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Original Article

Anemia after kidney transplantation

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Abstract

Background: Anemia is a major cardiovascular risk factor in renal disease. It might be appropriate to extrapolate this association of anemia with cardiovascular disease to renal transplant recipients who continue to have a significant cardiovascular risk.
The aim of our study was to elucidate the prevalence and risk factors of anemia after kidney transplantation.
Methods: We studied 118 stable adult kidney transplant recipients [age at transplant ranged between 22 and 58, 42 ± 12], 74 (62.7%) were males and 44 were females (37.3%) who received allograft between December 1998 and October 2008 and had at least 1 year of post-transplant follow up data at Sugar Medical Center, Theodor Bilharz Research Institute (TBRI), and Health Insurance Organization Cairo. Hemoglobin (Hb) level at 6 months, and 1 year after renal transplantation was recorded, the eGFR was calculated using the MDRD formula. Risk factors for anemia were evaluated using univariate and multivariate regression analysis.
Results: Anemia (Hb <12 g/dl in females and <13 g/dl in males) was common (28.8% at 6 months, 31.4% at 1 year). Significant anemia (Hb <11 g/dl in females and <12 g/dl in males) was also common (15.3% at 6 months, 16.8% at 1 year). Severe anemia (Hb <10 g/dl in both genders) at 6 months post-transplant was less common affecting 4 out of 118 (3.4%) patients. At 1 year, 8 out of 118 (6.8%) had 'severe' anemia. Univariate and multivariate analysis showed that a higher serum creatinine level and lower eGFR were significant risk factors at 6 months and 1 year post transplant. At 1 year, in addition to higher creatinine level and lower eGFR, female gender and immunosuppressive drugs (azathioprine and sirolimus) also were significant risk factors.
Conclusions: Anemia is common during the first year after kidney transplantation. High serum creatinine, low eGFR, female gender and immunosuppressive drugs [azathioprine, sirolimus] are independent risk factors for post-transplant anemia.

Key words: Anemia; kidney transplantation; immune-suppressive drugs.

Introduction

Anemia in chronic kidney disease (CKD) is strongly associated with significant cardiovascular morbidity [1], hospitalization [2] and mortality [3]. The development of erythropoiesis-stimulating agents (ESAs) has made anemia a central part of the management of patients with CKD stages III-V [4-6]. Following successful renal transplantation, some correction of anemia occurs via endogenous production of ESA from the engrafted kidney but a significant proportion, about one-third of the subjects, remain anemic [7-9]. Post-transplantation anemia (PTA) is important as the commonest cause of graft loss is death with a functioning graft, mostly due to an excess of cardiovascular disease, and anemia is a well-recognized and potent cardiovascular risk factor. Hence, it would be advisable to prevent and treat anemia in kidney transplant recipients.
Both 'early' and 'late' PTA has been identified in this context and the distinction is important in identifying etiological causes. 'Early' PTA refers to anemia persisting, or arising relatively soon after engraftment. Relevant potential etiological factors include iron deficiency, infectious agents, donor age, prophylactic and immunosuppressive therapy. 'Late' PTA is associated with the decline in renal function observed in the context of chronic allograft nephropathy or recurrent renal pathology [7,10].

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Aim of the study

The aim of our study was to elucidate the prevalence and risk factors for anemia during the first year after kidney transplantation.

Material and methods

We studied 118 stable adult kidney transplant recipients who received allograft between December 1998 and October 2008 and had at least 1 year of post-transplant follow up data at Sugar Medical Center, Theodor Bilharz Research Institute (TBRI) and Health Insurance Organization Cairo, Egypt. The recorded data base including: etiology of end stage renal disease, pre-transplant hemoglobin (Hb) level, age of the patients at time of transplant, Hb levels at 6 months and 1 year post transplant, serum creatinine and eGFR using MDRD formula at 6 months and 1 year post transplant, iron profiles (serum ferritin and transferin saturation), and immunosuppressive drugs and other medications.

Definition of anemia: We adopted three different definitions for anemia. One is the WHO criteria (Hb level <12 g/dl in females, and <13 g/dl in males). We also arbitrarily defined 'significant' anemia as Hb level <11g/dl in females and <12 g/dl in males and 'severe' anemia as Hb level <10 g/dl in both genders.

Methods: We recorded the Hb levels before transplantation, at 6 months' and at 1 year after transplantation. The eGFR was calculated using the MDRD formula. We performed univariate and multivariate analysis to find the risk factors for anemia. The various variables, which are typically recognized as risk factors for anemia were chosen for the univariate analysis. These were creatinine level and eGFR (at 6 months and 1 year after transplantation), pre-transplant Hb level, female gender, delayed graft function, acute rejection, use of ACEI or ARB, SLE as the underlying disease. We compared the Hb of patients who used AZA vs. MMF and cyclosporine vs sirolimus because most of the patients were on either of these medications.

Statistical analysis: Data were expressed as mean ± SD unless indicated otherwise. Partial correlation analysis was done to determine the independent correlation of the different factors affecting anemia/Hb levels after accounting for the different confounding factors. The continuous variables at different time points and in different groups of patients were compared using the Student's t-test and a P value of <0.05 was considered significant. Risk factors for anemia were evaluated using univariate and multivariate regression analysis. We used SPSS® software version 10.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient's demographics: Among 118 patients [age at transplant ranged between 22 and 58, 42±12 (mean±SD)], 74 (62.7%) were males and 44 were females (37.3%). Thirty-nine (33.1%), 38 (32.2%), 22 (18.6%) and 8(6.8%) patients, respectively, had diabetes mellitus (DM), hypertension (HTN), glomerulonephritis (GN) and systemic lupus erythematosus (SLE) as the cause of end-stage renal disease (ESRD). All 118 patients were living donor transplant recipients [16 living related and 102 living unrelated donors]. Twenty-one (17.8%) patients had been on angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) for 1 year after transplantation. Ten patients experienced delayed graft function and 20 patients experienced acute rejection. Only 6 out of 118 patients (5.1%) were on EPO and 14 (11.9%) were on oral iron supplementation.

Table 1. Patients characteristics.

Total number of patients	118		
Age at transplant(years)	22-58 (42±12 ; mean±SD)		
Gender	Male	74	62.7%
	Female	34	37.3%
Aetiology of ESRD	DM	39	33.1%
	HTN	38	32.2%
	GN	22	18.6%
	SLE	8	6.8%
	Others	11	9.3%
Type of transplant	Related living donars	16	13.6%
	Unrelated living donars	102	86.4%
Number of patients who had	Acute rejection	20	16.9%
	Delayed graft function	10	8.5%
Use of medications	ACEI or ARBS	21	17.8%
	MMF	54	45.8%
	Azathioprine	64	54.2%
	Cyclosporine	76	64.4%
	Tacrolimus(prograf)	12	10.2%
	Sirolimus(rapamycin)	30	25.4%
	Corticosteroids	118	100%
	Erythropiotin	6	5.1%
	Iron supplement	14	11.9%

Immunosuppressive regimens were as follows; steroid (methylprednisolone or prednisolone) was given to all the patients. Steroid was tapered down to a maintenance dose of 10 mg/day, by 6 months post-transplant unless they were treated for rejection. Eighty eight patients received calcineurin inhibitors (76 patients on cyclosporine and 12 patients on tacrolimus) and 30 patients received a sirolimus-based regimen. Target level of cyclosporine was 200–250 ng/ml during the first 3 months and 150–200 ng/ml thereafter; that of tacrolimus was 10–15 ng/ml during the first 3 months and 5–10 ng/ml thereafter and that of sirolimus was 5-15 ng/ml during the first 3 months and 5–10 ng/ml thereafter. Sixsty-four patients (54.2%) were on an azathioprine (AZA)-based immunosuppressive regimen and 54 (45.8%) were on a mycophenolate mofetil (MMF)-based immuno-suppressive regimen.

Iron profile was checked in 34 patients who had anemia by WHO definition during the first post-transplant year and 14 out of those 34 anemic patients had ferritin levels <100 mg/dl or transferrin saturation <20%. All patients of these iron deficient patients had iron supplementation. Only six out of 34 patients were treated with EPO and all of these patients had Hb <11 g/dl.

Prevalence of anemia (tables 2, 3 and figure 1):

Pre-transplant Hb level was 10.8±0.3 g/dl Hb level increased to 12.8±1.3 g/dl at 6 months and 12.6±1.4 g/dl at 1 year. The differences in Hb levels at both 6 months , 1 year with pre-transplant levels were significant (P<0.0001) but there was no significant difference in Hb level between 6 months and 1 year (P<0.2566).

Table 2. Hb levels in the pre-transplant, 6-month, and 1-year period after kidney transplantation.

Hemoglobin levels	*Total (n.118)*	*Male (n.74)*	*Female (n.44)*
Pre-transplant Hb levels	10.8±0.3 g/dl	11.6±0.5 g/dl	10.3±0.2 g/dl
6 month post-transplant Hb levels	12.8±1.3 g/dl	13.4±1.4 g/dl	12.3±1.2 g/dl
1 year post-transplant Hb levels	12.6±1.4 g/dl	13.2±1.5 g/dl	12.1±1.3 g/dl
P value 6 m post-tx vs pre-tx Hb levels	0.0001		
P value 6 month post-tx vs 1 yr post-tx Hb levels	0.2566		

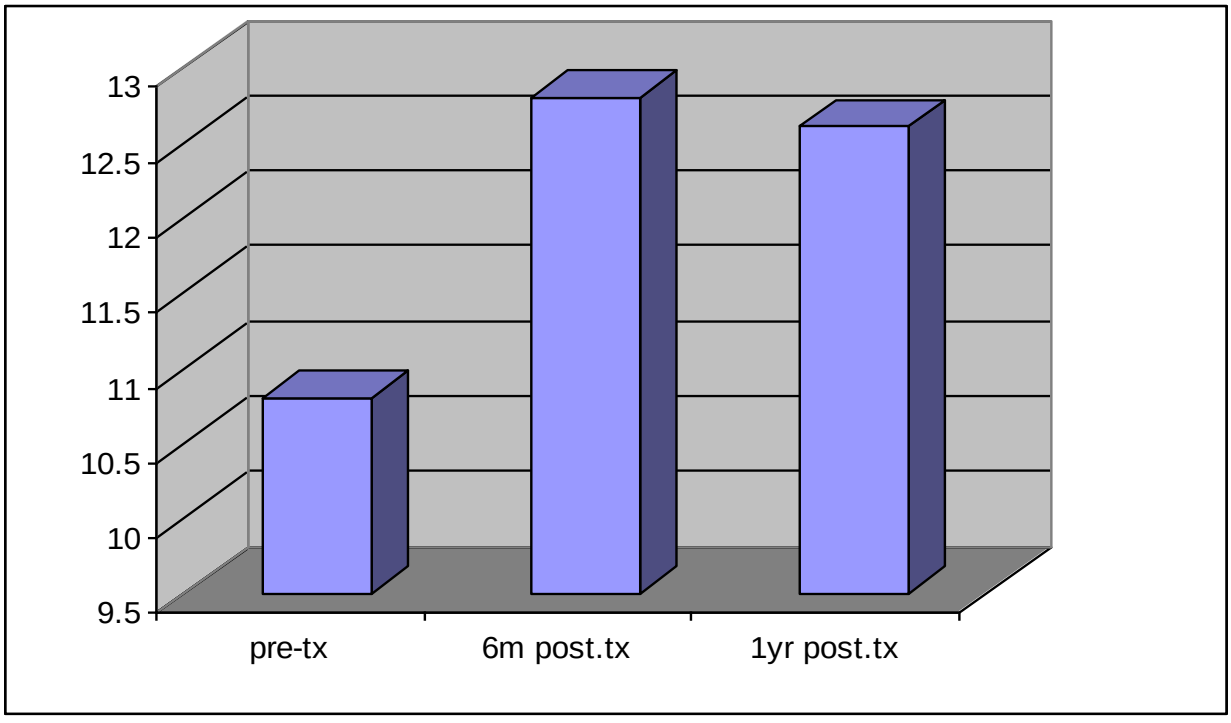

Fig. 1. Hb (g/dl) levels in the pre-transplant, 6-month and 1-year period after renal transplantation.

Prevalence of anemia defined by WHO (Hb <12 g/dl in females and <13 g/dl in males) was 28.8%% at 6 months (34 out of 118) and 31.4%% at 1 year (37 out of 118).

The prevalence of 'significant' anemia (Hb <11 g/dl in female and <12 g/dl in male) was still high: 15.3% at 6 months (14 out of 118) and 16.8% at 1 year (20 out of 118).

'Severe' anemia (Hb <10 g/dl in both genders) at 6 months post-transplant was less common affecting four out of 118(3.4%) patients. Among these, all were females, and all were on AZA. At 1 year, 8 out of 118 (6.8 %) had 'severe' anemia. Of these, six were females and using AZA and sirolimus (75%).

Table 3. Prevalence of anemia in our patients.

	At 6 months post-tx	*At 1 year post-tx*
Anemia as defined by WHO (Hb <12 g/dl in females and <13 g/dl in males)	28.8%	31.4%
Significant anemia (Hb <11 g/dl in female and <12 g/dl in male)	15.3%	16.8%
Severe anemia (Hb <10 g/dl in both genders)	3.4%	6.8 %

Risk factors for anemia (tables 4,5):

To elucidate the risk factors for anemia after transplantation, we conducted the univariate analysis of possible risk factors for 'significant' anemia defined as Hb level <11 g/dl in women and <12 g/dl in men. Univariate analysis showed that a higher creatinine level and lower eGFR were significant risk factors at 6 months and 1 year post transplant. At 1 year, in addition to higher creatinine level and lower eGFR, female gender and immunosuppressive drugs (AZA and sirolimus) also were a significant risk factors.

Table 4. Factors associated with 'significant' anemia by univariate analysis.

Variables	*6 months post-tx*		*1 year post-tx*	
	Relative risk (95% CI)	P value	Relative risk (95% CI)	P value
eGFR	3.86(2.34, 4.96)	0.04 [a]	4.46(2.7, 6.50)	0.02 [a]
Higher serum creatinine	1.98 (1.1, 3.82)	0.03[a]	2.24 (1.4, 3.2)	0.04 [a]
Female gender	1.7 (1.3, 2.6)	0.135	2.8 (1.9, 4.6)	0.01[a]
Lower pre-Tx Hb	1.4 (1.1, 1.7)	0.262	1.6 (1.3, 1.93)	0.073
Episode of acute rejection	1.02 (0.53, 2.23)	0.534	0.92 (0.46, 1.58)	0.686
Episode of DGF	0.98 (0.33, 2.1)	0.732	0.33 (0.09, 1.32)	0.152
SLE as a cause of ESRD	1.1 (0.33, 3.26)	0.628	1.4 (0.47, 3.68)	0.214
Use of AZA	0.57 (0.16, 1.45)	0.563	0.30 (0.21, 1.20)	0.05 [a]
Use of MMF	0.9(0.28, 2.36)	0.611	0.27 (0.12, 1.28)	0.246
Use of cyclosporine	1.12(0.48, 2.54)	0.521	0.37 (0.32, 1.48)	0.335
Use of sirolimus	1.07 (0.66, 1.95)	0.472	0.70 (0.61, 1.50)	0.05 [a]
Use of ACEI/ARBs	1.36 (0.86, 2.71)	0.574	1.64 (0.97, 2.93)	0.329

Pre-Tx, pre-transplant; DGF, delayed graft function.

Table 5. Factors associated with 'significant' anemia by multivariate analysis.

Variables	*Relative risk (95% CI)*	*P value*
Risk of 'significant' anemia at 6 month post-transplant:		
Higher serum creatinine	1.98 (1.1, 3.82)	0.03
eGFR	3.86(2.34, 4.96	0.04
Risk of 'significant' anaemia at 1 year post-transplant:		
Higher serum creatinine	2.10 (1.01, 4.12)	0.01
eGFR	4.46(2.7, 6.50)	0.02
Female gender	2.87 (1.12, 6.21)	0.01
Use of AZA	0.30 (0.21, 1.20)	0.05
Use of sirolimus	0.70 (0.61, 1.50)	0.05

Multivariate analysis showed that at 6 months, higher creatinine levels and lower eGFR were significant independent risk factors for anemia (p value = 0.03; p value=0.04 respectively) and at 1 year, significant independent risk factors for anemia included a higher creatinine level (P = 0.01), lower eGFR(p value=0.02), AZA and sirolimus(p value =0.05), and female gender (P = 0.01) even with a lower cut-off level of Hb by 1 g/dl in defining anemia compared with male gender.

Discussion

Over the last years, the renal transplant community has shown a growing interest in the incomplete correction of anemia by the transplanted kidney. Between 25% and 30% of these patients will be anemic at some time after transplantation. In addition to impaired kidney function, other factors may also play a role in the pathogenesis of post-transplant anemia: Immunosuppressive agents such as azathioprine, mycophenolate mofetil, and sirolimus; angiotensin-converting enzyme inhibitors and angiotensin-II receptor antagonists; impaired iron homeostasis; and donor and recipient age [11].

After successful transplantation, erythropoiesis begins and serum EPO level increases to a sustained level in a month and subsequently Hb level increases towards normal within 3 months [12]. This means that the Hb level should be completely normalized by 6 months for

most patients as long as they have a good allograft function. However, in some renal allograft recipients, anemia persists or develops following transplantation. Most of them are associated with preoperative blood loss, allograft dysfunction (delayed graft function, acute rejection, chronic allograft dysfunction) [13] although some have anemia with normal allograft function as well [14].

In our study, we have shown that anemia is common (28.8% at 6 month and 31.4% at 1 yea post-transplant by WHO criteria) and (15.6% at 6 month and 16.8% at 1 year by definition with Hb <11 g/dl in females and <12 g/dl in males, although 'severe' anemia (defined as Hb <10 g/dl) was not so common (3.4% at 6 month and 6.8% at 1 year).

The high prevalence of anemia in renal transplant recipients has been reported elsewhere. Yorgin et al. observed adult renal transplant recipients over a 5-year period and found 30% of the patients experienced anemia (Ht<33%) during study period [15]. In the study by Lorenz et al., prevalence of anemia (Hb<12 g/dl in females and <13 g/dl in males) was 39.7% [16]. Mix et al., observed a high prevalence of anemia (Ht <36%) at 1 year (21%) and at 4 years (36%) and found that treatment of anemia with iron or EPO was not common even among those with severe anemia [17]. An even large study from Europe confirmed this high prevalence of anemia (38.6% during a 5-year post-transplant enrolment period). Al-Khoury et al. identified anemia in 45.3% of adults and 22% in children post-transplant [18]. All the studies including ours confirmed the high prevalence of mild anemia after renal transplantation.

Among the possible risk factors, our study found that a higher creatinine value, lower eGFR, female gender, AZA and sirolimus were the only significant independent risk factors for posttransplant anemia.

Similar to our observations, other studies [19,20,7] have shown that poor renal allograft function is an independent risk factor for anemia. It is well described that production of EPO depends on allograft function [18].

Also, more females than males had mild anemia both at 6 months and 1 year even though we set a lower threshold for Hb level in females as a definition of anemia. The findings are consistent with other studies showed higher prevalence of anemia in females [9,18] and are inconsistent in other studies. The large European study did not show any gender difference in prevalence of anemia (defined as Hb ≤13 g/dl in males and ≤12 g/dl in females) [7]. Other studies showed higher prevalence of anaemia in males [15,16]. The negative effect of female gender on Hb level has been reported in dialysis [21] and CKD patients [22].

The European study showed use of ACEI, ARB or AZA, MMF was associated with higher prevalence of anemia [7]. Our study did not find the association of use of ACEI or ARB with anemia, but there was association of use of AZA and sirolimus with anemia.

In our study iron profile was checked in 34 patients who had anemia by WHO definition during the first post-transplant year and 14 out of those 34 anemic patients had ferritin levels <100 mg/dl or transferrin saturation <20%. All patients of these iron deficient patients had iron supplementation. Only six out of 34 patients were treated with EPO and all of these patients had Hb <11 g/dl. Mix et al., showed that among transplant recipients who had Ht <30%, only 36% had iron studies, with 46% being supplemented with iron and only 40% receiving EPO [17]. Vanrenterghem et al. showed only 17.8% of severely anemic patients received EPO [7,10,11]. EPO levels tend to be low in anemic renal transplant recipients irrespective of the allograft function [23,24] and several studies have shown the acceptable efficacy of EPO treatment in post-transplant anemia [17,24]. So early investigation of anemia and iron deficiency and its therapy with iron supplement or EPO should be considered in anaemic transplant recipients.

In conclusion, we found that anemia is common during the first year after transplantation and investigation and treatment of anemia is suboptimal. We think that the anemia check-up should be part of the long-term follow-up of the renal transplant patients. Controlled trials should investigate the impact of a better control of anemia on the patient morbidity and outcome.

References

1. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE.: The impact of anemia on cardiomyopathy, morbidity, and mortality in end-stage renal disease. Am J Kidney Dis 1996; 28: 53–61.
2. Holland DC, Lam M.: Predictors of hospitalization and death among pre-dialysis patients: a retrospective cohort study. Nephrol Dial Transplant 2000; 15: 650–658.
3. Hayashi T, Suzuki A, Shoji T et al.: Cardiovascular effect of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure. Am J Kidney Dis 2000; 35: 250–256.
4. Silverberg DS, Wexler D, Blum B et al.: Anaemia in chronic kidney disease and congestive heart failure. Blood Purif 2003; 21: 124–130.
5. Snyder JJ, Foley RN, Gilbertson DT et al.: Haemoglobin levels and erythropoietin doses in hemodialysis and peritoneal dialysis patients in the United States. J Am Soc Nephrol 2004; 15: 174–179.
6. Macdougall IC.: Erythropoietin and renal failure. Curr Hematol Rep 2003; 2: 459–464.
7. Vanrenterghem Y, Ponticelli C, Morales JM et al.: Prevalence and management of anaemia in renal transplant recipients: a European survey. Am J Transplant 2003; 3: 835–845.
8. Moore LW, Smith SO, Winsett RP et al.: Factors affecting erythropoietin production and correction of anaemia in kidney transplant recipients. Clin Transplant 1994; 8: 358–364.
9. Shibagaki Y, Shetty A.: Anaemia is common after kidney transplantation, especially among African Americans. Nephrol Dial Transplant 2004; 19: 2368–2373.
10. Vanrenterghem Y.: Anaemia after renal transplantation. Nephrol Dial Transplant 2004; 19 [Suppl 5]: V54–V58
11. Vanrenterghem Y.: Anemia after kidney transplantation. Transplantation. 2009; 15, 87(9):1265-7.
12. Sun CH, Ward HJ, Paul WL, Koyle MA, Yanagawa N, Lee DB.: Serum erythropoietin levels after renal transplantation. N Engl J Med 1989; 321:151–157.
13. Besarab A, Caro J, Jarrell BE, Francos G, Erslev AJ.: Dynamics of erythropoiesis following renal transplantation. Kidney Int 1987; 32: 526–536.

14. Miles AM, Markell MS, Daskalakis P et al.: Anemia following renal transplantation: erythropoietin response and iron deficiency. Clin Transplant 1997; 11: 313–315.
15. Yorgin PD, Scandling JD, Belson A, Sanchez J, Alexander SR, Andreoni KA.: Late post-transplant anemia in adult renal transplant recipients. An under-recognized problem? Am J Transplant 2002; 2: 429-435.
16. Lorenz M, Kletzmayr J, Perschl A, Furrer A, Horl WH, Sunder-Plassmann G.: Anemia and iron deficiencies among long-term renal transplant recipients. J Am Soc Nephrol 2002; 13: 794–797.
17. Mix TC, Kazmi W, Khan S et al.: Anemia: a continuing problem following kidney transplantation. Am J Transplant 2003; 3: 1426–1433.
18. Al-Khoury S, Shah N, Afzali B, Covic A, Taylor J and Goldsmith D.: Post-transplantation anaemia in adult and paediatric renal allograft recipients-Guy's Hospital experience. Nephrology Dialysis Transplantation 2006 21(7):1974-1980
19. Gossmann J, Kachel HG, Schoeppe W, Scheuermann EH.: Anemia in renal transplant recipients caused by concomitant therapy with azathioprine and angiotensin-converting enzyme inhibitors. Transplantation 1993; 56: 585–589.
20. Geetha D, Zachary JB, Baldado HM, Kronz JD, Kraus ES.: Pure red cell aplasia caused by Parvovirus B19 infection in solid organ transplant recipients: a case report and review of literature. Clin Transplant 2000; 14: 586–591.
21. Department of Health and Human Services, Health Care Financing Administration, Office of Clinical Standards and Quality; Health Care Financing Administration 1996 Annual Report, End Stage Renal Disease Core Indicators Project. Baltimore, MD: January 1997.
22. Howard AD, Moore J, Jr, Welch PG, Gouge SF.: Analysis of the quantitative relationship between anemia and chronic renal failure. Am J Med Sci 1989; 297: 309–313.
23. Miles AM, Markell MS, Daskalakis P et al.: Anemia following renal transplantation: erythropoietin response and iron deficiency. Clin Transplant 1997; 11: 313–315.
24. Nampoory MR, Johny KV, al-Hilali N, Seshadri MS, Kanagasabhapathy AS.: Erythropoietin deficiency and relative resistance cause anaemia in post-renal transplant recipients with normal renal function. Nephrol Dial Transplant 1996; 11: 177–181.