OPEN ACCESS Freely available online

Lupus: Open Access

Mini Review

Hydralazine Induced Lupus Nephritis

Timlin H[1*], Shiroky J[1], Wu M[2], Geetha D[3]

[1]Department of Rheumatology, Johns Hopkins Bayview Medical Center, Baltimore, USA; [2]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, USA; [3]Department of Nephrology, Johns Hopkins Bayview Medical Center, Baltimore, USA.

ABSTRACT

Renal involvement is uncommon in the hydralazine induced systemic lupus erythematosus. We conducted a retrospective study to identify patients with biopsy proven Hydralazine induced lupus nephritis.

Material and Methods: In this retrospective study, patients who had a diagnosis of hydralazine-induced lupus and were on hydralazine prior to their diagnosis of biopsy proven lupus nephritis were included. Clinical and laboratory data were obtained from review of medical records. The median follow-up time was 12 months.

Results: Medical records were reviewed between 2013 to 2017. Four patients had a diagnosis of biopsy proven hydralazine-induced lupus nephritis and were on hydralazine prior to their diagnosis. The median age was 68 years at the time of diagnosis. The majority of patients were Caucasian (75%). Three were female (75%) and three (75%) were exposed to hydralazine 100mg three times daily. All four patients had biopsy proven lupus nephritis (class II, III, IV, III/IV) with elevated serum creatinine and were positive for ANA (titer of 640-1280, homogenous pattern). Of the three patients tested, all were positive for anti-Histone antibody. Two patients had positive anti-dsDNA, and one of them had low C3 and C4. The level of Anti-dsDNA normalized at 3 months while low C3 in one patient persisted at 12months. All had negative C-ANCA and 3 of the 4 had positive P-ANCA. All had strong positive MPO titer and 2 of the 3 tested had positive PR3.In addition to withdrawal of hydralazine, all four patients were treated with steroids, hydroxychloroquine and mycophenolate mofetil. Two of four patients received PLEX and two received Cytoxan and hemodialysis.

Conclusion: A timely diagnosis of hydralazine induced lupus nephritis can be critical. In addition to withdrawal of hydralazine, all patients also require aggressive treatment similar to idiopathic lupus nephritis.

Keywords: Lupus nephritis; Hydralazine induced glomerular disease; Drug induced lupus

INTRODUCTION

Hydralazine has been implicated as an etiologic agent for drug induced lupus by production of multiple autoantibodies [1-3]. In addition for the treatment of essential hypertension, Hydralazine hydrochloride is also recommended by the American Heart Association (AHA) for the treatment of congestive heart failure in African-Americans. Recognizing and understanding this condition is critical due to increasing use of hydralazine for blood pressure control, particularly in patients with heart failure and renal injury; two conditions that continue to increase in incidence. Renal involvement is uncommon in the hydralazine induced systemic lupus erythematosus [4,5]. The diagnosis is made similarly to traditional lupus nephritis; based on presentation with renal injury, serology, and findings on kidney biopsy. The goal of this study is to raise attention to biopsy proven hydralazine-induced lupus nephritis. We present a retrospective case series of hydralazine-induced lupus nephritis.

[*]**Correspondence to:** Homa Timlin, Department of Rheumatology, Johns Hopkins Bayview Medical Center, Baltimore, USA; E-mail: htimlin1@jhmi.edu

Received: December 24, 2019; **Accepted:** January 16, 2020; **Published:** January 23, 2019

Citation: Timlin H, Shiroky J, Wu M, Geetha D (2020) Hydralazine Induced Lupus Nephritis. Lupus: Open Access 5:147. DOI: 10.35248/2684-1630.20.5.147.

METHODS

In this retrospective study, patients were required to have a history of antinuclear antibody (ANA) positivity, lupus nephritis based on the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) criteria and were on hydralazine prior to the diagnosis of lupus nephritis. The Office of Human Subjects Research and Institutional Review Board approved this study protocol as an exempt study. Patient demographics, clinical features, dose and duration of hydralazine exposure and details of immunosuppressive therapy were obtained retrospectively from the electronic medical records. Similar to our previous study, antibodies were considered positive if the ANA level was ≥ 1:160 and the anti-dsDNA level was twofold above the reference range. Proteinuria was defined by urine protein:creatinine ratio of >0.2 g/Cr.

RESULTS

Four patients had biopsy proven lupus nephritis ranging from Class II to IV. The majority were elderly (75% over age 60), with the median age of 68 years at the time of diagnosis, and caucasian (75%). Three were female (75%). Three were exposed to hydralazine 100mg three times daily for over twelve months. All patients required hospitalization and were diagnosed based on biopsy during that admission. At time of presentation to the hospital 3 presented with pulmonary, cardiac, and skin involvement, in addition to renal.Concerning laboratory findings, all four patients had lymphopenia, anemia, elevated serum creatinine, and a positive ANA (titer of 640-1280, homogenous pattern), and negative for anti-smith, GBM, and RNP at the time of diagnosis. Of the three patients tested, all were positive for anti-Histone antibody. All had negative C-ANCA and 3 of the 4 had positive P-ANCA. All had strong positive MPO titer and 2 of the 3 tested had positive PR3.

Severity of lupus nephritis ranged from class II to class IV. At presentation, the patient with lupus nephritis class II had low complements (C3, C4), strongly positive MPO/PR3, positive lupus anticoagulant but negative anti-dsDNA. Patient with lupus nephritis class III, had positive anti-dsDNA, lupus anticoagulant, strongly positive MPO/PR3 but normal complements. Patient with lupus nephritis class IV, had low complements (C3, C4), positive anti-dsDNA, and positive MPO. Patient with lupus nephritis class III/IV had strongly positive MPO but normal complements, negative anti-dsDNA, lupus anticoagulant, and PR3.

The level of Anti-dsDNA normalized at 3 months while low C3 in patient with class IV LN, persisted at 12 months. In addition to withdrawal of hydralazine, all four patients were treated with steroids, hydroxychloroquine and mycophenolate mofetil. Two of four patients received PLEX (LN class II, IV), and two received Cytoxan (LN class IV and III/IV) and hemodialysis (LN class II and III/IV). All patients showed some renal improvement following discontinuation of hydralazine and management of immunosuppression. At 3 months, one patient had resolution of proteinuria and improvement of renal function, with persistent CKD Stage 3 with eGFR 36 (LN Class IV). At 6 months one patient's renal function returned to normal with eGFR >60, however subsequently declined to CKD Stage 3 with eGFR 39. The two who required hemodialysis (LN Class II, III/VI) were able to come off dialysis and remain off with CKD Stage 3-4 within the first 6 months.

DISCUSSION

As hydralazine becomes increasingly utilized in both the inpatient and outpatient settings, it is critical that providers have a good understanding of its risks, including rare and potentially catastrophic ones [6]. Important characteristics of our case series include the majority of individuals were female and on high doses of hydralazine for over a year. Concerning serologic workup, while all patients had a positive ANA, the presence complement and anti-dsDNA values varied. Interestingly 3 of the 4 patients presented with extra-renal manifestations. The individuals in our series presented with a range of severity of lupus nephritis with all requiring varying forms of immunosuppression.

This case series is limited by retrospective analysis, small sample size, and lost to follow up. Most of the patients were transferred to our institution for diagnostic work up at a quaternary care center and did not live close. As a result, they returned to the local primary providers and only followed up as needed once stabilized. Providers must be wary of abnormal urinalysis and changes in renal function in individuals on hydralazine, making sure to keep hydralazine-induced lupus nephritis on their differential and avoid this medication in susceptible patients. If hydralazine-induced lupus nephritis is suspected, hydralazine should be immediately discontinued and work-up pursued to ensure timely diagnosis and initiation of aggressive treatment.

CONCLUSION

Hydralazine can aggravate and unmask incipient lupus. Hydralazine induced lupus nephritis is rare. Prompt diagnosis and institution of therapy is critical to prevent organ damage and associated morbidity. Further studies will help us better understand the autoimmunogenic capability of hydralazine and potentially the mechanisms triggering idiopathic lupus and its many organ manifestations.

REFERENCES

1. Timlin H, Wu M, Bosque CM, Geetha D, Ingolia A, Haque U, et al. Clinical Characteristics of Hydralazine-induced Lupus. Cureus. 2019;11(6):e4996.
2. Timlin H, Liebowitz JE, Jaggi K, Geetha D. Outcomes of hydralazine induced renal vasculitis. Eur J Rheumatol. 2018;5(1): 5-8.
3. Bjorck S, Svalander C, Westberg G. Hydralazineassociated Glomerulonephritis. Acta Medica Scandinavica. 1985;218(3): 261-269. Volume 218, Issue 3
4. Ihle BU, Whitworth JA, Dowling JP, Smith PK. Hydralazine and lupus nephritis. Clin Nephrol. 1984;22(5):230–238.
5. Shapiro K, Pinn V, Harrington JT, Levey AS. Immune Complex Glomerulonephritis in Hydralazine-Induced SLE. Am J Kidney Dis. 1984;3(4):270-274.
6. Radhakrishnan J, Perazella MA. Drug-Induced Glomerular Disease: Attention Required! Clin J Am Soc Nephrol. 2015;10(7): 1287-1290.