

## Post-renal transplant erythrocytosis; a case report and review of current concepts in pathogenesis and treatment

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### Abstract

Erythrocytosis post kidney transplant is known to have a prevalence of 2.5% to 22.2% among kidney recipients. The pathogenesis of this condition is multifactorial but not entirely clear. Over production of erythropoietin by retained native kidneys, renin angiotensin system activation among other factors have been implicated. Treatment modalities available include repeated phlebotomies, use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers and native kidney nephrectomy. We report the case of a 43 year old man who had kidney transplantation for end-stage renal disease secondary to chronic glomerulonephritis and developed erythrocytosis 26 months post-transplant. He became symptomatic at 32 months post-transplant and had elevated serum erythropoietin level. He was treated with repeated phlebotomy and ACE inhibitors with good results. Current concepts in the pathogenesis and treatment of post renal transplant erythrocytosis were reviewed also.

**Keywords:** Post-transplant, erythrocytosis, Angiotensin converting enzyme inhibitors, Phlebotomy, Erythropoietin,

### Introduction

Post renal transplant erythrocytosis (PTE) is defined as persistently elevated hemoglobin and hematocrit levels following renal transplantation which persist for more than six months in the absence of thrombocytosis, leukocytosis, or other potential cause of erythrocytosis.<sup>1</sup>

A haematocrit level greater than 51% in renal graft recipients have been generally used as a cut off value for definition of PTE.<sup>2</sup> Its prevalence varies from as low as 2.5% to as high as 22.2%. This wide variation in reported prevalence can be explained by different cut off values of haematocrit, (50% to 54%)<sup>3-5</sup> gender-specific cut-off values<sup>6,7</sup> used to define PTE, inclusion/exclusion of patients with transitory erythrocytosis in some studies<sup>2,8,9</sup> and variation in the nature and dose of immunosuppressive agents used.<sup>10</sup>

After renal transplantation and successful engraftment, PTE has been found to develop within a period of 8 to 24 months.<sup>2</sup> Predisposing factors include male gender, presence of native kidneys, smoking, transplant renal artery stenosis, type of immunosuppressant used (more frequently in cyclosporine-treated patients), rejection-free course with well-functioning renal graft and adequate erythropoiesis prior to transplantation.<sup>3</sup>

Although usually transient and benign, PTE can follow a protracted course and, in some instances, precipitate thrombo-embolic complications. We report this case to highlight this complication of renal transplantation. Current concepts in pathogenesis and treatment modalities will also be re-visited.

### Case report

Mr U.A, a 43 year old man, non-smoker, with end-stage renal disease secondary to chronic glomerulonephritis who received live-related kidney transplant in January 2013. Prior to this time he was regular on twice weekly maintenance hemodialysis for one year. The induction therapy was with anti-thymocyte globulin (thymoglobulin). His maintenance immunosuppressive regimen consisted of tapering doses of prednisolone till a dose of 10mg daily at 14<sup>th</sup> month, tacrolimus at 6.5mg (0.1 mg/kg/day) twice daily to maintain a trough level of between 5 and 20ng/ml after the third month, mycophenolate 1000mg twice daily and Pentodac 40mg twice daily.

He remained symptom free, in stable state of health and with normal blood pressure and renal function until 26 months post renal transplant when his haematocrit showed a steady increase (table 1) until he became symptomatic with headache and dizziness at exactly 32 months post renal transplant. There was no history of diarrhea, vomiting or polyuria, and he was not on any diuretic or hypertensive medication prior to this episode. Within this period, the blood pressure increased from average of 130/80mmHg to 156/90mmHg. His fasting blood sugar was within normal range. An abdominal ultrasound was done to exclude cystic kidneys, possible renal cell carcinoma and cystic liver disease. Doppler studies of renal vessels including that of the allograft was done and excluded renal artery stenosis. Liver function tests were normal and alpha fetoprotein level was within the normal limits. Viral serology was negative for hepatitis B and C. Serum erythropoietin (EPO) level was done by radio immune assay and the value was 39 mU/mL (normal value is 8 to 21 mU/mL). Phlebotomy was carried out on two occasions, each session one month apart with relief of symptoms of headache and dizziness. After the second session of phlebotomy, iron studies were conducted. Serum ferritin, serum iron and total iron binding capacity were all normal.

The patient was commenced on Tabs Lisinopril 5mg daily with minimal reduction in haematocrit to 48% after a month and to 39% at 2<sup>nd</sup> month of commencement of Lisinopril. Also the blood pressure normalized to an average of 130/86mmHg. He is currently symptom free and maintained on Tabs Lisinopril in addition to his maintenance immunosuppressive regimen.

**Table 1: Some haematological parameters and serum creatinine for the index patient**

Time post-transplant (months)	Haematocrit (%)	Mean cell volume (fL)	Reticulocyte count (%)	Serum creatinine (mg/dl)
6	36	72	2	1.2
9	38	72	2	1.1
17	37	79	2	1.4
22	39	82	1	1.2
26	52	79	4	1.3
32 <sup>+</sup>	54	75	5	1.3
34 <sup>+</sup>	53	61	4	1.2
36 <sup>\$</sup>	51	70	3	1.3
40	48	73	3	0.9
44	39	76	2	1.2

+: Phlebotomy performed, \$: angiotensin converting enzyme inhibitor commenced

### Discussion

Erythrocytosis can occur any time after a successful kidney engraftment. It has been reported to occur anytime from 1-90months post kidney transplant by several workers.<sup>3, 5, 12</sup> The index patient developed persistent erythrocytosis 32 months post-transplant which agrees with previous reports. Correction of anaemia post kidney transplant results from production of EPO by the transplanted kidney and removal of bone marrow suppression by uraemic toxins. EPO secretion by the kidney graft peaks within 3 days followed by reticulocytosis while correction of anaemia is expected by 3 months post successful transplant.

In a substantial subset of renal transplant patients such as the index patient, true polycythemia actually develops with increased red cell mass and enhanced reticulocytosis. Diagnosis of true polycythemia requires demonstration of increased red cell mass and EPO level with exclusion of secondary causes. The serum EPO level was elevated in the index patient and polycystic kidney disease, renal artery stenosis and liver disease were excluded as possible secondary causes. The finding of PTE and hypertension in our patient is not surprising as PTE generally carries an increased risk of hypertension, vascular accidents and thrombosis because of increased blood viscosity.<sup>13</sup>

### **Pathogenesis of post-renal transplant erythrocytosis**

Although the pathogenesis of PTE remains unclear, it is considered to result from an interplay of several factors. It also varies from patient to patient, so that, general conclusions may be difficult to draw. Considerable evidence points to the involvement of a minimum of three hormonal systems, namely erythropoietin, renin-angiotensin system (RAS) and endogenous androgens.<sup>2</sup>

#### ***Erythropoietin:***

In persons with normal kidney function, glomerular filtration rate (GFR) has an inverse relationship with haemoglobin concentration and serum EPO level. This relationship breaks down in chronic kidney disease where EPO levels are usually inappropriately in the normal range. In PTE, there is normal or excess erythropoietin secretion co-existing with erythrocytosis. Excess erythropoietin production have been shown to be from retained native kidneys.<sup>14</sup>

The native kidneys over secrete erythropoietin despite prevailing erythrocytosis which has been termed a form of "tertiary hypererythropoietinemia."<sup>2</sup> The following observations support this postulate. Dagher et al<sup>15</sup> demonstrated elevated serum

erythropoietin levels in six out of seven patients with PTE and venous blood sampling via selective catheterization of the native and transplanted kidney in three of the patients showed mean serum erythropoietin levels of 40.9 and 13.0 mu/mL, respectively. In the same study, one patient had bilateral native kidney nephrectomy which cured the erythrocytosis. Reduction in erythropoietin levels and correction of erythrocytosis following surgical removal of native kidneys has also been reported in other studies.<sup>3, 16, 17</sup>

Excess EPO can also arise from the transplanted kidney in the setting of cystic diseases (inherited or acquired), hydronephrosis or chronic ischemia. In addition, in vitro studies on erythroid progenitors from transplant recipients with PTE showed increased sensitivity to EPO compared to erythroid progenitors from transplant recipients without erythrocytosis.<sup>18</sup>

All treatment modalities of PTE (apart from phlebotomy) are generally accompanied by a reduction in plasma EPO levels and normalization of the erythropoietin/haematocrit relationship. The appearance of reticulocytosis and recurrence of PTE after discontinuation of pharmacotherapy are preceded and most likely mediated by EPO over-secretion.<sup>2, 19, 20</sup>

#### ***Renin-angiotensin system (RAS):***

Inhibition of the RAS either via ACE inhibition or blockade of angiotensin II receptors (specifically AT1 receptors), inhibits erythropoiesis in most patients with high-normal haematocrit, but not in their counterparts with normal haematocrit values.<sup>2</sup> As a result, it is believed that angiotensin II plays a role in the pathogenesis of PTE. Activation of angiotensin II receptors may enhance erythropoietin production in the graft or increase sensitivity of red cell precursors to erythropoietin.<sup>21</sup> Although not fully understood, It is postulated that angiotensin II plays this role by inappropriately sustaining secretion of EPO by directly stimulating the bone marrow or by

stimulating production of erythropoietic factors.

Previous findings of enalapril-associated anaemia in renal transplant patients<sup>20</sup> and successful treatment of PTE using Losartan<sup>22</sup> corroborate this postulate and, in the latter, indicate that interference with the action of angiotensin II rather than accumulation of bradykinin is mainly responsible for the haematocrit-lowering effect of RAS inhibition. There are other clinical conditions which demonstrate the direct relationship between RAS activation and increased red blood cell mass such that prolonged RAS inhibition in such patients lead to substantial decrease in red cell mass. These include hypertension (especially essential, malignant, or reno-vascular types), chronic obstructive pulmonary disease, congestive cardiac failure and in patients undergoing chronic haemodialysis.<sup>23-26</sup>

#### ***Androgens and other erythropoiesis stimulating factors:***

Some other factors, not related to EPO, appear to be responsible in some cases of PTE. This is probable since plasma EPO levels can be normal or even appropriately suppressed in some patients with PTE. Androgens have a direct and an indirect action on erythropoiesis. Directly, it exerts a dose-dependent stimulation of erythroid progenitors already differentiated by erythropoietin,<sup>27</sup> an effect that can be inhibited by androgen antagonists<sup>28</sup>. Indirectly, androgens promote erythropoiesis by stimulation of endogenous erythropoietin or by activation of RAS. These actions on erythropoiesis have enabled its use in the treatment of renal anaemia.<sup>29</sup>

In vitro studies have shown that insulin-like growth factor 1 (IGF-1) enhances erythropoietin-stimulated erythroid proliferation.<sup>30, 31</sup> Other studies have shown that plasma IGF-1 levels positively correlate with haematocrit levels in uraemic subjects and renal transplant recipients. In renal transplant recipients, higher IGF-1 levels were found in

patients with PTE compared with those who have normal haematocrit.<sup>32,33</sup>

The oligopeptide N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) is a normal inhibitor of entry of pluripotent stem cells into the S phase, thereby diminishing erythropoiesis.<sup>34</sup> Ac-SDKP is metabolized by angiotensin converting enzyme; it may accumulate therefore, in the presence of an ACE inhibitor with the potential of diminishing erythropoiesis.<sup>35</sup>

#### **Treatment of post-transplant erythrocytosis**

The target in treatment of PTE is to achieve a hemoglobin level less than 17.5g/dL. Modalities of treatment include pharmacotherapy, phlebotomy and bilateral native kidney nephrectomy. Pharmacotherapeutic agents target specific pathways in the pathogenesis of PTE as elucidated above. These include RAS inhibitors (ACE inhibitors, angiotensin II receptor antagonist) and theophylline.

#### ***RAS inhibition:***

Hiremath et al in their systematic review showed that the use of ACE inhibitors and ARBs in patients with PTE, effectively decreased hemoglobin levels.<sup>36</sup> A good number of studies have shown that relatively modest doses of captopril, enalapril, fosinopril, lisinopril, perindopril and ramipril are capable of reducing the haemoglobin in PTE.<sup>1, 2, 37, 38</sup> Similarly, Midtvedt et al<sup>22</sup> and Yildiz et al<sup>37</sup> demonstrated the efficacy of losartan, an ARB, in the treatment of PTE. The principle behind the action of RAS inhibitors can be adduced from the role of RAS activation in the pathogenesis of PTE as earlier stated. When these drugs are administered, there is a dose-dependent decrease in the haematocrit which starts within two to six weeks of therapy initiation and is complete in three to six months.<sup>1, 38</sup> After discontinuation of treatment, the haematocrit values rise gradually within a three month period to pretreatment levels.<sup>6, 8</sup> Both ACE inhibitors and ARBs can act through both EPO-dependent and EPO-independent pathways. In

our index patient, administration of lisinopril resulted in a reduction in haematocrit by 23% within a two-month period (table 1).

### **Theophylline**

Theophylline, a non-selective adenosine receptor blocker is an alternative drug to RAS inhibitors for the treatment of PTE. Adenosine through its renal A2 receptors stimulate EPO secretion. In a prospective drug trial of eight patients with PTE and five control subjects, Bakris et al showed that an eight week course of theophylline reduced the hematocrit from a pre-treatment level of 58% to 46% in those with PTE, and from 43 to 39% in the control group.<sup>39</sup> It has a narrow therapeutic window and is not as effective as ACE inhibitors.<sup>40, 41</sup> Hence its use is less favoured than the RAS inhibitors.

### **Ketanserin:**

Ketanserin is an antagonist of peripheral serotonin 5-HT receptors. It lowers plasma EPO level in some patients on chronic haemodialysis. Based on this finding, Borawski et al conducted a preliminary study to ascertain the effect of 3-week oral ketanserin administration on serum EPO concentration and relevant haematological parameters in four renal transplant patients with PTE.<sup>42</sup> The results showed a marked decrease in serum EPO levels from 48% to 76% following ketanserin administration. In three of the patients, there was a corresponding decrease or no rise in the erythrocyte count. Within the period of the study (6 weeks), the need for monthly phlebotomies was eliminated. Its use in treatment of PTE has not been generally accepted as a treatment modality.

### **Bilateral native kidney nephrectomy:**

The native kidneys in transplant recipients sometimes over produce EPO leading to PTE. This was demonstrated by Friman et al<sup>43</sup> who performed bilateral native kidney nephrectomy on 22 patients with PTE in which 20 of the patients had normalized haematocrit level after follow up for 36 months.

### **Phlebotomy:**

In patients with red cell mass expansion without a treatable secondary cause, phlebotomy remains an effective modality to lower the hematocrit but requires frequent monitoring, invasive needle punctures and the risk of iron deficiency anemia. The index patient in this report had two sessions of phlebotomy, hence may not have had considerable number of sessions to have developed iron deficiency. Development of iron deficiency following phlebotomy had been reported by Perazella and Bia in a 51-year old diabetic man who developed PTE and had frequent phlebotomies.<sup>44</sup>

In conclusion, erythrocytosis could occur in kidney transplant recipients and should be investigated to rule out causes not related to kidney transplant. Treatment is necessary to avoid thrombo-embolic complications. Useful therapeutic options include phlebotomy, use of RAS inhibitor drugs and bilateral native kidney nephrectomy.

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