Case Report

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Refractory interstitial granulomatous dermatitis in the setting of underlying diffuse large B-cell lymphoma

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ABSTRACT

Interstitial granulomatous dermatitis is a rare dermatologic condition characterized by erythematous papules, nodules, and plaques, most commonly on the trunk and limbs. It is commonly associated with comorbidities such as arthritis, autoimmune disease, lymphoproliferative disorders, and malignancies. In addition, the rash can be medicationinduced, which is differentiated by histopathologic results. Diagnosis is confirmed with skin biopsy, and treatment is individualized to each patient. Here we report an 89-year-old man with sudden onset lower extremity interstitial granulomatous dermatitis with the concurrent diagnosis of diffuse large B-cell lymphoma. Treatment of the skin lesions was attempted with a combination of steroids, antibiotics, antifungals, and disease-modifying anti-rheumatic drugs, without complete resolution.

Keywords: Interstitial granulomatous disease, Diffuse large B-cell lymphoma, Geriatric, Palisading infiltration of histiocytes, Necrotizing granulomatous inflammation

INTRODUCTION

Interstitial granulomatous dermatitis (IGD) describes an asymptomatic dermatologic condition displaying erythematous papules/nodules and polycyclic plaques within the trunk and limbs. Individual skin lesions are erythematous and violaceous in color, and often symmetrically distributed.¹ Of those with IGD, 90% present asymptomatically or with mild pruritus and burning.²

The pathogenesis of IGD remains unclear, although current paradigms suggest it arises secondary to immune complex deposition in dermal vessels.3 This deposition then activates the complement cascade causing subsequent neutrophil extravasation. These processes then inflict intrinsic damage to dermal collagen, which

can result in the formation of granulomatous infiltrate.³ The persistence of IGD lesions are strongly dependent on the cause of the rash and the treatment course, but studies suggest that most patients obtain remission within 3 months to 3 years.² Patients presenting with IGD have displayed strong associations with underlying medical conditions including arthritis, autoimmune disease, lymphoproliferative disorders, hematologic malignancies, and non-hematologic malignancies.^{2,4}

IGD can be difficult to delineate from other dermatologic conditions by physical examination. Thus, a skin biopsy is imperative to allow for clinical-pathologic correlation when examining the lesion to establish a diagnosis of IGD. Current treatment guidelines remain unclear for the proper medication regimen. To date, a majority of IGD cases have been successfully managed with systemic or

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topical glucocorticoids.⁵ Other successful reported therapies include hydroxychloroquine, dapsone, and tumor necrosis factor (TNF) inhibitors.⁵⁻⁷ In cases which patients have an associated underlying medical condition, management of the underlying condition has resulted in resolution of IGD lesions.⁵ In cases of drug-induced IGD, withdrawal of the offending agent can resolve the cutaneous manifestations.⁸ While the most appropriate treatment option is not always definitive given differing etiologies, most patients observe resolution of these lesions over time. This report describes a unique case in which a geriatric patient presented with persistent asymmetric lower extremity IGD lesions with underlying diffuse large B-cell lymphoma (DLBCL).

CASE REPORT

An 89-year-old male presented to the emergency department with profuse nocturnal diaphoresis. The patient was aware of a recent detection of lymphoma on laboratory testing, but was awaiting biopsy for diagnostic confirmation. Upon examination, the patient was During admitted for further follow-up. hospitalization, he underwent a biopsy and was diagnosed with diffuse large B-cell lymphoma. He was subsequently started on a chemotherapy regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP). On day 14 of hospital admission, the patient developed an atypical, asymptomatic rash which began on the left distal phalanges and slowly moved proximally.

Seven months after hospitalization, the patient presented to the dermatology clinic complaining of a rash on his left lower extremity. The skin lesions had progressed proximally to the left thigh. Significant past medical history included DLBCL, chronic lymphocytic leukemia, polycythemia vera, hypertension, type 2 diabetes mellitus, and severe osteoarthritis.



Figure 1: Physical examination revealing initial dermatologic lesions of the left lower extremity consistent with interstitial granulomatous dermatitis, located on the (A) anterior, (B) lateral, and (C) medial leg.

Physical examination revealed annular plaques and multiple erythematous, purpuric papules and nodules on the left lower extremity (Figure 1). A punch biopsy displayed deep dermal palisaded granulomatous dermatitis with central necrosis and neutrophils, along with a sparse perivascular lymphoid infiltrate. No polarizable foreign material was identified. A periodic acid-Schiff (PAS) stain was done to identify a potential fungal source, which yielded a negative result. An acid-fast bacilli (AFB) stain was negative, ruling out a mycobacterium infectious source.

Due to persistence of the rash, an exhaustive number of therapeutic interventions were attempted. Initial therapy consisted of triamcinolone cream, which showed no regression of his lesions. Next, a 6-months trial of doxycycline, fluconazole, and hydroxychloroquine combination again demonstrated no improvement in his rash. The third attempted intervention was intralesional triamcinolone, which demonstrated minimal improvement. The patient was then prescribed hydroxychloroquine which resulted in improvement in the clinical appearance of the rash by flattening out the lesions. Although flattened, the rash still persisted despite numerous treatments. Application of dapsone was attempted, again with no significant improvements. Given the persistent and refractory nature of the rash, additional care was sought at the wound clinic. The dermatitis led to progressive scarring over time, and the proximal lesions persisted for four years without complete remission.

DISCUSSION

IGD was originally outlined by Albert Ackerman in 1993. IGD inflicts women more commonly with an average age of diagnosis in the sixth decade of life. Despite over two decades of attempted research, IGD etiology remains partially unknown. In a 2008 literature review, only 97 cases of IGD were identified and reported. IGD

While a direct causal relationship has not been established, IGD has also shown an attributable association of diseases. Common associations of IGD include osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, various systemic vasculitides, drug reactions, myeloproliferative disorders, and malignancies. 11 The most common extracutaneous manifestations include arthralgias and arthritis in greater than 50% of patients with IGD.⁴ There is an association of IGD with malignancy, which insinuates that IGD may warrant further investigation into a potential new or progressing underlying cancer. 12 It is imperative to complete a full evaluation and stratify patients that carry a significant risk of underlying disease, specifically malignancy. In addition to medical history, medications play a role in the development of IGD, as outlined in (Table 1).

Table 1: Medications associated with interstitial granulomatous disease. 7,15,17,18

Class/category	Medication
Angiotensin converting enzyme inhibitors	Elanapril, Lisinopril
Angiotensin receptor blockers	Candesartan
Anticonvulsants	Carbamazepine
Antidepressants	Buproprion
Antihistamines	Brompheniramine, Ranitidine
Benzodiazepines	Diazepam
Beta-blocker	Atenolol, Propranolol, Labetalol
Calcium channel blockers	Verapamil, Diltiazem, Nifedipine
Diuretics	Furosemide
Anti-HER2 monoclonal antibodies	Trastuzumab
Lipid lowering agents	Gemfibrozil, Simvastatin, Pravastatin, Lovastatin, Atorvastatin
Stimulant laxatives	Sennoside
Tumor necrosis factor α (TNF-α) inhibitors	Lenalidomide, Infliximab, Etanercept, Adalimumab

IGD is histologically defined by the presence of necrotizing granulomatous inflammation, and diffuse palisading infiltration of histiocytes into the reticular dermis.² Histiocytes, polymorphonuclear leukocytes, and eosinophils are also identified circumferentially surrounding the degenerating collagen.² Histopathologic findings of medication-associated and disease-associated IGD are generally indiscernible. However, there are minor variations that allow differentiation of the two pathologies in some circumstances. Medication-associated IGD generally exhibits vacuolar interface dermatitis, exocytosis of lymphocytes, and the absence of neutrophils, while disease-associated will not.¹³ Differentiating these histopathologic findings can help determine the cause of IGD.

Management of IGD is dictated by the etiology of disease. The mainstay of treatment for medicationinduced IGD is discontinuation of the offending medication, which has been shown to result in complete resolution of skin lesions.8 However, appropriate treatment for non-medication-induced IGD is currently ill-defined and must be individualized based on medical comorbidities and health status. Typically, first-line treatment of localized lesions begins with a high potency topical corticosteroid, however, is not proven to be extremely effective.^{2,5} If first-line treatment fails, secondline treatment consists of a select combination of dapsone, hydroxychloroquine, methotrexate, and oral glucocorticoids.⁵ Dapsone has shown to be clinically effective particularly in patients with IGD and rheumatoid arthritis.¹⁴ TNF inhibitors, such as etanercept and infliximab, have also been shown to alleviate IGD symptomatology.^{6,7} Despite studies displaying their efficacy, The role of TNF inhibitors in treatment remains controversial given their ability to cause IGD as well.¹⁵ While several medications serve as potential therapeutic options, treatment of the underlying medical condition can also lead to regression of IGD lesions.⁵ Treatment of IGD generally confers favorable outcomes, with patients taking an average of approximately 9 months to show complete resolution of disease.²

This case varied from the current body of literature regarding IGD in several ways. First, this patient had an atypical presentation as the skin rash began with an asymmetric distal distribution on one lower extremity as opposed to the typical symmetric truncal presentation. Also, this patient's age of onset was significantly older than the mean age of diagnosis.

The patient's simultaneous onset of IGD and diagnosis of DLBCL renders the malignancy a potential cause. This case is noteworthy because it showed persistence of the IGD skin lesions with minimal to no signs of improvement after trying a multitude of treatment regimens. The rash persisted beyond 4 years after diagnosis.

To the author's knowledge, only one other case presents IGD with underlying DLBCL.¹⁶ The case described above differs from the previously documented case in etiology, patient demographic, and treatment outcome. The previous case documents medication-induced IGD, while this case was likely secondary to progression of the lymphoma. The previous patient with diagnosed DLBCL had no previous rash, but developed IGD lesions acutely after initiating anakinra of arthritic pain. This temporal relationship differed from our presentation, as no changes in medication occurred prior to precipitation of the rash. The demographic difference is also of note, as this patient was significantly older at 89 years of age, in comparison to the previously documented case at 56 years of age. The previously documented case obtained complete resolution after remission of lymphoma and discontinuation of anakinra. Our case documents an unusual case of refractory IGD in the setting of DLBCL, without resolution despite exhaustive interventions.

CONCLUSION

IGD describes a distinct dermatologic entity with a typical clinical pattern of patches, plaques, and erythematous papules. Most cases occur as a result of offending medications or precipitated by underlying disease, such as connective tissue disease, autoimmune processes, myeloproliferative disorders, and malignancies. Thus, screening these patients for extracutaneous disease can help unearth underlying processes, which may be treatable. Further research is needed to establish definitive treatment guidelines for IGD for alleviation of disease. It is imperative to uncover the etiologic cause of IGD, and remove offending agents

or treat concurrent associated disease to stop recurrence or persistence of IGD.

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