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Tacrolimus Treatment of Pure Red Cell Aplasia Due to Anti-Erythropoietin Antibodies Induced by COVID-19 In Hemodialysis Patient: A Case Report

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COVID-19; Pure red cell aplasia; Anti-erythropoietin antibodies; Tacrolimus; Hemodialysis patient

1. Abstract

Pure red cell aplasia (PRCA) caused by coronavirus disease 2019 (COVID-19) infection inducing anti-erythropoietin (anti-EPO) antibodies is rarely reported. In this article, a case of a hemodialysis patient who developed high titers of anti-EPO antibodies after COVID-19 infection leading to PRCA successful treatment with tacrolimus and Roxadustat. After infected with COVID-19 hemoglobin (Hb) levels of the patient continued to decline despite of increasing frequency of subcutaneous injection of EPO, and the patient had to depend on RBC transfusions. He was diagnosed pure red cell aplasia (PRCA) because of severe erythroid hypoplasia (rarely erythroblasts in bone marrow). the serum anti-EPO antibody was positive(titer1:625). Anemia remained unimproved with systemic prednisone and cyclosporine therapies. Retest positive for anti-EPO antibodies. We used tacrolimus instead of cyclosporine. No further RBC transfusions were required after 4 weeks of tacrolimus and renal anemia was corrected by treatment with Roxadustat. The anti-EPO antibodies turned negative. This report emphasized COVID-19 infection could induce anti-EPO antibodies, resulting in antibody-mediated PRCA.

2. Introduction

Coronaviruses disease 2019 outbroke in December 2019 and rapidly spread all over the world, leading a global pandemic. Although the most difficult period has been passed, it still continues to affect people's health, especially those with underlying diseases including end stage renal disease. The most common symptoms of COVID-19 are respiratory syndrome with dry cough, fever and fatigue. It also affects other organs, including renal, cardiovascular, and hematologic systems, so the patients have a diverse range of clinical manifestations [1]. Two cases reported that pure red cell aplasia (PRCA) presumably associated with preceding severe acute respiratory syndrome COVID-19 infection, but they do not test the anti-EPO antibody [2]. It has been shown that EPO values lower in deceased patients compared with survivors after COVID-19 infection [3]. It raises the possibility that COVID-19 infection may meditate an immunologic response resulting in production of autoimmune antibodies, which may include anti-EPO antibodies. Here we report a case of PRCA with anti-EPO antibodies linked to infection by COVID-19 and recovered after treatment with tacrolimus.

3. Case Report

A 49-year-old male, started hemodialysis in January 2022 due to chronic glomerulonephritis. The dialysis scheme was three times per week using his right forearm fistula for 4 hours, His residual urine volume about 700-1000 ml/day. Renal anemia was treated with subcutaneous injection of 10,000 IU of Erythropoietin once a week. Hemoglobin (Hb) recovered to 110 g/L and was monitored regularly. Hb fluctuated between 110 and 125 g/L. On December 27,2022, he visited a local hospital for fever and sore throat.

Self-tested antigen showed COVID-19 infection, without severe respiratory syndrome, and recovered by himself. Hemoglobin was 117 g/L. On February 6,2023, he fainted suddenly after amaurosis and looked pale and Hb level was 44g/L. He received 4U of Rh-B positive blood transfusion. The dose of EPO was adjusted to 10000iu every other day, the Hb level was 59 g/L after 6 times of treatment. On March 3,2023, hemoglobin level was 47g/L, he received blood transfusion again, and EPO 10000iu was injected subcutaneously every other day. From March 27,2023 to March 27,2023, he was admitted to the local hospital because of dizziness. The gastroscope showed chronic gastritis with protuberant erosion and duodenitis. He required frequent RBC transfusions. On April 12,2023, hemoglobin level was 52g/L. for further diagnosis and treatment, the patient was admitted to our hospital on April 22,2023. The patient was previously diagnosed hypertension, regularly treated with Nifedipine Controlled-release Tablets, Irbesartan, Metoprolol and Doxazosin Mesylate Controlled Release Tablets, blood pressure controlled at about 130/70mmHg. And he was a Hepatitis B virus carrier, no treatment. After admission, laboratory test results revealed red blood cell (RBC) count, 1.62×1012 L; hemoglobin, 42 g/L; fecal occult blood (FOB), negative; hemoglobin electrophoresis , normal; Lactate dehydrogenase (LDH), 224 u/L; direct and indirect Coombs test was negative; tumor markers, normal; cryoglobulins were negative; ANA and ANCA were negative; ferritin , 1012 ng/mL; Reticulocyte absolute count, 0.001×1012/L; erythropoietin level, < 0.60 MIU/mL; and erythropoietin antibody was positive, 1:625. Bone marrow (BM) revealed a hypercellular marrow. Erythroid precursor cells were notably absent. Granulomatous hyperplasia predominated. Other myeloid cells were all normal. After ruling out other causes of anemia, laboratory tests confirmed the production of anti-EPO antibodies, so we diagnosed PRCA.

The patient was treated with prednisone 15mg once per day and cyclosporine 75mg every 12 hours. Taking Roxadustat 120mg 3 times per week substitute for subcutaneous injection of 10,000 IU of Erythropoietin. Cyclosporine blood concentration was 191.5ng/ml. Hemoglobin fluctuates at 55-66 g/L. Anemia remained unimproved with systemic prednisone and cyclosporine therapies; the patient still required frequent RBC transfusions. On 23-June-2023, Hemoglobin level was 45 g/L, the patient readmitted to hospital. And three times double filtration plasmapheresis (DFPP) was performed. The erythropoietin antibodies titer was1:25. Then tacrolimus 1.5 mg every 12 hours was used instead of cyclosporine. No further RBC transfusions were required after 4 weeks of tacrolimus. Tacrolimus blood level was 4.6 ng/ml. On 22nd-July,2023, hemoglobin level was 70g/L. The erythropoietin antibody was negative. The patient recovered from anemia and showed increased reticulocyte absolute count 0.018×1012/L. And hemoglobin recovered to 120 g/L on 1st-December,2023. Oral prednisone and tacrolimus were gradually reduced during follow-up in the outpatient department owing to the patient's stable condition. Roxadustat 120mg 3 times a week is retained.

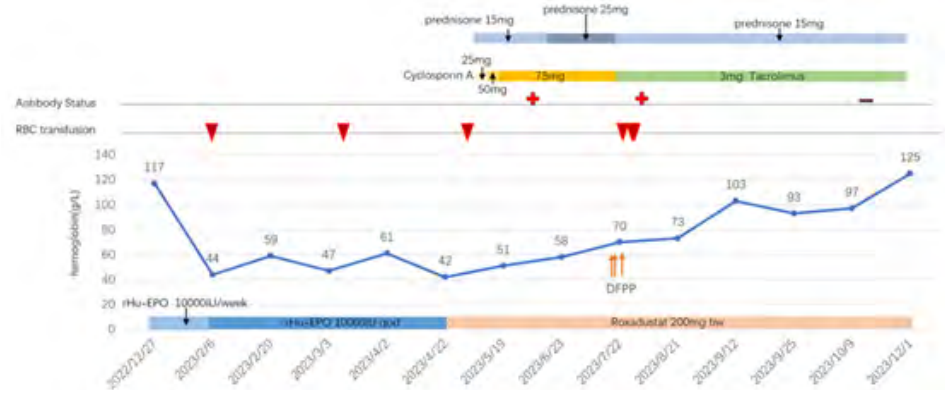

Figure 1: The change in hemoglobin during the whole course of the disease of patient. double filtration plasmapheresis (DFPP).

Table 1: Summary of laboratory investigations at the patient's first visit.

Investigation (Units)		Result (Normal Range)
Hemoglobin (g/L)		54 (135–175)
Mean corpuscular volume (MCV) (fL)		77.3 (82–100)
Mean corpuscular hemoglobin concentration (MCHC) (g/L)		323 (316–354)
Leukocytes (×109/L)		4.94(3.50–9.50)
Platelets (×109/L)		142(125–350)
	General Chemistry	
Sodium (mmol/L)		138.3 (137–147)

Potassium (mmol/L)		4.62 (3.50–5.30)
Chloride (mmol/L)		102.0 (96.0–108.0)
Bicarbonate (mmol/L)		26.2 (23.0–29.0)
Creatinine (μmol/L)		849.33 (57.00–111.00)
Urea (mmol/L)		24.71(3.10–8.00)
ALB(g/L)		32.09(40.00-55.00)
iPTH(pg/mL)		30.92(15.00-65.00)
Ca(mmol/L)		2.75(2.11-2.52)
P(mmol/L)		2.25(0.85-1.51)
Alanine aminotransferase (ALT) (U/L)		46(9-50)
Folate (ng/mL)		>23 (>5.90)
Coagulation		
International normalized ratio (INR)		1.08(0.95–1.15)
Activated partial thromboplastin time (APTT) (s)		34.6(30.0–45.0)
Fibrinogen (g/L)		3.09 (1.90–4.00)
Hemolytic Workup		
Total bilirubin (μmol/L)		9.6 (5.0-21.0)
Transferrin (g/L)		2.30(2.00-3.60)
Lactate dehydrogenase (LDH) (U/L)		224(120-250)
Reticulocyte absolute count (×10^12/L)		0.001(0.024-0.084)
Investigation (Units)		Result (Normal Range)
Reticulocyte percentage (%)		0.001(0.005-0.015)
Direct antiglobulin test (DAT)		Negative
Cryoglobulin qualitative		Negative
Peripheral blood smear		Negative
Urinalysis-Macroscopic		
Specific Gravity		1.015 (1.003–1.030)
pH		8.0 (4.5–8.0)
Protein (g/L)		0.75 (Negative)
Blood (Ery/μL)		1.5 (0.00-18.00)
WBC (/HPF)		26.90 (0–13)
RBC (/HPF)		0–2 (0–2)
Bacteria (/HPF)		0–20 (0–20)
Urine was negative for glucose, leukocytes, nitrites, and ketones		

4. Discussion

Almost all end stage renal disease (ESRD) patients combining with anemia because of reducing production of erythropoietin (EPO) [4]. EPO is a kidney-derived growth factor and essential growth factor for erythropoiesis. Since the late 1980s, patients with renal anemia have been treated with intravenous or subcutaneous recombinant human erythropoietin (rhEpo). The number of patients diagnosed with PRCA after anti-EPO antibodies induced by subcutaneous injection of rhEpo has gradually increased after the widespread use of subcutaneous injection of EPO [5]. PRCA is a syndrome characterized by reticulocytopenia and reduction or absence of erythroid precursors from the bone marrow. Anti-EPO antibodies cut off the interaction of EPO and its receptors by neutralizing all exogenous EPO and cross-reacting with endogenous, resulting in PRCA. The causes of acquired PRCA also include autoimmune vascular disorders; lymphoproliferative disorders; infections, especially B19 parvovirus; hematologic malignancies; thymoma; and drugs and toxic agents [6]. PRCA is a rare hematological condition characterized by selective reduction in BM erythroblasts and reticulocytes. PRCA has been reported as complication of COVID-19; however, very few studies elucidated the mechanism. Our patient was diagnosed with severe anemia

after 1 year of regular use of rhEpo, during which he was infected with COVID-19. We analyzed the causes of anemia one by one. Negative with direct and indirect Coombs, no bilirubin elevation, which could exclude the patient's autoimmune hemolysis. No malnutrition, and the pre-tests could exclude gastrointestinal hemorrhage, severe hyperparathyroidism, thalassemia, and pernicious tumors. Underlying diseases, and the use of special drugs which could cause anemia can be basically excluded. The patient was diagnosed with acquired PRCA based on the selective decrease in bone marrow erythroblasts and the remarkable decrease in reticulocytes. And COVID-19 infection was considered the only reason because other possible causes were ruled out. We speculated that the production of anti-EPO antibodies associated with COVID-19 may cause PRCA. He presented with fatigue 3 months later and was found to be anemic with positive for anti-EPO antibodies, which was corresponded to the point in time of the lifespan of erythrocyte. Some cases were reported that acquired PRCA occurs several weeks after recovery from acute COVID-19 infection [2]. PRCA may be a late complication of COVID-19 infection associated with disruption of normal erythropoiesis due to prolonged immune response. Studies have shown that infection with COVID-19 can cause a decrease in EPO and lead to anemia, and got improvement with EPO treatment [7]. COVID-19 vaccine injection also causes autoimmune hemolysis leading in anemia [8]. But they didn't mention the test ofnti-EPO antibodies. At present, there are reports that the occurrence of PRCA is related to COVID-19 infection, but the pathogenesis is not clear. Decreased hemoglobin may be associated with autoimmune disease. Lazarian reported seven patients with COVID-19 who had coexisting with autoimmune hemolytic anemia (AIHA) [9]. Some studies have suggested that the pathogenesis of PRCA may be related to the high inflammatory response induced by COVID-19 [10]. Moreover, the same sequence exists between the viral protein of COVID-19 and the human protein, and the possible mechanism of autoantibody production is molecular mimicry [11]. Production of anti-EPO antibodies may be molecular mimicry associated with immune-mediated infection with COVID-19, blocking the interaction of EPO and its receptors. Patients with anti-EPO antibodies -induced PRCA are managed by discontinuation of erythropoietin and they are typically treated with corticosteroids, cyclophosphamide, cyclosporine A, intravenous immunoglobulin, and renal transplantation [5]. Both tacrolimus and cyclosporine are calcineurin inhibitors with similar pharmacological actions but different receptors. Our patient didn't respond well by increasing cyclosporine doses with effective levels of cyclosporine, Workup turned negative for EPO antibodies after switching to tacrolimus. This case demonstrated that tacrolimus can be used as an alternative therapy for patients with anti-EPO antibodies -induced who don't effective with the treatment of cyclosporine. But we should be careful during the patient is treated with tacrolimus. Because some case reported that tacrolimus caused PRCA [12]. Therefore, attention should be paid to whether the anemia of the patient is recovery in the case of anti-EPO antibodies negative. When anti-EPO antibodies is positive, treating renal anemia with rhEpo is not effective and may lead to product anti-EPO antibodies again. Roxadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), regulates the expression of EPO, as well as other HIF stabilization, thus promoting erythropoiesis at multiple levels. Multiple studies have shown that Roxadustat is an effective treatment for anti-EPO antibodies -induced PRCA after immunosuppressive therapy [13-15]. In this case, we switched to Roxadustat to help correct anemia and did not produce EPO antibodies.

5. Conclusion

COVID-19 infection may induce Erythropoietin antibody and cause anti-EPO antibodies -induced PRCA. Immunosuppressive therapy with tacrolimus can make the antibodies turn negative. After started Roxadustat, renal anemia was successfully recovered. The COVID-19 era may continue for years, clinicians should be aware hemodialysis patient who combine with anemia requiring frequent RBC transfusions. This report emphasized COVID-19 infection can induce erythropoietin antibodies, resulting in antibody-mediated PRCA, of which the associated mechanisms remain unclearly defined.

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