

BRIEF ARTICLE

A Sweet Presentation of a Bitter Disease: Acute Febrile Neutrophilic Dermatitis Associated with Coccidioidomycoses

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ABSTRACT

Acute Febrile Neutrophilic Dermatitis, also known as Sweet Syndrome, is an uncommon inflammatory disorder. Though the exact etiology is unclear, it has been presented in association with various entities. The majority of cases present following upper respiratory infections or viral gastroenteritis. Other causes include drug-induced reactions, pregnancy-related manifestations, or in association with specific hematologic or solid tumors. Rarely, it has been associated with Coccidioidomycosis, a prevalent fungus endemic to the Southwestern regions of the United States with a literature review revealing only three previous cases of Coccidioidomycosis-associated Sweet Syndrome. Here we report two new cases in individuals residing in Arizona.

INTRODUCTION

Acute Febrile Neutrophilic Dermatitis (AFND) was first described by Robert Douglas Sweet in 1964 and thus eponymously termed Sweet Syndrome.^{1,2} AFND is subdivided into three categories based on clinical settings: classic, malignancy-associated, and drug-induced.^{3,4}

Classic AFND is described in association with infections, inflammatory bowel disease, and pregnancy. Most commonly, classic AFND follows upper respiratory infection but has also been associated with *Yersinia*, Tuberculosis, Histoplasmosis, and Toxoplasmosis. Coccidioidomycosis-associated AFND has rarely been reported in literature.

AFND is an uncommon inflammatory condition characterized clinically by sudden

onset of erythematous skin eruption, presenting as papules, nodules, and plaques commonly on the upper extremity, trunk, neck, and face.¹ The histological hallmark is variably dense dermal infiltrate largely composed of mature neutrophils, together with edema of the papillary dermis.⁵

Coccidioidomycosis, also known as Valley Fever, is an airborne, fungal disease caused by *Coccidioides immitis* or *Coccidioides posadasii*, a soil-dwelling fungus prevalent in regions of Southwestern North and Central America.⁷ During 1998-2014, there were ~147,000 coccidioidomycosis cases reported to the Centers for Disease Control and Prevention (CDC) with, approximately two thirds occurring among Arizona residents.⁸ This typically presents as a subclinical pulmonary infection, with self-resolution in immunocompetent individuals. The skin along with lymph nodes, meninges, and the musculoskeletal system, are the

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most common sites of disseminated infection. Cutaneous involvement generally presents as polymorphous lesions, resembling acne or rosacea.

Herein we examine two cases of AFND secondary to *Coccidioidomycosis*.

CASE PRESENTATION

Case Report One

A 55-year-old woman presented to her primary care physician with shortness of breath and rash. She was empirically treated with cefuroxime and amoxicillin without resolution in symptoms. Subsequently she presented to outpatient dermatology clinic a month later for evaluation of the rash. She presented with deep red, sharply demarcated nodules and papules that appeared edematous and vesiculated, some coalescing into larger groups, bilaterally on upper and lower extremities, back, chest and abdomen (Figure 1). No lesions appeared on the palms or soles. Two 4 mm punch biopsies were obtained from the thighs, and lab work was drawn. The biopsies returned with interstitial granulomatous dermatitis with papillary dermal edema and eosinophils, negative for fungal organisms, consistent with Histiocytoid Sweet Syndrome. Further workup resulted yielded positive serology for *Coccidioidomycosis* IgM and IgG antibodies. She was referred to the Infectious Disease team, who initiated treatment with oral fluconazole and oral corticosteroids. She continued to follow up, gradually tapering the oral steroids. At four months the rash had resolved leaving only post-inflammatory hyperpigmentation.

Case Report Two

A 57-year-old homeless gentleman presented to the Emergency Department



Figure 1. Left medial lower extremity revealing classic AFND architecture of erythematous plaques

complaining of a cough and a diffuse rash. He was initiated on ceftriaxone and azithromycin after being diagnosed with left lower lobe pneumonia. Review of systems was positive for headaches, fever, shaking chills, and nausea. The Dermatology service was consulted due to diffuse large, erythematous nodules coalescing into plaques on the left shoulder and neck (Figure 2). On physical examination firm nodules on the right forearm and chest were noted with several scattered vesicles on the extremities. Vesicles were swabbed for bacterial and viral cultures, with negative findings and several skin biopsies were obtained. Serology confirmed the presence of *Coccidioidomycosis* with a positive IgM. Biopsies revealed diffuse neutrophilic infiltrate with perivascular nuclear dust and massive papillary edema, all consistent with AFND. Infectious Disease and Pulmonology services were consulted, and the patient was initiated on intravenous corticosteroids with discussion of need for anti-fungal medications and careful monitoring. He

gradually improved throughout his hospital stay but was lost to follow up upon discharge.



Figure 2. Posterior neck. Indurated erythematous nodules and pseudovesicles

DISCUSSION

The diagnosis of classic AFND requires the presence of both major criteria and two out of the four minor criteria (Table 1).⁴

Symptoms and clinical manifestations typically respond rapidly to high-dose systemic corticosteroids. Second-line systemic agents include colchicine, dapsone, TNF-alpha antagonists and cyclosporine.^{4,6}

The pathogenesis for Acute Febrile Neutrophilic Dermatitis (AFND) is not fully elucidated but may be related to cytokine-mediated recruitment of neutrophils to the skin. For this reason, AFND is treated first-line with corticosteroids, especially with extensive involvement, and has historically shown dramatic resolution. This disease has been associated with several clinical settings, and treatment should be guided by the underlying cause. Though rare, in endemic areas underlying fungal etiologies

must be considered and diagnostic tests should be considered when index of suspicion is high, such as these two cases. Confirmatory testing for Coccidioidomycosis is needed for diagnosis. Diagnostic modalities such as serology, culture, and antibody screen are useful, as symptoms may be nonspecific.

Table 1. Sweet Syndrome Diagnostic Criteria

Criteria	
Major Criteria	1. Abrupt onset of painful erythematous plaques or nodules
	2. Histopathological evidence of dense neutrophil infiltrate in the dermis without evidence of leukocytoclastic vasculitis
Minor Criteria	1. Fever > 38 °C
	2. Association with an underlying hematological, or visceral malignancy, inflammatory disease, or pregnancy, or preceded by an upper respiratory or gastrointestinal infection or vaccination
	3. Response to treatment with potassium iodide or steroids
	4. Abnormal laboratory values (3 of the following 4) <ul style="list-style-type: none"> a. Erythrocyte sedimentation rate greater than 20 mm/h b. Positive C-reactive protein c. >8,000 leukocytes d. >70% neutrophils

Diagnosing the appropriate cause of AFND is critical in the treatment and management of the disease. General first-line therapy, corticosteroids, should be avoided as the sole treatment modality in infectious etiologies.⁹ Patients with AFND secondary to Coccidioidomycosis will typically require antifungal medication. Azole antifungals, specifically fluconazole and itraconazole are the initial therapy of choice for disseminated infections.⁷ Therefore, close monitoring and referral to Infectious Disease is recommended. In this setting consideration for optimization of therapy and management

of the overall infection will improve prognosis and reduce patient morbidity.

These unique cases of Coccidioidomycosis-associated Sweet Syndrome demonstrate the importance of consideration of this uncommon etiology. Importance should be given to individuals residing in the endemic regions, such as Southwestern regions of the United States or with recent travel to these areas.

CONCLUSION

In conclusion, until now, three cases of Coccidioidomycosis-associated Acute Febrile Neutrophilic Dermatitis (AFND) have been reported.¹⁰ Coccidioides, fungi endemic to the Southwestern regions of the United States, Central, and South America is a common pathogen that must be considered in patients presenting with clinical signs of AFND. These patients should be followed with a treatment plan of antifungal therapy, in addition to systemic corticosteroids, to appropriately treat these rare cutaneous manifestations.

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