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Erythrocytosis in renal allograft recipients. Benefit of staggered venous erythropoietin measurements

D. Chevet[1], F. Michel[2], Ch. Mousson[1], Y. Tanter[1], J. M. Rebibou[1], N. Casadeval[3], and G. Rifle[1]

[1] Department of Nephrology-Reanimation, [2] Department of Urology, University Hospital, Dijon, France; and
[3] Hôpital Cochin, Paris, France

Abstract. Two adult renal allograft recipients experienced erythrocytosis – one in acute form – within 3 months of grafting. Involvement of well functioning transplanted kidneys was unlikely whereas staggered erythropoietin measurements detected a high gradient in front of venous remnant kidneys. Because of these results bilateral nephrectomy was performed, which cured polycythaemia. Multiple events leading to polycythaemia after renal transplantation are reviewed and diagnosis and therapeutic schedules are proposed.

Key words: Erythrocytosis – Renal transplantation – Erythropoietin – Erythrapheresis – Bilateral nephrectomy.

The appearance of erythrocytosis after kidney transplantation was first described by Nies et al. in 1965 [15]. It is thought to be a rare and usually temporary post-transplant complication. Nevertheless, recent extensive reviews have indicated an incidence ranging from 8.6% [11] to 17.3% [23], with a risk of thromboembolic events in 18% of cases [23].

It is generally agreed that there are various causes of post-transplant polycythaemia. In 1979, Dagher et al. [7] drew attention to inappropriate production of erythropoietin (EPO) from native kidneys as a major contributing factor. Recently Aeberard et al. [1], Felle et al. [8], Qunibi et al. [18] and Garvin et al. [10] offered strong evidence for this cause–effect relationship in a majority of cases.

The recently-developed sensitive radioimmunoassay for EPO allows the localization of the site of exaggerated EPO production after selective catheterization of native or transplanted kidney veins.

Offprint requests to: Prof. D. Chevet, Service de Néphrologie-Réanimation, Hôpital du Bocage, 2bd de Lattre de Tassigny, 21034, Dijon, France

Case reports

Case 1

A 21-year-old female with Barraquer–Simons syndrome and dense deposits disease had been on maintenance haemodialysis for 1 year. She received rHEPO for 4 months. Then her blood haemoglobin level increased from 5.9 to 11.9 g/100 ml. Before treatment, blood EPO level was 7 mU/ml ($N < 22$ mU/ml). She underwent cadaveric renal transplantation in July 1989. Immunosuppressive therapy included ATG for 20 days, azathioprine and corticosteroids. Vasodilators and α-β blocking drugs were initiated for arterial hypertension (ABP, 170/110 mm Hg). Urine analyses were all normal, creatinine clearance was 77 ml/mn and haemoglobin level (Hb) 10.3 g/100 ml at the end of the first month. Two months later serum creatinine level (SCL) rose from 107 to 220 µmol/l. Transplant biopsy showed acute vascular rejection with interstitial haemorrhages. Cyclosporin A (4 mg/kg per day) was added to the previous regimen and SCL decreased to 164 µmol/l.

Within a 3-week period, facial erythrocytosis, headaches, epistaxis and hypertensive encephalopathy (ABP, 210/120 mm Hg) appeared. Hb was 19.6 g/100 ml and haematocrit value (Hct) 58%. Leucocyte and thrombocyte counts were in the normal range. No hypoxaemia was detected. Clinical, laboratory and X-ray investigations excluded morphological abnormalities of the transplanted kidney, visceral neoplasm or lymphoproliferative disorder. Bone marrow examination showed 46% of erythroblasts without cellular abnormality. Two erythrapheresis sessions dramatically improved consciousness state. However, 1 week later, Hb rose again from 12 to 16.5 g/100 ml. Blood EPO level was 94 mU/ml before blood removal. Figs. 1 and 2 show the results of staggered venous EPO measurements.

Because of the severity of the hypertensive crisis, the fast increase in Hb after erythrapheresis sessions and the strong evidence for remnant kidney EPO overproduction, bilateral native nephrectomy was performed. Light microscopic examination of these kidneys showed unidentifiable lesions. BP and Hb returned to normal values within 3 weeks without any antihypertensive drug. Two years later, BP was 130/80 mm Hg, Hb 12.9 g/100 ml, blood EPO level 8 mU/ml and SCL 96 µmol/l. In situ hybridization for human EPO mRNA in patient's kidneys was negative.

Case 2

A 46-year-old male patient underwent maintenance haemodialysis in July 1986 for idiopathic focal glomerulosclerosis. Initially uneventful renal cadaveric transplantation was carried out in January

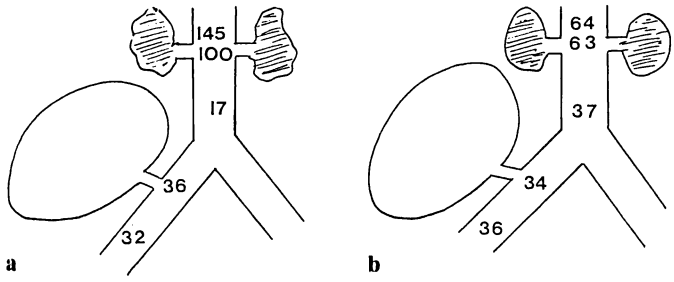

Fig. 1 a, b. Staggered erythropoietin levels (RIA control values 22 mU/ml). **a** case 1, 16 November 1989; **b** case 2, 22 November 1990

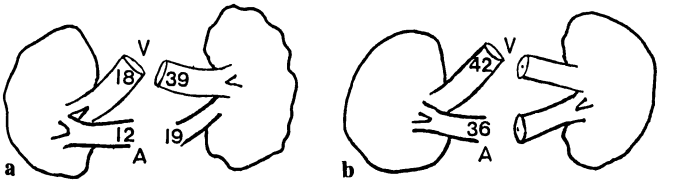

Fig. 2 a, b. EPO levels in arterial and venous samples taken during bilateral renal nephrectomy. Neither renal tumour nor cyst was found. **a** case 1; **b** case 2

1989. The immunosuppressive schedule included ATG (20 days), azathioprine and corticosteroids. Three months later, Hb reached 16.5 g/100 ml when SCL was 145 µmol/l. Chronic polycythaemia slowly progressed to a maximum of 19.1 g/100 ml with Hct 56.3%. The patient experienced mild symptoms such as headaches. Bone marrow aspirate showed 42% erythroblastic reaction and no malignant cells. Markers for haematological proliferative disease were all negative. This non-smoking patient did not have any respiratory disorder or haemoglobinopathy. Complete clinical and laboratory investigations excluded abnormalities of the transplanted kidney or at other sites of visceral neoplasm. Erythrocyte viscosity was 6.5 cP ($N < 4.5$). Blood EPO level was 38 mU/ml ($N < 7$ in matched controls) [20]. Immunosuppressive therapy was unchanged.

The patient was asymptomatic 1 year later except for facial erythrosis. Renal function and BP remained normal. On the other hand, Hb was still 18.8 g/100 ml. Isotopic ^{51}Cr red-cell mass was 53 ml/kg ($N = 42 + 2$). Staggered venous samplings in the iliac vein and vena cava showed an EPO gradient in front of native kidneys (Figs. 1 and 2). Bilateral nephrectomy was performed in November 1990. The weight of both kidneys was 30 g, and only a small cortical cyst was observed in the left one. Hb tapered to 12.6 g/100 ml quickly after surgery and remained in the normal range 1 year later. Post-operative blood EPO level was 14 mU/ml. In situ hybridization for EPO is still in progress.

Discussion

Various aetiological factors have been implicated in post-renal transplant erythrocytosis: acute and chronic rejection [14], transplant arterial stenosis [2], post-transplant hypertension [6], native kidney disease [23]. Other mechanisms have been proposed on theoretical or clinical grounds, including hydronephrosis, hepatic EPO production [13], pancreatic pseudocysts, resolution of hyperparathyroidism [3]. A drug-induced effect has been advocated such as contracted plasma volume by diuretics [16, 17], azathioprine [22] or cyclosporin therapy [5, 9, 21].

Usually, routine clinical and laboratory investigations permit an easy approach to such aetiological factors when the transplant is involved. In addition, the reversibility of the disorder after restoring the renal lesion when possible easily confirms the diagnosis. On the other hand, a successful renal transplantation can allow the appearance of a previously concealed polycythaemic syndrome. Such events can be observed in patients who smoke or in cases of chronic respiratory insufficiency, or sometimes in polycystic kidney disease, when the native kidneys were not removed before grafting. Polycythaemia can also be the first symptom of a myeloproliferative syndrome. Identification of such a syndrome does not pose particular difficulties. From a practical point of view, except in emergency circumstances as illustrated in case 1, measurement of red-cell mass remains, in all cases, an essential procedure before diagnosing a genuine erythrocytosis.

The recently available reliable estimation of EPO by radioimmunoassay or ELISA will certainly make it easier to recognize the cause of polycythaemia after renal transplantation. Indeed, a high level of circulating EPO demonstrates that EPO synthesis is no longer physiologically regulated. In the case of the kidneys, one can postulate that various lesions are able to generate local hypoxia which can stimulate secreting EPO target cells in the interstitium, probably located on peritubular capillary walls [19]. In transplanted erythrocytic patients, one of the main problems, in the absence of other causes, and when the graft is functioning well, is to localize the site of the hypersecretion: are the native kidneys or the grafted one involved? High levels of circulating EPO do not permit such a localization [8, 12, 18]. It was then logical to measure EPO levels in remnant and transplanted kidney veins [1, 7, 10]. We and others have observed a good correlation between the site of overproduction and recovery after surgery. Thus, it seems justified to recommend using this method before making any therapeutic decision. Human EPO mRNA was not identified by in situ hybridization in the removed kidneys (case 1). We have no clear-cut explanation for this failure, but technical reasons (late freezing of the specimens) could be concerned.

Historical and conventional therapy for post-transplant erythrocytosis still remains repeated phlebotomies for many months or years to maintain haematocrit at no more than 45%. Such a procedure avoids disabling symptoms such as headaches or water-induced pruritus, and above all protection from pulmonary embolism or cerebrovascular hazards, whose incidence has been emphasized [23]. This long-term protracted therapy is not always successful, as our case 1 demonstrates. Therefore, aetiological therapies are needed, which allow more constant and predictable results. When endogenous EPO overproduction by remnant kidneys is proved, surgical binephrectomy by a posterior procedure according to Gil-Vernet appears as the definitive therapy choice. Other promising methods include EPO-inhibiting drugs, as advocated for certain converting enzyme inhibitors or well demonstrated for theophylline [4].

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