POLYCYthaemia is Erythropoietin-Independent After Renal Transplantation

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Summary

Serum erythropoietin increased in 55 patients after transplantation. The serum erythropoietin decreased when the haematocrit and haemoglobin reached high levels, indicating recovery of a feed-back control system. Despite the diminution of erythropoietin, six patients demonstrated a state of erythrocytosis while the in vitro cultures of BFU-e revealed high sensitivity to the reduced doses of erythropoietin, using monocyte-free T-lymphocyte-depleted peripheral blood. In polycythaemic transplanted patients it is possible that cellular interactions stimulate an early hyperproliferation of BFR-e with a greater erythropoietin sensitivity and a partial capacity to grow in the absence of erythropoietin.

Introduction

Polycythaemia may temporarily complicate the course of a few patients after renal transplantation, but the mechanism is unclear. Acute or chronic rejection, renal artery stenosis or hydronephrosis of the transplanted kidney have been implicated as causes [1,2].

Local hypoxia, in all cases, may lead to an increased erythropoietin production with consequent erythrocytosis.

In many transplanted patients, however, the polycythaemia has been found in the absence of the abnormalities mentioned above, suggesting that other factors may contribute to the pathogenesis of erythrocytosis.

With the aim of contributing to the knowledge of the pathogenesis of this erythrocytosis, the present study reports the modifications of early erythroid progenitor growth in vitro and those of some haematological parameters in vivo, observed in kidney transplant patients with or without polycythaemia.

Patients and methods

Erythrocytosis was detected in six out of 55 patients who underwent kidney transplantation. The haematocrit, haemoglobin and erythrocyte mass (Cr$^{51}$)
mean values were respectively 60.6 per cent, 21.4g/100ml and 44.16ml/kg body weight, with white blood cells and platelets within the normal range. The original renal diseases were chronic glomerulonephritis in three, chronic pyelonephritis in one, Alport's syndrome in one, lupus erythematosus systemicus in one.

The following parameters were determined monthly in the patients with erythrocytosis and in 12 out of 49 transplanted patients without erythrocytosis, from the dialysis phase up until 24 months after renal transplantation; haematocrit (Hct%), haemoglobin (Hb g/100ml), reticulocytes (Ret. μLitre), serum erythropoietin (sEp μU/ml) [3] and proliferative growth of Burst Forming Unit Erythroid (BFU-e per plate) using mononuclear cells from peripheral blood isolated on Ficoll-Hypaque gradient and incubated in in vitro cultures with progressively reduced doses of sheep plasma erythropoietin (2–1.5–1–0.5–0.1U/ml medium) [4].

Various culture patterns were employed: incubating 2x10^5 whole mononuclear cells (A), incubating 2x10^5 mononuclear cells depleted of monocytes (B), incubating T-lymphocytes (C) and by incubating 2x10^5 monocytes or T-lymphocytes alone (D) [5,6].

All patients showed a normal serum creatinine, blood pressure, and respiratory function, and received the same patterns of immunosuppressive treatment. The mean age was 33.16 ± 10.7 years.

Twelve normal volunteers were also studied as controls. All subjects gave their consent to this study.

Statistics. All data obtained under various experimental conditions, expressed as mean ± SD, underwent statistical analysis by the Student’s ‘t’ test. Statistical significance was accepted at 0.05 level.

Results

In the patients with erythrocytosis, at four months the Hct, Hb and Ret. increased significantly in comparison with those of control subjects 40 per cent, 41 per cent and 380 per cent (p<0.005) and the dialysis phase, 186 per cent, 205 per cent, 2156 per cent (p<0.005). These figures remained significantly higher until the twelfth month, while from the twelfth month to the twenty-fourth month, they decreased slightly.

In the patients without erythrocytosis, the increases of Hct, Hb and Ret. over the levels observed during dialysis phase were lower than those of polycythaemic patients and did not exceed the normal range.

The sEp values increased similarly in both types of subjects, 400 and 480 per cent over the basal levels in non-uraemic anaemic patients, from the first month, with a successive feed-back dependent decrease.

The in vitro cultures of type A with reducing doses of Ep in patients with erythrocytosis at the fourth month showed percentage increases of the number of BFU-e colonies developed per plate which were greater than to those observed in the dialysis phase and in normal subjects, 635 per cent, 680 per cent, 800 per cent, 2500 per cent (p<0.005) and 131 per cent, 143 per cent, 400 per cent and 2500 per cent (p<0.005) respectively. A mean number of 13 ± 2.5 BFU-e colonies per plate was also obtained in the absence of Ep, while no cellular
TABLE I. Erythropoietin (Ep) dose-response growth of BFU-e colonies in ‘in vitro cultures’ performed by incubating whole peripheral mononuclear cells (A type cultures), monocyte-depleted peripheral mononuclear cells (B type cultures) or T-lymphocyte-depleted peripheral mononuclear cells (C type cultures) from six erythrocytic (E) and 12 non-erythrocytic (non-E) after renal transplantation. (Values expressed as mean ± SD)

<table>
<thead>
<tr>
<th>Erythropoietin concentration</th>
<th>Controls(^a)</th>
<th>E Patients(^b)</th>
<th>Non E Patients(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) IU/ml</td>
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<td>(A) IU/ml</td>
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<tr>
<td>0</td>
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<tr>
<td>0.5</td>
<td>2 ±1.2</td>
<td>52 ±4.9</td>
<td>0 f</td>
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<tr>
<td>1</td>
<td>18 ±3</td>
<td>90 ±6.1</td>
<td>25 ±2.2</td>
</tr>
<tr>
<td>1.5</td>
<td>48 ±5</td>
<td>117 ±3.9</td>
<td>43 ±1.9</td>
</tr>
<tr>
<td>2</td>
<td>54 ±4.26</td>
<td>125 ±6.4</td>
<td>57 ±4.3</td>
</tr>
</tbody>
</table>

\(^a\) Values are the mean ± SD for 12 normal subjects
\(^b\) Values are the mean ± SD for 6 subjects with erythrocytosis after renal transplantation
\(^c\) Values are the mean ± SD for 12 subjects without erythrocytosis after renal transplantation
\(^d\) Significantly different from control values (p<0.005)
\(^e\) Significantly different from DP values (p<0.005)
\(^f\) Significantly different from erythrocytic patient values (p<0.005)
\(^g\) Dialysis phase
growth was found under similar conditions in the dialysis phase and in normal subjects (Table I).

At the same time, in type A cultures of patients without erythrocytosis, the BFU-e colony growth, with the addition of progressively reduced doses of Ep, was higher than in the dialysis phases and normal subjects, but noticeably lower than those of the patients with erythrocytosis. In the absence of Ep from cultures no BFU-e development was observed in these cases.

In types B or C cultures in patients with or without erythrocytosis, the BFU-e growth was significantly less than that seen in type A cultures. In the patients without erythrocytosis, however, this reduction was less than in patients with erythrocytosis and no BFU-e developed on adding small doses of Ep to the cultures, as occurred with normal subjects (Table I).

In all patients the type D cultures did not result in any significant BFU-e development, irrespective of the Ep dose added.

Discussion

Our results demonstrate that the sEp increases in the same period and in the same proportion in transplanted patients with or without erythrocytosis, and successively undergoes a feed-back dependent decrease. This suggests a restoration of normal intrarenal secretion [7]. However, despite these sEp changes a few transplanted patients (10.9%) show a further elevation of the Hct values which remain at high levels for a few months. This finding appears to be associated with a greater capacity for the development of erythroid progenitors in the erythrocytotic patients, this may be due to an early increase in Ep receptors on the cell surface and consequently to a greater Ep sensitivity [8].

Such a particular sensitivity appears to be accompanied by the presence of the adherent mononuclear cell fraction and/or T-lymphocytes in the medium. In fact, the removal of these cells, particularly the monocytes, is followed by a reduction in the number of BFU-e colonies per plate.

These results, therefore, confirm that Ep cannot be considered the most important regulatory factor in early BFU-e development. A primary role in this mechanism is played by cellular interactions which, in a few transplanted patients, assume a greater capacity for stimulating BFU-e maturation. Up to the present time the mechanism for this was largely unknown but appears to be almost completely independent of the presence of Ep.

References

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931