

## ERYTHROCYTOSIS IN A HEMODIALYSIS PATIENT TREATED WITH IRON SUCROSE

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**SUMMARY** – A 59-year-old Caucasian male started intermittent hemodialysis in March 1995 for the treatment of end-stage renal disease of unknown etiology. In December 2002, he started receiving parenteral iron sucrose, 100 mg every two weeks, for iron deficiency. He did not receive erythropoietin. One month later he experienced severe pruritus. Blood analysis revealed erythrocytosis. Iron therapy was discontinued immediately, and four venepunctures were performed to avoid thrombosis of AV fistula. Malignant disease was excluded. It was decided to apply an angiotensin convertase enzyme inhibitor (ACEi), ramipril, in a dose of 2.5 mg/day. However, the patient developed severe cough as a side effect of ramipril and was switched to an angiotensin receptor type II antagonist (AAR), losartan, in a dose of 25 mg/day. While the patient was prone to hypotension during the dialysis sessions, losartan was administered every evening at bedtime. One month after the introduction of AAR, a stable hemoglobin level was achieved. On control MSCT six months later, there was no sign of malignant disease. Oral ACEi and AAR are appropriate treatment in the control of erythrocytosis in dialysis patients.

**Key words:** *hemodialysis, erythrocytosis, losartan, ramipril* (molim ključne riječi kao i u drugim člancima)

### Introduction

Anemia is one of the cardinal features of end-stage renal disease (ESRD). It is considered to be the consequence of structural changes of the failing kidney with interstitial fibrosis and destruction of erythropoietin (EPO) producing cells<sup>1</sup>. However, recent observations have shown that a failing kidney may retain the ability to produce EPO. Erythropoietin concentration is within the normal range in many of dialysis patients, although low for the level of hemoglobin<sup>2,3</sup>. Anemia worsens after bilateral nephrectomy<sup>4,5</sup>. Acute hypoxic or hemorrhagic stress causes an increase in serum EPO concentration<sup>6,7</sup>. Finally, EPO causing erythrocytosis in patients with kidney transplant is mostly derived from native kidneys<sup>8,9</sup>.

Erythrocytosis in hemodialysis patients is rare. We describe a case of a man with ESRD treated with hemodi-

alysis who developed erythrocytosis after the administration of intravenous iron sucrose for severe iron deficiency.

### Case Report

A 59-year-old Caucasian male started intermittent hemodialysis in March 1995 for the treatment of ESRD of unknown etiology. Several months later he had developed thrombosis of a distal left arteriovenous (AV) fistula, and from then he was treated with oral anticoagulants. In December 2002, he started receiving parenteral iron sucrose, 100 mg every two weeks, for iron deficiency (Table 1). One month later he experienced severe pruritus. Blood analysis revealed erythrocytosis ( $6.05 \times 10^9/l$ ) with hemoglobin (Hb) concentration of 192 g/L and hematocrit level of 0.56 L/L. Skin plethora was prominent on physical examination. Auscultation revealed vesicular breathing and normal heart tones with no murmurs. There was no splenomegaly or hepatomegaly.

Laboratory tests demonstrated erythrocytosis with an increased number of reticulocytes, erythropoietin level within the normal range, and increased ferritin level (Ta-

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ble 1). Prothrombin time was 0.22, activated partial thromboplastin time 41.3 s, and fibrinogen level 4 g/L (the patient was treated with oral anticoagulants). Urea was 25.6 mmol/L, creatinine 956 mmol/L, uric acid 423 mmol/L, and liver enzymes were within the normal range. Chest x-rays were normal. Spirometry was within the normal range, with a normal diffusion capacity for carbon monoxide. Electrocardiogram showed normal sinus rhythm, 80/min. His body mass index was 27 kg/m<sup>2</sup>.

Abdominal ultrasound demonstrated a normal liver and spleen. Kidneys were 4.5 cm long with anechogenic zones that primarily corresponded to cysts and marked reduction of renal parenchyma. To further evaluate the kidney structure and screen for the presence of a malignant disease, contrast enhanced multislice computed tomography (MSCT) of the abdomen and thorax were performed. There was no sign of malignant disease in the thoracic cavity. Parapelvic cysts (of 2-2.2 cm in diameter) and cortical cysts (1 cm in diameter) were present in both kidneys. This finding was consistent with the acquired cystic disease of ESRD. There was no sign of malignant disease in the abdominal cavity or retroperitoneum.

Sternal puncture demonstrated intermediately abundant hematopoiesis, with the white to red blood cell line ratio of 2.3:1. Erythropoiesis was mature, with a small percentage of erythroblasts. Thrombocytopenia was normal. Leukocyte alkaline phosphatase and blood volume were normal. The patient failed to fulfill the criteria for polycythemia rubra vera.

Iron therapy was discontinued immediately after the finding of erythrocytosis. Four venepunctures of 450 ml whole blood each were performed, however, it seemed that it would be necessary to perform venepunctures at least once a week to avoid thrombosis of the AV fistula. We decided to apply an angiotensin convertase enzyme inhibitor (ACEi), ramipril, in a dose of 2.5 mg/day. The patient developed severe cough as a side effect of ramipril and was switched to an angiotensin receptor type II antagonist (AAR), losartan, in a dose of 25 mg/day. While the patient was prone to hypotension during dialysis sessions, losartan was administered every evening at bedtime. One month after the introduction of AAR, a stable hemoglobin level was achieved. On control MSCT 6 months later, there was no sign of malignant disease.

## Discussion

This report documents development of severe erythrocytosis secondary to intravenous iron therapy in the pa-

*Table 1. Laboratory values before the administration of iron-sucrose, two months after the introduction of iron when severe erythrocytosis was present, and the last control measurements during the treatment with losartan; nd-not done.*

	December 2002	February 2003	July 2003
E (x10 <sup>12</sup> /l)	4.36	6.02	3.74
Hb (g/l)	123	192	124
Htc (l/l)	0.398	0.560	0.362
Rtc (/1000 E)	nd	22	2
Epo (IU/l)	nd	34	25
Fe (mmol/l)	5	15	8
Ferritin (ng/ml)	1.04	320	75.21

tient with ESRD treated with intermittent hemodialysis. Four urgent venepunctures were necessary to maintain hemoglobin concentration below 170 g/L, to avoid thrombosis of AV fistula. Stable hemoglobin concentration of 140 g/l was achieved one month after the introduction of AAR.

There are few reports of erythrocytosis in patients treated with dialysis. Erythrocytosis has been reported in several patients treated with continuous ambulatory peritoneal dialysis, with volume depletion and iron therapy suggested as the possible cause for the development of erythrocytosis in this group of patients<sup>10-12</sup>.

Erythrocytosis may be found in almost 20% of patients after kidney transplantation<sup>13</sup>. It can be controlled with ACEi<sup>14,15</sup>, AAR<sup>16</sup>, or theophylline derivatives<sup>17</sup>. The mechanisms associated with an increased post-transplant erythropoietin production, apart from the acute and chronic graft rejection, or malignant diseases, include diabetes, amyloidosis, renal artery stenosis, hepatic erythropoietin production, androgens, and hypoxia<sup>18-20</sup>. The same predisposing conditions may play a role in the development of erythrocytosis in patients treated with dialysis, including the polycystic kidney disease as the most common cause<sup>21-24</sup>. Some novel hypotheses propose abnormalities in insulin-like growth factor (IGF-I) and IGF-I receptor production as a cause of erythrocytosis after renal transplantation<sup>25</sup>.

Erythrocytosis is rare in hemodialysis patients. However, it is well known that some of dialysis patients do not need erythropoietin therapy to maintain appropriate erythropoiesis. Our daily practice shows the patients who do not need erythropoietin therapy for the treatment of anemia to be mostly overweight, or at least to have good nutritional status. The question is: which factor might be responsible for substituting for EPO in dialysis patients? Leptin is

a small peptide hormone, mainly produced in adipose tissue, thus reflecting the amount of body fat<sup>26</sup>. Together with its receptor B219/OB it constitutes a novel hematopoietic pathway<sup>27</sup>. It is increased in patients with ESRD due to either increased synthesis or reduced clearance<sup>28</sup>. An increased blood concentration of leptin may be responsible for the increased hemoglobin concentration in some of dialysis patients<sup>29</sup>.

The most probable cause of erythrocytosis in our patient was the treatment with intravenous iron sucrose. With the severe iron depletion, there was no substrate for the production of erythrocytes, and after the introduction of iron sucrose, red blood cells started to proliferate as seen from the increased reticulocyte count in the peripheral blood smear. The normal erythropoietin concentration indicated that epithelial cells of the kidney cysts produced erythropoietin, and once there was enough substrate for cell production (iron administration), erythrocytosis developed. It is also possible that iron may induce expression of some factors that are capable of inducing erythropoiesis. The possible candidates include insulin-like growth factor I, leptin, or angiotensin II. Unfortunately, we had no possibility to investigate their expression.

Oral ACEi and AAR are appropriate treatment for the control of erythrocytosis in dialysis patients. Monitoring of serum potassium and good patient compliance are necessary because these medications may cause hyperkalemia. Iron is an invaluable medication in the treatment of renal anemia. However, caution is necessary when administering intravenous iron in patients with secondary cysts, as they can produce erythropoietin and induce erythrocytosis, which will increase the risk of thrombosis of the vascular access or small to medium blood vessels. Special attention is necessary when prescribing iron in patients with diabetes, amyloidosis, those on androgen therapy, and in patients suffering from hypoxia, as these conditions were found to be associated with an increased risk for the development of erythrocytosis.

Investigations in patients with kidney failure who retain the ability of normal hematopoiesis may improve the understanding of erythrocyte production, ultimately leading to the improvement in the treatment of renal anemia.

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#### Sažetak

### ERITROCITOZA U BOLESNIKA NA HEMODIJALIZI LIJEČENOG ŽELJEZKOM SUKROZOM

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Bijelac u dobi od 59 godina započeo je s primjenom hemodijalize s prekidima u ožujku 1995. radi liječenja terminalne bubrežne bolesti nepoznate etiologije. U prosincu 2002. počeo je primati parenteralnu željeznu sukrozu, 100 mg svaka dva tjedna, zbog nedostatka željeza. Nije primao eritropoetin. Nakon mjesec dana nastupio je svrbež, a krvne pretrage su ukazale na eritrocitozu. Liječenje željezom smjesta je prekinuto i napravljena su četiri vađenja krvi kako bi se izbjegla tromboza AV fistule. Zloćudna bolest bila je isključena. Odlučeno je da se primijeni inhibitor enzima konvertaze angiotenzina (ACEi), ramipril, u dozi od 2,5 mg/dan. Međutim, u bolesnika se je razvio težak kašalj kao nuspojava ramiprila, pa je bolesnik prešao na terapiju antagonistom tipa II. receptora angiotenzina (AAR), losartanom, u dozi od 25 mg/dan. Za vrijeme dok je bolesnik bio sklon hipotenziji tijekom postupaka dijalize, losartan je dobivao svake večeri prije spavanja. Mjesec dana nakon uvođenja AAR postignuta je stabilna razina hemoglobina. Kontrolna MSCCT nakon šest mjeseci nije pokazala nikakvih znakova zloćudne bolesti. Oralni ACEi i AAR su primjerena terapija za reguliranje eritrocitoze u bolesnika na dijalizi.

Ključne riječi: *hemodijaliza, eritrocitoza, losartan, ramipril* (molim ključne riječi kao i u drugim člancima)