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CASE REPORT

Hydralazine Induced Vasculitis: A Case Report

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Abstract:

Background:

Hydralazine has been used in the treatment of hypertension and heart failure for a long time. It has been associated with the development of Vasculitis and Drug induced lupus. This is a male patient in his sixties who was admitted at the hospital and prescribed hydralazine. He developed Hydralazine-induced lupus with Pancytopenia and renal failure. This case report has been written to raise awareness about the hydralazine side effects.

Case Presentation:

This case report describes a 68-year-old male, transferred to our hospital for rehabilitation. He was tracheostomized. He is hypertensive with a history of CVA. BP was elevated during the admission. He has no family history of immunological diseases or any allergies. 6 months after hydralazine, the patient started to have a purpuric rash over the lower limbs and an elevated renal profile. Only Direct Coomb's test was positive. He had hematuria and pancytopenia also. He was started on steroids and he became edematous. On March 2021, the hydralazine was stopped and the patient's blood tests improved, the rash disappeared and hematuria stopped. Unfortunately, he got fungemia and septicemia with pneumonia. He became hypotensive and anuric. The patient kept deteriorating and passed away.

Discussion:

Hydralazine is not a first line choice for the treatment of hypertension. Common side effects include tachycardia and headache. It can also cause drug-induced lupus.

Conclusion:

Hydralazine has been used in the treatment of hypertension and heart failure for a long time. It has been associated with the development of Vasculitis and Drug induced lupus.

Keywords: Hydralazine, Hypertension, AKI, Vasculitis, Hematuria, Thrombocytopenia.

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1. INTRODUCTION

Hydralazine has been in use as a treatment for hypertension and heart failure since 1951 [1]. The drug is a known cause of autoimmune disease, most specifically hydralazine-induced lupus. Recent report indicating the emergence of drug-induced anti-neutrophil cytoplasmic antibodies associated vasculitis [2]. Drug-induced lupus associated with the use of hydralazine was first described in 1953 [3], the incidence of hydralazine-induced lupus is about 5 to 8%. The typical symptoms include arthralgia, myalgia, fever, rash, pruritus, and leukopenia, renal injury is uncommon, encountered in 5 to 10% of reported cases; however, cases demonstrating drug-induced vasculitis limited to the kidney associated with the hydralazine use were reported in the literature beginning in the early 1980 [4, 5]. Hydralazine was one of the first drugs reported to induce SLE and has since been frequently cited in the literature, hydralazine induced SLE continues to be an important topic due to its use in heart failure and hypertension. The purpose of reporting this case is to raise awareness of the need to maintain vigilance for this drug-induced disease.

2. CASE PRESENTATION

68-year-old gentleman transferred to our hospital on 16 March 2021 for rehabilitation presented to the referring

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hospital with right-sided weakness. On 8 of March 2021, initial investigation and management were done. He was intubated and ventilated through mechanical ventilation. His chest was clear. He had a PEG tube, his abdomen was soft and not tender. His GCS was 11 out of 15. CT scan showed hypo dense area in the temporoparietal region indicative of infarctions.

He had a past medical history of old CVA, hypertension, diabetes mellitus, asthma, hyperlipidemia, epilepsy, Benign prostatic hypertrophy, PEG tube, suprapubic catheter, and low vitamin D.

He was ventilated through endotracheal tube, tracheostomy tube was inserted on 21 March 2021 and continued on mechanical ventilation. He was treated a couple of times for aspiration pneumonia and urinary tract infection with antibiotics. He was taking the following medication on admission: Clopidogrel 75 mg, aspirin 75 mg, amlodipine/valsartan 10/80 mg once a day dapagliflozin /Metformin 5/500 mg twice daily, atorvastatin 80 mg, sodium valproate 500 mg twice daily, citalopram 20 mg daily, omeprazole 20 mg daily, bisoprolol 5 mg daily, tamsulosin 0.4 mg once daily, baclofen 5 mg 3 times daily. Cholecalciferol 50,000 international unit once a week Routine blood tests were normal, including CBC, CRP, renal function, and liver function tests on admission. During his stay in the hospital, his blood pressure remained very high, *i.e.* 177/81. Hydralazine 25 mg 4 times a day was added on 10 of June 2021. On November 2021, after around 6 months, he developed a purpuric rash on his lower limbs and upper body, typical of vasculitic rash. Investigation was sent for vasculitic screen. He was started on hydrocortisone 100 mg injections twice daily. Because of massive edema secondary to the steroid. Slowly, we started weaning him from the steroid and introduced azathioprine, initially 50 mg, Then increased to 100 mg once a day. His creatinine level slowly deteriorated from 179 mmol/l to 309 mmol/l (Fig. **1**). His urea slowly deteriorated from 42 mmol/L to 76 mmol/L (Fig. **2**).

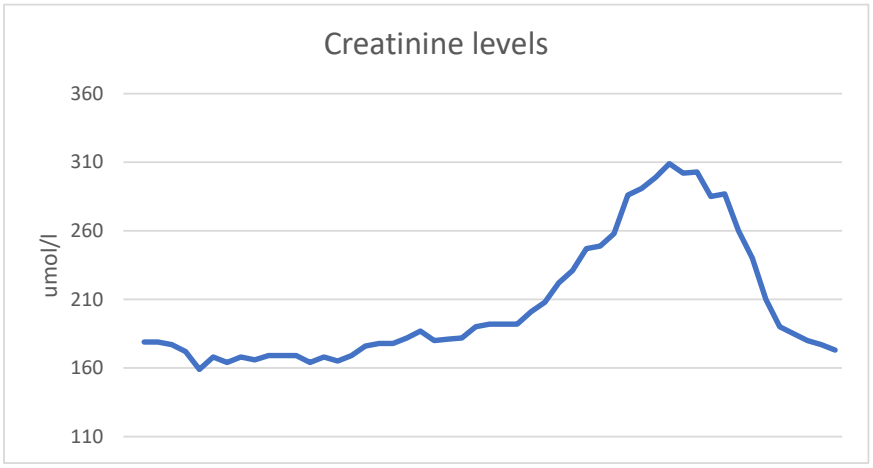

Fig. (1). The figure shows the variation of creatinine levels throughout the admission with an apparent increase. The levels settle to a value of 150 umol/l after stopping the hydralazine.

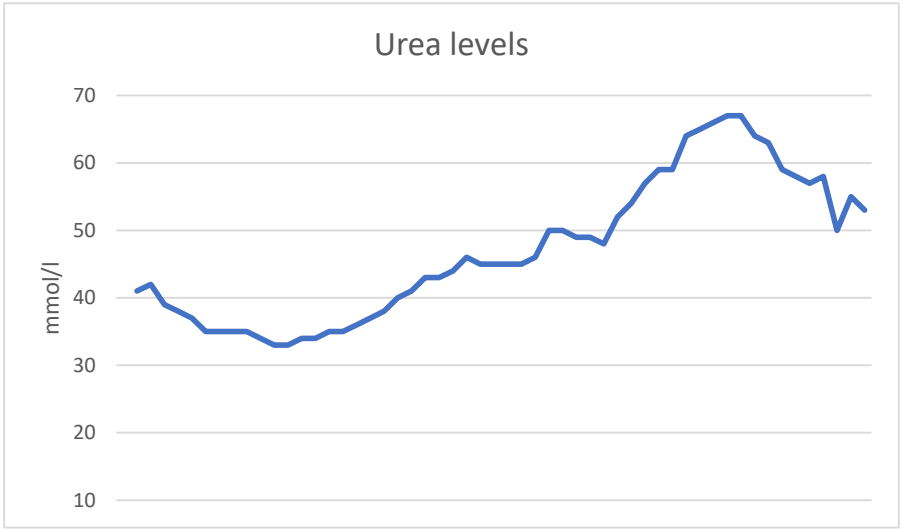

Fig. (2). This figure shows the serum urea levels during the admission. We can notice the increase in the serum urea levels which correlates with the onset of Hydralazine induced lupus. After stopping the Hydralazine, the urea levels settled down to around 50 mmol/l.

White cell count dropped from 5.6 × 10 9/L to 2.3 × 109/L (Fig. **3**).

His hemoglobin dropped from 8.8 mg/dl to 5.3 mg/dl (Fig. **4**).

His platelets dropped from 172 × 10^9/L to 45 × 10^9/L (Fig. **5**). CRP increased from 67 mg/L to….-225 mg/L Liver function test was normal. Antinuclear antibody was negative. Anticardiolipin was negative. Antiphospholipid was negative. Myeloma screen showed no evidence of a monoclonal band. Reticulocyte count was high 3.57%. Blood film showed evidence of normochromic normocytic anemia with thrombocytopenia. G6PD test was normal. ANCA test was negative for both P and C ANCA. Direct Coombs test was positive. Rheumatoid factor was negative. Antihistone antibody was requested but no results were received. Hepatitis B and C screening were negative, HIV test was negative. Thyroid function test was normal Vitamin D level was 17 ng/mL. Random cortisol level was 237 nmol/L. Urine examination showed 4+ blood and 1+ protein and negative for nitrate. Ultrasound abdomen showed chronic renal parenchymal disease and prostatomegaly. His purpuric rash improved with the steroid injections. But unfortunately, his renal function and CBC deteriorated. He required blood transfusions many times to keep his hemoglobin above 8. He had severe hematuria with clots, treated with regular flush of the catheter with normal saline and platelet transfusion. He requires a lot of platelets transfusion to keep his platelets above 50,000. On 4 March 2022 his hydralazine was stopped. We started gradually weaning him from the steroids. As a side effect of the steroid, he became very edematous, requiring IV furosemide by infusions; he lost almost 10 kg in weight within 2 weeks' time. Immediately after stopping the hydralazine, his blood test improved dramatically. He did not require any blood transfusion or platelet transfusion. His hematuria stopped. His skin petechial rash disappeared.

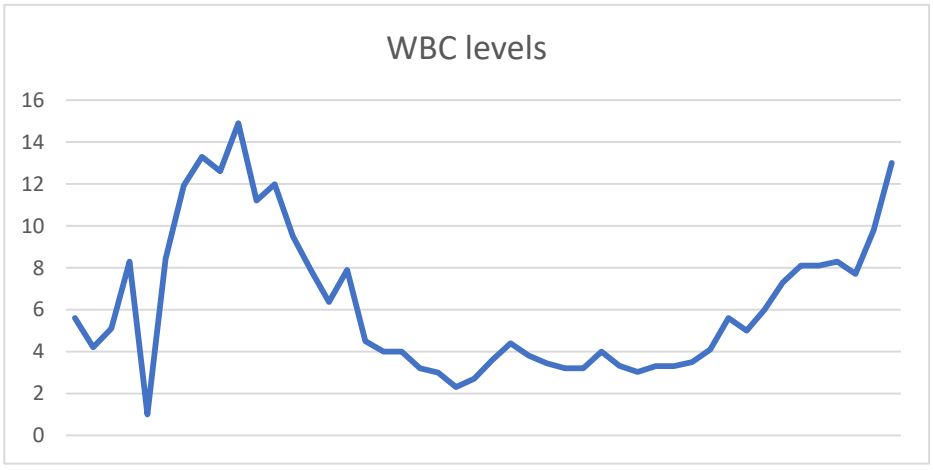

Fig. (3). The figure demonstrates the variation of White blood count levels during the patient's course of illness. The drop in the count correlated with Hydralazine induced lupus. The changes have been reverted after withdrawing the Hydralazine.

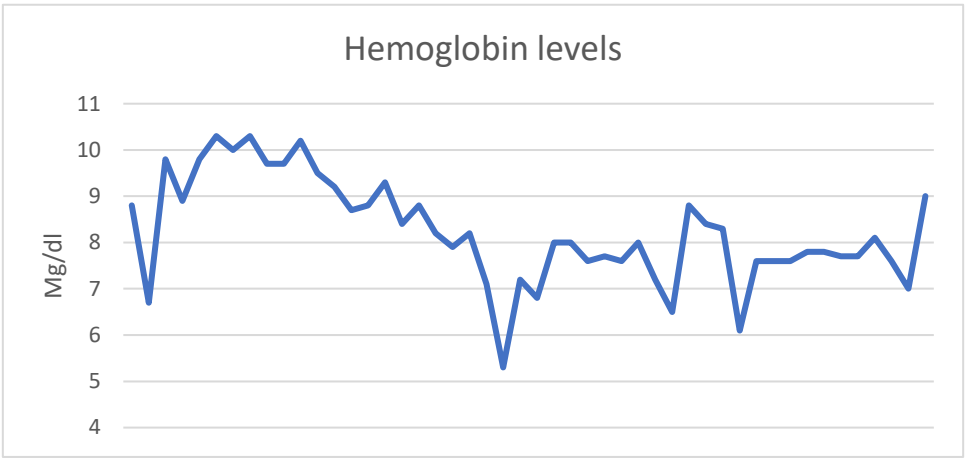

Fig. (4). The figure illustrates the Hemoglobin levels throughout the admission period. It is noticeable that there is a drop in Hb levels which occurred mainly during the period of the lupus like syndrome.

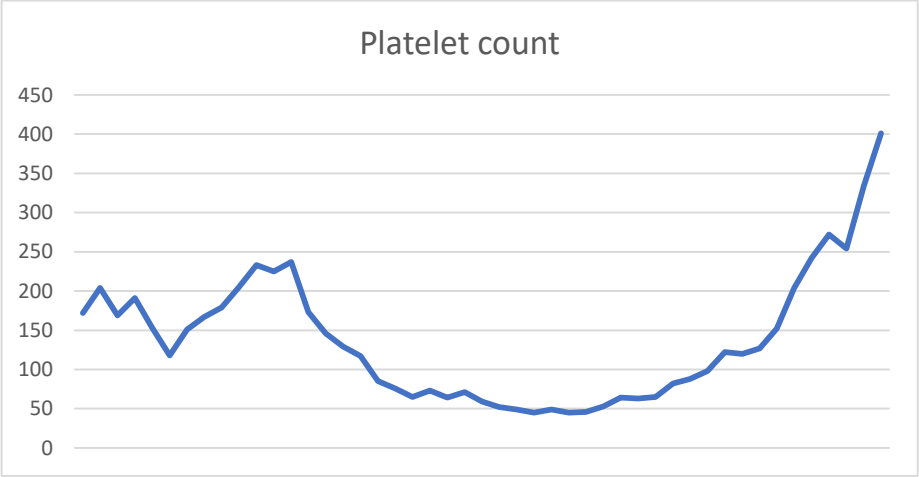

Fig. (5). This line graph demonstrates shows the platelt levels which has been declining through the period after the onset of Hydralazine Induced Lupus. The count jumped up to the normal levels after stopping the Hydralazine.

His renal function remained stable, with a urea of around 50 and creatinine of around 180 ((Figs. **1** and **2**)

His white cell count improved from 2.3-……..9.8 (Fig. **3**).

His hemoglobin remained around 8 (Fig. **4**). His platelets improved from 52-……..400 (Fig. **5**). Unfortunately he developed septicemia and fungemia. Blood culture grew Klebsiella pneumonia and Candi. His chest x-ray showed effusion on the right with pneumonia on the left lung. Central line was removed and started on antibiotics and antifungals (caspofungin) His condition deteriorated and his blood pressure dropped and became anuric And in spite of inotropic support, he died in peace on 2nd May 2022.

3. DISCUSSION

BHydralazine is a medication used to treat high blood pressure and heart failure including high blood pressure in pregnancy [6, 7]. Hydralazine has been found to be particularly useful in heart failure together with isosorbide nitrates [8]; it can be given orally or by injections. Common side effects, including headache and fast heart rate, it is not recommended in people with coronary artery disease or in those with rheumatic heart disease that affects the mitral valve [6]. The mechanism of action is through vasodilatation [6]. Hydralazine was discovered in 1949 while scientists were trying to find treatment for malaria [9, 10] and was approved for use by the FDA in 1953. Hydralazine is on the list of world health organization of essential medicines [11]; statistics from 2019 showed that it is the 99th most commonly prescribed medication in the United States, with more than 6 million prescriptions [12, 13]. Hydralazine can cause drug-induced lupus and drug-induced vasculitis, because of this, its use was on the decline. Hydralazine is not a first-line therapy for hypertension, and is often used to treat hypertension in pregnancy [14]. It should not be used in people with tachycardia, pericarditis, SLE, dissecting aortic aneurysm or porphyria [15].

The onset is slow, at least 3 to 6 months, with the usual range of 9 to 14 months. Musculoskeletal symptoms are the most common clinical manifestations especially arthritis of hands and wrist. Dose limitation of hydralazine reduces risk but low-doses are well documented to be associated with SLE, antinuclear antibody level should be determined on initiation of hydralazine, but routine checks are not warranted.

Laboratory results that lead to the diagnosis of drug-induced lupus include antinuclear antibody, antihistone antibodies and rheumatoid factor. Antihistone antibody has a sensitivity of up to 90% in DILE (drug induced lupus erythematosus) and 50% sensitivity to idiopathic SLE.

At each visit patient should be monitored if any signs and symptoms of SLE develop, hydralazine should be discontinued immediately.

Our patient had very poor blood pressure control and started on hydralazine 25mg 6 hourly, and after almost 6 months, he developed a petechial skin rash, renal function deteriorated, developed pancytopenia, he required blood transfusion and platelets transfusion, he did not respond to hydrocortisone and azathioprine. His investigation results showed positive Coombs test and high reticulocyte count supporting the diagnosis of hemolytic anemia, his urine examination showed hematuria and proteinuria.

Vasculitis screening tests were negative, including antinuclear antibody, ANCA test, antiphospholipid antibodies, and rheumatoid factor. Antihistone antibody which is more specific for hydralazine induced lupus was requested, but unfortunately the result wasn't reported back. After stopping his hydralazine his condition improved and after 4 weeks from stopping medication, his platelets were back to normal, his hemoglobin remained stable at around 8 mg/dl and, did not require any blood transfusion, his white cell count improved from 2.3×10^9/L to 9.8×10^9/L (Fig. **4**). His renal function improved but he remained in renal failure (Figs. **1** and **2**).

The gold standard of diagnosing SLE induced lupus is the resolution of the clinical manifestation of the disease typically within several weeks to months after the offending drug has been discontinued. Our patient has developed septicemia and fungemia and in the last few days of his life his blood pressure dropped and in spite of antibiotic and inotropic support, he died.

Hydralazine can cause serious side effects like drug-induced lupus and drug-induced vasculitis. We should think about lupus-like syndrome in all patients taking hydralazine therapy if they develop pancytopenia, skin rash, and deteriorated renal function.

Hydralazine should be avoided as much as possible as it is not first or second line treatment for hypertension. Stopping the hydralazine as soon as possible is the mainstay for the treatment.

CONCLUSION

The paper has been written to illustrate this serious side effect of hydralazine, which limits the use of this drug. It shows the case presentation along with the investigation figures showing the trends before and after stopping the hydralazine. The conclusion also addresses the main take-away messages about hydralazine and Hydralazine induced lupus.

LIST OF ABBREVIATIONS

DILE	=	Drug Induced Lupus Erythematosus
CT	=	Computed tomography

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Informed consent was obtained.

STANDARDS OF REPORTING

CARE guideline has been followed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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