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Roxarestat for treatment of erythropoietin (EPO)-induced pure red cell aplasia in a hemodialysis patient: a case report

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Short Report

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Abstract

Anemia is a prevalent complication in patients with chronic kidney disease (CKD), particularly those undergoing dialysis. Recombinant human erythropoietin (rhEPO) is widely administered to patients both on and off dialysis to manage this anemia. However, despite an initial favorable therapeutic response, a sudden and unexplained decline in hemoglobin levels (Hb) often prompts the need for further diagnostic evaluation. In this context, we report a clinical case involving a 48-year-old male patient who had been undergoing hemodialysis (HD) for two years. During the course of his rhEPO treatment regimen, he developed pure red cell aplasia (PRCA), a rare but serious adverse reaction. Upon recognition of this complication, the administration of rhEPO was promptly discontinued, and the patient was initiated on roxarestat therapy. Remarkably, following nine months of continuous roxarestat treatment, the patient experienced a significant and sustained increase in his Hb levels. This clinical outcome underscores the importance of prompt diagnosis and intervention in cases of EPO-induced PRCA. Furthermore, our findings suggest that roxarestat may serve as a viable and effective therapeutic option for patients with EPO-induced PRCA, potentially obviating the need for immunosuppressive therapy and its associated risks.

Introduction

Anemia is a prevalent complication encountered by individuals suffering from chronic kidney disease (CKD), becoming particularly pronounced when the glomerular filtration rate (GFR) drops below 60 mL/min/1.73 m². This condition is significant, as it impacts approximately 20% of patients in stage 3 CKD and affects nearly all (at least 90%) individuals who progress to require dialysis.[1,2] The onset of anemia in such patients constitutes a critical health issue that necessitates effective intervention. To combat this complication, recombinant human erythropoietin (rhEPO) has been widely used as a therapeutic measure, with the objective of enhancing the overall quality of life for CKD patients receiving both dialysis and non-dialysis treatments. Moreover, the utilization of rhEPO can contribute to a reduction in the dependence on blood transfusions, which are often required in instances of severe anemia.[3,4] However, despite the benefits it provides, rhEPO is associated with a rare but serious side effect known as pure red cell aplasia (PRCA). Initially reported in the early 1990s[5–7], PRCA has mainly been documented in kidney failure patients across various regions, including Europe, the UK, Canada, Australia, and Asia.[8] Recently, there have also been documented cases of PRCA in China that are linked to the use of erythropoiesis-stimulating agents (ESAs).[3,9,10]

In recent years, roxarestat has emerged as a novel and promising treatment for addressing renal anemia in patients with CKD. This medication functions as an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, which in turn stimulates erythropoiesis by enhancing the production of endogenous erythropoietin, enhancing iron bioavailability, and reducing hepcidin levels. The increasing application of roxarestat in the management of renal anemia reflects a shift towards more targeted therapies that aim to improve patient outcomes.[11,12]

This report details a clinical case study that highlights the critical importance of early detection, timely intervention, and careful nursing care in the management of PRCA that arises as a consequence of epoetin therapy. In this particular case, we focus on a middle-aged male patient from China, tracing his journey through the diagnosis of PRCA and the subsequent management of his condition utilizing roxarestat. This case not only underscores the challenges presented by side effects of treatment but also illuminates the potential for effective alternatives in the management of renal anemia.

Case Presentation

A 48-year-old male patient was diagnosed with stage 5 CKD along with secondary anemia attributable to CKD in January 5 2023. His baseline serum creatinine and hemoglobin (Hb) levels were recorded as 2366.5 umol/L and 53.0 g/L, respectively. And he had been diagnosed with grade 3 hypertension five years and was on a daily regimen of sacubitril/valsartan sodium tablets (50 mg). Subsequently, he commenced hemodialysis (HD) via a temporary catheter inserted into the right femoral vein and later transitioned to a semi-permanent catheter in the right jugular vein, facilitating a shift from induction dialysis to regular HD sessions three times per week. Besides, he began receiving subcutaneous injections of rhEPO at a dose of 5,000 IU weekly, along with oral medications for anemia management. On March 28, 2023, he underwent arteriovenous fistula surgery and began maintenance HD (three times per week). Subsequently, he began receiving subcutaneous injections of rhEPO at a dose of 6,000 IU weekly. His anemia demonstrated a favorable response to this treatment, with his Hb level rising to 135 g/L over the course of seven months. During this period, he continued with conservative treatment. Unexpectedly, his Hb level concentration declined to 99 g/L in December 2023. In response, the erythropoietin dosage was increased to 10,000 units weekly for a duration of three months. However, in May 2024, his Hb level concentration further dropped to 76 g/L, despite the absence of any clinical signs indicative of bleeding, hemolysis, or infection. Consequently, the erythropoietin dosage was further escalated to 13,000 units weekly, but only minimal improvement was observed, and this dosage adjustment was maintained for just one month. After that, his Hb levels declined rapidly, falling below 34 g/L in July 2024, which necessitated a thorough investigation into the underlying cause of his anemia, involving four separate hospitalizations.

Upon admission, the patient received multiple blood transfusions, rhEPO (16000 U/W), adequate dialysis, and other symptomatic treatments. However, his anemia remained refractory to these interventions. On August 13, 2024, we conducted a series of tests, including serum ferritin (1993.45 ng/mL), transferrin (1.82 g/L), reticulocyte percentage (0.05%), seven cytokine tests (all negative), anti-nuclear antibody (negative), and EPO (0.75 mIU/mL). Additionally, given the history of intermittent blood transfusions, the patient was suspected of suffering from iron overload. Gastrointestinal bleeding was excluded as a potential cause. His liver function test results were within the normal range. Computed tomography of the chest revealed no abnormalities. Furthermore, his complement levels were normal, his coagulation function was unaffected, and his B19-IgG and B19-IgM levels were within the established normal reference range. Peripheral blood cells revealed anisocytosis of mature red blood cells and the presence of easily discernible, scattered platelets. A bone marrow biopsy (Fig. 1 and Fig. 2) demonstrated the

following cellular composition: late erythroblasts (0.5%), granulocytic lines (85.5%), monocytic lines (2.0%), lymphocytic lines (11.0%), and other cells (1%). Based on the results of peripheral blood cell morphology and bone marrow cytology tests, PRCA was considered to be the most likely diagnosis.

Surprisingly, the anti-erythropoietin (anti-EPO) antibody titer was assessed using an enzyme-linked immunosorbent assay (ELISA), and the results indicated a negative serological response. Notwithstanding these findings, the potential contribution of EPO to the pathogenesis of PRCA cannot be definitively excluded.

Consequently, rhEPO was promptly discontinued, and roxarestat was initiated at a dose of 100 mg daily as an alternative therapeutic intervention. Based on the patient's medical history, the hematologist recommended immunosuppressant therapy consisting of 1 mg of sirolimus and 625 mg of deferasirox daily. However, after two weeks of treatment, the patient's anemia continued to be refractory to these interventions. Subsequently, the patient discontinued immunosuppressive therapy and continued to take roxarestat (100 mg) to monitor changes in Hb levels.

During the follow-up assessment, the patient had adhered to the above medications. After four weeks of treatment, laboratory investigations revealed a significant increase in Hb levels from 62 g/L to 77 g/L. EPO levels normalized to 21.3 mIU/mL (Fig. 3), and the reticulocyte percentage returned to within the reference range (1.03%). Additionally, serum ferritin levels exhibited a gradual decline, decreasing by nearly 50% to 797.69 ng/mL. No treatment-related adverse effects were observed throughout the follow-up period. Currently, the patient was on continuous oral roxarestat treatment, with his Hb level measuring 106 g/L (Fig. 4), a reticulocyte percentage of 1.62% (within near-normal limits; Fig. 5), and ferritin levels further normalized to 307.6 ng/mL (Fig. 6).

Based on a systematic assessment of the patient's clinical course, including treatment response patterns and a comprehensive differential diagnosis, we used a process of diagnosis exclusion to ultimately conclude that the patient had EPO-induced PRCA.

Discussion

PRCA is an uncommon hematological disorder marked by a significant decrease or complete absence of erythroid precursors in the bone marrow, which subsequently results in a substantial reduction in red blood cell production[13]. While some cases of PRCA are idiopathic, others are associated with underlying medical conditions, such as thymoma, myelodysplastic syndromes, lymphoma, leukemia, systemic autoimmune disorders, and viral infections (e.g., parvovirus B19 infection). This case ruled out the influence of these diseases. Additionally, drug-induced PRCA can occur due to the use of certain medications, including phenytoin and chloramphenicol[14–16]. Notably, the administration of rhEPO and ESAs has also been implicated as a contributing factor[17].

Casadevall et al. defined rhEPO-associated PRCA as a rare clinical entity characterized by three diagnostic criteria: resistance to EPO therapy; anemia accompanied by reticulocytopenia (< 10×10^9/L)

during rHuEPO treatment, which may or may not necessitate blood transfusions due to erythroblastopenia in a morphologically normal bone marrow; and the detection of neutralizing anti-EPO antibodies[5]. In our patient, due to the patient's limited financial resources and lack of testing equipment, anti-EPO antibody repeated testing was not performed; however, the first two criteria were satisfied. Furthermore, based on reverse deduction, it can be concluded that the patient belongs to the EPO-mediated PRCA category.

Since 1989, erythropoietin has been extensively utilized to alleviate anemia in patients with chronic renal failure. With the increasing use of EPO, cases of anti-EPO antibody formation have been documented in individuals with chronic renal failure[18]. These anti-EPO antibodies possess neutralizing activity against endogenous erythropoietin, thereby inducing PRCA. The pathophysiological mechanisms underlying rhEPO-induced PRCA are intricate. Macdougall et al. proposed that a breakdown in immunological tolerance leads to heightened antigen recognition by autoreactive T cells. This, in turn, triggers a B-cell-mediated antibody response in genetically predisposed individuals[19]. A multitude of factors, such as advanced age, concurrent infections, intermittent illnesses, adjuvant therapies, comorbidities, and immune status, may collectively contribute to immune dysregulation, thereby playing a role in the development of rhEPO-induced PRCA. Anti-EPO antibodies can impede the binding of EPO to its receptor, thereby obstructing the differentiation of erythroid progenitor cells[20]. Despite the patient testing negative for anti-EPO antibodies, the possibility of a false negative cannot be completely dismissed. The reasons are multifaceted: First, the testing method may lack sufficient sensitivity. Techniques like ELISA struggle to detect low antibody concentrations, potentially missing antibodies when their levels are low in the patient. Second, there may be incomplete coverage of antibody types; antibodies could form stable complexes with EPO or bind to other proteins, hindering effective detection. Third, the sample was sent for external testing, risking improper storage or contamination with interfering substances. Lastly, during early disease stages or remission, antibodies may not yet have formed or may have been cleared from the body.

The immunogenicity of rhEPO can be influenced by various factors, including different packaging, storage, and transportation conditions, the subcutaneous route of administration, the formulation, and the type of the epoetin preparation[8,13]. All human erythropoietin injections administered to patients at this HD center are sourced from a pharmaceutical conglomerate in China, with human erythropoietin alpha as their principal active ingredient. These injections are uniformly stored at a temperature range of 2–8 degrees Celsius and are delivered via intravenous or subcutaneous routes. Anti-EPO antibody-mediated PRCA represents a prevalent subtype of secondary PRCA observed within the CKD patient cohort, with the majority of documented cases associated with the use of α-erythropoietin, specifically Epoetin. Nevertheless, there exists a body of evidence indicating that certain individual brands of erythropoietin in China may exhibit a comparatively higher incidence of PRCA.[21]

The management of rhEPO-induced PRCA necessitates the immediate cessation of EPO or ESAs, blood transfusion as needed, immunosuppressive therapy, and, in some cases, kidney transplantation[9,22].

Previous research indicates that immunosuppression represents the preferred therapeutic approach for patients diagnosed with primary or secondary acquired PRCA.[23] However, alterations in renal function or the presence of severe hypertension may necessitate a prompt transition from cyclosporine A, which poses risks of acute and long-term nephrotoxicity, to sirolimus or other second-line immunosuppressive agents.[24] Together with years of clinical experience, the hematologist recommended treatment with an immunosuppressant such as sirolimus. Sirolimus is a frequently employed drug for the treatment of PRCA. It exerts immunosuppressive effects by modulating the proliferative capacity of T cells, thereby promoting erythropoiesis[25]. Additionally, it has been observed to improve creatinine levels in PRCA patients with concurrent renal insufficiency[26]. However, the patients in this study did not respond to this treatment modality.

Roxarestat is a hypoxia-inducible factor-prolyl hydroxylase inhibitor (HIF-PHI) that mimics the hypoxic state, thereby enhancing EPO expression and improving anemia. Wu et al.[14] reported a case of a peritoneal dialysis patient who developed EPO-mediated PRCA, was treated with immunosuppressive therapy, and was then treated with roxarestat for 2 months, resulting in a rapid increase in Hb to normal levels. Wan et al.[27] described a patient with EPO antibody-mediated PRCA who was not treated with immunosuppressive therapy but instead received roxarestat therapy for 3.5 months. The anti-EPO antibody test results shifted to negative, and the patient's Hb levels demonstrated a significant recovery. Xiaoe You et al.[28] documented cases of PRCA in two male patients undergoing HD and receiving rHuEPO treatment. Patient 1, with confirmed anti-EPO antibodies, showed no improvement after one year on roxarestat. Patient 2, suspected of PRCA, improved following three months of combined roxarestat and rituximab therapy. Sijia Li et al.[3] documented a case involving an HD patient with PCRA and positive anti-EPO antibodies who declined immunosuppressant therapy. Following 6 months of roxarestat treatment, the EPO antibodies subsided, and the patient's Hb levels normalized. Hongsha Yang et al. [29] described in a case report that roxarestat monotherapy did not sufficiently elevate Hb levels in a patient with acquired PRCA and anti-EPO antibody-negative CKD.

However, unlike some previous reports, the patient was treated with roxarestat for 9 months before his Hb levels returned to a satisfactory state, an effective time span that is much longer than in other studies, which was one of the strengths of this case. In this particular case, drawing upon the laboratory results, it is reasonable to postulate that roxarestat combats anemia via two principal biological pathways. Firstly, it serves as a powerful activator of EPO synthesis, boosting the expression of genes associated with EPO production in the kidneys and other pertinent tissues. Secondly, it regulates the intracellular events governing ferritin breakdown and iron liberation, consequently enhancing the supply of iron for Hb synthesis. Through these two cooperative mechanisms, roxarestat effectively ameliorated this patient's anemia.

Roxarestat has demonstrated efficacy within this specific clinical scenario[27], aligning with prior studies that have reported its effectiveness in dialysis-dependent patients[30]. However, it is important to emphasize that our case differs from those documented in the literature in the lack of detection of anti-

EPO antibodies. Frequent antibody testing can strongly validate the study's results, highlighting one of the limitations of this study. To date, roxarestat has been less well studied in similar cases. Therefore, no conclusive conclusions can be drawn about the efficacy of roxarestat in the treatment of acquired PRCA in dialysis patients. Further collection and summarization of clinical cases are needed to elucidate roxarestat's treatment mechanism for anti-EPO antibody-mediated PRCA.

Conclusions

Management of anemia with maintenance HD patients, especially those unable to maintain Hb levels with subcutaneous injections of high-dose rhEPO, requires careful consideration. The potential occurrence of EPO-induced PRCA adds a critical dimension to the clinical landscape. This case report illustrated the importance of early diagnosis, treatment, and personalized management of such patients. Roxarestat may be an additional treatment option for anemia in patients undergoing maintenance HD. Treatment of anemia in patients should be individualized. It is necessary to closely examine the risks and carefully monitor adverse events.

Declarations

Author Contributions

All the authors designed the study. Methodology, data analyses and writing-Original Draft were performed by Sufang Jiang and Yumei Zhou. Data collection were performed by Yunhan Xie, Shaowei Song and Xinjie jin. Review and editing were performed by Ying Jiang. All the authors read and approved the final manuscript.

Statement of Ethics

Because it is a case report, this study was exempted from research ethics committee review (the biomedical ethics committee of the Xiangyang No.1 People's Hospital). Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Clinical trial number: not applicable.

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Conflict of Interest Statement

The authors declare they have no conflicts of interest.

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Figures

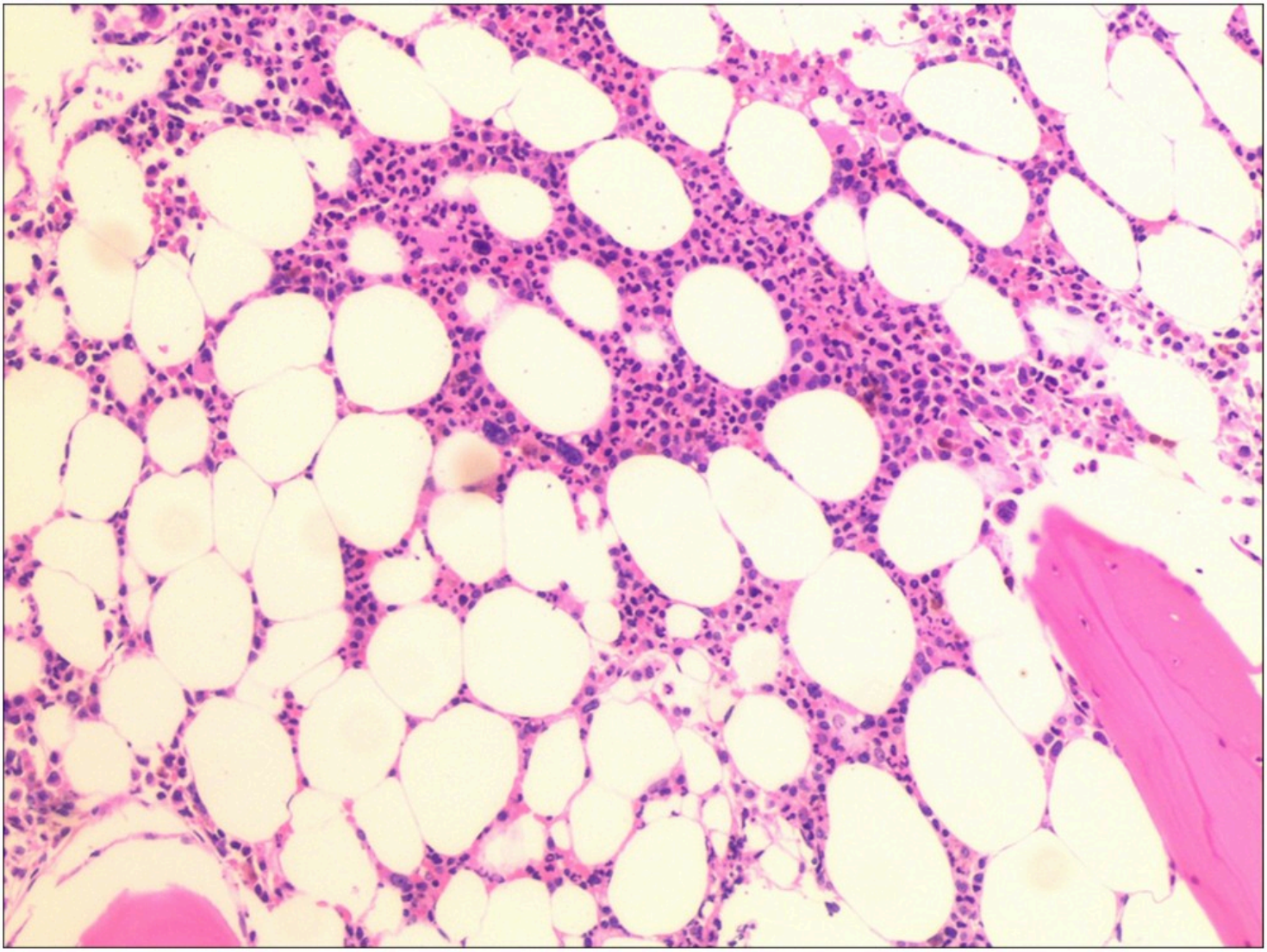


Figure 1

The results of the bone marrow biopsy of patient.

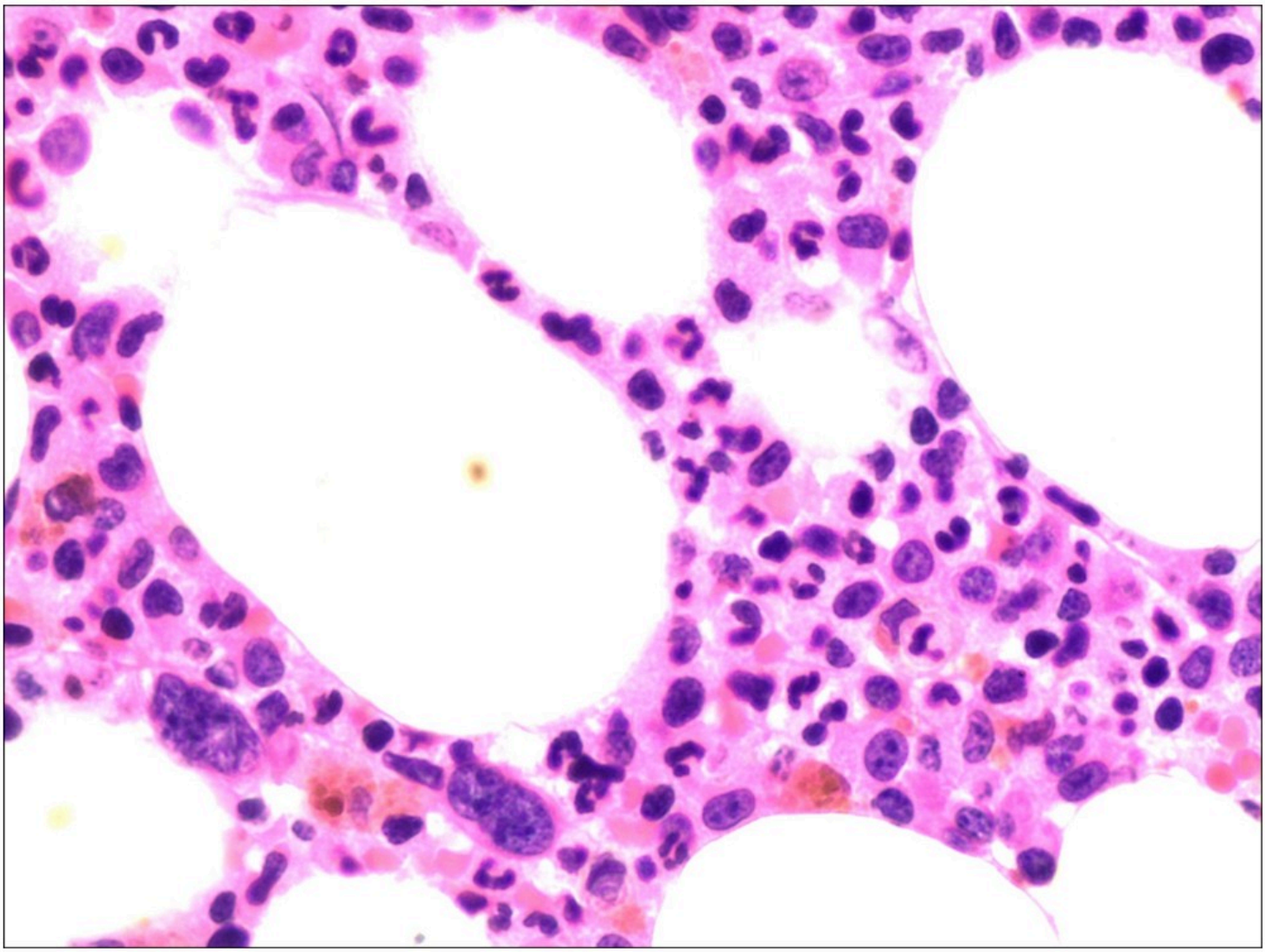


Figure 2

The results of the bone marrow biopsy of patient.

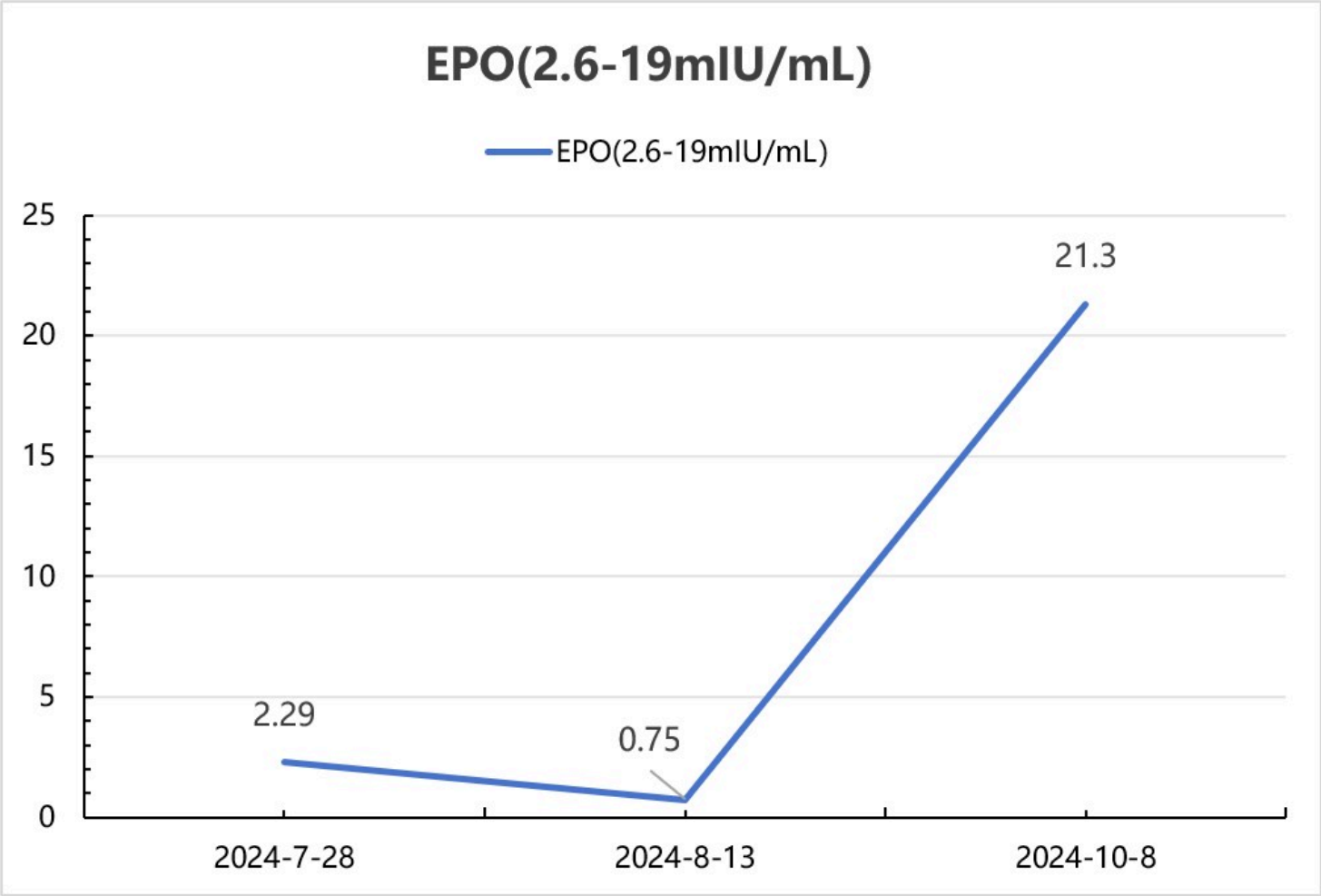


Figure 3

The change in EPO values during the whole course of the disease of patient.

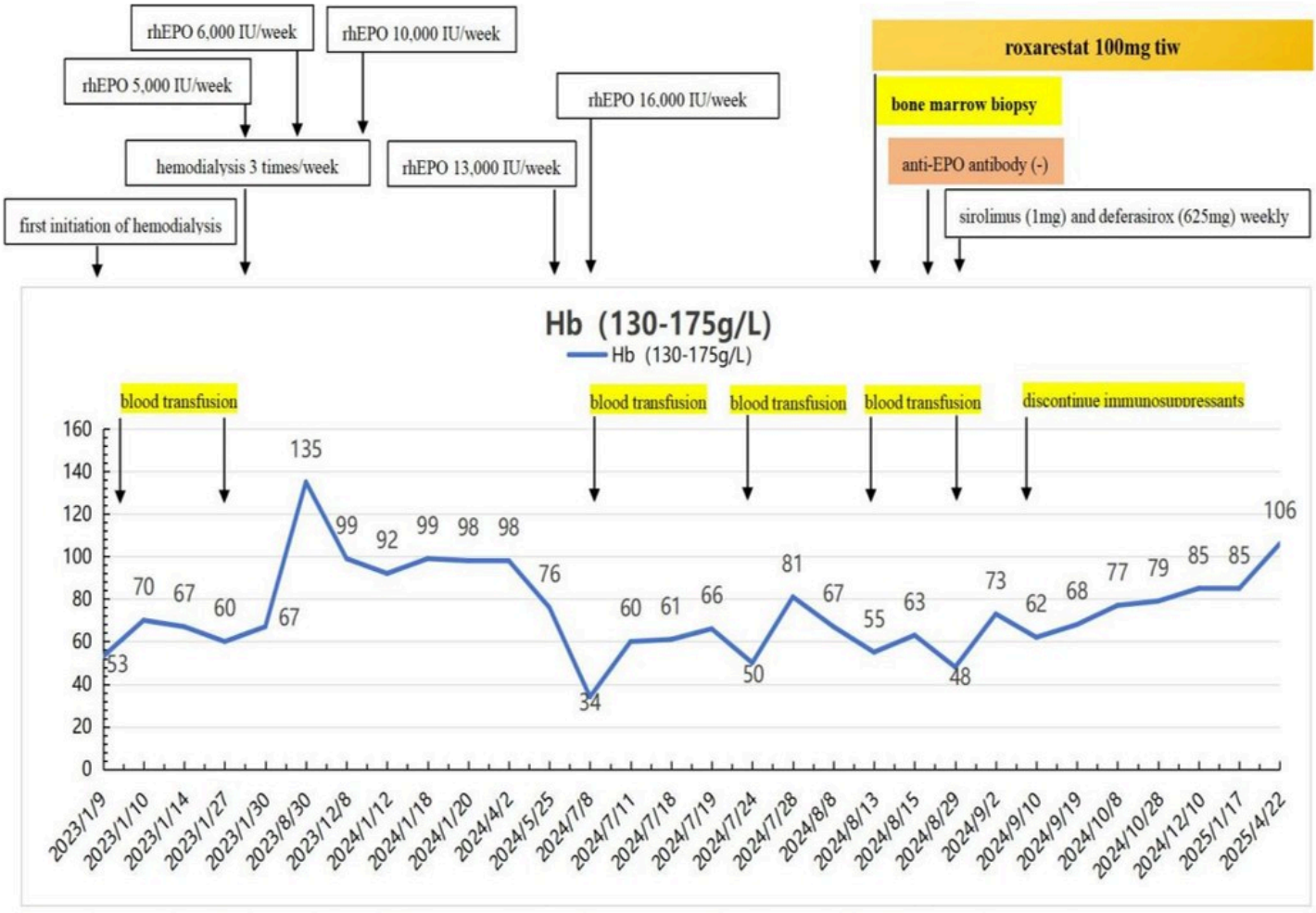


Figure 4

Temporal trends in hemoglobin (Hb) levels throughout the disease course of this patient, with key clinical events annotated.

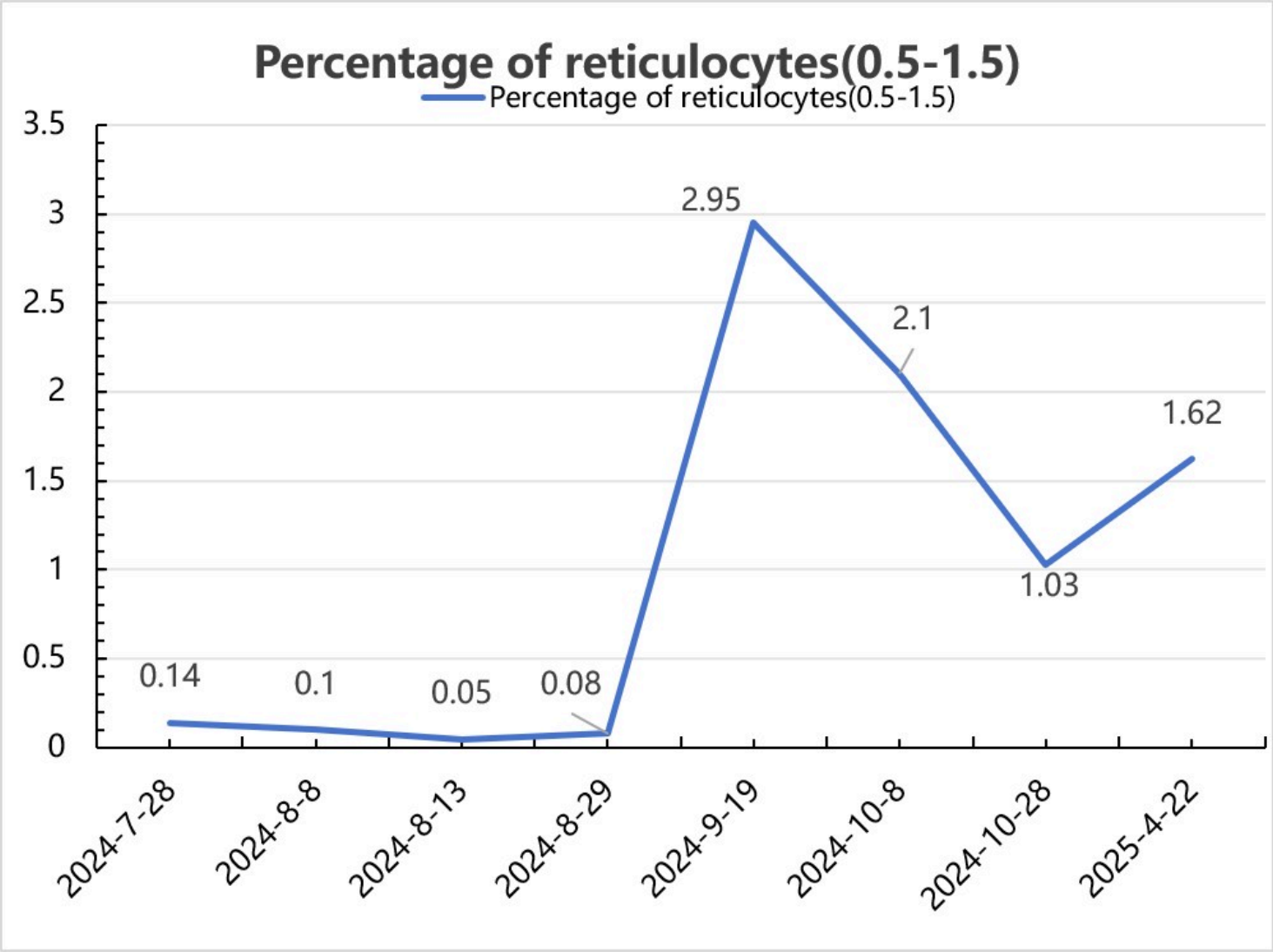


Figure 5

The change in reticulocyte absolute values during the whole course of the disease of patient.

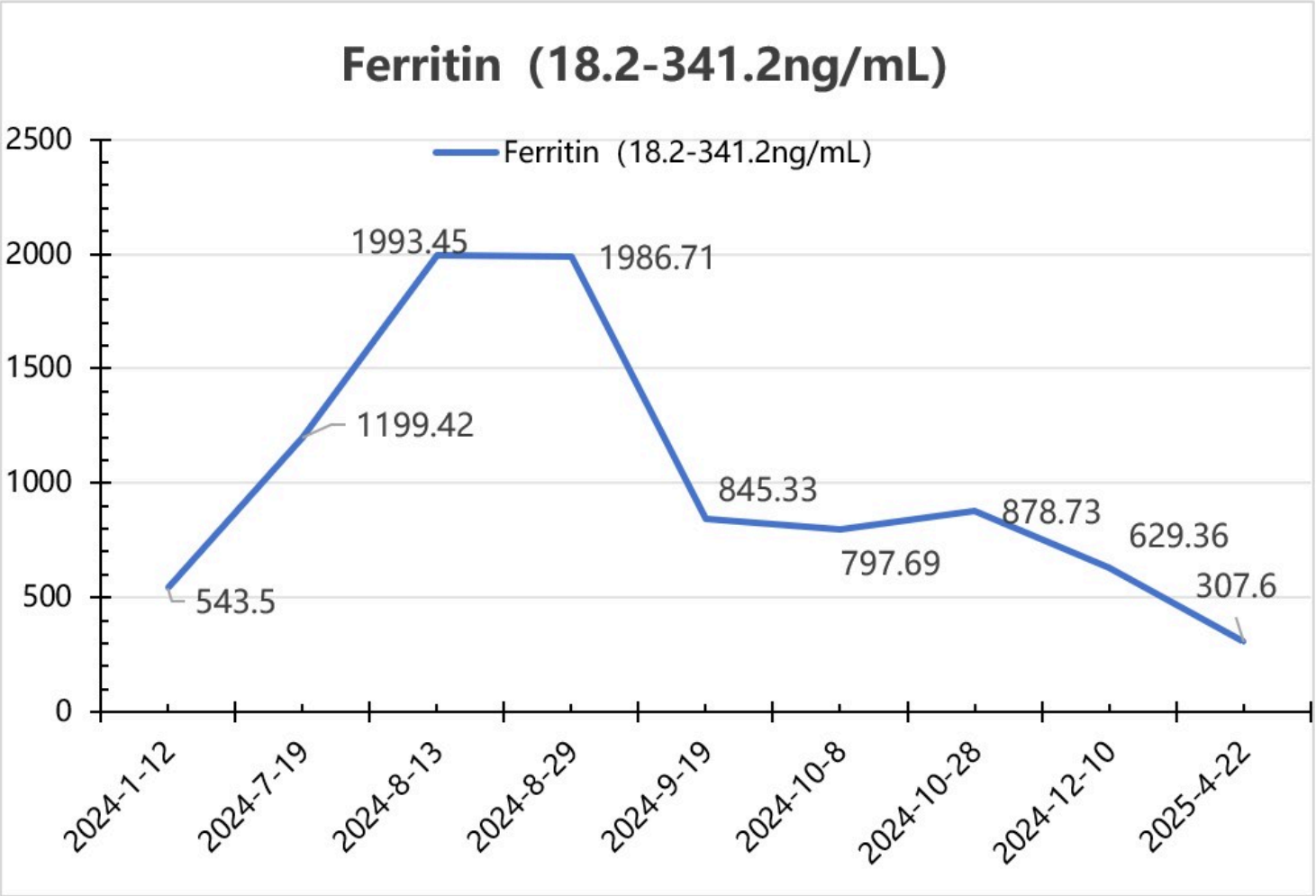


Figure 6

The change in ferritin values during the whole course of the disease of patient.