Jam-A, Plasminogen and Fibrinogen Reactivity in a Case of a Lupus Erythematosus-Like Allergic Drug Reaction to Lisinopril

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Abstract

**Background:** Drug-induced lupus erythematosus is a lupus variant that resolves within days to months after withdrawal of the eliciting drug, in patients without other major underlying immune system dysfunction.

**Case report:** A 71 year old Caucasian female presented following sudden onset of an erythematous, desquamative, polycyclic, scaling and pruritic rash in sun exposed areas, 4 days after taking Lisinopril®. Skin biopsies for hematoxylin and eosin analysis, as well as for direct immunofluorescence (DIF) were obtained.

**Results:** The hematoxylin and eosin staining revealed basal layer vacuolar degeneration, basilar apoptotic and dyskeratotic keratinocytes, and a lymphocytic interface dermatitis with an additional superficial and deep, perivascular and perineural lymphohistiocytic infiltrate. A significant presence of eosinophils was noted in the inflammatory infiltrate. DIF demonstrated positive reactivity with FITC conjugated anti-human fibrinogen, especially directed against dermal neurovascular plexus components and appendageal neurovascular supply structures; this staining colocalized with glial fibrillary acidic protein staining. Overexpression of anti-plasminogen and anti-junctional adhesion molecule A was also noted in these areas.

**Conclusion:** In this case of a lupus-like allergic drug reaction, the strong presence of dermal eosinophils, lack of basement membrane zone deposition of IgM and C3 and strong reactivity to dermal vessels with fibrinogen assisted in addressing the differential diagnosis of lupus erythematosus.

Keywords: Lupus-like drug reaction; Direct immunofluorescence; Fibrinogen; Plasminogen; Lisinopril; Glial acidic fibrillary protein; JAM-A

Abbreviations: H&E: Hematoxylin and Eosin; DIF: Direct Immunofluorescence; DLE: Discoid Lupus Erythematosus, BMZ: Basement Membrane Zone, GFAP: Glial Fibrillary Acidic Protein

Introduction

Drug induced lupus erythematosus (DILE) can arise months to years after exposure to eliciting drugs (eg, selected antihypertensives, antibiotics and anticonvulsants). The most common eliciting medications include hydralazine, procainamide, quinidine, isoniazid, diltiazem, and minocycline [1-4]. Drug induced subacute cutaneous lupus erythematosus represents a subvariant with predominant skin involvement [1-4]. Care must be taken to correctly diagnose the symptoms of drug induced lupus, and to differentiate it from classic systemic lupus erythematosus via clinical, serologic and pathologic data.

Case Report

Our patient exhibited rapidly presenting constitutional symptoms of fever, weight loss, fatigue, joint pain and myalgias after taking Lisinopril® for 5 days. The patient denied taking other medications or vitamins, as well as over the counter or natural medications. Serologic testing revealed antihistone antibodies to be positive at >95%, and low anti-dsDNA antibodies titers. Her C3/C4 levels and a complete blood count were within normal limits. Anti-Sm, ENP, ribosomal protein, ANCA and VDRL testing were negative.

A lesional skin biopsy was taken for hematoxylin and eosin (H&E) analysis. A DIF biopsy was taken from the upper arm, and from the edge of the lesions. The constellation of clinical, histologic and immunofluorescence features favored the differential diagnosis of 1) DILE, or 2) early lupus erythematosus, with a concomitant, nosologically unrelated allergic reaction present. After biopsy interpretation, we favored the diagnosis of a DILE, and suggested cessation of Lisinopril®. Follow up of the patient demonstrated that her antihistamine antibodies diminished 6 weeks after Lisinopril® cessation and addition of antihistaminics and topical betamethasone. The patient’s lesions began to recede clinically one week after these therapeutic changes. The patient was further advised to avoid future Lisinopril® therapy.

Methods

DIF

Our DIF was prepared and incubated with multiple fluorochromes, as previously described [5-9]. In brief, we transferred our biopsy from Michel’s transport medium into OCT media, and froze at minus 20 degrees Celsius. We used a cryostat to cut multiple frozen section sets, at four micron thickness. DIF was then performed utilizing antibodies directed to FITC conjugated polyclonal rabbit anti-human IgG, IgA,

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IgM, complement/C1q, complement/C3, albumin and fibrinogen, all from Dako (Carpinteria, California, USA) as previously described [6-10]. We utilized FITC conjugated monoclonal goat anti human FITC IgE from Vector Laboratories (Burlingame, California, USA), and FITC conjugated mouse monoclonal anti-human IgG3 from Sigma (Saint Louis, Missouri, USA). We also utilized FITC conjugated anti-plasminogen from Academy Biomedical (Houston, Texas, USA). We utilized FITC conjugated anti-human haptoglobin from Rockland Immunonchemicals (Gilbertsville, Pennsylvania, USA). We selected this antibody because haptoglobin is typically increased in hypertensive patients, and wished to evaluate alterations of this molecule in the skin biopsy. Finally, we utilized Cy3 conjugated anti-human glial fibrillary acidic protein (GFAP) from Sigma, and FITC conjugated anti-human polyclonal junctional adhesion molecule-A (JAM-A) from Invitrogen (Carlsbad, California, USA).

Results

Microscopic examination

Examination of the H&E tissue sections demonstrated mild epidermal hyperkeratosis with minimal follicular plugging. A mild interface infiltrate of lymphocytes and histiocytes was noted. Within the dermis, a prominent, superficial and deep, perivascular and periadnexal infiltrate of lymphocytes, histiocytes, plasma cells, occasional mast cells, neutrophils and eosinophils was also observed. Increased dermal mucin was not appreciated. A PAS special stain revealed focal reinforcement of the epidermal basement membrane zone (BMZ), as well as around sebaceous glands, eccrine sweat glands and hair follicles. Notably, these sites represented the same places that positive deposits of fibrinogen were later identified via DIF. The PAS special stain revealed no fungal organisms. DIF studies displayed the following results: IgG (-); IgA (+; focal superficial perivascular dermal deposits); IgM (focal +, deposits on the sebaceous gland base membrane zone (BMZ)); IgE (focal +, at the superficial dermal neurovascular plexus); complement/C1q(-); complement/C3(-); albumin (focal +, linear deposits on sebaceous gland BMZ); fibrinogen (+ + +, shaggy linear BMZ, and ++, at the dermal neurovascular plexus); plasminogen (+, focal deposits in some areas around the sebaceous glands and hair follicular units) and haptoglobin (-). Thus, the primary findings in our case included strong focal reactivity of the BMZ with fibrinogen and to dermal neurovascular areas and vessels, in contradistinction to conventional lupus band reactivity that favors BMZ deposition of multiple immunoreactants. Further, reactivity with anti-human fibrinogen was positive in several neurovascular supply structures of dermal appendages. 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Figure 1: a) H&E. Low magnification (10X) demonstrates edema and an inflammatory infiltrate in the superficial dermis, and subepidermal clefing at the basement membrane zone (black arrows). b) H&E highlighting spongiosis in the epidermis (black arrow) and the lymphohistiocitic infiltrate in the papillary dermis (red arrow) (40X). c) Demonstrates the patient’s clinical lesions. d) DIF documenting a positive pseudo-lupus band at the BMZ (red arrow), visualized via FITC conjugated anti-human fibrinogen (green staining; red and yellow arrows). e) Dual DIF staining, highlighting overexpression of Cy5 conjugated JAM-A (pink) in the same areas where the pseudo-lupus fibrinogen band is present. Note the JAM-1 staining overlaps with the FITC conjugated anti-human fibrinogen staining (yellow/green staining; blue arrow). f) Higher magnification of the DIF pseudo-lupus band (red arrow).

Figure 2: All DIF, except e. a) positive staining of blood vessels around a hair follicular unit using FITC conjugated anti-human fibrinogen (green staining; white arrow). b) Antibody to Cy5 conjugated JAM-A on dermal blood vessels (red staining; white arrows). Additional, colocalizing FITC conjugated anti-human plasminogen antibody staining is present (green-yellow staining; white arrows). c) Similar to b, but shows staining with FITC conjugated anti-plasminogen alone (green staining; white arrows). d) Positive staining of blood vessels around a dermal eccrine gland duct using Cy5 conjugated anti-JAM-A (red staining; white arrows). e) H&E demonstrating the dermal inflammatory infiltrate, including eosinophils (black arrow) (40x). f) Dermal blood vessels demonstrating positive staining with FITC conjugated anti-human fibrinogen (green staining; red arrow; g), h) Dermal blood vessel perivascular areas displaying positive staining with FITC conjugated anti-human IgG3 (green staining; white arrows). i) Positive staining of blood vessels near a hair follicular unit with FITC conjugated anti-human IgG (green staining; red arrows). Note-Keratinocyte nuclei were also counterstained with DAPI in b, d, f and i (light blue staining).

We investigated IgG3 deposition, because in allergic asthma IgG3 has been shown to play a role in eosinophil degranulation. Few studies on skin allergic reactions have included investigation of this immunoglobulin [15]. Indeed, our DIF findings were positive for this antibody.

Lisinopril® is an angiotensin converting enzyme (ACE) inhibitor used for treating high blood pressure, heart failure and preventing renal failure due to high blood pressure and diabetes. In our skin biopsy, we found weakly positive plasminogen deposition, thus raising the possibility that in our patient Lisinopril did not reach the serum levels necessary to modulate the fibrinolytic balance.

Drug-induced lupus erythematosus differs from its idiopathic counterpart in terms of clinical, histologic, immunologic and prognostic characteristics, including the presence of eosinophils in the dermal inflammatory infiltrate (Figure 1), and prominent epidermal spongiosis (Figure 2).

In Table 1, we compare some DIF findings in these differential variants of lupus erythematosus, and in sun exposed skin. One cardinal DIF finding in our DILE case is strong fibrinogen reactivity at the BMZ, with further, focal reactivity in the superficial dermis. In contrast to conventional lupus band reactivity, we found that fibrinogen BMZ reactivity in our case was stronger than IgM or C3 BMZ reactivity. Drug allergies often present a significant immune response, demonstrated by fibrinogen deposition. Notably, the dermal fibrinogen reactivity was paralleled by expression of anti-human GFAP in the same area.

We further noted that the dermal fibrinogen reactivity was present in several neurovascular areas that supply the skin appendageal structures; overexpression of JAM-A and deposits of plasminogen were also noted in these areas. The pathophysiologic significance of these findings remains unclear. In the workup of allergic drug reaction patients, we recommend clear communication between primary care providers and consultant dermatologists regarding the medications each patient is taking. Often, drug related skin conditions will rapidly clear following cessation of the eliciting medication. In our case, the patient’s Lisinopril® was discontinued; subsequent treatment with topical clobetasol led to rapid improvement of her skin lesions. Serologic followup noted that her antihistone antibodies decreased over 6 weeks following cessation. For the clinician, is important to remember that antihistone antibodies have been demonstrated to be of value in the management of drug induced lupus [3,16].

Funding

Georgia Dermatopathology Associates, Atlanta, Georgia, USA
References


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