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A Case Report on Phenytoin Induced Agranulocytosis and Rash

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Abstract

Agranulocytosis is a rare condition which is defined as reduction or an absolute lack of circulating granulocytes, typically neutrophil count less than 0.5×10^9/L. Phenytoin is a therapeutically effective anticonvulsant agent but it may causes adverse drug reactions as well. In rare cases, it may cause idiosyncratic reactions in the form of agranulocytosis. Over the years, skin rash also been identified as a hypersensitivity reaction to phenytoin. We present a case of a 59 year old male who suffered from an injury to the head and dorsum of right foot in a road traffic accident one month ago. He was admitted to a local hospital and was started on Phenytoin 100 mg for seizure prophylaxis as CT scan showed signs of subarachnoid hemorrhage (SAH). After taking the medication for two weeks, it was observed that his White blood cells (WBC) levels had serially decreased to 550/mm^3 along with rash on trunk and generalized itching.

Keywords: Phenytoin, Agranulocytosis, Rash, White blood cells (WBC), Subarachnoid hemorrhage (SAH), Granulocyte colony-stimulating factor (G-CSF).

INTRODUCTION

Phenytoin is the most common and widely used antiepileptic drug. It is used for the prevention and treatment of generalized seizures, partial seizures and status epileptics. The etiological factors of seizure vary widely from infection or injury to the brain tissues.[1] Hematological problems have been rarely reported with phenytoin and includes macrocytosis, granulocytopenia, leukopenia, pancytopenia, thrombocytopenia, agranulocytosis.[2] Agranulocytosis is defined as reduction or an utter lack of circulating granulocytes, typically neutrophil count less than 0.5×10^9/L . [3] Drug –induced agranulocytosis is identified as a very rare condition. Annual incidence rates in Europe usually ranges from of 1.6 to 9.2 cases per million population per year.[4] The symptoms usually arise from risk that was increased due to the lack of WBCs and include fever, sore throat, weakness, and chills. There are two basic mechanisms in agranulocytosis, i.e. by destruction of circulating neutrophils through a process that is immune-mediated by drug- dependent or drug –induced antibodies by direct toxicity. Direct toxic effect of the drug and cellular immunity play an important part in phenytoin induced agranulocytosis .[5] Prognosis of events depend on variety of factors like age, co morbidity and duration of granulocytopenia.[6]

CASE REPORT

A 59 year old male diagnosed with type 2DM and dyslipidemia came to the tertiary care teaching hospital with complaints of intermittent fever with rash since 1 week. On admission ,he was afebrile, vitals were stable and examination revealed diffuse erythematous rash all over the body .Blood tests on admission revealed elevated inflammatory markers (CRP 92mg/l) [normal level (<1mg/l)], with severe leucopenia (TC 550,Absolute neutrophil count 176(1500-8000 cells/µL). He was empirically started on IV Cefoperazone –sulbactam along with strict neutrop enic care, IV fluids, anti-pyretic and other supportive measures. A Dermatology consultation was sought in view of persisting rash with few bullous lesions. A Tzanck smear was taken from the same and they opined a diagnosis of Phenytoin induced Rash and advised treatment with anti-histamines.

His serial counts were monitored and it is explained in Table 1 &Figure 1. The figures and table depict worsening leucopenia with eventual agranulocytosis .A hematology consultation for the same was sought and a bone marrow aspiration and biopsy was conducted which reported only an erythroid preponderance. Having ruled out the possibility of hematological malignancy he was then started on G-CSF. It was stopped once his counts were normalized .

Table 1: Laboratory investigations

Date	Tests	
	WBC(Reference range: 4.0-10.0 K/ µL)	NEUTROPHILS (Reference range: 60-80%)
13/2/17	0.55 K/ µL	32.7%
15/2/17	0.38 K/ µL	13.2%
16/2/17	0.62 K/ µL	8.0%
19/2/17	0.83 K/ µL	16.9%
21/2/17	5.5 K/ µL	56.1%
22/2/17	18.6 K/ µL	77.7%
23/2/17	26.2 K/ µL	85.0%
25/2/17	27.03 K/ µL	85.91%

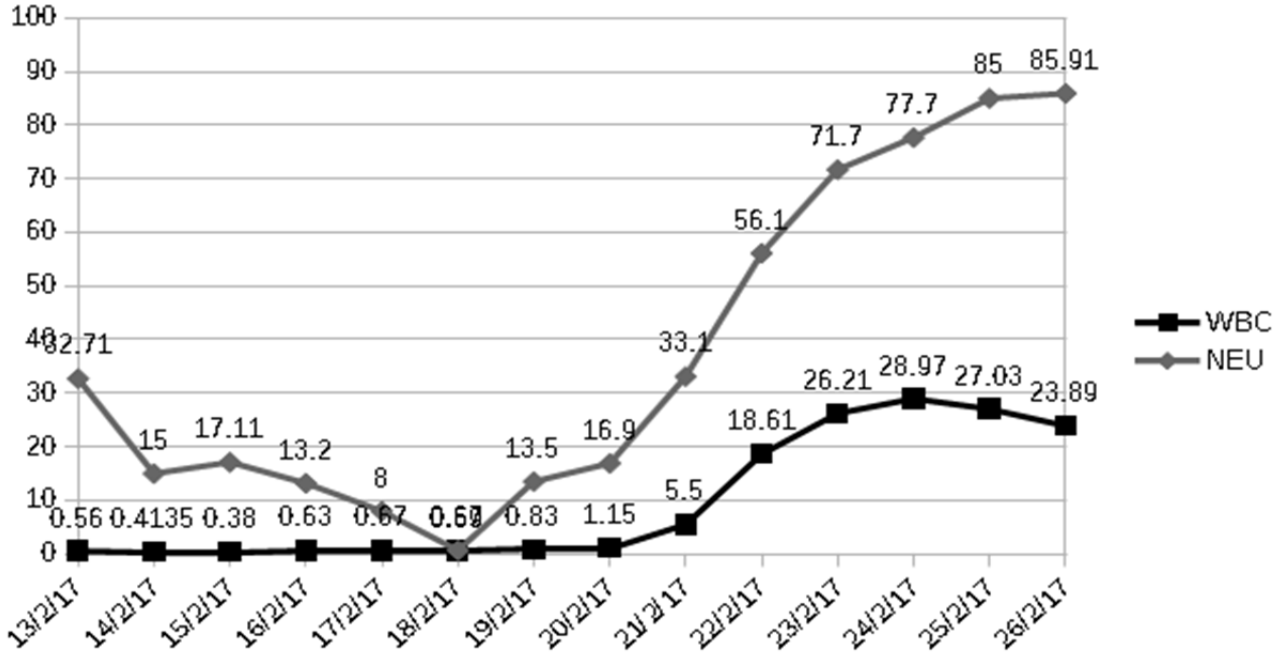

Figure 1: Lab result

DISCUSSION

Agranulocytosis is marked by a profound reduction in circulating granulocytes. The process of destruction of neutrophils is mediated by the immune system through the production of antibodies that are either induced by drug or drug dependent and also through direct toxicity. We are reporting a case of phenytoin associated agranulocytosis and rash. In this case agranulocytosis developed after the initiation of phenytoin therapy for seizure prophylaxis. The median duration of exposure prior to the advancement of agranulocytosis can vary from 19 to 60 days. In our case, approximately 20 days elapsed before development of agranulocytosis. Drug induced Agranulocytosis recover over time and the time for neutrophil recovery is between 4 to 24 days. In this case a Naranjo ADR probability scale was applied for causality assessment and the score was 8 (probable) and the Common Terminology Criteria for Adverse Events (CTCAE) V4.03 was used to classify the severity of rash, which was grade 2. The patient was managed with removal of the offending drug and started G-CSF 300 mcg s/c BD. For treating drug induced rash, antihistamines (Desloratadine) was administered. Various studies have shown that primary treatment of drug induced Agarnulocytosis is stopping the offending agent. After the withdrawal of phenytoin majority of the cases of neutropenia resolves over time. In this particular case neutropenia resolved within 8 days. Granulocyte colony stimulating factor reduces the duration of neutropenia. Early detection of the risk of Agranulocytosis is done by monitoring the WBC count and differential count.[7]

CONCLUSION

Phenytoin is a frequently used anticonvulsant. Rarely it may be related with serious complications such as agranulocytosis. Routine monitoring of blood count help to identify these complications. Therefore it is important to educate the patient regarding the offending drug and to avoid further exposure. Clinical pharmacist and clinicians should have adequate knowledge regarding this reaction and they must give careful attention to such patients.

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