

CLINICAL VIGNETTE

Post-Transplant Erythrocytosis

Evangelia Kirmis, MD

A 54-year-old patient with history of end stage renal disease related to focal sclerosing glomerulonephritis was referred to hematology with elevated red blood cell indices. He underwent a kidney transplant almost one year prior to referral. Prior to surgery, the patient had stable anemia with hemoglobins around 9 g/dL. After surgery he initially remained anemic but was noted to have steady improvement of hemoglobin into normal range as he improved from his transplant. However, his blood count continued to increase above the normal range, and his last several hemoglobins had increased to 18.5 g/dL, hemocrit of 63.2%, and red blood cell count of $8.2 \times 10^6/\text{microL}$. His other blood elements were unremarkable. Janus Kinase 2 (JAK2) V617F and reflex testing for additional exons 12-15 showed no mutations. Erythropoietin was normal. His physical exam was unremarkable and he remained asymptomatic other than residual symptoms related to his prior transplant.

Posttransplant erythrocytosis (PTE) is a well-noted phenomenon which is described as a persistent elevation in hemoglobin/hematocrit levels after renal transplantation.¹⁻³ In general, PTE is noted when a hemoglobin is greater than 17g/dL and/or hematocrit is greater than 51% for more than six months after transplantation and other causes are ruled out.^{1,3} It is expected that patients have otherwise normal white blood cell and platelet counts and no other underlying causes to explain the erythrocytosis such as renal cell carcinoma, renal artery stenosis, myeloproliferative disease, breast cancer, hepatocellular carcinoma, cardiopulmonary disease, etc.¹ The erythrocytosis usually develops within the first two years after kidney transplant.¹ It has been noted in 10-20% of renal transplant patients.^{1,2} Known risk factors include: male gender, preserved glomerular filtration rate (GFR), retained native kidneys, renal artery stenosis in the transplanted kidney, and no evidence of rejection.^{1,2} Male gender has been reported as a strong risk factor. While most cases occur in patients with retained native kidneys, there have been a few reports in patients after nephrectomy.¹ There are some associations with smoking and diabetes.¹ It is not clear if transplant related medications such as cyclosporine, azathioprine, and steroids may be associated, as studies have shown conflicting results.^{1,2} Interestingly, limited need for erythropoietin-stimulating agents with dialysis prior to transplant may indicate a patient with good erythropoiesis and predisposition for PTE after surgery.¹ The process can self-resolve in 25% of patients within the initial two years or, it can persist indefinitely.^{1,2} Loss of allograft function due to rejection can also cause a drop in red blood cell numbers.¹ If left untreated, patients can develop lethargy,

headaches, malaise or thromboembolic events.¹ Stroke or pulmonary embolus occurs in 10-30% of PTE patients and can lead to death in 1-2% of this population.¹

The exact mechanism underlying PTE is not clear.^{1,3} The process seems to be multifactorial and likely is related to undefined factors related to the recipient.¹ Certain hormonal pathways seem to be involved including erythropoietin, renin-angiotensin system, and androgens.^{1,3} Excess erythropoietin from the native kidney may explain why most cases were in patients who retained their kidneys.¹ The old, injured kidneys may not respond to the appropriate feedback to diminish erythropoietin production.¹ However, measuring erythropoietin levels is not generally helpful for diagnosis as they usually remain normal despite PTE.¹ Given normal erythropoietin values, other mechanisms clearly are also at work.¹ Theories include growth factors that increase sensitivity to erythropoietin or activation of the renin-angiotensin system may stimulate erythropoietin secretion.¹ Effective pharmacologic therapies do lower erythropoietin levels and subsequently hemoglobin/hematocrit as well.¹ Androgen effects may explain the male predominance of PTE.¹

Treatment is very effective in the majority of PTE cases and includes angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).^{1,3} Published reports suggest ACE inhibitors can be more effective than ARBs but are associated with more toxicity.¹ Either class can be utilized with low initial dosing low and titration to maximize benefit.¹ In the small proportion of patients that do not respond to ACE and ARB medications, can respond to phlebotomy.¹ Alternatives such as theophylline, azathioprine, mTOR inhibitors can be used but have more toxicity.¹ Therapy should be continued indefinitely given potential for relapse with discontinuation.¹

In this case, while the patient was asymptomatic, the steady rise in hemoglobin was concerning with potential for long term risks. His normal erythropoietin suggested no secondary etiology and the lack of a JAK2 mutation also made a myeloproliferative disorder less likely. He had no other clinical evidence to suggest a secondary erythrocytosis. He was started on losartan 50 milligrams every day. His hemoglobin steadily decreased and plateaued around 15 g/dL in the subsequent months.

REFERENCES

1. **Vlahakos DV, Marathias KP, Agroyannis B, Madias NE.** Posttransplant erythrocytosis. *Kidney Int.* 2003 Apr;63(4):1187-94. Review. PubMed PMID: 12631334.
2. **Razeghi E, Kaboli A, Pezeshki ML, Meysamie AP, Khatami MR, Khashayar P.** Risk factors of erythrocytosis post renal transplantation. *Saudi J Kidney Dis Transpl.* 2008 Jul;19(4):559-63. PubMed PMID: 18580013.
3. **Gaston RS, Julian BA, Curtis JJ.** Posttransplant erythrocytosis: an enigma revisited. *Am J Kidney Dis.* 1994 Jul;24(1):1-11. Review. PubMed PMID: 8023814.