Brazilian Journal of TRANSPLANTATION

https://doi.org/10.53855/bjt.v28i1.669_ENG

CASE REPORT

Post-Kidney Transplant Erythrocytosis: Case Report

Renato André Digieri[1,*], Américo Lourenço Cuvello Neto[2], Andréa Santos Galvão[1], Leonardo Victor Barbosa Pereira[1], Precil Diego Miranda de Menezes Neves[2], Pedro Renato Chocair[1], Érico Souza de Oliveira[1]

1.Hospital Alemão Oswaldo Cruz – Serviço de Medicina Interna – São Paulo (SP) – Brazil.

2.Hospital Alemão Oswaldo Cruz – Centro de Nefrologia e Diálise – São Paulo (SP) – Brazil.

*Corresponding author: rd.haoc@gmail.com

Seccion editor: Ilka de Fátima Santana F. Boin

Received: Jan. 03, 2025 | Approved: Feb. 03, 2025

ABSTRACT

We present the case report of a patient diagnosed with erythrocytosis after kidney transplantation, the occurrence of which must be known so that it can be accurately diagnosed and correctly treated, preserving patients from consequences related to blood hyperviscosity. It has several risk factors and can be asymptomatic or manifest in a typical form. The pathogenesis of erythrocytosis after kidney transplantation is multifactorial. The diagnosis is made in the appropriate clinical context, and other possible causes must necessarily be ruled out, some of which are potentially serious, such as proliferative diseases. The mainstay of treatment for erythrocytosis after kidney transplantation is the administration of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. With appropriate treatment, its prognosis is good.

Descriptors: Polycythemia; Erythrocytosis; Kidney Transplant; Angiotensin-Converting Enzyme Inhibitor.

Eritrocitose Pós-Transplante Renal: Relato de Caso

RESUMO

Apresentamos o relato de caso de um paciente diagnosticado com eritrocitose pós-transplante renal, cuja ocorrência deve ser conhecida para que possa ser diagnosticada de forma acurada e corretamente tratada, preservando os pacientes de consequências relacionadas à hiperviscosidade sanguínea. A eritrocitose pós-transplante renal apresenta diversos fatores de risco, podendo ser assintomática ou manifestar-se de forma típica. Sua patogênese é multifatorial. O diagnóstico é realizado no contexto clínico apropriado, devendo necessariamente ser descartadas outras possíveis causas, algumas das quais potencialmente graves, como doenças proliferativas. A base do tratamento reside na administração de inibidores da enzima conversora de angiotensina ou bloqueadores do receptor de angiotensina. Com tratamento adequado, tem bom prognóstico.

Descritores: Policitemia; Eritrocitose; Transplante Renal; Inibidor da Enzima Conversora de Angiotensina.

INTRODUCTION

Post-kidney transplant erythrocytosis (PTE) has been discussed in the medical literature for many years. Its incidence, which is probably decreasing, may make its identification more time-consuming. However, it persists in a significant percentage of patients; therefore, it should be known so that the diagnostic process can be conducted appropriately and adequate treatment can be instituted. We report a case of PTE in a patient investigated at the Hospital Alemão Oswaldo Cruz, followed by a brief literature review covering epidemiology, risk factors, clinical manifestations, pathogenesis, diagnosis, treatment and prognosis of this disorder.

CASE REPORT

A 66-year-old male patient presented to the Emergency Department in June 2024, complaining of fatigue and dyspnea on minimal exertion for 5 days. When questioned about other respiratory symptoms, he reported a mild dry cough. He denied fever or chest pain.

The physical examination revealed no striking alterations except for bibasal crackles, predominantly at the left base, and mild hypoxemia.

As relevant antecedents, the patient reported systemic arterial hypertension, dyslipidemia, gout and a kidney transplant that occurred in March 2023. He did not have diabetes and denied smoking. His donor was deceased, with zero antibody reactivity against the human leukocyte antigen (HLA) panel. The cold ischemia time was 23 hours, and induction was performed with basiliximab.

The chronic kidney disease (CKD) that led to end-stage renal failure was related to long-standing hypertension, aggravated by excessive use of nonsteroidal anti-inflammatory drugs due to gout. He started dialysis in June 2021 with stage V CKD [Kidney Disease: Improving Global Outcomes (KDIGO) criteria]. During his dialysis, the patient never required erythropoietin (EPO) replacement.

The patient's continuous medications included mycophenolate sodium, tacrolimus and prednisone, in addition to allopurinol, metoprolol and rosuvastatin.

He was admitted for investigation and treatment. His admission laboratory tests are shown in Table 1.

Table 1. Admission laboratory tests.

Requested tests	Results and reference values
Erythrocytes	6.83 million/mm^3 (4.32-5.67)
Hemoglobin	20 g/dL (13.3-16.5)
Hematocrit	60.70% (39.2-49)
Mean corpuscular hemoglobin	29.3 pg (27.7-32.7)
Mean corpuscular volume	88.9 fL (81.7-95.3)
Red cell distribution width	14.30% (11.8-14.1)
Leukocytes	10.990/mm^3 (3.650-8.120)
Platelets	244 thousand/mm^3 (151 thousand-304 thousand)
Prothrombin time (International Normalized Ratio)	1.2 (0.9-1.1)
Activated partial thromboplastin time (Patient/Standard)	1.22 (0.91-1.20)
D-dimers	541 ng/mL FEU (up to 500)
C-reactive protein	2.24 mg/dL (> 1 for inflammatory or infectious processes)
Urea	68 mg/dL (10-50)
Creatinine	1.44 mg/dL (0.7-1.3)
CKD-EPI glomerular filtration	54 mL/min/1.73 m^2 (> 60)
Troponin I – Ultrasensitive	11 ng/L (< 19.8)
Sodium	134 mEq/L (136-145)
Potassium	3,8 mEq/L (3.5-4.5)
B-type natriuretic peptide	42 pg/mL (up to 100)
Influenza A and B – Rapid test	Negative (negative)
PCR Sars-Cov-2	Not detected (not detected)

Source: Elaborated by the authors.

The hemoglobin (Hb) and hematocrit (HT) levels attracted attention, and a curve of these parameters was recovered: in October 2023, Hb = 14.8 g/dL with HT = 51.1%; in January 2024, Hb = 16.6 g/dL with HT = 55.4%.

A computed tomography (CT) scan of the chest was performed, which indicated diffuse ground-glass opacities associated with a discrete mosaic attenuation pattern. No consolidations or signs of chronic obstructive pulmonary disease (COPD) were observed.

The transthoracic Doppler echocardiogram showed no dysfunctions relevant to the clinical picture.

The patient developed tachypnea and diffuse rales. New laboratory tests were requested, including iron (Fe) profile and lactic dehydrogenase (LDH), respiratory viruses screening by molecular detection, an entire abdominal ultrasound (USG), a search for the p.V617F mutation in the *JAK2* gene, cytomegalovirus (CMV) screening by polymerase chain reaction (PCR) and plasma EPO dosage. Three phlebotomies were performed, taking advantage of the ease of the procedure since the patient was hospitalized and had no contraindications.

The abdominal USG did not suggest liver or kidney nodules or any splenomegaly as well. In the viral search, rhinovirus/enterovirus was isolated (the available viral panel did not differentiate between the two viruses). The CMV search was negative. The Fe profile and DHL results are shown in Table 2.

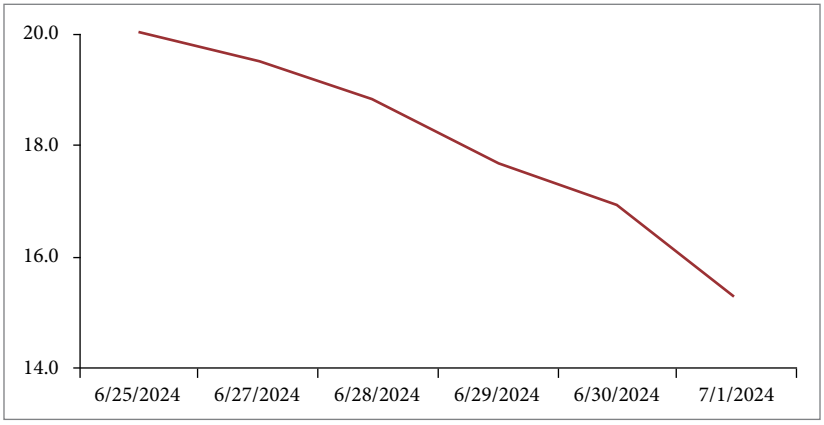
Table 2. Fe profile and DHL.

Requested tests	Results and reference values
Serum iron	87 mcg/dL (65-175)
Transferrin saturation	34% (20-50)
DHL	195 U/L (135-225)

Source: Elaborated by the authors.

The patient had previously undergone a Doppler ultrasound of the renal arteries (native and transplanted) with normal results. He had no history of obstructive sleep apnea.

After clinical support for the respiratory viral infection, with a reduction in C-reactive protein to 0.52 mg/dL, as well as measures to reduce Hb to 15.3 g/dL, as shown in Fig. 1, the patient was discharged from the hospital on the 7th. day of hospitalization in good condition, with diagnostic hypotheses of (a) rhinovirus/enterovirus pneumonia and (b) PTE for the high Hb/HT concentration detected in the admission tests.



Source: Elaborated by the authors.

Figure 1. Evolution of Hb (g/dL).

He was prescribed enalapril (a medication that was actually started in the last few days of his hospitalization), in addition to guidance and a request for tests scheduled for outpatient follow-up. One day after his discharge, the results of the pending tests were known, as shown in Table 3.

Table 3. EPO and JAK2 mutation.

Requested tests	Results and reference values
EPO	2.4 miU/mL (4.3-29)
JAK2, p.V617F mutation	Absent (absent)

Source: Elaborated by the authors.

DISCUSSION

KDIGO defines PTE as the finding of Hb concentration above 17 g/dL or HT higher than 51% in patients who received the graft. It occurs in a minority of transplant patients, in a variable percentage range from 2.5 to 22.2% of cases, depending on the chosen definition criteria, usually between 8 and 24 months after grafting[1]. However, its incidence may be decreasing, with the widespread use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), in addition to antiproliferative immunosuppression itself, being plausible explanations for that trend[2].

Associated risk factors are not always coincident in the literature and include male sex, retention of native kidneys, adequate erythropoiesis before transplantation, a rejection-free course with preserved glomerular filtration, younger age, the existence of a previous period of dialysis and the underlying cause of kidney disease (notably polycystic kidney disease)[1,3-6]. Simultaneous double kidney-pancreas transplantation also appears to increase the risk of PTE[7].

The patient may show typical signs and symptoms of erythrocytosis or be simply asymptomatic, in the latter case with the diagnosis based on an incidental finding. Typical signs and symptoms include malaise, headache, fatigue, plethora, lethargy and dizziness[5,8]. Due to blood hyperviscosity, potential thromboembolic events, whether venous or arterial, constitute a source of concern for untreated patients.

The pathogenesis of PTE is multifactorial. The involved mechanisms include EPO levels, the renin-angiotensin-aldosterone system (RAAS), endogenous androgens, and other erythropoiesis-stimulating factors, such as insulin-like growth factor 1 (IGF-1) and stem cell factor (SCF). The mechanisms described may have an isolated and direct influence on erythropoiesis or act combined and dependently.

EPO is a powerful hormone that regulates erythropoiesis. Renal retention can generate an excess of EPO since, although grafts are subject to the typical negative hormonal feedback, native kidneys appear to secrete EPO in an "insensitive" manner, in a kind of "tertiary hypererythropoietinemia"[1]. However, it is necessary to mention that not every patient with PTE has high EPO levels [9,10]. The RAAS is also a stimulator of erythropoiesis, as suggested by several observations in patients with congestive heart failure, hypertension and COPD, whose high erythrocyte mass is reduced when ACEIs are used for a long time.[1] Angiotensin II, in particular, is a growth factor for erythroid progenitor cells. Still, it stimulates EPO secretion even in states of elevated HT.[11]. Androgens exert dose-dependent direct stimulation on erythroid progenitors, which is inhibited when androgen antagonists are administered[1,5,6]. Levels of IGF-1 are positively correlated with HT values in uremic and transplant patients. In dialysis patients with undetectable EPO, IGF-1 is considered an essential erythropoiesis-stimulating factor[1]. SCF is a cytokine produced by fibroblasts, stromal cells, keratinocytes, endothelial cells and other cells of tumor lineages that, bound to its receptor, called c-kit, acts synergistically with other erythroid precursor stimulating factors. Its increased serum levels and inadequate EPO suppression also impact PTE[12].

The diagnosis of PTE involves confirmation of Hb and/or HT concentrations greater than 17 g/dL and 51%, respectively, in the appropriate clinical context. Non-transplant causes of erythrocytosis should be excluded, including neoplasms such as breast, renal or hepatocellular cancer, obstructive sleep apnea and significant lung disease. Possible renal artery stenosis should be evaluated. EPO measurement is not commonly part of the diagnostic evaluation since, as mentioned in the previous paragraph, PTE is not always associated with high EPO levels[5].

Although there are cases of spontaneous remission estimated in less than a quarter of patients, the basis of treatment for PTE lies in the administration of ACEIs or ARBs [1,3,4,5,8]. The nadir of HT usually reaches within 3 months of treatment, and recurrence may occur after discontinuation of therapy, although there are reported cases (20 to 30%) of non-recurrence[1]. Additionally, treatment also contributes to the reduction of microalbuminuria, which sometimes develops post-transplant along with PTE[3]. There are reports, however, of refractoriness to treatment with ACEIs or ARBs, the percentage of which varies, reaching 22% of cases[8]. The second line of treatment involves phlebotomy or theophylline[5]. Phlebotomy can cause Fe deficiency, while theophylline, an adenosine antagonist drug, has side effects that can impact quality of life, such as headache, anxiety and insomnia[1,5]. As a last option, one can consider replacing immunosuppression, using, for example, sirolimus, an mTOR inhibitor that, however, also has a significant potential for side effects[5].

Regarding the prognostic impacts of PTE, a meta-analysis indicates that, with early diagnosis and appropriate treatment, graft survival and patient mortality do not change significantly in the long term in comparison with those of transplant patients who do not develop PTE[13].

CONCLUSION

Knowledge of PTE is necessary so that diagnostic investigations in the suggestive clinical context can be performed in a targeted, appropriate manner and with less time and resources. The treatment, which is generally simple and low-cost, tends to ensure an unalterable long-term prognosis for the transplant patient when compared to the transplant patient who does not develop this condition.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Digieri RA, Chocair PR, Oliveira ES; **Conception and design:** Digieri RA, Galvão AS, Oliveira ES; **Data analysis and interpretation:** Digieri RA, Oliveira ES; **Article writing:** Digieri RA, Neves PDMM, Oliveira ES, Chocair PR; **Critical revision:** Digieri RA, Chocair PR, Oliveira ES; **Final approval:** Digieri RA, Cuvello Neto AL, Pereira LVB, Chocair PR, Oliveira ES.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study.

FUNDING

Not applicable.

ACKNOWLEDGEMENT

Not applicable.

REFERENCES

1. Vlahakos DV, Marathias KP, Agroyannis B, Madias NE. Posttransplant erythrocytosis. Kidney Int, 2003; 63(4): 1187-94. https://doi.org/10.1046/j.1523-1755.2003.00850.x
2. Kiberd BA. Post-transplant erythrocytosis: a disappearing phenomenon? Clin Transplant, 2009; 23(6): 800-6. https://doi.org/10.1111/j.1399-0012.2008.00947.x
3. Mulhern JG, Lipkowitz GS, Braden GL, Madden RL, O'Shea MH, Harvilchuck H, et al. Association of post-renal transplant erythrocytosis and microalbuminuria: response to angiotensin-converting enzyme inhibition. Am J Nephrol, 1995; 15(4): 318-22. https://doi.org/10.1159/000168856
4. Galvão MM, Romão Júnior JE, Sabbaga E. Tratamento da eritrocitose pós-transplante renal com bloqueadores da enzima de conversão. J Bras Nefrol, 1996 [access on 02 Jan. 2025]; 18(3): 243-7. Available at: https://docs.bvsalud.org/biblioref/2023/12/269678/jbn_v18n3-1-243-247.pdf
5. Alzoubi B, Kharel A, Machhi R, Aziz F, Swanson KJ, Parajuli S. Post-transplant erythrocytosis after kidney transplantation: a review. World J Transplant, 2021;11(6): 220-30. https://doi.org/10.5500/wjt.v11.i6.220
6. Hofstetter L, Rozen-Zvi B, Schechter A, Raanani P, Itzhaki O, Rahamimov R, et al. Post-transplantation erythrocytosis in kidney transplant recipients – A retrospective cohort study. Eur J Haematol, 2021; 107(6): 595-601. https://doi.org/10.1111/ejh.13696
7. Guerra G, Indahyung R, Bucci CM, Schold JD, Magliocca JF, Meier-Kriesche HU. Elevated incidence of posttransplant erythrocytosis after simultaneous pancreas-kidney transplantation. Am J Transplant, 2010; 10(4): 938-42. https://doi.org/10.1111/j.1600-6143.2010.03012.x
8. Vishnu P, Moreno Vanegas Y, Wadei HM, Rivera CE. Post-transplant erythrocytosis refractory to ACE inhibitors and angiotensin receptor blockers. BMJ Case Rep, 2018; 2018: bcr2018224622. https://doi.org/10.1136/bcr-2018-224622
9. Gaston RS, Julian BA, Curtis JJ. Posttransplant erythrocytosis: an enigma revisited. Am J Kidney Dis. 1994 Jul; 24(1):1-11. https://doi.org/10.1016/S0272-6386(12)80153-3
10. Wang AY, Yu AW, Lam CW, Yu LM, Li PK, Goh J, et al. Effects of losartan or enalapril on hemoglobin, circulating erythropoietin, and insulin-like growth factor-1 in patients with and without posttransplant erythrocytosis. Am J Kidney Dis, 2002; 39(3): 600-8. https://doi.org/10.1053/ajkd.2002.31404
11. Vlahakos DV, Marathias KP, Madias NE. The role of the renin-angiotensin system in the regulation of erythropoiesis. Am J Kidney Dis, 2010; 56(3): 558-65. https://doi.org/10.1053/j.ajkd.2009.12.042
12. Kiykim AA, Genctoy G, Horoz M, Tiftik NE, Gok E, Altun B, et al. Serum stem cell factor level in renal transplant recipients with posttransplant erythrocytosis. Artif Organs, 2009; 33(12): 1086-90. https://doi.org/10.1111/j.1525-1594.2009.00823.x
13. Mekraksakit P, Boonpheng B, Leelaviwat N, Duangkham S, Deb A, Kewcharoen J, Nugent K, Cheungpasitporn W. Risk factors and outcomes of post-transplant erythrocytosis among adult kidney transplant recipients: a systematic review and meta-analysis. Transpl Int. 2021 Nov; 34(11): 2071-2086. https://doi.org/10.1111/tri.14016