Clinical Vignettes

Cutaneous Manifestation of Kikuchi–Fujimoto Disease in the Setting of Granulomatosis with Polyangiitis (Wegener's)

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INTRODUCTION

Kikuchi–Fujimoto disease (histiocytic necrotizing lymphadenitis) is a rare, self limited, benign necrotizing lymphadenitis. Although originally described in young Asian women, numerous cases have since been documented among various genders, ages, and races. Kikuchi–Fujimoto disease typically presents as fever, lymphadenopathy, and rash. The rash is variable in appearance and biopsy is required to confirm the diagnosis. This vignette describes a unique case of a Caucasian man with a history of granulomatosis with polyangiitis (Wegener's)¹ who presented with recurrent rash, flu-like illness, and acute kidney injury, suspicious for relapse of the disease. However, by skin biopsy, he was found to have Kikuchi–Fujimoto disease. This is the first reported case of Kikuchi–Fujimoto disease in a patient with known granulomatosis with polyangiitis (Wegener's).

CASE REPORT

A 56-year-old Caucasian man with a history of granulomatosis with polyangiitis (GPA) and associated renal insufficiency was admitted with subjective fever, nausea, vomiting, and a rash on his bilateral upper extremities. He had been hospitalized for similar symptoms one week prior. At that time, his symptoms were attributed to suspected viral syndrome, and he was discharged after receiving supportive care. Since that time, he continued to experience intermittent low-grade fevers and nausea. He reported that the rash, described as nonpruritic and nonpainful, was more pronounced than it had been on his previous admission. He

denied chills, night sweats, abdominal pain or diarrhea. He had not experienced chest pain or shortness of breath. He denied sick contacts, recent travel or recent change of medications. Six months prior, he was diagnosed with GPA after presenting with dyspnea and hematuria. Renal biopsy showed pauci-immune necrotizing crescentic glomerulonephritis, with noted absence of immune complex deposition. Cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA) and antiproteinase 3 antibodies were positive at that time. His current medical regimen consisted of azathioprine, trimethoprim/sulfamethoxazole, and low dose prednisone.

On examination, the patient was slightly fatigued. His temperature was 36.9°C, blood pressure was 119/70 mm Hg, pulse was 117 beats/min, respiratory rate was 18 breaths/min, and oxygen saturation was 96% on room air. His body mass index (BMI) was 31. Head and neck examination revealed dry mucous membranes. Cervical lymphadenopathy was difficult to appreciate. Cardiovascular and respiratory examinations were unremarkable. His abdomen was obese, but otherwise benign. The patient had lower extremity edema. There was a red, nonscaly, non-blanching maculopapular rash on the bilateral upper and lower extremities. No pustules or blisters were present. Neurologic exam revealed residual right-sided motor weakness in the upper and lower extremities as a result of a previous hemorrhagic CVA. Initial laboratory findings (Table 1) showed acute on chronic kidney injury (baseline creatinine of 2.0 mg/dL), as well as a mild leukocytosis.

Further workup was warranted, as this was his second presentation with rash, flu-like symptoms and acute kidney injury. Initially, the differential diagnosis included viral exanthem, fungal infection, drug hypersensitivity reaction, as well as collagen vascular diseases, such as systemic lupus erythematosus (SLE). However, he recently had a negative antinuclear antibody (ANA) screening for SLE and denied recent changes in his medications. Most concerning was that the rash and acute kidney injury represented a flare of GPA. Therefore, a skin biopsy was performed. Dermatopathology reported superficial perivascular inflammatory infiltrates of the dermis consisting of histiocytes, lymphocytes, and very few neutrophils (Fig. 1). The histiocytic cells showed diffuse positivity with CD68 immunostain and exhibited focal myeloperoxidase positivity. No evidence of vasculitis was seen on immunofluorescence examination.

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Table 1. Initial Laboratory Results

Basic Metabolic Panel		
Sodium	140	Reference Range 134-142 mmol/L
Potassium	4.4	3.5-5.0 mmol/L
Chloride	109	98-107 mmol/L
CO ₂	18	22-30 mmol/L
BUN	47	9-20 mg/dL
Creatinine	2.93	0.7-1.5 mg/dL
Glucose	132	70-99 mg/dL
Complete Blood Count		
White Blood Cells	15.2	Reference Range 4.4-11.3 k/mcL
Hemoglobin	9.0	14-17.4 g/dL
Hematocrit	27.8	41.5-50.4 %
Platelets	150	145-445 k/mcL
Other		
C-ANCA	<1:20	Reference Range <1:20

Fungal stains were negative. These results were consistent with Kikuchi–Fujimoto disease (KFD).

DISCUSSION

KFD is a benign, necrotizing lymphadenitis first described separately by Kikuchi and Fujimoto in 1972.^{2,3} Classic presentation includes fever, cervical lymphadenopathy, and rash. This patient had an atypical presentation of KFD with absent lymphadenopathy on physical exam. In a retrospective analysis of 195 patients with KFD, 53% of patients presented with tender lymphadenitis. Furthermore, every patient in the review had either cervical or axillary lymphadenopathy.⁴ This patient's large body habitus impaired detection of presumed cervical lymphadenopathy on exam. KFD is typically diagnosed via lymph node biopsy. The disease is self limited, usually resolving in one to four months, although recurrent cases have been reported.^{5,6} Appropriate management consists of supportive measures and outpatient follow up.

The etiology of KFD remains unclear. The identified histological pattern of disease resolution is suggestive of an infectious process.^{7,8} Implicated infectious etiologies in-

clude Epstein–Barr virus (EBV), parvovirus B-19, human immunodeficiency virus (HIV), and human herpesvirus 6 (HHSV6).⁹ However, no sole infectious agent has been proven. Possible immune reactions have also been proposed. There is a reported association between KFD and SLE; however, the nature of the relationship is unclear. Some propose it could be an attenuated form of SLE, while others suggest it could be a self-limited SLE-like autoimmune reaction.^{10,11} Patients with KFD have an increased incidence of developing autoimmune diseases and require close follow up as outpatients.⁴ There are no prior case reports documenting association between KFD and GPA, though one report describes a case originally misdiagnosed as GPA later found to be KFD associated with SLE.¹² This case alone does not establish an association between the diseases, but surveillance should continue for further cases given the suggested autoimmune nature of GPA.¹³

GPA is a necrotizing granulomatous vasculitis of the small vessels. Classically, it is characterized by upper respiratory, lower respiratory, and kidney involvement. However, all organ systems can be affected, including the skin. In GPA, antineutrophil cytoplasmic antibodies are directed against proteinase 3, a component of neutrophil granules. One hypothesis is that these antibodies induce degranulation of neutrophils and monocytes, causing necrotizing vasculitis via endothelial injury.^{14,15} While autoimmune phenomena likely occur, the pathogenicity of ANCA remains unproven.¹³ GPA was considered to be a fatal condition until the introduction of cyclophosphamide and immunosuppressive therapies. Despite appropriate treatment, 25-40% of patients experience disease flares and morbidity and mortality are substantial.¹⁴

Cutaneous manifestations of KFD and GPA are clinically similar. Rash is present in 40% of KFD cases and 46% of GPA cases. Skin eruptions associated with KFD are typically located on the scalp, face, trunk, and upper extremities. Rash associated with GPA frequently manifests on the upper and lower extremities.¹⁶ Table 2 lists the common cutaneous findings in KFD and GPA.^{17,18} Although some trends have been identified, the rash still tends to be quite variable and non-specific. Therefore, differentiating these two disease processes based on dermatologic findings alone is difficult.

Figure 1. The patient's skin biopsy demonstrating dermal infiltrates.

Table 2. Common Cutaneous Findings in Kikuchi–Fujimoto Disease and Granulomatosis with Polyangiitis (Wegener's)

Kikuchi–Fujimoto Disease ¹⁷	Granulomatosis with Polyangiitis ¹⁸
"Rash"	Palpable purpura
Erythematous macules or patches	Pyoderma-like ulcer
Erythematous papules or plaques	Papule
Erythematous macules and papules	Petechiae
Malar erythema	Nodules
Oral ulcers	Superficial ulcerations
Pruritis	Bullae
Alopecia	Maculae and erythema

The histological characteristics of KFD and GPA are much more distinct. Typical histologic traits of KFD include dermal and epidermal histiocytic infiltrates, presence of non-neutrophilic karyorrhectic debris, basal vacuolar change, and papillary dermal edema.¹⁷ Histiocytes are the predominant inflammatory cells, with neutrophils usually being absent.¹⁹ These histiocytes typically stain positive for myeloperoxidase, indicating their myeloid lineage.²⁰ Nearly all of the infiltrating cells stain positive for CD68 and CD163, histiocyte antigen-markers commonly seen in inflammatory conditions.^{19,21} The histopathologic hallmark of cutaneous GPA is leukocytoclastic vasculitis, seen in up to 80% of patients. It often leads to epidermal necrosis and ulcer formation. Additionally, C-ANCA serology has been shown to be positive in 81% of patients with cutaneous manifestations of GPA.¹⁸

The rashes of KFD and GPA are difficult to differentiate from physical exam alone. Further complicating the clinical picture, both diseases are associated with nonspecific symptoms, such as malaise, weakness, arthralgias, anorexia, and weight loss. Tissue biopsy can provide valuable information regarding a diagnosis. The patient's skin biopsy was consistent with findings of KFD, as there were numerous histiocytic cells which were CD68 and myeloperoxidase positive. No signs of vasculitis were seen, excluding a flare of GPA as the source of the rash. His acute kidney injury improved with IV fluids, compatible with pre-renal factors. The rash and fevers resolved within two weeks of discharge. Maintenance therapy for GPA continued as an outpatient with azathioprine, trimethoprim/sulfamethoxazole, and chronic low dose prednisone.

CONCLUSION

This patient's rare systemic disease was confounded by a rare acute illness. The insight provided from the skin biopsy helped direct the course of treatment. Had the rash been consistent with GPA, his maintenance therapy may have been altered to better control the disease. However, biopsy results allowed for accurate diagnosis and avoidance of unnecessary treatment. This is the first reported case of KFD in a patient with known GPA. While no association has been established between these diagnoses, surveillance for further cases should continue.

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Conflict of Interest: The author declares that he does not have a conflict of interest.

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