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Expanding the histological findings in postvaccinial non-viral folliculitis

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Abstract

Postvaccinial non-viral folliculitis has been recognized in the past decade as a new adverse cutaneous reaction to the smallpox vaccination. Contrary to more serious smallpox vaccine reactions, postvaccinial non-viral folliculitis has a benign course resolving spontaneously within approximately seven days. We describe additional histopathological findings associated with postvaccinial non-viral folliculitis, which has only been described once previously. New findings include the presence of neutrophilic or lymphohistiocytic infiltrates that concentrate around the hair follicles. We compare our findings to the follicular nature of varicella and herpes zoster infections, generating the hypothesis of deposition of vaccinia protein within folliculosebaceous units as a potential pathophysiologic mechanism behind postvaccinial non-viral folliculitis.

Introduction

Since the tragic events of September 2001, there has been a renewed interest in protecting military personnel using the smallpox (vaccinia virus) vaccine as well as generating enough supply for the entire American population in the event of a bioterrorist attack. Several studies in the past decade have explored the possibility of diluting current smallpox vaccine stocks to increase the effective supply and have investigated the frequency and types of adverse events associated with the vaccine (1, 2). In one randomized, single-blind, prospective study of 680 adults, 14.3% of vaccinees developed some type of cutaneous eruption at a location other than the vaccination site (1). Different types of cutaneous eruptions reported after smallpox vaccine include: papulovesicular, erythema multiforme, generalized vaccinia, eczema vaccinatum, and progressive vaccinia (1–3).

The papulovesicular eruption was first characterized as a neutrophil-rich folliculitis in 2003 (2), but also was reported subsequently as “vaccinia-associated folliculitis” (3) or “postvaccinial non-viral pustulosis” (4). Perhaps the most accurate descriptor is postvaccinial non-viral folliculitis, a term which addresses the timing (postvaccinial), the lack of vaccinia virus isolation from culture (non-viral), and the histopathology (folliculitis). To date, however, there is minimal information in the literature regarding the histopathology of this papulovesicular (or also described as papulopustular) eruption (2). This report describes the histopathological features of biopsy specimens from two different patients with postvaccinial non-viral folliculitis, demonstrating the variability between presentations.

Case Reports

Case 1

A 21-year-old Air Force reserve airman with a remote history of childhood eczema presented 11 days after receiving the smallpox vaccination to the left upper arm (in preparation for deployment to Iraq) with complaints of a “rash.” His clinical exam was notable for approximately fifty, 3 to 4 mm diameter pink papules on an erythematous base across the chest and upper back. The patient reported fatigue and malaise with flu-like symptoms and a headache alleviated by acetaminophen. He denied pruritus, but did have pain at the smallpox vaccine injection site with associated lymphadenopathy in the left axilla.

Skin biopsy demonstrated inflammation centered around a hair follicle characterized by acute neutrophilic infiltrates in the infundibulum along with rupture of the follicular epithelium. There were no viral cytopathic changes. A PAS stain was negative for fungi.

Case 2

A previously healthy 43-year-old man presented 10 days after receiving the smallpox vaccination to the left upper arm (in preparation for deployment to Afghanistan) with complaints of a progressive skin “rash.” He reported the appearance of pruritic lesions 7 days after the smallpox vaccine. Since he continued to develop more lesion during the following three days, he presented to the university emergency department. His clinical examination was notable for over one hundred 2–3 mm diameter pink papules and papulovesicles on the trunk (upper and lower back; mid-chest and abdomen) more so than the proximal upper extremities. The papules and vesicles appeared to involve both follicular and non-follicular skin; they were not arranged in a dermatomal or grouped fashion. Over the left deltoid was a central 7–8 mm gray ulcer at the smallpox vaccine administration site surrounded by a tender, 1–2 cm red patch.

Skin biopsy demonstrated a mixed inflammatory infiltrate, including abundant lymphocytes and histiocytes, many of which were perifollicular. There was focal extension of the lymphocytes into the hair follicle. Areas of the epidermis showed focal spongiosis and a “pustule-like” appearance, but with intraepidermal lymphocytes. An Alcian-blue stained section failed to reveal significant mucin. PAS stained sections failed to reveal fungi.

Discussion

We describe the histological findings in two additional cases of postvaccinial non-viral folliculitis, expanding our understanding of the range of histological findings that may be seen in patients after smallpox vaccination. Neither of the patients reported here were involved in a smallpox vaccine clinical trial, and thus presented to either the regular Veterans Affairs dermatology clinic (Case 1) or the local emergency department (Case 2) for medical care. Thus, it is important for medical practitioners to be aware of this entity.

Importantly, the clinical history of smallpox vaccine alone raises significant concerns for more serious smallpox vaccine-related entities such as generalized vaccinia, eczema

vaccinatum, and progressive vaccinia. Progressive vaccinia is a rare, although frequently fatal reaction in immunocompromised individuals in which the initial site of vaccination fails to heal. The non-healing site develops an ulcer with central necrosis and dark eschars, gradually spreading in a metastatic-like fashion with the appearance of similar satellite and secondary lesions; systemic symptoms occur late in the course of the illness and death ensues due to overwhelming viremia or septicemia (5). Eczema vaccinatum is a postvaccinial adverse reaction described as a sudden and not uncommonly severely painful eruption of disseminated vesicles or pustules within dermatitic skin of individuals afflicted with atopic dermatitis. Positive viral cultures or direct observation of infected cells by direct fluorescent antibody staining solidifies the diagnosis; tissue biopsy shows ballooning degeneration of keratinocytes with multinucleated epithelial cells (6). Finally, generalized vaccinia was historically diagnosed solely on a clinical basis as a benign vesicular, pustular, or maculopapular eruption in healthy skin at areas distant to the initial site of vaccination, presumably through hematologic spread of the virus; however, in recent years stricter diagnostic criteria precluded that vaccinia must be confirmed in these lesions by viral culture, immunohistology, or polymerase chain reaction (4). Due to the stricter criteria, recent studies have downplayed the true incidence of generalized vaccinia (4), as many of the cases thought to be generalized vaccinia more likely represented postvaccinial non-viral folliculitis. Understanding the cutaneous histopathology is thus vital to help clinicians differentiate among diagnostic possibilities (and in the case of military personnel, to potentially help determine whether he or she is fit for deployment).

The differential diagnosis for a primarily truncal, follicular, papulovesicular or papulopustular eruption is broad, including bacterial or fungal or *Pityrosporum* folliculitis, herpes simplex or varicella infection, Grover's disease, acute generalized exanthematous pustulosis (pustular drug eruption), and pustular psoriasis. Histopathologic features will distinguish many of these entities (Table 1).

The histopathological samples from these two cases demonstrated a spectrum of possible infiltrates. The first patient had a similar acute neutrophilic follicular infiltrate as the initial study case (2), with actual rupture of the follicular epithelium. The second case, however, had a more lymphohistiocytic perifollicular infiltrate with extension of the lymphocytes into the hair follicle itself.

This predilection of the inflammatory infiltrate to the follicular unit is a phenomenon that also has been observed histologically in varicella and herpes zoster infections. Walsh and colleagues described three cases in which the patients presented initially with baffling non-vesicular lesions generating broad and vague differential diagnoses. Biopsies of these initial lesions showed specific manifestations typical of herpes virus infections limited to and around the folliculosebaceous unit; these changes included ballooning of keratinocytes, steel grey nuclei, and multinucleated giant cells. Within days of the biopsy, each of the three patients developed a typical herpes zoster eruption at the site of concern, suggesting that the early manifestations of herpes zoster infections are limited to the pilosebaceous unit (7). In addition, several other studies have demonstrated that skin in the early stages of herpes zoster infection demonstrated a high concentration of viral antigens, proteins, and nucleic acids exclusively in follicular and sebaceous epithelium on immunohistochemistry (7).

Considering these prior clinical and microscopic observations of the follicular nature of varicella and herpes zoster infections, a possible hypothesis to the pathophysiology of postvaccinial non-viral folliculitis may include the deposition of vaccinia protein within folliculosebaceous units. Further research is necessary to investigate the presence of these deposits to validate or refute this hypothesis.

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