Kidney Medicine

EPO-Mimetic Peptide Pegmolesatide Therapy for Pure Red Cell Aplasia in a Patient with Non-dialysis-dependent Type 1 Diabetic Nephropathy: A Case Report

Qiong Chen, Xuan Liu,* Juan Wang, Man Yang, and Qiu-ling Fan*

Pure red cell aplasia (PRCA) is a rare complication of erythropoietin (EPO) therapy, characterized by a severe deficiency in red blood cell production. There is no guideline on the treatment for PRCA because there have been too few cases to perform prospective cohort studies. The main treatments for PRCA include immediate cessation of EPO, restrictive transfusion, and immunosuppressive therapies. A 35-year-old male patient with type 1 diabetic nephropathy was diagnosed with PRCA. Enarodustat and roxadustat were administered successively after discontinuation of EPO, but anemia did not improve, and the patient was maintained with weekly blood transfusions. Subsequently, the EPO-mimetic peptide pegmolesatide was administered, and the patient's hemoglobin started to increase after 1 week and increased from 50 g/L to 92 g/L over approximately 3 months. Based on these findings, we speculate that pegmolesatide can provide a safe, effective, and convenient therapeutic strategy for PRCA in Chinese patients with chronic kidney disease.

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INTRODUCTION

Anemia is a common complication of chronic kidney disease (CKD). In China, the prevalence of anemia is approximately 28.5% to 51.5% in patients with non-dialysis-dependent CKD.[1,2] Erythropoiesis-stimulating agents are the standard treatment for CKD-associated anemia[3] and can effectively increase hemoglobin levels to avoid transfusion dependence.[4] Although definitive data are not available in China, the rate of achieving target levels of hemoglobin in non-dialysis-dependent CKD patients is unsatisfactory. Several factors may contribute to this low target-achieving rate, including imbalanced economic and medical resources, poor patient compliance with short-acting erythropoietin (EPO), iron deficiency, and pure red cell aplasia (PRCA) resulting from anti-EPO antibodies.[5,6]

EPO-mimetic peptides are synthetic chemical compounds that act as agonists of the EPO receptor. Despite lacking sequence homology with EPO, EPO-mimetic peptides can bind to and activate the EPO receptor, stimulating erythropoiesis through the same intracellular signaling pathways.[7,8] Pegmolesatide (R&D code: HS-20039, previously known as pegol-sihematide or EPO-018B) is a novel pegylated EPO-mimetic peptide developed by Hansoh Pharmaceutical Group Co, Ltd. It offers advantages such as reduced immunogenicity and an extended duration of action.[9] A randomized, open-label, active-comparator, non-inferiority phase 3 trial was conducted at 43 dialysis centers in China between May 17, 2019, and March 28, 2022. The results of this clinical trial demonstrated that monthly subcutaneous injection of pegmolesatide was as effective and safe as conventional epoetin alfa administered 1-3 times a week for treating anemia in Chinese dialysis patients. In addition, pegmolesatide was found to be noninferior to EPO, with consistent results observed across all predefined subgroups.[10] Currently, pegmolesatide has been approved in mainland China for the treatment of anemia in both dialysis and non-dialysis CKD patients.

Our case is the first to present pegmolesatide treatment for PRCA in a Chinese patient with non-dialysis-dependent type 1 diabetic nephropathy. The use of pegmolesatide in this case led to a marked improvement in hemoglobin levels and clinical symptoms with no side effects, offering a promising alternative for patients with this condition.

CASE REPORT

A male in his mid-30s was admitted to the hospital on February 7, 2024, for "diagnosed type 1 diabetes mellitus for 17 years, elevated blood creatinine for more than a year, and chest tightness for 1 day." The patient had been diagnosed with type 1 diabetes mellitus 17 years ago and was currently on insulin pump therapy. One year ago, he was found to have mildly elevated blood creatinine (details unknown) and urinary albumin-creatinine ratio of 2000 mg/g. In June 2023, during treatment for diabetic retinopathy, his serum creatinine level was 1.584 mg/dL (140 μmol/L), estimated glomerular filtration rate (calculated using the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] formula) was 56.07 mL/min/1.73 m^2, and hemoglobin level was 122 g/L. On September 14, his hemoglobin level dropped to 90 g/L, and the patient was given 10,000 U of EPO-α (Shenyang Sansheng Pharmaceutical Co, Ltd) once a week and ferrous succinate as an oral treatment. On October 27, 2023, the patient's hemoglobin level increased to 124 g/L, and the treatment with EPO-α was stopped. However, after his hemoglobin level decreased to 106 g/L in 1 week, the patient restarted EPO-α therapy. On January 5, 2024, the patient's hemoglobin level was 89 g/L, and he was switched to roxadustat 50 mg 3 times a week and oral

ferrous succinate, as he preferred oral medication. In February 2024, the patient presented to the clinic with chest tightness and fatigue, and his hemoglobin level was 65 g/L, creatinine level 2.033 mg/dL (179.7 μmol/L), estimated glomerular filtration rate (calculated by CKD-EPI formula) 41.47 mL/min/1.73 m^2, and serum albumin 32.7 g/L.

The patient's past history included type 1 diabetes mellitus for 17 years, hypertension for 5 years, and recurrent hypotension in the last 2 months. Antihypertensive medication has been discontinued. He also had a history of hypothyroidism, treated long-term with oral levothyroxine 50 μg once a day. Regular monitoring showed thyroid function was normal. Since June 2023, he had underwent surgery several times in our ophthalmology department for diabetic retinopathy and vitreous hemorrhage in the right eye. The patient had not previously been administered drugs that may cause PRCA (eg, diphenylhydantoin, rifampicin, azathioprine, and isoniazid) and did not have any secondary causes of PRCA including thymoma history, infections (eg, parvovirus B19, Epstein-Barr virus), lymphoproliferative disorders (eg, chronic lymphocytic leukemia, lymphoma, and T-large granular lymphocyte disorders), systemic autoimmune disease (eg, systemic lupus erythematosus, rheumatoid arthritis), myelodysplastic syndrome, hemolysis, or liver dysfunction. At admission, his temperature was 36.5°C, pulse rate 96 beats/min, respiratory rate: 20 beats/min, blood pressure 107/59 mm Hg, height 168 cm, weight 73 kg, and body mass index 25.5 kg/m^2. When he entered the ward, the patient had no enlarged superficial lymph nodes, no subcutaneous hemorrhages, and no skin rash. The eyelids and conjunctiva were pale, and there was no yellowing of the sclera. The thyroid gland was not enlarged. Breath sounds of both lungs were clear, and no dry or wet rhonchi were heard. His heart rate was rhythmic at 96 beats/min, abdomen was flat and soft, no pressure pain, liver and spleen were not felt under the ribs, and both lower limbs were mildly edematous.

Baseline clinical and laboratory characteristics were obtained on April 3, 2024: red blood cells 2.33 × 10^{12}/L (reference interval: 3.8-5.1 × 10^{12}/L), hemoglobin 65 g/L (1 week progressive decline to 53 g/L; reference interval: 115-150 g/L), mean corpuscular volume 87.4fL (reference interval: 80-100 fL), mean corpuscular hemoglobin 29.5 pg (reference interval: 27-34 pg), mean corpuscular hemoglobin concentration 345 g/L (reference interval: 316-354 g/L), reticulocytes 0.2% (reference interval: 0.5%-1.5%), platelets 191 × 10^9/L (reference interval: 125-350 × 10^9/L), leukocytes 5.72 × 10^9/L (reference interval: 3.5-9.5 × 10^9/L), C-reactive protein 6.7 mg/L (reference interval: 0-10 mg/L), serum creatinine 179.7 μmol/L (reference interval: 41-73 μmol/L), albumin 29.5 g/L (reference interval: 40-55 g/L), glycated hemoglobin 8.5% (reference interval: 4%-6%), intact parathyroid hormone 32.4 pg/mL (reference interval: 18.5-88 pg/mL), fecal occult blood negative, urinary protein 2+, urinary glucose positive, and urinary albumin-creatinine ratio 1,635 μg/mg. In addition, although oral ferrous succinate treatment was suspended on March 2, ferritin was still extremely high (>1,500 μg/L; reference interval: 23.9-336.2 μg/L), serum iron was 26.7 μmol/L (reference interval: 10.6-36.7 μmol/L), total iron binding capacity 28.95 μmol/L (reference interval: 50-77 μmol/L), transferrin saturation 92.2%, transferrin 1.3 g/L (reference interval: 2-3.6 g/L), folate 8.8 ng/mL (reference interval: 3.1-19.9 ng/mL), and vitamin B12 858 pg/mL (reference interval: 180-914 pg/mL) (Table 1).

Thyroid function markers, transaminases, and bilirubin were at normal levels. Complement, immunoglobulin, antinuclear antibody, antineutrophil cytoplasmic antibody, anti-double-stranded DNA antibody, and anticardiolipin antibody were normal. M-protein, tumor marker, human immunodeficiency virus, hepatitis B virus, and hepatitis C virus were not detected. No abnormal red blood cells were found in peripheral blood. Direct and indirect human immunoglobulin test was negative. Cytomegalovirus and Epstein-Barr virus DNA were not detected. Renal ultrasound showed cortical echo enhancement in both kidneys with clear corticomedullary demarcation. Computed tomography showed scattered striations in both lungs, hypodensity of cardiac chambers, and anemia. No abnormalities were found in thymic computed tomographic examination.

To treat the patient, EPO was first discontinued, and enarodustat was subsequently administered. His anemia did

Table 1. Laboratory Characteristics of the Patient During the Clinical Course

	Date		
Characteristics	**February 7**	**April 3**	**June 1**
TIBC (RI: 50-77 μmol/L)	36.72	28.95	34.63
Serum iron (RI: 10.6-36.7 μmol/L)	29.2	26.7	26.1
Ferritin (RI: 23.9-336.2 μg/L)	891.1	>1,500	>1,500
Transferrin (RI: 2-3.6 g/L)	1.6	1.3	1.4
TSAT (%)	79.5%	92.2%	75.4%
Folate (RI: 3.1-19.9 ng/mL)	8.58	8.8	16.77
Vitamin B12 (RI: 180-914 pg/mL)	>1,500	858	803
Reticulocytes (RI: 0.5%-1.5%)	0.76%	0.2%	1.32%
CRP (RI: 0-10 mg/L)	22.3	6.7	1.2

Abbreviations: CRP, C-reactive protein; RI, reference interval; TIBC, total iron binding capacity; TSAT, transferrin saturation.

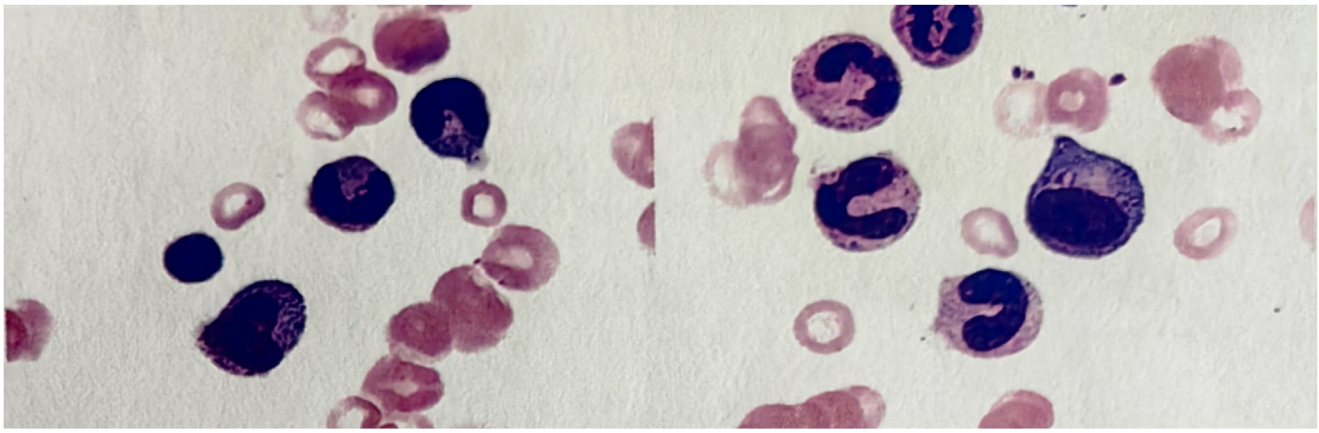

Figure 1. Hematologic staining of the bone marrow of this patient shows the absence of erythroblasts.

not improve, and he was maintained by weekly blood transfusions, receiving a total of 9 units of red blood from February 12-March 22. A further examination was performed, and bone marrow aspirate revealed severe erythroid hypoplasia, with 5.1% red blood cell precursors, evidence that a block in the maturation of erythroid precursors may be present. Platelet and white cell precursors were normal. There was no evidence to suggest T-cell large granular lymphocyte leukemia or B cell dyscrasia, which commonly cause the induction of idiopathic PRCA (Fig 1). Anti-EPO antibody was negative (19.62 IU/L; reference interval: ≤28 IU/L) by enzyme-linked immunosorbent assay (ELISA) on April 3. Although the anti-EPO antibody level was normal, PRCA was still considered in conjunction with the bone puncture and clinical manifestations. Thus, EPO-mimetic peptide treatment was given, specifically pegmolesatide (trade name: San Lorelai), with a dosage of 4 mg (0.04 mg/kg of body weight) once every 4 weeks injected subcutaneously.

The patient was discharged from the hospital on April 9 after the first subcutaneous administration of 4 mg pegmolesatide. On the day of discharge, his hemoglobin level was 50 g/L and reticulocytes were 0.19%. After the second treatment with 4 mg pegmolesatide, hemoglobin was rechecked at 69 g/L and reticulocytes were 2.71%. On June 1, after the third pegmolesatide treatment, the hemoglobin level of the patient had further increased to 76 g/L and reticulocytes were 1.32%. Furthermore, the patient's symptoms of chest tightness and dizziness were

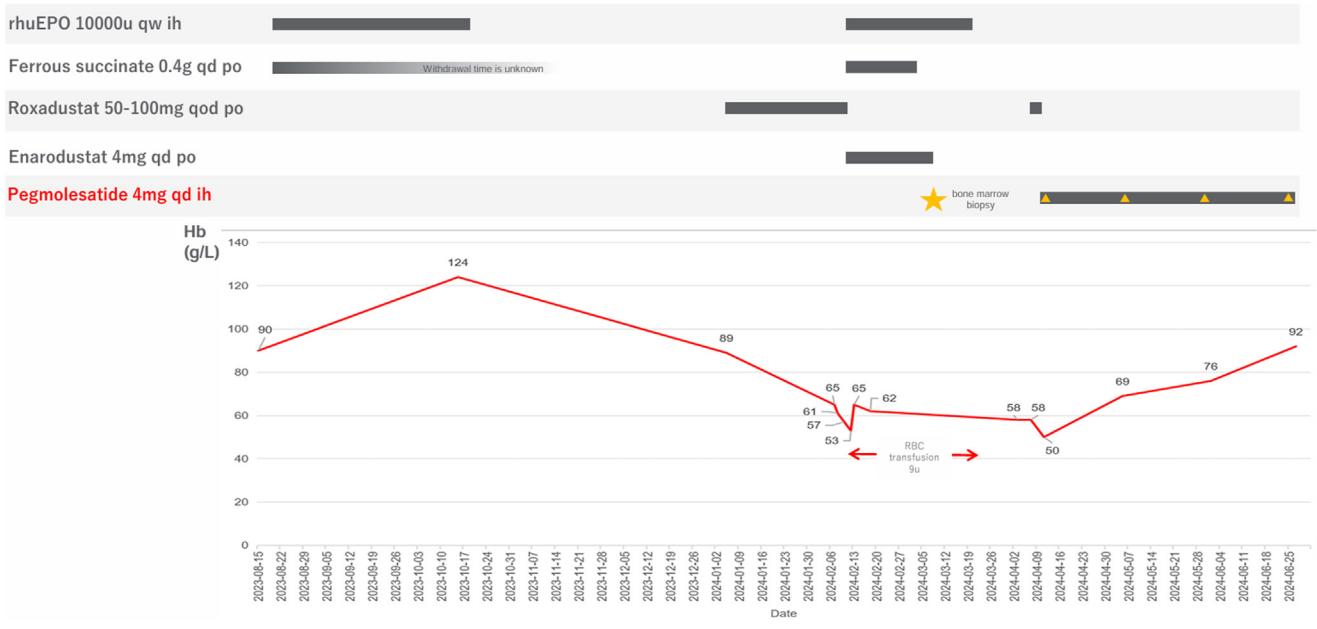

Figure 2. A summary diagram of clinical course including hemoglobin levels and different treatments (EPO, transfusion, enarodustat, roxadustat, and pegmolesatide) over time. ih, hypodermic injection; po, orally; qd, once a day; qod, every other day; qw, weekly; RBC, red blood cell; rhuEPO, recombinant human erythropoietin.

obviously improved. Serum creatinine was 2.44 mg/dL (216.4 μmol/L), estimated glomerular filtration rate (calculated using the CKD-EPI formula) was 33.12 mL/min/1.73 m^2, and serum albumin 32.1 g/L. On June 27, after the patient had received another subcutaneous injection of 4 mg pegmolesatide, his hemoglobin level had increased to 92 g/L (Fig 2). Ferritin was 1,784 μg/L on June 27.

PRCA is a rare but devastating drug-induced disease caused by EPO, a drug used for the treatment of anemia. Previously, the main treatment was immunosuppressive therapy. Because the glucose level was difficult to control in this patient with type 1 diabetes, even though insulin pump therapy was already in use, and anti-EPO antibody was negative, prednisolone was not administered. In consideration of his serum creatine, cyclosporine was also not administered. It has been previously reported that roxadustat may be an alternative treatment for PRCA; however, in this case, the treatment was ineffective, and the patient was maintained with weekly blood transfusions. The EPO-mimetic peptide pegmolesatide was given, and on review, the hemoglobin level of the patient began to increase after 1 week, increasing from 50 g/L to 92 g/L during the course of approximately 3 months.

DISCUSSION

PRCA is a complication of EPO therapy, described as a syndrome characterized by normochromic normocytic anemia, with a reticulocyte count <10,000/μL and an almost complete absence of erythroblasts from the bone marrow, without evidence of hemolysis.[11] PRCA is a very

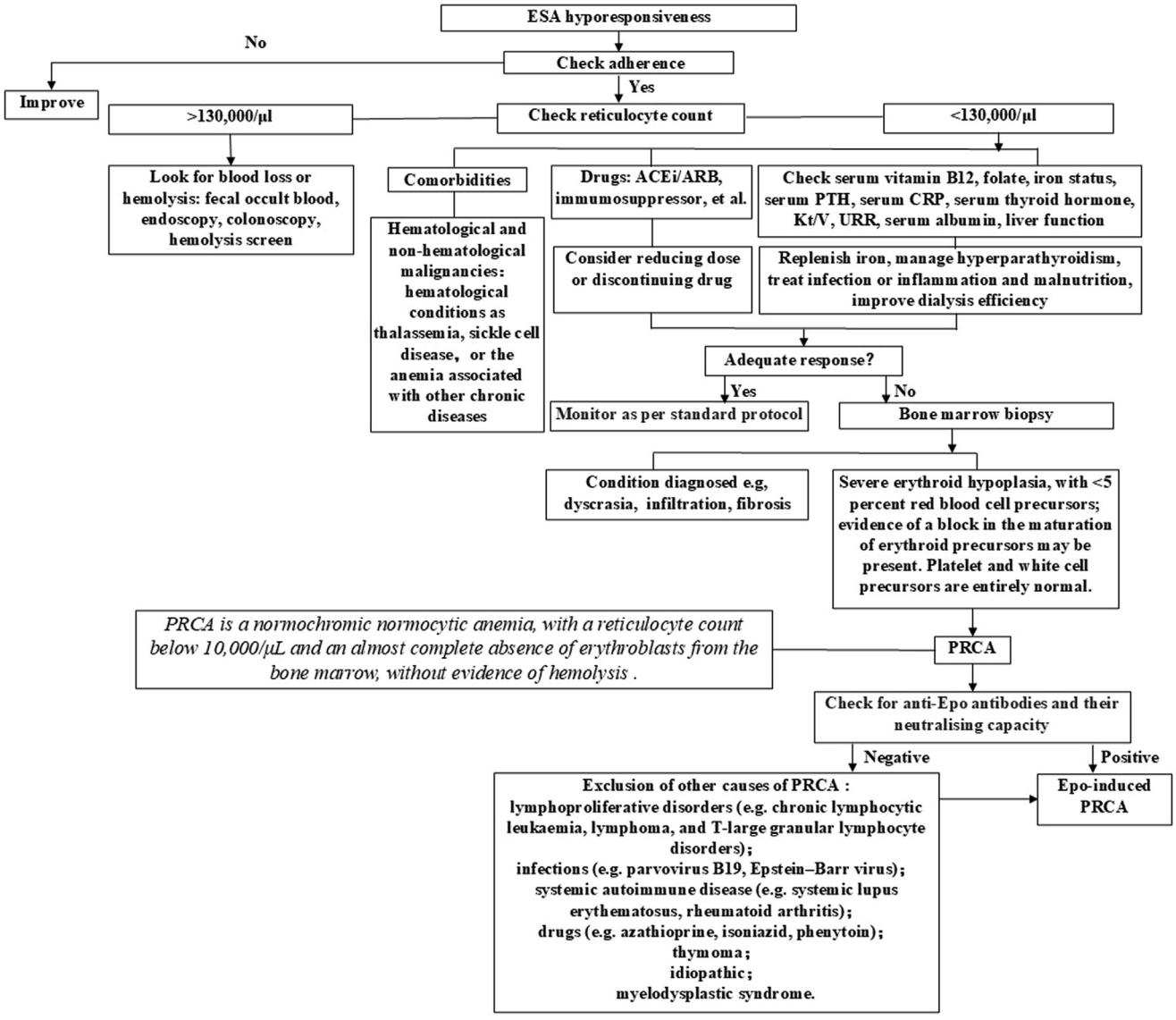

Figure 3. A flowchart that guides distinction from EPO resistance and criteria for PRCA. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CRP, C-reactive protein; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; PRCA, pure red cell aplasia; PTH, parathyroid hormone; URR, urea reduction ratio.

rare but severe transfusion-dependent anemia with an incidence of 0.02-0.03 per 1,000 person-years.[11,12] The flowchart in Fig 3 shows the distinction from EPO resistance and criteria for PRCA diagnosis based on the current recommendations.[13,14] There was no guideline for the treatment for PRCA, because there have been too few cases to perform prospective cohort studies.[15] The main treatments for PRCA include immediate cessation of EPO, restrictive transfusion, and immunosuppressive therapies.[16] Antibodies to EPO, detectable in the serum of such patients, neutralize not only the biologic activity of the therapeutic erythropoiesis-stimulating agent but also endogenous EPO, thus obliterating red cell production in the bone marrow. However, long-term blood transfusions are resource-consuming and may increase the risk of infection and antibody development.[17] In this case, this male patient in his mid-30s with type 1 diabetic nephropathy was diagnosed as PRCA. Enarodustat and roxadustat were successively given after discontinuation of EPO. Anemia did not improve and was maintained with weekly blood transfusions. Subsequently, the EPO-mimetic peptide pegmolesatide was given, and the patient's hemoglobin level started to increase after 1 week and increased from 50 g/L to 92 g/L during the course of approximately 3 months.

Interestingly, we did not find anti-EPO antibody in the case. However, the diagnosis of PRCA was reliable based on his clinical presentation, laboratory findings, and bone marrow biopsy results. Because there was no immune response with endogenous and exogenous EPO in this patient, we still consider his diagnosis as PRCA, although anti-EPO antibody was negative. A positive antibody test may not be necessary for the diagnosis of PRCA. The possible reasons for negative anti-EPO antibody are as follows: (1) False negatives due to poor testing techniques. In this case, the anti-EPO antibody of this patient was negative (19.62 IU/L; reference interval: ≤28 IU/L) by ELISA. The various tests available to detect the presence of anti-EPO antibody include radioimmunoprecipitation assays, ELISA, and surface plasmon resonance methods (BIACORE biosensor immunoassays). Radioimmunoprecipitation assays and ELISA are the most widely used but may give misleading results if incorrectly formatted. All of these assays vary in sensitivity and specificity, and it should be remembered that a negative result from antibody testing, particularly with ELISA, might reflect an inability of the assay used to detect such antibodies in a given patient. (2) Low antibody titer in body. The antibody titer depends on the amount of antibody produced and binding to EPO. If a large amount of antibody binds to EPO and is consumed, the antibody titer may be low or even undetectable, even if the amount of antibody produced is relatively large. Therefore, we suggest that a negative antibody test does not invalidate the diagnosis of PRCA.

The new EPO-mimetic peptide pegmolesatide, which consists of 44 amino acids and has a completely different peptide chain structure from peginesatide and EPO (Fig 4), was independently developed in China. It can bind the EPO receptor with high selectivity and high affinity, and then promotes erythrocyte production efficiently. Importantly, pegmolesatide has no homology to the known sequences of endogenous or exogenous EPO. Thus, there is no cross-immune response between pegmolesatide and EPO. In addition, pegmolesatide rarely produces drug antibodies, attributed to the low immunogenicity. Recently, a randomized, open-label, active-comparator, noninferiority phase 3 trial was conducted at 43 dialysis centers in China and demonstrated that subcutaneous injection of pegmolesatide once a month is noninferior to conventional epoetin alfa administered 1-3 times a week for the treatment of anemia in Chinese patients treated with dialysis.[10] Moreover, the trial showed an acceptable safety profile of pegmolesatide, without severe allergic reactions.[10] In our case, the EPO-mimetic peptide pegmolesatide was given, and the hemoglobin level of patient with PRCA began to increase on review after 1 week, increasing from 50 g/L to 92 g/L during the course of approximately 3 months. Although the anemia in this case was not completely corrected, we still consider the treatment to be successful because of the increased hemoglobin concentration. This male patient with PRCA only required a monthly subcutaneous injection to achieve stable hemoglobin target levels. Based on these findings, we speculate that pegmolesatide can provide a safe, effective, and convenient therapeutic strategy for PRCA. Pegmolesatide is expected to be a treatment option for patients with PRCA who cannot tolerate long-term blood transfusions.

The safety of pegmolesatide is also closely monitored. Before pegmolesatide, peginesatide (also referred to as Hematid), the first EPO-mimetic peptide developed by Affymax, was approved by the US Food and Drug Administration for treating anemia in CKD patients.[18] Peginesatide corrected antibody-induced anemia in a rat

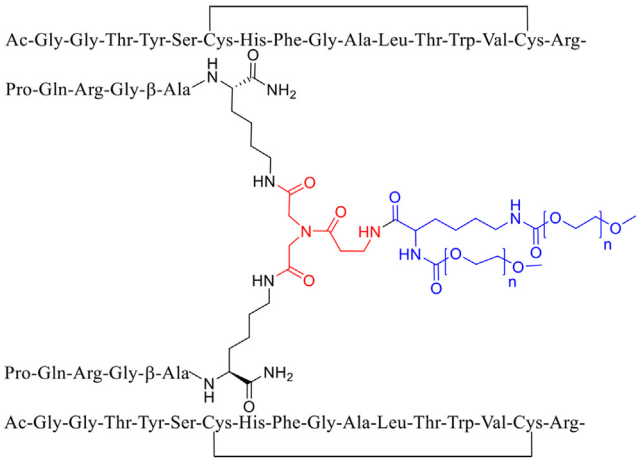

Figure 4. The chemical constitution of pegmolesatide. Pegmolesatide, which consists of 44 amino acids, was independently developed in China. It can bind the erythropoietin receptor with high selectivity and high affinity and then promotes erythrocyte production efficiently.

PRCA model, suggesting that antibodies to EPO do not cross react with peginesatide and, conversely, antibodies to peginesatide do not cross react with EPO.[19] In an open-label, single-group trial, 14 patients with CKD who had PRCA or hypoplasia due to anti-EPO antibodies were treated with peginesatide. The results further showed that peginesatide, which has a completely different peptide chain structure from EPO, cannot be bound by anti-EPO antibodies and can correct anemia in patients with PRCA caused by anti-EPO antibodies.[20] Although peginesatide has been delisted due to anaphylactic reaction and hypotension, the emergence of EPO-mimetic peptides still offer a ray of light to PRCA patients.[21] The results of the phase 3 trial of pegmolesatide demonstrated that monthly subcutaneous injection of pegmolesatide is as safe as conventional epoetin alfa administered 1-3 times a week in treating anemia in Chinese dialysis patients [10]. Fortunately, we have not observed any adverse event in this case. However, ongoing adverse reaction monitoring is still warranted.

To our knowledge, our case is the first to present pegmolesatide treatment of PRCA in a Chinese patient with non-dialysis-dependent CKD. In the future, our team will conduct a multicenter clinical trial to establish whether these initial findings can be confirmed and to further investigate the adverse drug reactions of pegmolesatide.

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