

Palisaded Neutrophilic and Granulomatous Dermatitis-Like Reaction Associated with Wilms Tumor 1 Protein-Derived Peptide Vaccine: A Case and Review of the Literature

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Abstract

Palisaded neutrophilic and granulomatous dermatitis (PNGD) is an inflammatory cutaneous reaction that is associated with underlying autoimmune diseases. In rare cases, PNGD has been attributed to systemic medications. Here we report one case of a cutaneous injection-site reaction that occurred after intradermal administration of an experimental Wilms Tumor 1 (WT1) protein-derived peptide vaccine in a woman being treated for recurrent ovarian cancer. This is the first reported case of a PNGD-like reaction associated with immunotherapy injections. In this article, we discuss this case and summarize the literature related to the diagnosis and management of PNGD, as well as other injection site reactions related to immunotherapies and experimental vaccines.

Keywords: Palisaded neutrophilic and granulomatous disease; experimental vaccine; cancer vaccine

Academic Dermatology (2024) 2:1-6 | <https://doi.org/10.18061/ad.v2i1.9639>

Published: April 8, 2024.

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INTRODUCTION

PNGD is a rare pathologic condition that is widely associated with various diseases and therapeutics.¹ Patients diagnosed with PNGD most commonly have underlying connective tissue disorders, malignancies, or gastrointestinal diseases.²⁻⁴ In the absence of underlying diseases, certain medications can cause PNGD and PNGD-like reactions. In particular, several studies have shown a connection between allopurinol, ledipasvir, and sofosbuvir and PNGD.^{5,6} To date, there have been no cases of PNGD or PNGD-like reactions due to viral or bacterial vaccines. Furthermore, there are no reported cases of PNGD-like reactions at sites of immunotherapy injections, such as the WT1 tumor vaccine. This article aims to present a case of a PNGD-like reaction secondary to a novel vaccine and to summarize existing knowledge on PNGD and other injection site reactions from immunotherapies.

CASE

A female in her 60s presented with concerns for repeated injection site reactions (ISR) and subsequent ulcerations after injection with an experimental vaccine for treatment of recurrent ovarian cancer. She was enrolled in a clinical trial that involved an intradermal injection with 10.5 mg of the experimental vaccine DSP-7888 Emulsion, also known as Ombipepimut-S, weekly for three weeks, followed by an injection every three weeks (in three-week cycles). At each visit, a total of six injections were administered, consisting of an injection on each upper arm, each side of the abdomen, and each thigh. She denied associated pain or itchiness, only stating that the appearance of this lesions was bothersome. In addition to the experimental vaccine, she was also receiving pembrolizumab (programmed death receptor-1 inhibitor) every three weeks throughout the duration of this clinical trial. She presented to a dermatology clinic after six cycles of treatments. ISRs had been present since the first cycle of the injections.

On physical examination, many brightly erythematous papulonodules and plaques ranging from 0.5 cm to 1.5 cm in diameter were noted at all injection sites (Figures 1A and 1B). Several lesions were ulcerated or eroded. There were no new skin findings in areas other than injection sites. The patient had been applying topical triamcinolone without improvement. Two biopsies were taken at the right upper arm and the left lower abdomen. Microscopic examination depicted an interstitial dermal inflammatory response composed of an ill-defined palisade, a loosely organized histiocytic response, and variable numbers of neutrophils and lymphocytes (Figure 2A). On high magnification, palisaded histiocytes surround individual collagen bundles with a neutrophilic infiltrate in the background. Many multinucleated giant cells are noted along with areas of necrobiosis (Figures 2B). A foreign body reaction was also considered as part of the differential diagnosis. A foreign body reaction was less favored, as, with polarization, there was no foreign body material visualized. Additionally, the neutrophil-rich infiltrate was less characteristic of a foreign body reaction. Infectious stains and universal PCR were sent to evaluate for infectious agents, though both were negative. The biopsy findings and negative infectious studies were consistent with a PNGD-like reaction.



Figure 1. *Brightly erythematous juicy papulonodules with central ulceration were present on the abdomen (A), and bilateral arms (B), at injection sites.*

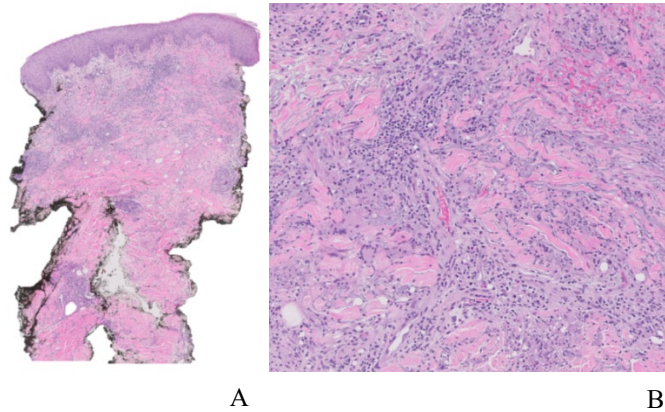


Figure 2. The low power image (A) depicts an interstitial dermal inflammatory response composed of an ill-defined palisade, a loosely organized histiocytic response, and variable numbers of neutrophils and lymphocytes. The high power image (B) depicts palisaded histiocytes surrounding individual collagen bundles with a neutrophilic infiltrate in the background. Many multinucleated giant cells are noted along with areas of necrobiosis.

Over the next seven months, she was treated with intralesional triamcinolone (ILT) injections at two-week intervals at indurated injection sites with the goal to flatten the ulcers. ILT was used to treat new lesions approximately two weeks after DSP-7888 Emulsion injections to ensure that the ILT would not affect the initial vaccine response. The vaccine study was ended after her first dose of ILT, so it is unlikely that future rounds of ILT had any effects of the vaccine. The initial concentration of ILT was 20 mg/ml, but it was decreased to 10 mg/ml as lesions improved and flattened. She also started 50 mg of dapsone daily, which was titrated up to 100 mg daily within one month, and 200 mg of hydroxychloroquine. After the first month, she reported significant improvements in lesions, stating they had faded and were sloughing off. Her hemoglobin levels dropped from 11.4 to 8.1 g/dL, prompting discontinuation of dapsone. She continued taking hydroxychloroquine daily and received intralesional ILT injections twice per month for an additional seven months.

After three months of receiving the experimental vaccine and the first round of ILT, the clinical trial in which she was enrolled ended due to a low probability of meeting the primary endpoint of partial or complete response as determined by the Response Evaluation Criteria in Solid Tumors measure. She discontinued the experimental vaccine DSP-7888 but continued pembrolizumab monotherapy.

Following discontinuation of the experimental vaccine, she continued daily hydroxychloroquine and received a total of nine ILT injections for three additional months. After three months of treatment, the lesions became flattened with only mild desquamation (Figure 3).

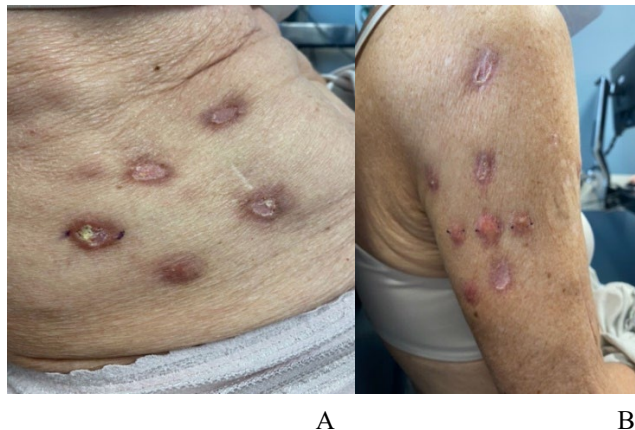


Figure 3. Significant clinical improvement of the lesions with flattening and reepithelialization of the bases was noted after 3 months of treatment (A) and has continued at 6 months of treatment (B).

METHODS

We completed a search through PubMed to identify other reported cases of PNGD secondary to vaccines. The search strategy was (("Palisaded neutrophilic and granulomatous dermatitis"[Mesh] OR "PNGD")) AND (("vaccines"[Mesh] OR "injections OR "immunomodulating" OR "immunotherapy")). We included articles where: 1) a formal diagnosis of PNGD was made from biopsy results, and 2) PNGD was associated with either an injection, vaccine, or other immunotherapy.

We also completed a search through PubMed to identify the clinical features, diagnosis, and management of PNGD. We included articles that were related to either: 1) physical exam findings, 2) underlying diseases associated with PNGD, 3) drugs or vaccines that have been associated with PNGD, 4) diagnosis of PNGD, and 5) treatments for PNGD.

Lastly, we completed a search through PubMed to identify articles related to injection site reactions secondary to Wilms Tumor Vaccine DSP-7888 Emulsion (Ombipepimut-S) and its ingredient, Montanide ISA 51. The search strategy was (("Wilms tumor" [Mesh] OR "Ombipepimut-S" OR "Montanide ISA" OR "ISA 51")) AND (("injection site reaction" [MESH] OR "adverse events" OR "cutaneous")). We only included articles that were related to clinical trials for Wilms Tumor Vaccine DSP-7888 Emulsion (Ombipepimut-S) and Montanide ISA 51.

RESULTS

No cases of PNGD secondary to a vaccine were identified, making our patient the first reported case of PNGD associated with an immunomodulating vaccine.

DSP-7888 Emulsion and Injection Site Reactions

DSP-7888 Emulsion is an investigative vaccine that contains three epitopes from Wilms Tumor 1 (WT1).^{7,8} This mechanism of action of DSP-7888 Emulsion involves the induction of cytotoxic T cells and helper T cells against WT1, thereby reducing the volume of tumors that grow in response to WT1.⁹ Many solid tumors and tumors of hematologic origin express WT1, making the DSP-7888 Emulsion a promising candidate for cancers such as ovarian cancer.^{10,11}

When analyzing this experimental vaccine for adverse reactions, the most common side effect were ISRs.⁷ The National Cancer Institute Common Terminology Criteria for Adverse Events uses a scale of grades 1-5 for ISR.¹² One study noted when given intradermally, DSP-7888 Emulsion caused ISR in all patients, though all were grades 1 or 2.⁷ A second study noted an injection site reaction in 91% of patients, of which 58% met criteria for a grade 3 ISR.⁸ Though ISRs are common occurrences in patients who receive the DSP-7888 Emulsion vaccine, a grade 3 ISR with associated histology for a PNGD-like reaction, as in the case of our patient, has not been reported in the literature. Furthermore, this is the first reported case of a grade 3 ISR due to an immunotherapy injection that was adequately treated with ILK injections, hydroxychloroquine, and dapsone.

Role of Adjuvant Therapy in Adverse Effects

Montanide ISATM 51 (ISA 51) is an ingredient and adjuvant therapy in the DSP-7888 Emulsion. A systematic review found that ISRs were more common in vaccines that contained a combination of vaccines and ISA 51, both in healthy and unhealthy subjects.¹³ Interestingly, two clinical trials were even discontinued due to skin-related adverse reactions from ISA 51.^{14,15} Graham et al. reported four cases of sterile abscesses, leading to trial suspension.¹⁴ Wu et al. was halted due to two reports of erythema nodosum secondary to ISA 51.¹⁵ A third study noted 5.3% of patients experienced severe abscesses after an experimental breast cancer vaccine that contained an antigen and ISA 51.¹⁶ These studies highlight the significant need for clinical trials to address the safest ISA 51 portion to be used in therapeutic vaccines, in addition to surveying patients about associated reactions.

DISCUSSION

Clinical Examination of PNGD

On physical examination, PNGD appears as erythematous papules on the flexor surfaces of extremities, most commonly on the elbows or knees.⁴ These papules are typically asymptomatic, though they can be associated with pain and discomfort. Alternatively, the "rope sign" may be present on examination, which describes a cord-like pattern of lesions in a linear fashion.¹⁷ Given the variety of skin presentations of PNGD, the diagnosis in the absence of biopsy can be challenging. In this patient, examination showed erythematous papulonodules and

plaques on flexor surfaces, rather than the classic “rope sign.” Because of initial concern for infection, two biopsies were obtained, which both supported a diagnosis of a PNGD-like reaction.

Management of PNGD

There is a wide variety in the potential therapies for PNGD. In cases of any underlying disease state, such as connective tissue disease, vasculopathies, or autoimmune diseases, it is important to manage acute flares. In this patient, we discussed the possibility of discontinuing the experimental vaccine in hopes of preventing the formation of new lesions. If the onset of a drug is associated with PNGD, discontinuation of the drug may induce remission.^{5,6} Other potential therapeutics involve topical corticosteroid, non-steroidal anti-inflammatory drugs (NSAIDs), dapsone, colchicine, prednisone, oral tacrolimus, and tumor necrosis factor (TNF) inhibitors.¹⁸ Despite the many possible therapies, topical corticosteroids and dapsone are the most frequently used.¹⁹ Interestingly, a review article noted spontaneous resolution in 20 to 25% of cases.²⁰

Our patient achieved significant improvement after treatment with ILT injections, hydroxychloroquine, and dapsone. There is still limited data on the use of many systemic immunomodulating medications in patients on checkpoint inhibitors, but reports of dapsone used to manage PD1-inhibitor-induced bullous pemphigoid and hydroxychloroquine used to manage PD1-inhibitor-induced lupus suggest that these agents can be safely combined with checkpoint inhibitors. A risk-benefit discussion of immunodulatory medications is recommended with both the patient and their treating oncologist.

The Association of Pembrolizumab with Injection Site Reactions

Though pembrolizumab has been associated with injection site reactions²¹⁻²³ as well as granulomatous skin changes, there are several pieces of evidence that suggest a reaction secondary to the WT1 vaccine itself. First, the papulonodules occurred exclusively in the areas where the WT1 vaccine were administered. Furthermore, she developed no new lesions after WT1 vaccine administration was halted, despite still receiving pembrolizumab. Yet, it cannot be discounted that the co-administration of pembrolizumab and the experimental vaccine may have led to a more pronounced skin reaction due to an additive immunomodulatory effect of checkpoint therapy.

CONCLUSIONS

While DSP-7888 Emulsion injection site reactions have been described in clinical trials, this is the first reported case of a reaction with histology diagnostic of a PNGD-like reaction. To date, PNGD has never been reported with association to cancer vaccines. Common treatment options for PNGD include topical corticosteroids, non-steroidal anti-inflammatory drugs, and tumor necrosis factor inhibitors. Our patient experienced significant improvement in lesions after treatment with ILT injections, hydroxychloroquine, and dapsone. As immunotherapy agents have an increasing utility in the management of cancers, it is important for dermatologists to have a high clinical suspicion for cutaneous reactions that mimic PNGD, as well as knowledge for effective treatments.

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