolymphoma) [51]
Granuloma annulare [81]
Tetanus and diphtheria vaccine
Granuloma annulare [26]
Tetanus, diphtheria, and pertussis vaccine
Abscess (*Mycobacterium tuberculosis*) [82]
Deep reactive nodular infiltrates of mixed inflammation [83]
Necrotizing granuloma [83]
Tetanus, diphtheria, pertussis, and polio vaccine
Abscess (*Mycobacterium chelonei*) [84]
Tetanus, diphtheria, pertussis, polio, and *Haemophilus influenza* type B vaccine
Itching granuloma[a] [14]
Subcutaneous nodule (sterile abscess)[b] [85]
Tetanus, plague, and yellow fever vaccine
Dermatofibrosarcoma protuberans [86]

[a] Itching granuloma occurred in 38 of 4758 children (0.83%) who received Infanrix or Pentavac alone or concomitant with pneumococcal conjugate (Prevnar). Accompanying clinical features at the injection site in some of the patients also included bluish discoloration, dermatitis, excoriations, hyperpigmentation, hypertrichosis, and scar. Contact allergy to aluminum was verified in 29 of the 34 children (85%) who were evaluated by epicutaneous testing with aluminum

[b] The patient received the Pentacel vaccine

Table 6 Other vaccination site reactions

Early summer meningitis
Subcutaneous nodule (cutaneous B-cell pseudolymphoma) [51]
Influenza vaccine
Psoriasis [36]
Sweet's syndrome [87–89]
Leishmaniasis vaccine
Dermatofibrosarcoma protuberans [90]
Varicella-zoster virus vaccine
Burning [91]
Erythema [91]
Pruritus [91]
Subcutaneous nodule (pseudolymphoma) [92]
Zosteriform eruption [93]
Vaccine not specified
Basal cell carcinoma [55, 73]
Dermatofibrosarcoma protuberans[a] [55, 94, 95]
Lentigo maligna [96]
Lichen sclerosus et atrophicus [97]
Melanoma [55]
Squamous cell carcinoma [55, 73]

[a] Includes pigmented dermatofibrosarcoma also referred to as Bednar tumor [55, 94]

Ruocco et al. proposed the immunocompromised district as a unifying concept for the development of skin disorders and cancer at lymphoedematous, herpes-infected, and otherwise damaged cutaneous sites in 2009 [99]. The concept has subsequently been expanded with regards to not only the factors responsible for the regional immune dysregulation (which also include burns, ionizing and ultraviolet radiation, neurologic disorders such as paralytic stroke and poliomyelitis, tattooing, and trauma such as amputation), but also the skin diseases arising in the affected sites (such as granulomatous reactions, immunity-related disorders, infections, and tumors) [100–102]. The occurrence of cutaneous dermatoses or skin cancers at vaccination sites is another example of an immunocompromised cutaneous district that has been created by local immunologic changes induced by the vaccine.

Table 7 Cancers at vaccination sites

Basal cell carcinoma
Bacillus Calmette-Guerin vaccine [33, 38]
Smallpox vaccine [55–57]
Not specified [55, 72]
Dermatofibrosarcoma protuberans[a]
Leishmaniasis immunization [90]
Smallpox vaccine [55, 57, 60, 61]
Tetanus, plague, and yellow fever vaccines [86]
Travel immunization [94]
Not specified [55, 95]
Fibrosarcoma
Smallpox vaccine [57, 62]
Keratoacanthoma
Pneumococcal vaccine [15]
Smallpox vaccine [69]
Malignant fibrous histiocytoma
Smallpox vaccine [55, 57, 72]
Melanoma
Smallpox vaccine [55, 57, 73]
Not specified [55, 96]
Squamous cell carcinoma
Bacillus Calmette-Guerin vaccine [33, 38]
Smallpox vaccine [54, 55, 57]
Not specified [55, 73]

[a] These also include pigmented dermatofibrosarcoma protuberans (Bednar tumors) [55, 94]

CONCLUSION

Vaccination site reactions have been observed following immunization with several vaccines including Bacillus Calmette-Guerin, hepatitis B, influenza, leishmaniasis, meningitis, pneumococcal, smallpox, tetanus (alone and in combination with diphtheria, pertussis, polio, *Haemophilus influenza* type B or plague and yellow fever), and varicella-zoster. The reactions at the vaccine injection sites are either cutaneous dermatoses or neoplasms. In this report, a man is described who developed a lichenoid dermatitis that occurred at the pneumococcal vaccine injection site within 2 weeks after PCV13 vaccination; the erythematous nodule resolved spontaneously within 9 weeks following immunization. Dermatoses at the injection sites of vaccines can be granulomatous, immunity-related conditions, infections, lichenoid, neutrophilic, or pseudolymphomatous. Vaccination site-associated malignancies most commonly are basal cell carcinoma or squamous cell carcinoma; however, smallpox vaccine-related site neoplasms also include melanoma and sarcomas (dermatofibrosarcoma protuberans, fibrosarcoma, and malignant fibrous histiocytoma). The pathogenesis of vaccination site reactions is hypothesized to be the result of a cutaneous immunocompromised district created by vaccine-induced local immunologic changes.

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Compliance with Ethics Guidelines. Informed consent was obtained from the patient for being included in the study.

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