Case report

Phenytoin-induced pure red cell aplasia: a rare and challenging diagnosis

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Abstract:

Pure Red Cell Aplasia (PRCA) is a rare hematologic disorder characterized by normochromic, normocytic anemia with reticulocytopenia, while the white blood cell and platelet counts remain generally normal. Bone marrow biopsy typically shows a lack of erythroblasts but normal granulopoiesis and megakaryopoiesis. We report a case of a 72-year-old male who developed severe anemia following phenytoin administration for post-traumatic seizure prophylaxis. The patient's hemoglobin dropped from 11.1 g/dL to 6.6 g/dL within 32 days of phenytoin initiation. Bone marrow examination revealed markedly decreased erythroid precursors (4%) with preserved other cell lineages, confirming the diagnosis of PRCA. Following discontinuation of phenytoin and supportive transfusions, the patient showed complete hematologic recovery. This case represents the oldest reported patient with phenytoin-induced PRCA to date and demonstrates that elderly patients may develop this complication more rapidly than younger individuals. This emphasizes the importance of monitoring for rare but serious hematologic complications among patients receiving phenytoin therapy, particularly during the initial months of treatment.

Keywords : ● *Pure Red cell aplasia (PRCA)* ● *Phenytoin* ● *Drug-induced anemia* ● *Anticonvulsant*

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รายงานผู้ป่วย

ภาวะ pure red cell aplasia จากยา phenytoin: กรณีศึกษาที่พบได้ยากและท้าทายในการวินิจฉัย

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บทคัดย่อ

ภาวะ Pure Red Cell Aplasia (PRCA) เป็นความผิดปกติทางโลหิตวิทยาที่พบได้ยาก มีลักษณะเฉพาะคือภาวะโลหิตจางแบบ normochromic normocytic ร่วมกับ reticulocytopenia โดยที่จำนวนเม็ดเลือดขาวและเกล็ดเลือดยังคงปกติ การตรวจไขกระดูกมักพบการขาดหายไปของ erythroblasts แต่ granulopoiesis และ megakaryopoiesis ยังคงปกติ รายงานนี้นำเสนอเคสผู้ป่วยชายอายุ 72 ปี มีภาวะโลหิตจางรุนแรงภายหลังได้รับยา phenytoin เพื่อป้องกันอาการชักหลังการบาดเจ็บที่ศีรษะ ระดับฮีโมโกลบินลดลงจาก 11.1 g/dL เป็น 6.6 g/dL ภายใน 32 วัน การตรวจไขกระดูกพบ erythroid precursor ลดลงมาก (4%) โดยที่ granulopoiesis และ megakaryopoiesis ยังปกติ ยืนยันการวินิจฉัยภาวะ pure red cell aplasia ผู้ป่วยได้รับการหยุดยา phenytoin และให้เลือดทดแทน จนมีการฟื้นตัวของระบบเลือดอย่างสมบูรณ์ กรณีนี้เป็นผู้ป่วยสูงอายุที่สุดที่มีรายงานภาวะ PRCA จากยา phenytoin และแสดงให้เห็นว่าผู้ป่วยสูงอายุอาจเกิดภาวะแทรกซ้อนนี้ได้เร็วกว่าผู้ป่วยอายุน้อย กรณีนี้เน้นย้ำความสำคัญของการเฝ้าระวังผลข้างเคียงทางโลหิตวิทยาที่รุนแรงในผู้ป่วยที่ได้รับยา phenytoin โดยเฉพาะในช่วงเดือนแรกของการรักษา

คำสำคัญ : ● *Pure red cell aplasia* ● *Phenytoin* ● *ภาวะซีดจากยา* ● *ยากันชัก*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2568;36:73-81.

Introduction

Pure red cell aplasia (PRCA) is an uncommon hematologic disorder with an estimated incidence of 1.06 cases per million per year based on nationwide epidemiologic studies[1]. The condition is characterized by severe normochromic, normocytic anemia accompanied by marked reticulocytopenia, while white blood cell and platelet counts typically remain within normal limits. Bone marrow examination characteristically reveals an absence or near-absence of erythroblasts with preservation of granulopoiesis and megakaryopoiesis.

The etiology of PRCA is diverse, encompassing both congenital and acquired forms. Approximately one half of acquired cases are associated with thymoma, while other causes include hematologic malignancies, solid tumors, infections particularly human parvovirus B19, autoimmune diseases, and certain medications[1,6]. Although over 30 different medications have been implicated in causing PRCA, most reports describe only isolated cases, and the pathogenic mechanisms remain incompletely understood for many of these drugs. Phenytoin, azathioprine, and isoniazid are among the few medications for which the mechanisms of PRCA induction have been more clearly elucidated[2,3].

While drug-induced PRCA is well-documented, phenytoin-induced PRCA specifically remains exceptionally rare, with fewer than 20 cases reported in the literature to date[6]. This rarity contributes to diagnostic challenges and potential delays in recognition. The incidence of phenytoin-induced PRCA is estimated to be less than 0.01% of patients receiving the medication, yet its consequences can be severe if not promptly identified[2].

The temporal relationship between phenytoin initiation and PRCA development varies considerably in the literature, ranging from as early as 30 days to as late as 4 years after drug commencement[2,5]. This wide variability suggests that individual susceptibility factors may play a crucial role in developing this adverse reaction. Statistical analysis of reported cases reveals a significant negative correlation between patient age and time to PRCA onset ($r = -0.63$, $p = 0.012$), suggesting that elderly patients develop this complication more rapidly. We present a case of phenytoin-induced PRCA that developed within one month of drug initiation, along with a comprehensive discussion of the diagnostic approach and management strategies employed.

Case report

A 72-year-old male with a past medical history of type 2 diabetes mellitus, hypertension, dyslipidemia, and a prior transient ischemic attack was admitted after a motorcycle accident. Initial evaluation revealed a Glasgow Coma Scale score of E1V2M4 and brain CT demonstrated multiple traumatic injuries including extradural and subdural hematomas. Baseline laboratory values showed a hemoglobin of 11.1 g/dL with normal white blood cell and platelet counts.

The patient received a loading dose of phenytoin 1000 mg intravenously for seizure prophylaxis and underwent emergent right decompressive craniectomy. Postoperatively, he was maintained on phenytoin 300 mg daily intravenously (100 mg intravenous every 8 hours) from July 6 to July 16, 2024, then switched to oral phenytoin 300 mg daily (100 mg oral every 8 hours) from July 16 to August 16, 2024.

Throughout hospitalization, the patient received multiple concomitant medications, including omeprazole, paracetamol, amlodipine, hydralazine, various antibiotics (cefazolin, ceftazidime, meropenem), baclofen, senokot, metoprolol, NPH insulin, lactulose, lorazepam, quetiapine, sodium chloride tablets, N-acetylcysteine, trazodone, haloperidol, and thiamine. Several of these medications, particularly omeprazole (CYP inhibitor), are known to potentially increase phenytoin levels through inhibition of cytochrome P450 metabolism. Laboratory evaluation showed impaired renal function with a baseline creatinine of 1.74 mg/dL, which remained relatively stable during hospitalization (1.89 mg/dL at the time of hematology consultation). Serum albumin was 4.1 g/dL at admission, decreasing to 2.9 g/dL at the time of hematology consultation, which is significant as reduced albumin levels increase the free (active) fraction of phenytoin due to its high protein binding properties.

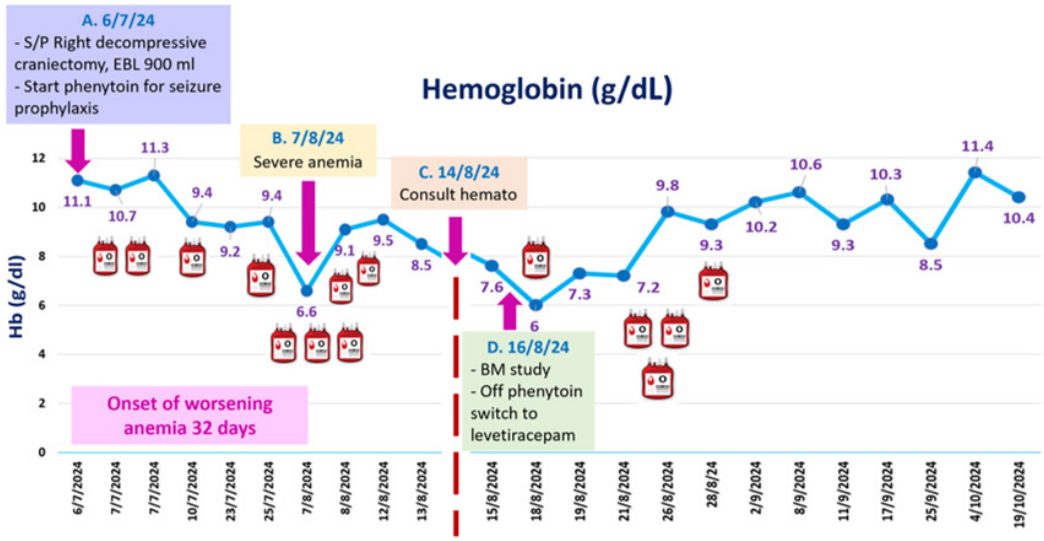
On day 32 (August 7, 2024) after phenytoin initiation, preoperative laboratory studies for a planned tracheostomy revealed a dramatic decline in hemoglobin to 6.6 g/dL. Review of prior laboratory values showed a progressive decline over the preceding two weeks, with hemoglobin of 9.4 g/dL on day 19 (July 25, 2024) of phenytoin therapy (Figure 1). The initial hemoglobin decline to 9.4 g/dL was initially attributed to anemia of inflammation, as the patient was in the ICU on mechanical ventilation with multiple medical issues including pneumonia and atrial fibrillation with rapid ventricular response. Careful clinical assessment revealed no evidence of overt bleeding.

The patient received a total of five units of packed red blood cells between August 7 and 10, 2024. Despite these multiple transfusions, follow-up laboratory evaluation on August 13 showed a hemoglobin level of 8.5 g/dL, prompting hematology consultation (Figure 1). Further laboratory investigation demonstrated persistent anemia with a strikingly low reticulocyte count of 0.3% (absolute reticulocyte count 8,760/μL). Peripheral blood smear showed normochromic, normocytic red blood cells with mild anisopoikilocytosis but no schistocytes, spherocytes, or polychromasia.

Bone marrow aspiration and biopsy performed on day 41 (August 16, 2024) showed normocellular trilineage hematopoiesis with approximately 40% cellularity. However, a striking paucity of erythroid precursors was noted, comprising only 4% of nucleated marrow cells, resulting in an elevated myeloid-to-erythroid ratio of 10:1. Granulopoiesis and megakaryopoiesis were preserved and morphologically normal. No blasts, abnormal infiltrates, fibrosis, or evidence of malignancy were identified (Figure 2). These findings of selective erythroid hypoplasia with preservation of other lineages confirmed the diagnosis of pure red cell aplasia.

Although testing for parvovirus B19 infection and autoimmune markers was not performed, these etiologies were considered less likely given the patient's clinical context as an immunocompetent host without risk factors for parvovirus infection or clinical signs suggestive of autoimmune disease.

Based on the clinical presentation and bone marrow findings, a diagnosis of phenytoin-induced pure red cell



S/P, Status post; EBL, Estimate blood loss; Consult hemato, Consult hematologist; BM study, bone marrow study

Figure 1 Hemoglobin trend during hospitalization. Box A: Day of phenytoin initiation following decompressive craniectomy (July 6, 2024). Box B: Day of severe anemia detection, occurring 32 days after admission and phenytoin administration (August 7, 2024). Box C: Day of hematology consultation (August 14, 2024). Box D: Day of phenytoin discontinuation and switch to levetiracetam (August 16, 2024). Red blood bag icons indicate transfusion events. Note the significant hemoglobin decline following phenytoin initiation and gradual recovery after its discontinuation.

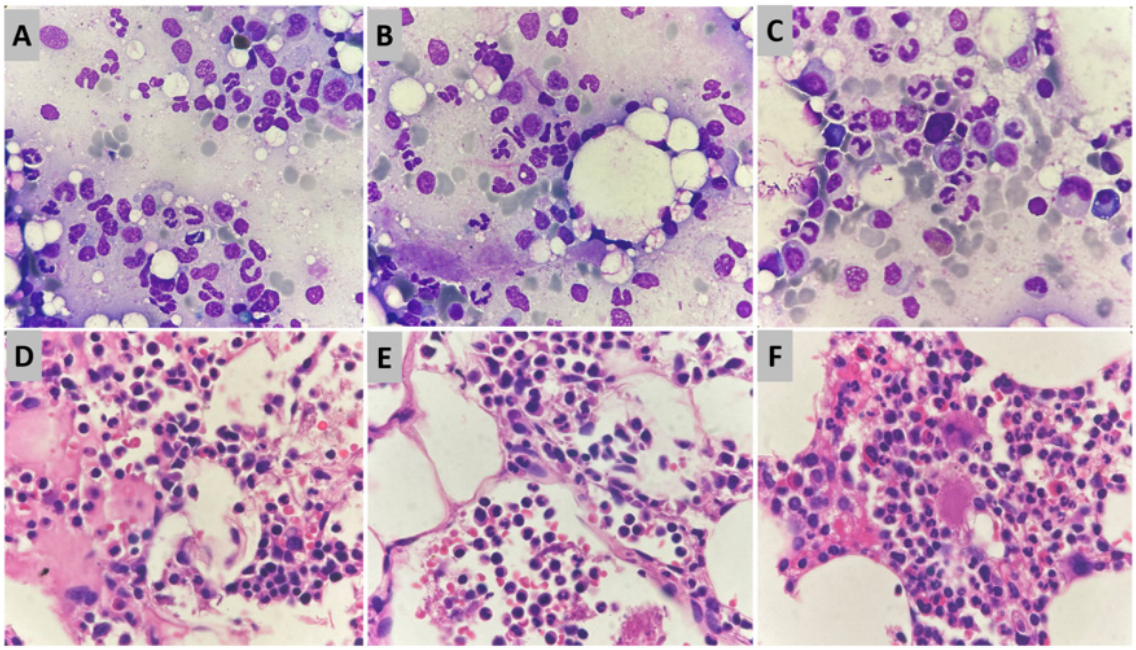


Figure 2 Bone marrow morphology in phenytoin-induced PRCA. A-C: Wright-stained aspirate (x100, oil immersion) shows normocellular marrow (40% cellularity) with markedly decreased erythroid precursors (comprising only 4% of nucleated cells) and elevated M:E ratio of 10:1. The conspicuous absence of erythroid precursors contrasts with the preserved myeloid lineage. D-F: H&E-stained biopsy (x400) confirms selective erythroid hypoplasia with preserved granulopoiesis and megakaryopoiesis.

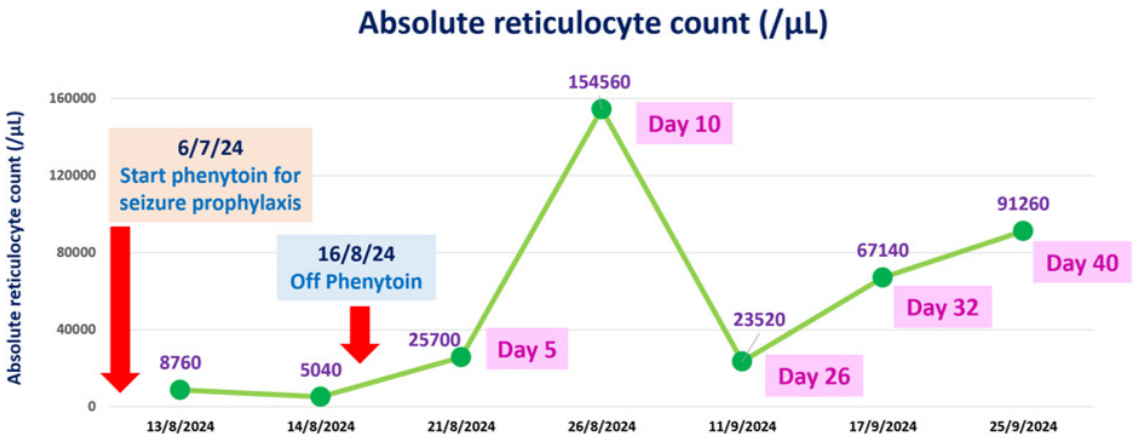


Figure 3 Serial absolute reticulocyte count measurements throughout treatment. Note the profound reticulocytopenia during phenytoin therapy and the robust recovery beginning 5 days after drug discontinuation, demonstrating the reversible nature of phenytoin-induced erythroid suppression.

aplasia was established. Phenytoin was immediately discontinued and replaced with levetiracetam for seizure prophylaxis. The patient's hematologic parameters showed gradual improvement following phenytoin discontinuation. Five days after stopping the drug, the reticulocyte count increased to 1.0% with an absolute count of 25,700/µL. By day 10 after drug discontinuation, the reticulocyte count had increased to 4.6% (absolute count: 154,560/µL), with hemoglobin improving to 9.8 g/dL. Follow-up one month after phenytoin discontinuation showed continued recovery with hemoglobin of 10.3 g/dL and an absolute reticulocyte count of 67,140/µL. The last transfusion was three weeks before follow-up, and no further transfusions were required, providing strong evidence of sustained marrow recovery (Figures 1 and 3).

Table 1 Summary of published cases of phenytoin-induced PRCA

Author (Year)	Age/Sex	Indication for Phenytoin	Phenytoin dosage (mg/day)	Time to Onset	Nadir Hb (g/dL)	Treatment	Recovery Time
Brittingham, et al. (1964)[7]	17 M	Epilepsy	400	2.5 years	2.2	Stopped DPH, transfusion	19 days
Jeong, et al. (1974)[8]							
Case 1	50 F	Seizure Prophylaxis	ND	52 days	6.5	Stopped DPH, transfusion, steroids	4 weeks
Case 2	40 F	Seizure Prophylaxis	ND	4 months	5.4	Stopped DPH, transfusion, steroids	1 week
Huijgens, et al. (1978)[9]	16 F	Headache	180	1 month	6.1	Stopped DPH	3 weeks
Pritchard, et al. (1979)[10]	19 F	Seizure	300	52 days	4.1	Stopped DPH, transfusion	23 days
Yoshida, et al. (1980)[11]	54 F	Epilepsy	100-170	72 days	7.8	Stopped DPH	1 month
Dessypris, et al. (1985)[2]	32 M	Seizure Prophylaxis	500	407 days	PRV 19%	Stopped DPH	2 weeks
Kueh, et al. (1991)[12]	36 M	Seizure Prophylaxis	300	2 months	6	Stopped DPH	1 month
Singh, et al. (1993)[13]	16 M	Epilepsy	ND	4 months	3	Stopped DPH, oxymetholone	56 days
Tanaka, et al. (2000)[14]							
Case 1	46 F	Seizure Prophylaxis	150	35 days	4.5	Stopped DPH, transfusion, steroids	1 month
Case 2	66 F	Seizure Prophylaxis	200	50 days	3.7	Stopped DPH, transfusion	1 month
Rusia, et al. (2006)[15]	58 M	Seizure Prophylaxis	300	3 months	5.8	Stopped DPH, transfusion	3 months
Sugaya, et al. (2010)[16]	26 F (pregnant)	Seizure	300	1 month	3.8	Stopped DPH, transfusion	1 month
Paul, et al. (2011)[5]	25 M	Seizure Prophylaxis	ND	1 month	1.9	Stopped DPH, transfusion	3 weeks
Present, case (2024)	72 M	Seizure Prophylaxis	300	32 days	6.6	Stopped DPH, transfusion	1 month

M, Male; F, Female; Hb, Hemoglobin; DHP, Diphenylhydantoin (phenytoin); PRV, Packed cell volume; ND, Not described

Discussion

Pure red cell aplasia represents a rare but potentially severe complication of phenytoin therapy. The disorder is characterized by the triad of anemia, reticulocytopenia, and isolated erythroblastopenia on bone marrow examination. While PRCA can arise from various etiologies, including primary marrow disorders, thymoma, infections, and autoimmune conditions[1], drug-induced PRCA typically presents as an acute, reversible form of isolated erythroid aplasia following exposure to the offending medication[6].

Our patient developed severe anemia within 32 days of initiating phenytoin therapy, representing a relatively rapid onset compared with most related reported cases. Review of the literature revealed considerable variability in the time to onset of phenytoin-induced PRCA, ranging from 30 days to 4 years, with most cases occurring after several months of therapy (Table 1). Statistical analysis of reported cases demonstrates a significant negative correlation between patient age and time to PRCA onset ($r = -0.63$, $p = 0.012$), with patients over 55 years developing PRCA significantly earlier (mean onset 43.5 days) compared with younger patients aged 31 to 55 years (mean onset 124.0 days) and those under 30 years (mean onset 240.5 days). Additionally, a significant positive correlation was found between phenytoin dosage and time to PRCA onset ($r = 0.67$, $p = 0.024$), with lower doses associated with earlier onset. Our patient's recovery timeline - with reticulocyte response within five days of drug discontinuation - appears consistent with most related reported cases, suggesting a direct and reversible effect of phenytoin on erythropoiesis[2,5].

At 72 years of age, our patient represents the oldest documented case of phenytoin-induced PRCA in the literature, extending the demographic range of this rare adverse reaction and providing important insights into its presentation in the geriatric population. The rapid onset in our elderly patient aligns with the statistical

trend observed across reported cases and supports the hypothesis that age may be an important risk factor for accelerated development of this complication.

In our case, several patient-specific risk factors likely contributed to the rapid onset of PRCA. The patient had impaired renal function (creatinine 1.74 to 1.89 mg/dL) which, although stable, could have reduced phenytoin clearance. More significantly, his serum albumin decreased from 4.1 g/dL at admission to 2.9 g/dL at the time of hematology consultation. Given that phenytoin is approximately 90% bound to albumin in the blood, this marked hypoalbuminemia would substantially increase the free (active) phenytoin concentration despite unchanged total drug levels. Furthermore, the patient received omeprazole throughout his hospitalization, which inhibits cytochrome P450 enzymes responsible for phenytoin metabolism, potentially further increasing phenytoin levels. This combination of factors - advanced age, renal impairment, hypoalbuminemia, and medication interactions - likely created a "perfect storm" for rapid development of immune-mediated PRCA.

The pathogenesis of phenytoin-induced PRCA involves several proposed mechanisms. Immune-mediated processes appear central with evidence supporting formation of drug-dependent antibodies targeting erythroid progenitors[2]. These antibodies may directly lyse erythroid cells or interfere with their differentiation[1]. Additionally, in vitro studies suggest phenytoin can directly inhibit DNA synthesis in erythroid precursors[3]. The observed relationship between lower phenytoin doses and earlier PRCA onset supports an immune-mediated mechanism rather than direct toxicity, as idiosyncratic immune reactions often do not follow typical dose-response relationships.

While phenytoin drug levels were not measured in our patient, the relationship between serum concentrations and PRCA development remains unclear. Current evidence suggests that phenytoin-induced PRCA is an idiosyncratic immune-mediated reaction rather than a dose-dependent phenomenon. PRCA can occur within therapeutic phenytoin levels (10-20 μg/mL) among susceptible individuals, suggesting that individual genetic and immunologic factors play a more significant role than absolute drug concentrations. Nevertheless, factors that increase free phenytoin concentrations - as observed in our patient - may accelerate or amplify this immune-mediated process.

Several factors may influence phenytoin pharmacokinetics and potentially increase risk among elderly patients. These include age-related reductions in phenytoin clearance (15-30% lower), decreased serum albumin levels leading to higher free (active) phenytoin concentrations and genetic polymorphisms in CYP2C9 (particularly variants 2 and 3) that reduce phenytoin metabolism. HLA associations (HLA-B15:02 and HLA-B51:01) have also been linked to severe phenytoin reactions, though specific associations with PRCA remain to be established.

The diagnosis of drug-induced PRCA requires a high index of suspicion and systematic exclusion of other causes. In our patient, the temporal relationship between phenytoin exposure and anemia development, combined with the characteristic findings of severe reticulocytopenia and selective erythroid hypoplasia on bone marrow examination, strongly supported the diagnosis. The absence of other causes such as viral infections, autoimmune diseases, or malignancies, along with the subsequent recovery following drug discontinuation, further confirmed phenytoin as the causative agent. A limitation of our diagnostic approach was the lack of testing for drug-dependent antibodies, which could have provided additional confirmation of the immune-mediated mechanism.

Management of phenytoin-induced PRCA centers on immediate discontinuation of the offending drug. Unlike some other forms of drug-induced cytopenia, phenytoin-induced PRCA typically does not require immunosuppressive therapy, and most patients recover with supportive care alone.[2,6] Red blood cell transfusions should be administered as clinically indicated

to maintain adequate oxygen delivery. The time to hematologic recovery varies but generally occurs within several weeks of drug discontinuation, as observed in our patient showing reticulocyte response within five days and near-normalization of hemoglobin within one month.

The patient's recovery showed two distinct phases: a rapid initial reticulocyte response within five days of drug discontinuation, followed by gradual hemoglobin recovery to near-normal levels (10.3 g/dL) by one month. This biphasic pattern is characteristic of PRCA recovery and is attributed to several favorable factors: the relatively short drug exposure duration (32 days), absence of concurrent nutritional deficiencies and prompt drug discontinuation upon recognition of the condition. A similar recovery pattern was observed in the case reported by Kueh, et al. (1991) of a 36-year-old male showing reticulocyte response within six days and complete hemoglobin recovery at one month. This consistency in recovery timelines across different age groups suggests that once the offending drug is removed, the bone marrow's capacity to regenerate erythroid precursors remains remarkably preserved even in elderly patients.

This case highlights several important clinical considerations. First, current guidelines recommend limiting phenytoin use for post-traumatic seizure prophylaxis to seven days, which would have prevented this complication in our patient.[4] Second, alternative anticonvulsants such as levetiracetam may be preferred among patients requiring prolonged therapy, particularly those with multiple comorbidities or advanced age.[4] Third, regular monitoring of complete blood counts during the initial months of phenytoin therapy may facilitate early detection of hematologic toxicity.[5,6]

Finally, our findings suggest that elderly patients require more vigilant monitoring during phenytoin therapy due to their significantly increased risk for earlier onset of PRCA. Based on our statistical analysis of reported cases, we propose an intensified monitoring protocol for patients aged 55 years or older, including baseline CBC with reticulocyte count before phenytoin initiation, followed by weekly CBC monitoring during the first month of therapy, and biweekly monitoring in the second month. This monitoring schedule is justified by the significantly earlier onset of PRCA observed among elderly patients (mean onset 43.5 days) compared to with that of younger patients. Prompt evaluation of any unexplained decline in hemoglobin, even in the absence of clinical symptoms, may facilitate early detection and intervention before severe anemia develops.

Conclusion

Phenytoin-induced PRCA represents a rare but potentially life-threatening complication requiring prompt recognition and management. Clinicians should maintain awareness of this adverse effect, particularly among patients developing unexplained anemia during phenytoin therapy. Our case expands the documented demographic range of this rare adverse reaction to include advanced age (72 years) and provides statistical evidence supporting a significant negative correlation between patient age and time to PRCA onset, suggesting that elderly patients develop this complication more rapidly than younger individuals.

Early recognition, immediate drug discontinuation, and appropriate supportive care typically result in complete recovery.[2,5,6] This case underscores the importance of adhering to current guidelines limiting phenytoin use for seizure prophylaxis[4] and considering alternative agents when prolonged therapy is required. Regular hematologic monitoring during the initial months of therapy may facilitate early detection and intervention, potentially preventing severe complications. Further studies investigating genetic predispositions and immunologic markers that may identify patients at higher risk for this complication would be valuable to optimize phenytoin therapy in vulnerable populations, particularly the elderly.

Conflict of interest

The author declares no conflict of interest relevant to this article.

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