More than just a coincidence: Herpes zoster and acne rosacea appearing together as Wolf’s isotopic response in an Asian female

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ABSTRACT

Introduction: Wolf’s isotopic response is a rare dermatologic phenomenon defined as the occurrence of a new, unrelated disease at the site of healed lesions of some other disease. We report the first case of Wolf’s isotopic response in a female presenting with rosacea localized to the site of healing zoster lesions. Case Report: A 35-year-old previously healthy Filipino-American woman with no prior history of a dermatologic condition presented to our clinic with a 9-month history of a painful and pruritic unilateral erythematous papular eruption on her right upper cutaneous lip and cheek that respected the midline. At initial presentation she was started on 800 mg acyclovir five times daily for one week for presumed zoster. Four days into her seven-day acyclovir course, her primary care physician obtained cultures for VZV and HSV, but these tests were negative. The vesicular eruptions completely resolved following treatment with acyclovir, leaving only hyperpigmented scars in the unilateral maxillary distribution. Two months after the completion of her acyclovir treatment, she noticed pink dots, which had a prickly and itchy sensation located in the same unilateral distribution as her previous eruptions. Her condition was refractory to a myriad of topical treatments and a skin biopsy was performed which suggested acne rosacea. She was started on isotretinoin and continued for five months with almost complete resolution of papules and symptoms. Conclusion: The pathogenesis of Wolf’s isotopic response is unknown. We review the various etiologies that have been postulated including direct action of viral, particles, immune activation, alterations in neurologic system and vascular changes. Early recognition of Wolf’s isotopic response may result in more timely and effective treatment for patients. Further studies are needed to define the pathogenesis of isotopic response.

Keywords: Wolf’s isotopic response, Rosacea, Herpes zoster

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INTRODUCTION

Wolf’s isotopic response is a rare dermatologic phenomenon defined as the occurrence of a new, unrelated disease at the site of healed lesions of some
other disease [1]. The initial infection is usually herpes zoster followed by a secondary condition, most commonly carcinoma or granuloma annulare [1]. In 2006, the first report of post-herpetic rosacea was published in an Indian male [2]. We report the first case of Wolf's isotopic response in a female presenting with rosacea localized to the site of healing zoster lesions.

CASE REPORT

A 35-year-old previously healthy Filipino-American woman (Fitzpatrick photo skin type 4) presented to our clinic with a 9-month history of an initially painful and pruritic unilateral erythematous papular eruption on her right upper cutaneous lip and cheek. She had no history of dermatologic disease or previous facial erythema.

The patient’s rash started one week after a dental procedure (deep cleaning). She was noted to have a cluster of pinpoint vesicles in the right maxillary cheek region starting from the area adjacent to the nasal ala to mid cheek and including the upper lip on the right side. She was started on 800 mg acyclovir five times daily for one week for presumed zoster. Viral direct fluorescent antibody and viral cultures were sent but were negative for Herpes Simplex Virus (HSV). After completion of her acyclovir course the vesicles cleared and she was only left with hyperpigmented scars limited to the right maxillary distribution. Two months following resolution of the zoster, she noticed pink dots, which had a “prickly and itchy” sensation as reported by the patient. She was given hydrocortisone cream 2.5% to use twice daily, but she stopped after three days because it made her rash worse. She denied eye symptoms but was sent for an ophthalmologic exam for headaches, and this was normal.

Because the papules were follicle-centered and pricky, she was treated for presumptive acne rosacea. Since the distribution was unilateral, the differential diagnosis included contact dermatitis from a topical agent as well as unilateral rosacea. The patient denied any exogenous topical agents besides her prescription medications. She was started on metronidazole 0.75% gel, which she discontinued after three days because of worsening of the rash. She was then started on minocycline 100 mg orally twice daily and pimecrolimus cream 1% twice daily, but she only used this regimen for one week because her face continued to worsen. She then switched her oral antibiotic to oral doxycycline 100 mg twice daily, which she took consistently for two months without improvement.

Due to the refractory nature of the condition, and the fact that the lesions occurred only at sites of previous blisters (with perfectly appearing normal skin on the left side of her face) (figure 1), a skin biopsy was performed by 4 mm punch technique to better diagnose the condition. The skin biopsy (figure 2) showed a dense perivascular and perifollicular lymphocytic and granulomatous infiltrate in the superficial and deep reticular dermis. Mild spongiosis involving the epidermis and follicular epithelium was noted. Additionally, there were dilated thin-walled telangiectatic vessels in the superficial dermis. There was no evidence of viral cytopathic effect. These findings, along with the clinical presentation, were felt to be most consistent with a diagnosis of acne rosacea. A second independent dermatopathology consultation concurred with this impression.

She was started on isotretinoin and continued for five months (cumulative dose 57 mg/kg) with almost complete resolution of papules and itch symptoms. There were some residual hyperpigmented scars (figure 3). Three months into the isotretinoin, she continued to have unilateral tingling and itching on the right face. She was started on amitriptyline for presumed post-herpetic neuralgia, titrated up from 10 mg initially to 50 mg daily by mouth with resolution of the tingling and itching after two months of use. Amitriptyline was discontinued at the same time as her isotretinoin course ended. She has been asymptomatic and without lesions since then. We have

**Figure 1:** A) Unilateral erythematous papular eruptions at the right upper cutaneous lip and cheek occurring only at the sites of previous zoster lesions with normal appearing skin on the left side of the face, B) Closer image of same view.

**Figure 2:** A) Skin biopsy showed a dense perivascular and perifollicular lymphocytic and granulomatous infiltrate in the superficial and deep reticular dermis. Mild spongiosis involving the epidermis and follicular epithelium was noted (H&E, x40), B) Higher power view exhibits dilated thin-walled telangiectatic vessels in the superficial dermis. There was no evidence of viral cytopathic effect (H&E, x100).
advised her to start valacyclovir 2 g orally twice daily with her next dental procedure to prophylax against zoster.

DISCUSSION

Wyburn-Mason first described the occurrence of malignant transformation in the location of a previous herpes virus infection in 1955 [3]. Following this publication, over a hundred cases have been published detailing inflammatory diseases, malignancies and infections occurring at the exact distribution of a previously healed site of an unrelated disease. In 1995, Wolf et al. coined the term “Isotopic Response” to clearly define the phenomenon, which was described as the occurrence of a new, unrelated disease at the site of healing or healed lesions of some other disease [1]. Since Wolf’s isotopic response is a relatively rare phenomenon our clinical experience with these cases is limited, however, reports have been written summarizing intervals from initial infection to secondary disease, ranging from days to decades. Notably, when Wolf et al. first reported the isotopic response they published the largest case review (table 1 from Reference 1) that described the initial infection, secondary disease and latency interval for over 60 cases. [1] The interval from initial infection to the development of secondary disease in the aforementioned review and other publications falls within a range of one month to five years. Our patient falls within the range of reported development of secondary disease.

Of the cases described in the literature, the most common secondary diseases reported have been granuloma annulare, malignancy (breast carcinoma, squamous cell carcinoma, and basal cell carcinoma), leukemic/lymphomatous infiltration, inflammatory reactions (lichen planus, contact dermatitis, psoriasis) and infections. The first report of post-herpetic rosacea was published in an Indian male in 2006 by E. Sezer et al. [2]. Our patient demonstrates the first reported case of post-herpetic rosacea in a female.

The pathogenesis of Wolf’s isotopic response is unknown, however, several etiologies have been postulated including direct action of viral particles, immune activation, alterations in neurologic system and vascular changes [4].

Initially, it was thought that virus particles themselves were causing the inflammatory changes often seen in the isotopic response when Serfling et al. [5] isolated VZV DNA from an isotopic lesion. However, direct viral action has fallen out of favor as VZV DNA isolation has not been frequently reported since. Ruocco et al. [4] suggested that DNA isolations from isotopic responses which form a short interval following herpes infection simply represent the remaining infectious particles.

Another hypothesis suggests a neuroimmunological interaction between the nerve fibers and the immune system at the site of infection. Herpes virus has long been known to cause destruction of A-delta and C nerve fibers in the mid and lower dermis [6]. Damage to the peripheral sensory nerves may alter the neuropeptide and neurotransmitter expression profile (eg. substance P, calcitonin gene-related peptide, neuropeptide Y) of these nerves [7]. These neuropeptides have been demonstrated to have receptors on monocytes and mediate immune functions such as mast cell degranulation and release of pro-inflammatory cytokines via other immune system components [8]. This neuroimmunological reaction creates an invisible scar of immune dysregulation confined to the area of initial infection and has been termed a “locus minorus resistentiae”, where healthy appearing skin is increasingly susceptible to subsequent disease. It is unknown how herpes virus infection can lead to such a diversity of secondary disease and why most people do not have an isotopic response; however, it has been postulated to be a multifactorial contribution of genetics, environmental exposures, age, nutrition and other unknown factors.

In 2005, the Shingles Prevention Study demonstrated the efficacy of a live, attenuated OKA/Merck VZV Vaccine “Zostavax” in reducing the incidence of VZV reactivation by 51 percent among immunocompetent individuals 60 years of age or older [9]. The significant decrease in morbidity and mortality offered by vaccination led to the Center for Disease Control to recommend that all individuals 60 years or older be vaccinated. Although the vaccine has proved efficacious in decreasing the incidence of zoster, the direct role of vaccination in prevention of PHN (beyond reducing zoster incidence) has yet to be determined [10].

It is important to note in our case of Wolf’s isotopic response (with rosacea in the location of a previous herpes zoster infection) that unilateral rosacea remains in the differential diagnosis. The prevalence of unilateral rosacea has been reported to be as high as 14% in an epidemiologic study of 81 persons with rosacea [11]. Several case reports have suggested a
pathogenic role of Demodex folliculorum [12]. Of note, our patient’s clinical history and histologic features were not consistent with demodidiosis.

Given our patient’s PHN and headaches, another diagnostic consideration is a recently proposed subset of rosacea termed “neurological rosacea”. Scharscheidt et al. hypothesized that the pathogenesis of rosacea among select patients with prominent neurological features (such as dysesthesias and headaches) was neural dysregulation causing vasomotor instability and neuronal injury from a proinflammatory environment [13]. Neurological rosacea is a still a new concept that warrants further research and our patient’s history and clinical presentation appear more consistent with Wolf’s isotopic response.

CONCLUSION

Wolf’s isotopic response is a rare, and not well-recognized entity among many dermatologists. These cases can pose clinical dilemmas, because the initial skin condition and the superimposed second condition can seem unrelated. Recognition of this phenomenon will likely result in more timely and more effective care for patients. It is possible that molecular studies on this entity may shed light on the pathogenesis of this isotopic response.

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Author Contributions

Natalia Fijalkowski – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting of the article, Critical revision of the article, Final approval of the version to be published
Ashley Wysong – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published
Phuong Khuu – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published
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Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.