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Clinical Reviews & Cases

Hydralazine induced Membranous Nephritis and RPGN

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ABSTRACT

It is already well known that Hydralazine can induce ANCA associated vasculitis(mentioned as AAV) and Pauci-Immune RPGN which is sometimes associated with pulmonary renal syndrome [1,2]. Hydralazine induced membranous nephritis has never been documented before. We present a case of hydralazine induced RPGN, with biopsy findings of Membranous Glomerulonephritis. This is a unique presentation of hydralazine induced renal failure and helps us to study the spectrum of pathological reactions induced from this drug. This case study also reviews the pathological similarities in the hydralazine induced reactions and SLE and discusses the treatment of such pathology.

Keywords

Hydralazine, Hypertension, Liver enzymes, Endoscopy.

Case Report

41 y old male was admitted for evaluation of shortness of breath of 1week duration, hemoptysis and one-episode bloody bowel movement. His symptoms started about 1 month ago, with abdominal discomfort, associated with loss of appetite, malaise, night sweats, loss of weight of 20lbs. The symptoms progressed to cause dyspnea, chest discomfort, pleuritic chest pain and hemoptysis associated with a purpuric rash on the lower extremities, low grade fever and chills. His past medical history was significant for hypertension for 1 year which was well controlled with hydralazine and amlodipine. He denied any drug or alcohol use. The initial presentation in ER indicated hypertension with BP is 170/90, fever of 100.6 f, RR 23. The significant exam findings were presence of a purpuric rash and 1+ edema in the bilateral lower extremities and bilateral crackles on chest auscultation. Further investigations showed presence of an acute DVT in the left leg, an elevated creatinine of 2.1 and albumin of 2.6 with normal liver enzymes.

There were bilateral alveolar infiltrates on CT Chest (Figure a) An echocardiogram effectively ruled out an underlying CHF but was positive for a small pericardial effusion. An upper endoscopy was positive for active duodenitis (Figure b). Since the clinical and lab findings in the patient were worrisome for a pulmonary renal syndrome, more specific autoimmune labs and a renal biopsy was ordered.

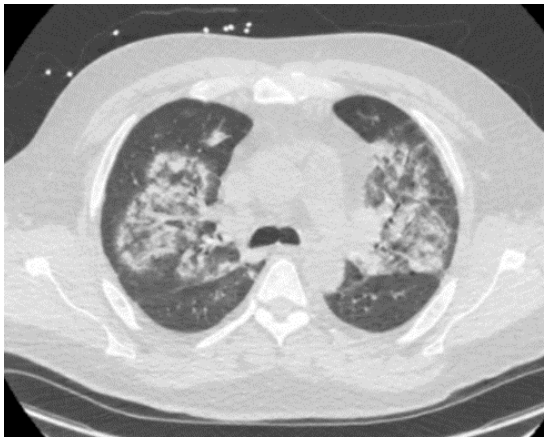

Figure a: Bilateral fluffy alveolar infiltrates, no Pulmonary embolism.

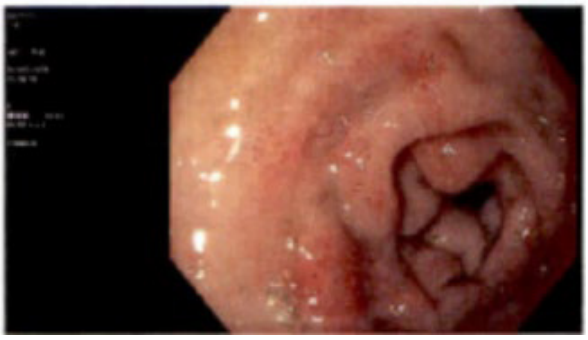

Figure b: Upper endoscopy shows duodenitis.

The Lab results are summarized in Tables 1, 2 and 3.

Table 1

Urine Analysis	
Specific gravity	1.008
pH	5.5
leucocyte esterase	negative
nitrite	negative
glucose	negative
hemoglobin	large
RBC	64
Cellular cast	present
Urine protein /creatinine	2.7

Table 2

Beta-2 gp1 IgA	0.0-19.9 u/mL	2.3
Beta-2 gp1 IgM	0.0 - 19.9 u/mL	0.2
Beta-2 gp1 IgG	0.0 - 19.9 u/mL	<1.4
Anticardiolipin IgA	0 - 19.9 APL	1.0
Anticardiolipin IgM	0 - 19.9 MPL	0.9
Anticardiolipin IgG	0 - 19.9 GPL	<1.6

Table 3

Immunology	
ANA Titer	1:1280 (homogenous)
Anti-ds DNA	Negative
Crithidia luciliae	Negative
Anti-chromatin IgG	Elevated 5.1
Anti-Histone Ab	Elevated 5.2
ANCA	Positive
Anti RNP	Negative
Myeloperoxidase Ab	> 8 Positive
Protéinase 3 IgG Ab	<0.2 (negative)
Complement C3	134
Complement C4	22
HIV	Negative
Hepatitis BsAg	Negative
Hepatitis B anti c ab	Negative
Hepatitis C ab	Negative
Cryoglobulins	Negative
Anti GBM	Negative
PLA2R	Negative

Renal biopsy

Focal disease activity, with cellular crescents or necrosis in 3 of 8 glomeruli on the light microscopy sample. In addition, immunofluorescence staining shows an immune complex glomerulonephritis with a membranous pattern. The features were compatible with necrotizing and Crescentic Glomerulonephritis and Immune Complex Glomerulonephritis, membranous nephropathy.

Immunofluorescence staining: + staining for IGG, IGM, IGA, C1Q, C3, C4 in the basement membrane, Negative for PLA2R antibody.

Electron Microscopy: Diffuse presence of sub epithelial immune deposits (figure 2)

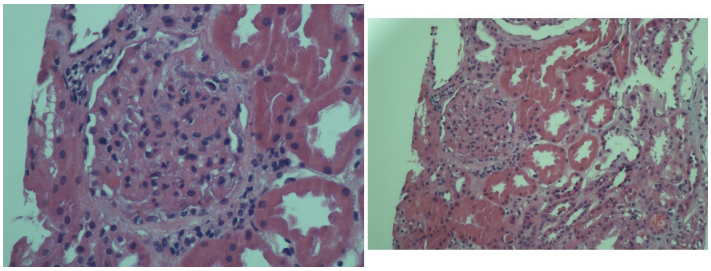

Figure 1: Focal necrotizing and crescentic glomerulonephritis.

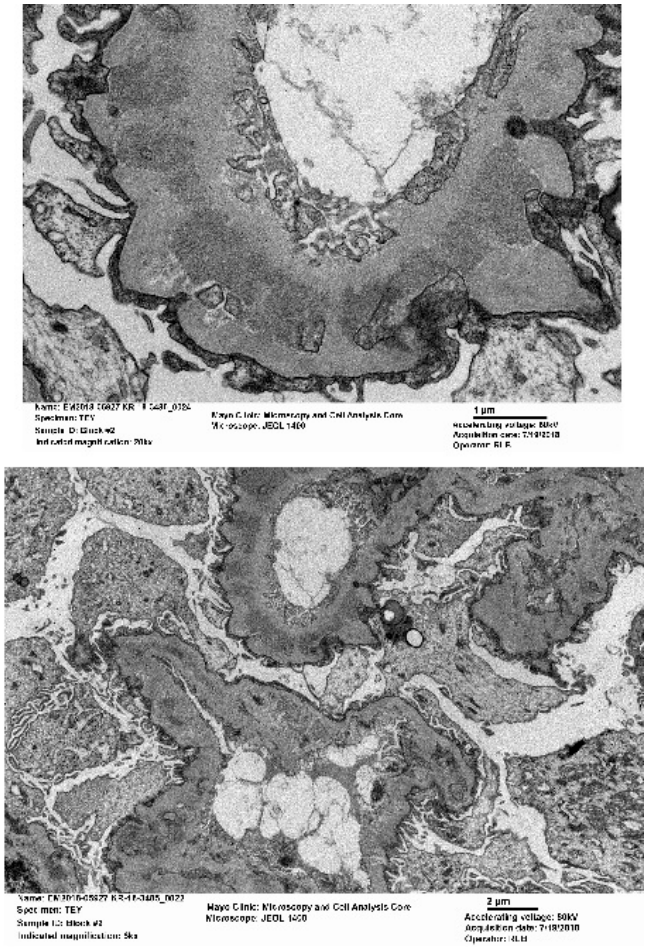

Figure 2: Immune complex glomerulonephritis with membranous features.

Clinical Course

The clinical presentation of our patient was multiorgan involvement, a cutaneous and pulmonary vasculitis, anemia, mild pericardial effusion and acute renal failure. In addition there were renal pathology findings of Rapidly Progressive Glomerulonephritis, Immune complex deposition and Membranous nephropathy.

These features are often seen in the SLE. The panel of blood test with a negative double stranded DNA, a negative antichromatin level, normal complements and absence of a full house effect on immunofluorescence rules out SLE as the underlying cause. The absence of Anti Phospholipase A2 Receptor (PLA2R) antibody both in serum and renal biopsy rules out primary membranous nephropathy. After ruling out all the other de novo and viral induced autoimmune reaction we concluded the etiology of the above presentation as Hydralazine induced autoimmune reaction. We started the treatment with pulse dose steroids solumedrol 500 mg ivy for 3 days followed by 1 gram of Rituximab on day 5 of admission. Hydralazine was stopped. His treatment was complicated with a serum sickness like reaction with Rituximab. Over the course of next 2 month his proteinuria increased from 2.9 grams and peaked at 6.7 grams His creatinine increased to 2.6. He was then started on 0.5g/kg every 3 weeks of i.v cyclophosphamide for 6 doses with 60 mg oral prednisone daily. After completing 6 doses of i.v cyclophosphamide his serum creatinine has improved to 1.5 with decrease in proteinuria to 3 gm. He continued to have persistent elevate ANA, ANCA levels and anti-histone antibodies. Currently the patient he is on mycophenolate mofetil 1500 mg bid with prednisone 20 mg daily.

Discussion

Hydralazine has been in use to treat hypertension for more than 50 years. Strong evidence is available in literature associating hydralazine and autoimmune reactions [1-6]. Hydralazine is known to cause 2 types of autoimmune reactions.

ANCA /MPO associated vasculitis

Characterized by pauci- immune RPGN and Pulmonary Renal Syndrome. The pathogenesis is described as:

a) Neutrophil apoptosis in response to hydralazine MPO binding, resulting in the production of multiple autoantibodies.

b) Increased expression of neutrophil autoantigens through hydralazine-induced reversal of epigenic silencing of MPO and PR3.

c) Break in tolerance in slow versus fast acetylators of Hydralazine.

Hydralazine induced Lupus Syndrome (HIL)

The mechanism behind this SLE like reaction is presence of antibodies against d DNA (also known as denatured DNA). Patients with SLE high titers of mainly anti-native DNA (100%) times and sometimes have anti-d DNA(6a) Hydralazine can produce high titers of anti d DNA (not against native DNA) to cause a Lupus like reaction(6b)Hydralazine Induced Lupus (HIL) is known for more than 30 years with clinical presentation ranging from being asymptomatic to arthralgia, low grade fever, rash.

HIL is not a known cause for renal failure and current guidelines do not support treating HIL with immunosuppressant agents due to lack of a true incidence of renal failure from HIL. Historically renal failure in HIL was first described in 1988 [7]. This work was further studied by Shapiro, Hess and Dustan [8,9] where they found an abnormal urine sediment and proteinuria in the patients taking hydralazine. Interestingly the abnormal sediment and proteinuria in these patients persisted after discontinuation of the drug.

Subsequently many case reports were published which described renal failure with Hydralazine use. Renal biopsy in these patients showed a wide range of renal pathology like focal and segmental necrotizing glomerulonephritis along with immune complex deposits [7,10]. Proliferative GN with mesangial electron dense deposits [11], hemorrhages in kidney, thickening of capillary walls and wire loops lesions [12]. Interestingly all these pathological findings in Hydralazine induced renal failure closely resembled Lupus Nephritis [13-18]. The Immune complex GN and its resemblance to Lupus Nephritis was also studied and confirmed in animal models [14,19].

The autoimmune panel in all these patients reported a positive ANA with variable values for complement c3, c4 and double ds DNA. Some patients had a positive MPO/ ANCA with or without clinical evidence of vasculitis.

Hydralazine induced autoimmunity can have a variable but severe presentation with multiorgan involvement. Our patient had evidence of clinical vasculitis with acute presentation of GI bleed, alveolar hemorrhage, cutaneous vasculitis and renal failure. The renal biopsy had significant findings of crescentic necrosis in GN, but there was no evidence of vasculitis in the renal blood vessels. The immunofluorescence and EM were significantly positive for immune complex deposits consistent with a secondary membranous nephritis. The negative staining for PLA2R ruled out primary membranous nephropathy effectively. This case has the classical findings of an autoimmune reaction involving multiple organs including an Immune Complex type of Membranous GN which is very similar to SLE.

The course of renal failure in this case was aggressive. He attained partial remission with improvement in serum creatinine from 2.6 to 1.5 and improvement in proteinuria from 6 gm to 3 gm after treatment with i.v cyclophosphamide. He continues to have a positive ANA, ANCA and Anti-histone Ab even after 6 months of treatment.

Further studies are needed to study the rate of remission and relapse of hydralazine induced renal disease. It will also be interesting to investigate if patients with HIL are more prone to develop SLE later in life.

Conclusion

This case supports that Hydralazine can cause an Immune complex vasculitis with Membranous GN, which requires prompt identification and treatment with immunosuppression. Disease spectrum from Hydralazine induced Lupus Syndrome can range from being completely asymptomatic incidental rise in ANA titers [2] to severe Vasculitis and Pulmonary Renal Syndrome. The actual pathology behind the Hydralazine induced renal failure is still undetermined but there is a striking resemblance in its presentation to SLE. Positive serum ANA is a sensitive marker to rule in HIL but a negative ds DNA and normal complements does not rule

it out. Presence of an abnormal urine sediment or urine protein may indicate underlying Hydralazine induced nephritis [4]. We believe that Hydralazine induced renal failure is an underreported event which often gets overlooked due to presence of confounding factors like long standing severe hypertension or chronic renal insufficiency in these patients.

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