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Case Report

# RARE SIDE EFFECTS OF PHENYTOIN: CASE REPORT

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## ABSTRACT

Phenytoin is known for its antiseizure activity. It is used for management of tonic-clonic and partial seizures. Chronic treatment with phenytoin can be associated with side effects. This is a case report of 27 years old male who is a known case of seizure disorder since 3 months on phenytoin (300m/day) treatment, came to our hospital with history of fever, cough and generalized weakness for 3 days. Patient's systemic examination was normal except for laboratory investigations which revealed anemia, thrombocytopenia, elevated serum creatinine and positive anti histone antibodies. Renal biopsy proved to be having acute interstitial nephritis. Diagnosed as phenytoin induced rare and multiple complications and hence phenytoin was stopped and managed with steroids, hemodialysis (short term) and other supportive medications. Patient condition improved significantly with normalization of serum creatinine levels. This case report highlights about rare side effects of phenytoin. Early diagnosis and management can reduce morbidity and mortality.

**Key words:** Phenytoin, Seizures, Interstitial Nephritis, Bicytopenia, Lupus.

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## INTRODUCTION

Phenytoin sodium has a chemical name of sodium 5,5-diphenyl-2, 4-imidazolidinedione, and is related to barbiturates in chemical structure. It is commonly used as prophylactic or therapeutic drug for seizures. Chronic use of phenytoin is not without complications. The acute interstitial nephritis (AIN), drug induced lupus (DIL) and bicytopenia in a same patient on phenytoin treatment are quite rare.

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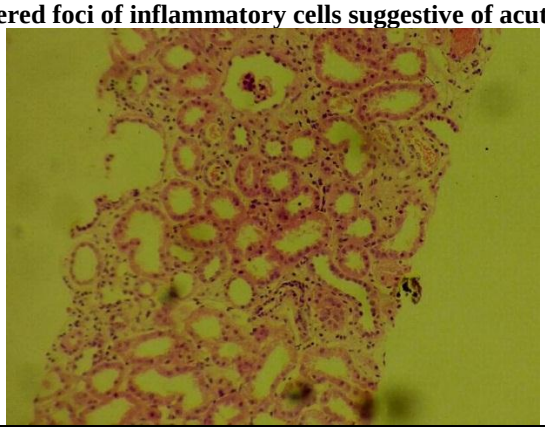
**CASE REPORT:** A 27 years old male who is a known case of seizure disorder since 3 months on phenytoin (300m/day) treatment, came to our hospital with history of Fever, cough and generalized weakness for 3 days. On initial evaluation, patient was conscious, afebrile, pulse rate – 78 beats / min, blood pressure – 124/56 mmHg, respiratory rate – 26 /min, spo2 of 96% (room air) and anemic. Initial lab investigations revealed Hb-7.3gm/dl, TLC-4800 cells/cumm, PLT-98,000, INR-1.09, Urea-109, Sr. Creatinine - 6.1, Folic acid - 0.9 ng/ml (2-20 ng/ml), S.ferritin - >2000, S.Transferin-119.6%, Serum. Vitamin B 250 pg/ml (200-500 pg/ml), and CPK-304U/L. Malaria, Dengue, Leptospira, Weil Felix, ASO titer and Coomb's test were negative. Blood, sputum and Urine culture showed no growth. Anti histone antibody was positive suggestive of drug induced lupus. USG Abdomen revealed mild coarse echo texture of liver with mild increased renal

cortical echogenicity. Renal biopsy (Figure-1) showed acute interstitial nephritis.

Conditions which can increase phenytoin toxicity such as alcohol consumption, drugs (Cimetidine, Amiodarone, Anti-tubercular drugs and Metronidazole) which inhibit hepatic mono-oxygenase activity causing reduction in phenytoin metabolism and (Aspirin and Sodium Valproate) which can displace phenytoin from plasma albumin were not used by our patient. Short term phenytoin treatment related acute kidney injury (AKI), bicytopenia and drug induced lupus was suspected and phenytoin treatment was stopped. Patient was managed with levetiracetam (for seizure prevention), blood transfusion (for anemia), Hemodialysis (seven times), methyl prednisolone and other supportive measures. General condition improved significantly with normalization of serum creatinine levels (1.3 mg/dl) without hemodialysis and later discharged home with tablet prednisolone (20mg BD tapering dose) and levetiracetam (500mg BD).

**Figure 1. Histopathology of the patient (Renal biopsy) showing pigmentary acute tubular necrosis and edematous interstitium with scattered foci of inflammatory cells suggestive of acute interstitial nephritis.**



**DISCUSSION**

Phenytoin has a narrow therapeutic index (10-20 mcg/ml concentration). Half life after oral administration varies from 7 to 42 hours. The intravenous form is effective after 30 minutes of administration up to 24 hours [1]. Phenytoin acts by blocking inactive form of voltage gated sodium channels on the motor cortex [2]. It abolishes post tetanic potentiation and avoids seizure foci from detonating adjacent cortical areas. Other uses of phenytoin are in status epilepticus, trigeminal neuralgia and cardiac arrhythmias. It is a class 1b antiarrhythmic medication used in ventricular or atrial tachycardia following failure of primary drugs and cardioversion. Common side effects are nausea, loss of appetite, poor coordination, increased hair growth and gum enlargement. Rare and serious side effects are seen with chronic use which includes bone marrow suppression, toxic epidermal necrolysis, bone fractures, interstitial kidney disease, and DIL. All rare side effects occurring in a single patient has not been reported till date.

On hematological system, it can cause thrombocytopenia, megaloblastic anemia [3], lymphoma, aplastic anemia, leucopenia and agranulocytosis. Anemia and thrombocytopenia was seen in our patient. Anemia is secondary to folate deficiency and thrombocytopenia secondary to bone marrow depression and phenytoin dependent antiplatelets antibodies [4]. Thrombocytopenia known to occur after 1-3 weeks of treatment [5]. Treatment includes discontinuation of offending drug and platelet transfusion (in case of hemorrhage). Intravenous immunoglobulin has been tried for rapid improvement of platelet count [6].

Drug-induced lupus erythematosus is also a rare side effect following long term treatment with phenytoin. It is commonly seen with chronic use of drugs such as Hydralazine, Procainamide, and Isoniazid [7]. It is an autoimmune disorder similar to systemic lupus erythematosus (not as severe as SLE). Symptoms of DIL include fatigue, muscle and joint pain. Anti-histone antibodies are seen in 95% of cases. Symptoms usually disappear days to weeks after discontinuation of medicine. Corticosteroids may be used in severe cases of DIL.

Acute interstitial nephritis has been reported in 1% of patients who were evaluated for causes for hematuria or proteinuria. The causes of acute AIL has been broadly classified into drugs, infections and immune or neoplastic disorder related. Most common drugs causing acute interstitial nephritis are penicillins, cephalosporins, sulfonamides, NSAIDs, loop and thiazide diuretics. Phenytoin is one of the rare causes of acute interstitial nephritis [8].

Patients usually presents with nausea, vomiting, malaise and oliguria. Laboratory features show elevated serum creatitine, blood urea nitrogen and potassium. Urine analysis may reveal proteinuria, hematuria, pyuria or eosinophiluria. Diagnosis of AIN is usually based on clinical features, laboratory findings and renal biopsy (gold standard). In case of AIL, withdrawal of causative drug

with maintenance of adequate fluid status, avoidance of nephrotoxic drugs and hemodialysis are required. Prednisone 1m/kg/day orally for 2-3 weeks and tapered over 3-4 weeks [9] has been used by few clinicians and Cyclophosphamide in patients who fail to respond to steroids.

This case report highlights about multiple rare side effects in a patient on treatment with phenytoin. Early diagnosis and supportive treatment can reduce morbidity and mortality.

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**DECLARATION OF INTEREST:** None declared.

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