CASE REPORT

Post-transplant erythrocytosis refractory to ACE inhibitors and angiotensin receptor blockers

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SUMMARY

Post-transplant erythrocytosis (PTE) is a condition with elevated haematocrit (hct) in renal allograft recipients. The mainstay of treatment is ACE inhibitors (ACEi) or angiotensin II receptor blockers (ARB), but seldom phlebotomy. PTE must be recognised early to prevent major thromboembolic events. We present a case of PTE that was refractory to blockade of renin–angiotensin system (RAS) by ACEi and ARB and required phlebotomy for control of hct. Our review of medical literature about prevalence and pathophysiology of PTE suggests that approximately 22% of patients with PTE are refractory to ACEi/ARB treatment. There are four plausible pathways that appear to play a role in causing PTE: disruption of erythropoietin regulation, mitogenic effect of the RAS on erythroid lineage, insulin-like growth factor 1 and androgenic stimulation. Presently, there is no unifying hypothesis involving these factors, but refractoriness to ACEi/ARB may represent a distinct subcategory of PTE.

BACKGROUND

Post-transplant erythrocytosis (PTE) is a well-described condition occurring in kidney transplant recipients.¹ It was first described in 1965 by Nies *et al* in a case report of a 22-year-old woman who had undergone kidney transplant with bilateral native kidney nephrectomy and splenectomy.² The prevalence of PTE is highly variable: it ranges from 2.5% to 22.5%.^{1,3} This variation can be explained by the different definitions used to diagnose this condition including different levels of haematocrit (hct), gender variations of hct and length of time of persistence of disease.³ There are no clearly defined criteria for diagnosis of PTE; however, the consensus seem to favour a hct level $\geq 53\%$ in men and $\geq 51\%$ in women that persists over a period of 3 to 6 months in a patient who has undergone a kidney transplantation.⁴ This rise in hct level must be independent of other pathological conditions.⁴ PTE occurs most often in male patients with excellent allograft function and in diabetics.^{4,5} Spontaneous resolution is uncommon and occurs in less than 25% of patients, and hence it is necessary to recognise this condition and begin prompt management.⁴ Post-kidney transplant patients will usually develop PTE in the first 2 years after transplant with a median of 13 months.^{3,6} They may have an asymptomatic increase in hct level, but when it is higher than 60%, patients present with malaise, dizziness, headache, plethora and lethargy.^{3,7} It is essential to rule out any other plausible cause of primary

or secondary erythrocytosis. Causes such as polycythaemia vera (PCV), hypoxia, liver disease, renal artery stenosis and cystic kidney disease should be excluded.⁸ Genetic mutations in the erythropoietin receptor (EPO-R), VHL gene, PHD2, HIF-2 α and bisphosphoglycerate mutase deficiency should be investigated.⁸ Secondary malignancies such as cerebellar haemangioblastoma, meningioma, parathyroid carcinoma/adenoma, hepatocellular carcinoma, renal cell carcinoma, pheochromocytoma and uterine leiomyomas must be excluded as well.⁸ EPO level tends to be inappropriately high and may not be helpful in the diagnosis of PTE; nevertheless, it does help to rule out primary PCV and an EPO-producing tumour.^{9,10} It is necessary to manage PTE early since it represents an increase in morbidity and mortality due to thromboembolic events and cardiovascular disease.¹¹ About 10%–30% of patients can have thromboembolic complications, which can involve digital or branchial arteries, thrombophlebitis, stroke, deep vein thrombosis or pulmonary embolus, with a 1%–2% mortality rate.⁶ The mainstay of treatment includes ACE inhibitors (ACEi), angiotensin II receptor blockers (ARB) and in case of refractory disease, phlebotomy with a goal of maintaining hct below 45% to reduce the risk of thromboembolic complications.^{7,12} Treatment with ACEi and ARB tends to be very efficacious and is usually sufficient in the majority of cases; nonetheless, several patients with PTE are refractory to ACEi and ARB, and will only respond to phlebotomy.¹³ Since the pathophysiology of this disease still remains to be elucidated, the mechanism of ACEi/ARB refractoriness is not known. In this article, we present a case report of PTE refractory to ACEi and ARB therapy, and also perform a review of the medical literature published during the years 1991 to 2016 to determine the proportion of patients with PTE who are refractory to ACEi/ARB. Furthermore, we also explored the pathophysiological mechanisms for PTE and features that distinguish ACEi/ARB responders and non-responders. Perhaps, an earlier distinction between these two groups may help institution of appropriate therapy and avoid the use of ineffective treatments.

CASE PRESENTATION

A 59-year-old man was evaluated in our institution's transplant nephrology clinic in July 2013 for a history of diabetes-related end-stage renal disease and was on haemodialysis for about 2 years. He subsequently underwent a simultaneous pancreas

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and kidney transplant in November 2014. Prior to the transplant, he had anaemia related to chronic kidney disease with a haemoglobin (hgb) level of 11.3 g/dL that did not require treatment. Other pre-transplant antihypertensive medications included amlodipine 10 mg once a day, clonidine 0.1 mg four times a day, hydralazine 25 mg three times a day and losartan 50 mg once a day. Immunosuppressive therapy included alemtuzumab induction and maintenance treatment with tacrolimus, mycophenolate mofetil and prednisone. He had an uncomplicated postoperative course with a good establishment of pancreas and kidney allograft function; estimated glomerular filtration rate was 56.5 mL/min, amylase level of 46 U/L and lipase level of 20 U/L at 1 month post-transplant.

About 18 months post-transplant, he was noted to have a hgb level of 19.2 g/dL with a hct of 59%, and hence was referred to haematology clinic for further evaluation of erythrocytosis. He was asymptomatic and denied any headache, dizziness, vertigo, tinnitus, pruritus, visual disturbances, angina or intermittent claudication. His physical examination was unremarkable without any plethora or hepatosplenomegaly.

INVESTIGATIONS

Several tests were undertaken for evaluation of polycythaemia: serum EPO was normal (7.8 mIU/mL; range 2.6–18.5 mIU/mL), and urine catecholamines, dopamine, epinephrine and norepinephrine levels were normal. CT of abdomen and pelvis did not show any vascular tumours, or cystic lesions in the liver or kidney. MRI of the brain did not show any evidence of intracranial anomalies. Molecular tests for myeloproliferative disorders (JAK2V617F mutation, CALR exon 9, MPL exon 10, BCR-ABL) and familial erythrocytosis (EPOR, HIF2a, PHD2, BPGM, VHL) did not demonstrate any pathogenic mutations.

DIFFERENTIAL DIAGNOSIS

We also evaluated the patient for other possible secondary causes of erythrocytosis such as chronic obstructive pulmonary disease, sleep apnoea, renal artery stenosis, cystic kidney or liver disease, and kidney, liver and intracranial malignancies and anomalies. Furthermore, the patient did not have any history of using anabolic steroids or exogenous erythropoietin that could be a pharmacological cause for his erythrocytosis.

TREATMENT

The dose of losartan was increased to 100 mg daily, and low-dose aspirin (81 mg once a day) was started for thromboprophylaxis.

OUTCOME AND FOLLOW-UP

The erythrocytosis did not respond despite therapy with an ARB at a maximal dose for 4 weeks, and hence required weekly phlebotomy (with removal of 500 mL of blood each session) until the hct normalised (~45%) after four sessions, and since then, he has maintained a hct of <45% with phlebotomies as needed once every 1 to 2 months.

DISCUSSION

Review of literature

Three online databases (PubMed, Web of Science and Google Scholar) were searched for published medical literature about PTE using the following keywords: 'erythrocytosis' AND 'post-transplant' OR 'polycythemia' OR 'Post-renal transplant' NOT 'vera'. Full original articles published in the English language between January 1991 and December 2016 were included. On the initial search, a total of 1927 articles were found, but further

review yielded 66 articles that were relevant to our topic of study. These 66 articles were screened by abstract and methodology taking into account the studies that described at least one patient with PTE, treated with ACEi or ARB and was followed until remission or for at least 6 months. Size of patient cohort or study design restrictions was not applied. From each article, we extracted data about the nature of the study, study population, hct and EPO levels, treatment strategy and outcomes. Our main interest was to define the proportion of cases in these studies that were ACEi/ARB refractory and also explore a plausible mechanism to the refractoriness to renin-angiotensin system (RAS) blockade.

Discussion

We present a case of ACEi/ARB refractory PTE. The patient received RAS blockade therapy for hypertension in his pre-transplant course. He developed PTE while on ACEi therapy; he was switched to an ARB, and despite increasing to the maximum dosage, he did not achieve adequate response and required several phlebotomy sessions to reach the target hct levels. There is very limited information in the medical literature about ACEi/ARB-refractory PTE cases. By review of medical literature, we procured 20 studies, of which 6 were either case reports or case series, 3 were retrospective cohort studies and 11 were prospective trials. The characteristics of each study and study population are as described in [table 1](#). The majority of these studies had a patient follow-up length of at least 6 months. Although refractoriness was not the focus of any of these articles, most of them presented with the proportion of patients with PTE who had not responded adequately to ACEi/ARB, some of which required phlebotomy. Based on the appraisal of these studies, it appears that about 22% of patients with PTE are indeed refractory to ACEi/ARB.

The mechanisms for refractoriness remain unknown. Perhaps, it is related to underlying pathophysiological mechanism and pre-transplant management of hypertension and anaemia, and also associated with the widespread use of ACEi/ARB in the pre-transplant and post-transplant period.³ In order to determine a plausible mechanism of resistance, we performed a complete review of all pathogenic mechanisms of PTE explored to date. From the current understanding, PTE appears to result from the combined trophic effect of multiple and mutually dependent erythropoietic factors such as EPO, angiotensin II, androgens and insulin-like growth factor 1 (IGF-1) ([figure 1](#)). Although erythropoiesis is a very well-studied pathway in vitro and in vivo, many specific steps still remain unknown. Several studies have confirmed that EPO levels are increased in patients with PTE and that there may be a disorderly production of EPO and a disruption of normal EPO homeostasis.^{14 15} Nonetheless there is also evidence that some of the patients with PTE have similar or, in some cases, even lower EPO levels when compared with control patients.^{16 17} This raises the question of whether there are other EPO-independent mechanisms involved in the PTE pathogenesis. Due to the finding that ACEi could cause anaemia in hypertensive patients, studies have focused on the effects of the RAS on erythroid development.¹⁸ Renin has been closely associated with changes in the levels of EPO.¹⁹ Nonetheless, Mrug *et al* in 1997 determined that angiotensin II (AngII) increased proliferation of BFU-E in vitro, an effect that could be blocked by the addition of losartan.²⁰ Also, in vitro studies by Naito *et al* indicated that patients with PTE developed higher numbers of BFU-E cells compared with patients with no PTE and that there was an increased number of angiotensin receptor

Table 1 Patients with PTE who are refractory to ACE inhibitors/ARB: literature review

Author	Year	Study type	Sample size	Refractory patients	Mean hct (%) or mean hgb level (mg/dL)	Mean EPO (mIU/L) at diagnosis	Treatment strategy
Brouhard <i>et al</i>	1992	Case report	1	0	19.1±0.6	Not specified	Enalapril 5 mg
Rell <i>et al</i>	1994	Prospective	17	3	51.1	12.2	Enalapril 2.5–20 mg/day
Torregosa <i>et al</i>	1994	Prospective	19	0	56.2±1.9	13.5±9.48	Captopril 25 mg/day
Mulhern <i>et al</i>	1995	Prospective trial	8	1	53.7±0.6	22.8±8.4	Different ACE inhibitors
Perazella <i>et al</i>	1995	Prospective trial	10	0	52±2	20±11	Enalapril 2.5–5 mg/day
Rostaing <i>et al</i>	1995	Prospective trial	12	2	51.14±2	17.41±13.5	Enalapril 5–20 mg/day
Midtveddt <i>et al</i>	1996	Case report	1	0	52	<12	Lisinopril 2.5 mg/day
MacGregor <i>et al</i>	1996	Prospective	52	3	16.7±0.8	Not specified	Lisinopril or enalapril 2.5–5 mg/day
Ducloux <i>et al</i>	1997	Case series	3	0	49	15.6	Losartan 100 mg/day
Ducloux <i>et al</i>	1998	Case series	4	0	52±0.01	17±3.7	Losartan 100 mg/day
Tsang <i>et al</i>	1998	Prospective trial	11	0	52.5±1.5	Not specified	Losartan 12.5–25 mg/day
Iñigo <i>et al</i>	1999	Prospective trial	20	0	54.6±3.5	Not specified	Losartan 50 mg/day
Javid <i>et al</i>	1999	Case series	20	2	Not specified	Not specified	Enalapril 15 mg/day
Colak <i>et al</i>	2001	Case series	23	3	41%	Not specified	Losartan 50 mg/day
Singh <i>et al</i>	2002	Prospective trial	11	1	57.7±5.4	Not specified	Losartan 25 mg/day
Wang <i>et al</i>	2002	Prospective trial	8	2	52.1±1.1	10.49±7.64	Losartan 50 mg/day and enalapril 5 mg/day
Jimeno <i>et al</i>	2005	Prospective trial	21	0	Not specified	Not specified	Enalapril 2.5–5 mg/day
Basri <i>et al</i>	2007	Retrospective cohort	29	0	Not specified	Not specified	Different ACE inhibitors
Kiberd	2009	Retrospective cohort	59	37	18.1±9	Not specified	Different ACE inhibitors and ARB
Ahmed <i>et al</i>	2012	Retrospective cohort	40	28	54.78±1.96	Not specified	Different ACE inhibitors
Moreno <i>et al</i> (this article)	2017	Case report	1	1	59.35	8.1	Enalapril and losartan
Total			370	83			

ARB, angiotensin II receptor blocker; EPO, erythropoietin; hct, haematocrit; hgb, haemoglobin; PTE, post-transplant erythrocytosis.

I (AT1R) in BFU-E of patients with PTE compared with patients with no PTE.²¹ The correlation between the RAS and erythropoiesis is even further consolidated with the finding that activation of the AT1R by AngII can activate Jak2/Stat, IRS2 and p70 S6 kinase pathways, a pathway common to activation of EPO-R raising the question of whether the cross-talk between these two pathways on erythroid progenitor cells may have a functional role in erythropoiesis and PTE.²²

Although EPO and AngII each seem to play a vital role in PTE pathogenesis, resistance to ACEi and ARB suggests that there are alternative factors involved in the pathogenesis of this disease. Previous studies in PCV had demonstrated the importance of IGF-1 in the regulation of erythropoiesis in vitro and there is evidence demonstrating that it is a main stimulator of erythropoiesis in patients with anaemia and renal failure.^{23–24} Patients with PTE have increased levels of IGF-1 compared with control patients both under ACEi therapy and after ACEi discontinuation.²⁵ IGF-1 stimulation of erythropoiesis is most probably an EPO-independent mechanism, but there is evidence to suggest that it may be associated in some way with the RAS pathway.²⁵ During ACEi treatment, there was decrease in IGF-1 levels in patients with PTE compared with controls, which suggests a common pathway between ACEi and IGF-1.²⁶ Moreover, IGF-1 may be a key player in pathophysiology of ACEi/ARB refractoriness. Other factors, such as hormones, have been known to affect hb and hct levels. Androgens have long been successfully used for the treatment of anaemia.³ The association between androgens and erythropoiesis has been thoroughly studied finding that androgens exert a dose-dependent stimulation of erythroid progenitors, an effect that can be blunted by androgen

antagonists.²⁷ Testosterone and its metabolites such as 5- α -androstanes increase EPO production in vivo while other metabolites will enhance colony-forming units erythroid in vitro in the presence of EPO.^{28–29} Nonetheless, a study by Chan *et al* in 1992, which examined the androgenic and sexual hormone profile of patients with PTE, did not find any significant differences between the levels of testosterone.²⁸ Although there is no clear correlation between PTE and androgen levels, the importance of testosterone in erythropoiesis is clear and thus cannot be ruled out as a player in the pathogenesis of PTE. Other factors such as stem cell factor, N-acetyl-seryl-aspartyl-lysyl-proline, hypercalcaemia and ACE polymorphisms have also been associated with the pathogenesis of PTE, but further studies are necessary to completely elucidate the molecular pathways involved.^{3–30}

Standard pharmacological treatment of PTE includes ACEi and/or ARB starting with a low dose that can be adjusted every few months depending on the progression of the hct.^{31–32} ACE inhibition is usually well tolerated by patients. Other treatments such as theophylline, although effective, cause many side effects such as headache, nervousness, insomnia and gastrointestinal discomfort.^{33–35} A recent randomised cross-over trial comparing fosinopril and theophylline demonstrated that fosinopril was superior to theophylline in terms of controlling hct.³⁴ Patients in the fosinopril arm had better tolerance to the medication and experienced greater and sustained hct control.³⁴ Another therapeutic option that has been explored is ketanserin, a 5HT₂ receptor antagonist.³⁶ Although it seems to be effective in controlling hct, there is only one report in the literature about the value of its use in patients with PTE.³⁶ Based on these pathophysiological mechanisms, it appears that those patients who

Figure 1 Mechanistic pathways with causal roles in post-transplant erythrocytosis (PTE), present therapies and pharmacological targets EPO, RAS, IGF-1 and androgens are the main pathways involved in the pathogenesis of PTE. Other factors such as SCF, Ac-SDKP and ACE polymorphisms might also play a role in PTE, but further molecular evidence is lacking. ACEi and ARB are the mainstay therapy for PTE, which blocks the RAS, but may also have an effect on EPO and IGF-1 pathways, and BFU-E/CFU-E erythroid progenitor cells. ACEi, ACE inhibitor; Ac-SDKP, *N*-acetyl-seryl-aspartyl-lysyl-proline; ARB, angiotensin II receptor blocker; AT1R, angiotensin II receptor type 1; BFU-E, burst-forming unit erythroid; CFU-E, colony-forming unit erythroid; EPO, erythropoietin; IGF-1, insulin-like growth factor 1; IGF1R, insulin-like growth factor 1 receptor; RAS, renin-angiotensin system; SCF, stem cell factor.

are refractory to ACEi/ARB have a distinct entity of PTE, which has been described in several case series and prospective trials (table 1). A subgroup of patients with PTE fail to respond to ACEi, and they are equally unresponsive to ARB.³ Our literature review suggests that the prevalence of ACEi/ARB PTE refractoriness is about 22%. Considering the possible pathways of disease described previously, we hypothesise that use of ACEi and/or ARB administered before transplant may also influence the responsiveness of PTE to ACEi/ARB therapy. Since patients with advanced-stage kidney disease have low to no renal synthesis of EPO, other pathways such as the RAS through AngII and/or IGF-1 may be up-regulated to support erythropoiesis. Once the new kidney has been engrafted and the levels of EPO normalise,

the BFU-E and CFU-E initiate proliferation with EPO from the allograft and native kidneys and simultaneously receive stimulation in a parallel fashion from the up-regulated AT1R and/or IGF-1 pathways. Treatment with ACEi or ARB pre-transplant may blunt the response through the RAS pathway. Once they develop PTE, the mechanism will be AngII/AT1R independent rendering the treatment with ACEi and ARB unsuccessful.

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Learning points

- Post-transplant erythrocytosis (PTE) is a complication of kidney transplantation with heterogeneous pathogenic mechanisms, usually occurring in a subset of transplant recipients within the first 8 to 24 months after surgery.
- The role of importance of erythropoietin, renin-angiotensin system, insulin-like growth factor 1 and androgen pathways has been investigated, but there are still several questions that remain unanswered.
- Use of ACE inhibitors (ACEi)/angiotensin II receptor blockers (ARB) during the pre-transplant clinical course may predict for the primarily refractoriness of PTE to ACEi or ARB treatment.
- Early recognition of this entity and timely initiation of therapy would prevent long-term impact and thromboembolic complications.

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