

Brief Communication

Angiogenic Activity in the Sera of Patients with Post-Kidney Transplant Erythrocytosis

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ABSTRACT. Post-kidney transplant erythrocytosis (PTE) is one of the hematological complications in the renal transplant patients. While its pathogenesis still remains to be elucidated completely, a number of therapies are available for the management of PTE. The aim of this prospective study was to investigate whether angiogenesis may be involved in the pathogenesis of post-transplant erythrocytosis by comparing its level with those of different classes of erythrocytosis [polycythemia vera (PV), idiopathic erythrocytosis and secondary erythrocytosis]. The angiogenic activity was evaluated by the assessment of the serum vascular endothelial growth factor (VEGF) levels, as one of circulating angiogenic factor, using a standardized enzyme-linked immunosorbent assay commercial kit in 13 PTE (2 F/11 M), in 75 untreated erythrocytosis non-transplant patients and in 21 healthy subjects controls. The results indicated that VEGF was overproduced in advanced and untreated PV patients and to a lesser degree in idiopathic erythrocytosis thus confirming an increased angiogenic activity. However, there is no evidence of increased angiogenesis in PTE and in secondary erythrocytosis. The absence of angiogenesis in PTE and its presence in PV is another argument that the pathogenesis of these two entities is different.

Introduction

Post-kidney transplant erythrocytosis (PTE) is one of the hematological complications in kidney transplant patients, and it is characterized

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by persistent hematocrit levels above 51% after kidney transplantation.¹ This complication is reported to develop in 10–20% of the kidney recipients within eight to 24 months after successful transplantation.^{2–6} While the pathogenesis of PTE still remains to be elucidated completely, a number of therapies are available for its management.

The aim of this prospective study was to investigate whether angiogenesis was involved in the pathogenesis of PTE by comparing its

level with those of the different classes of erythrocytosis [polycythemia vera (PV), idiopathic erythrocytosis and secondary erythrocytosis].

Patients and Methods

All patients of our study underwent red cell mass and plasma volume measurement with a standardized radionuclide method (^{51}Cr -labeled erythrocytes, ^{125}I -labeled human serum albumin) to confirm or exclude absolute erythrocytosis. True PTE was defined as an RBC mass $>125\%$ of the theoretical values allowed for sex, weight and height with no evidence of PV or secondary polycythemia due to reduced arterial oxygen or kidney and hepatic tumors.

The study patients were divided into three groups. The first group included 13 PTE patients (2 F/11 M, mean age 39.4 ± 11.6 years). The second group comprised 75 absolute erythrocytosis non-transplant patients divided by a standardized series of investigations [complete blood count, bone marrow tests, serum erythropoietin level, measurement of arterial oxygen saturation (SaO) abdominal ultrasound and JAK2 mutation assays] into a primary erythrocytosis (PV) (23 M–22 F; mean age 59.3 ± 13.7 years), secondary erythrocytosis (14 M; mean age 53.2 ± 13.0 years) and idiopathic pure erythrocytosis (16 M; mean age $41.1 \pm$

15.1 years), which was a heterogeneous subgroup where the cause could not be established. Finally, the third group comprised 21 healthy control individuals (normal RCM) (21 M; mean age 45.5 ± 14.7 years).

The angiogenic activity was evaluated by the assessment of the serum levels of vascular endothelial growth factor (VEGF), a circulating angiogenic factor. An enzyme-linked immuno-sorbent assay (ELISA) using a standardized commercial kit (Quantikine; R&D Systems, Minneapolis, MN, USA) was used to measure the VEGF levels.

Results

The average serum level of VEGF was 278 ± 121 pg/mL in the control group, demonstrating a progressive rise to 634 ± 271 pg/mL in the idiopathic erythrocytosis patients and 2233 ± 1861 pg/mL in the PV patients, while it was not increased in the secondary erythrocytosis patients (350 ± 174 pg/mL) and in the PTE patients (378 ± 181 pg/mL) compared with that in the control group (Figure 1).

Discussion

Our results indicated that serum VEGF was overproduced in advanced and untreated PV patients and, to a lesser degree, in idiopathic

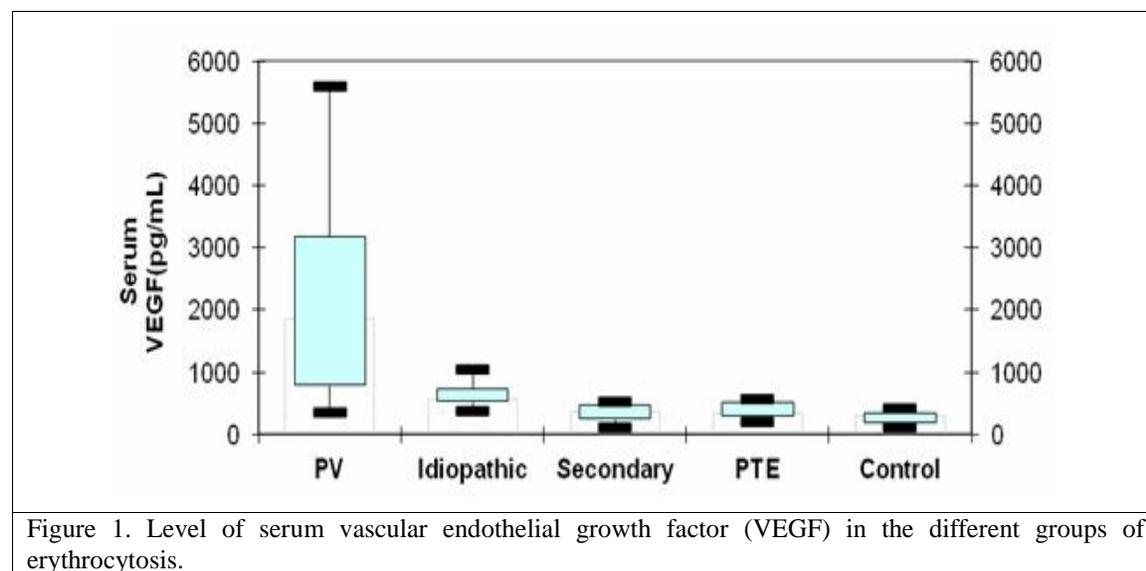


Figure 1. Level of serum vascular endothelial growth factor (VEGF) in the different groups of erythrocytosis.

PTE: Post-transplant erythrocytosis, PV: Polycythemia vera.

erythrocytosis thus confirming an increased angiogenic activity. However, there was no evidence of increased angiogenesis in PTE and in secondary erythrocytosis.

In our study, we studied only true erythrocytosis cases by measuring the RBC mass. PTE remains an enigmatic syndrome unique to renal transplant recipients. Predisposing factors include male gender,⁷ retention of native kidneys, cyclosporine use⁴ and a rejection-free course with a well-functioning renal graft.^{2,7,8} Its etiology is incompletely understood, and the most frequently suggested causative factors are still a matter of controversy. It was suggested that PTE results from the combined trophic effect of multiple and interrelated erythropoietic factors, inappropriately excessive production of erythropoietin either by the native or transplanted kidneys, enhanced sensitivity of erythroid stem cells to erythropoietin or altered regulation of the hematocrit-EPO feedback system. Increased production of erythropoietin may be caused by ischemia in the renal artery and/or use of cyclosporine. However, erythropoietin levels in most PTE patients are within the normal range. Erythrocytosis may ensue the contributory action of additional growth factors on erythroid progenitors, such as angiotensin II,⁹ androgens⁷ and insulin-like growth factor 1 (IGF-1).¹⁰⁻¹⁵ The role of the oligopeptide *N*-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP), a natural inhibitor of the pluripotent stem cell in the hematocrit-lowering effect of angiotensin-converting enzyme inhibition, in the development of PTE is still controversial.¹ Increased serum-soluble stem cell factor (sSCF) levels seem to have a role in the pathogenesis of PTE.¹⁶

The evaluation of angiogenesis may add some important pathophysiological and prognostic information of some diseases and may, with clinical-therapeutic implication, that anti-angiogenic agent may be a useful therapy of angiogenesis-dependent diseases. Several studies have shown that angiogenesis is an event in myeloproliferative diseases and reported a significant elevation in the serum levels of the VEGF, which is the fundamental regulator of differentiation of the hemangioblast (common

precursor for endothelial and hematopoietic cells) in PV. We have confirmed and discussed this in a previous study.¹⁷

In the present study, despite the fact that the number of transplanted patients examined was small, we have demonstrated that this VEGF does not play an angiogenic role in PTE. The absence of angiogenesis in PTE and its presence in PV is another argument that the pathogenesis of these two entities is different.

Conflict of interest: None

References

1. Vlahakos DV, Marathias KP, Agroyannis B, Madias NE. Posttransplant erythrocytosis. *Kidney Int* 2003;63:1187-94.
2. Wickre CG, Norman DJ, Bennison A, Barry JM, Bennett WM. Postrenal transplant erythrocytosis: A review of 53 patients. *Kidney Int* 1983;23:731-7.
3. Morrone LF, Di Paolo S, Logoluso F, et al. Interference of angiotensin-converting enzyme inhibitors on erythropoiesis in kidney transplant recipients: Role of growth factors and cytokines. *Transplantation* 1997;64:913-8.
4. Perazella, M, McPhedran, P, Kliger, A, Lorber M, Levy E, Bia MJ. Enalapril treatment of posttransplant erythrocytosis: Efficacy independent of circulating erythropoietin levels. *Am J Kidney Dis* 1995;26:495-500.
5. Koziak K, Rell K, Lao M, Baczkowska T, Gaciong Z. Does erythropoietin production after renal transplantation depend on the type of immunosuppression? *Nephron* 1995;71:236-7.
6. Gaston RS, Julian BA, Curtis JJ. Posttransplant erythrocytosis: An enigma revisited. *Am J Kidney Dis* 1994;24:1-11.
7. Kessler M, Hestin D, Mayeux D, Mertes PM, Renoult E. Factors predisposing to post-renal transplant erythrocytosis. A prospective matched-pair control study. *Clin Nephrol* 1996;45:83-9.
8. Dagher FJ, Ramos E, Erslev A, Karmi S, Alongi SV. Erythrocytosis after renal allotransplantation: Treatment by removal of the native kidneys. *South Med J* 1980;73:940-2.
9. Gupta M, Miller BA, Ahsan N, Ulsh PJ, Zhang MY, Cheung JY. Expression of angiotensin II type I receptor on erythroid progenitors of patients with posttransplant erythrocytosis.

- Transplantation 2000;70:1188-94.
10. Gaston RS, Julian BA, Barker CV, Diethelm AG, Curtis JJ. Enalapril: Safe and effective therapy for posttransplant erythrocytosis. *Transplant Proc* 1993;25:1029-31.
 11. Azizi M, Rousseau A, Ezan E, et al. Acute angiotensin-converting enzyme inhibition increases the plasma level of the natural stem cell regulator N-acetyl-seryl-aspartyl-lysyl-proline. *J Clin Invest* 1996;97:839-44.
 12. Correa PN, Axelrad AA. Production of erythropoietin bursts by progenitor cells from adult human peripheral blood in an improved serum free medium: Role of insulin-like growth factor 1. *Blood* 1991;78:2823-33.
 13. Sanders M, Sorba S, Dainiak N. Insulin-like growth factors stimulate erythropoiesis in serum-substituted umbilical cord blood cultures. *Exp Hematol* 1993;21:25-30.
 14. Congote LF, Brox A, Lin FK, Lu HS, Fauser AA. The N-terminal sequence of the major erythropoietic factor of an anephric patient is identical to insulin-like growth factor 1. *J Clin Endocrinol Metab* 1991;72:727-9.
 15. Urena P, Bonnardeaux A, Eckardt KU, Kurtz A, Drüeke TB. Insulin-like growth factor I: A modulator of erythropoiesis in uraemic patients? *Nephrol Dial Transplant* 1992;7:40-4.
 16. Kiykim AA, Genctoy G, Horoz M, et al. Serum stem cell factor level in renal transplant recipients with posttransplant erythrocytosis. *Artif Organs* 2009;33:1086-90.
 17. Maktouf C, Bounemra A, Mahjoub S, et al. Evaluation of serum VEGF levels in untreated erythrocytosis patients. *Pathol Biol (Paris)* 2011;59:240-2.

