Idiopathic Erythrocytosis in Dialysis Patients: A Case Report and Literature Review

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Key Words
Idiopathic erythrocytosis · Erythrocytosis · End-stage renal disease · Erythropoietin · Hemodialysis

Abstract
Anemia is a common complication in end-stage renal disease (ESRD) patients. On the other hand, idiopathic erythrocytosis is extremely rare, with only a few cases reported in the literature. We present a case of erythrocytosis that developed after initiating hemodialysis. A 68-year-old male with a history of ESRD secondary to diabetes presented with erythrocytosis that started a few months after initiating dialysis in the absence of having received erythropoietin-stimulating agents or iron supplements. His erythropoietin level was elevated, with a negative JAK2 mutation. Blood gases showed normal oxygen and CO\textsubscript{2}, with slightly elevated carboxyhemoglobin. Tiny foci in both kidneys were noted, representing vascular calcifications or renolithiasis. There was no radiological evidence of neoplasms or cysts. After excluding secondary causes, a diagnosis of idiopathic erythrocytosis was made. The patient underwent intermittent phlebotomies during dialysis, and his hemoglobin went from 18.5 to 14 mg/dl. Erythrocytosis in ESRD patients is very rare. So far, there is no complete understanding of the underlying pathophysiology; however, there seem to be multiple possible reasons for an increased erythropoietin level. Phlebotomy is a successful and easy way to control erythrocytosis in such patients. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, currently being used in posttransplant erythrocytosis, might also be considered.

Introduction

Anemia is a common complication in patients with end-stage renal disease (ESRD). Most patients on dialysis are started on erythropoietin-stimulating agents when their hemoglobin level falls below 10 g/dl. On the other hand, idiopathic erythrocytosis is extremely rare. It can be caused by the same conditions causing erythrocytosis in the general population or any condition specific to chronic kidney failure [1]. However, it may also develop in the absence of any clear explanation for its occurrence. Idiopathic erythrocytosis in ESRD patients undergoing dialysis has been reported in the literature. Herein, we present one such case of erythrocytosis that developed after initiating hemodialysis in an ESRD patient.
A 68-year-old Hispanic male with a history of ESRD second-
ary to diabetic nephropathy was started on hemodialysis in May
2010. At that time, he was anemic with hemoglobin of 9.8 g/dl.
Iron studies were consistent with anemia of chronic disease (as
iron levels were 39 μg/dl, total iron binding capacity was 213 μg/
dl and ferritin was 394 ng/ml). A few months after starting he-
modialysis, his hemoglobin level started to rise gradually, even
though he had never received an erythropoietin-stimulating
agent or any form of iron supplements. Twenty-two months lat-
er he developed erythrocytosis with hemoglobin of 18.5 g/dl and
hematocrit of 58.2%. His past medical history was significant for
hypotension with no previous history of erythrocytosis or heart
or lung disease.

The patient’s regular medications were Lantus insulin, calcium
acetate and midodrine. He had never received a blood transfusion
nor taken anabolic steroids or cobalt supplements. He used to
smoke cigarettes but stopped smoking at the age of 30. Workup for
an underlying cause of erythrocytosis showed an elevated erythro-
poietin level of 49.45 mU/ml, along with negative JAK2 V617F
mutation and normal white blood and platelet counts. Thus,
poietin level of 49.45 mU/ml, along with negative JAK2 V617F
an underlying cause of erythrocytosis showed an elevated erythro-

Discussion

The primary site of erythropoietin production is the
kidney. Erythropoietin is detectable in surgically ane-
phic patients, which suggests an extrarenal source of
erythropoietin, with liver being the most probable source.
Erythropoietin levels have been reported to be elevated,
normal or decreased in the serum of renal failure patients
[2].

Erythrocytosis in ESRD patients has been reported in the
literature in different settings. Eight to fifteen percent
of post-renal transplant patients develop erythrocytosis
[3]. The pathogenesis of erythrocytosis in posttransplant
patients is multifactorial and not well understood [3].
Erythropoietin secretion by native kidneys secondary to
chronic kidney hypoxia is one of the explanations for id-
opathic erythrocytosis. This has been well studied in
posttransplant patients. In one study, analysis of renal
venous plasma collected from both allograft and native
kidneys showed that erythropoietin levels were clearly
higher in renal venous plasma from the native kidney
when compared to that from the transplanted kidney in
3 patients [4]. In 1 patient who had nephrectomy, eryth-
ropoietin levels and hematocrit values fell to normal [4].
Other suggested etiologies beside elevated erythropoietin
are hematopoietic growth factors such as insulin-like
growth factor-1 and its binding proteins, serum-soluble
stem cell factor, endogenous androgens and activation of
the renin-angiotensin system [3]. On the other hand,
erythrocytosis in dialysis patients who have not under-
gone a kidney transplant is rare and poorly studied. Sev-
eral writers have described polycythemia vera or second-
ary erythrocytosis in patients who are on hemodialysis or
continuous ambulatory peritoneal dialysis (CAPD).
Polycythemia vera was reported in patients who had sus-
tained elevated hemoglobin levels despite being on dialy-

We performed a search in the English language litera-
ture using the electronic database PubMed. The follow-
ing terms were used in our search: (‘polycythemia’[MeSH
Terms] OR ‘polycythemia’[All Fields] OR ‘erythro-
cytosis’[All Fields]) AND (‘renal dialysis’[MeSH Terms]
OR (‘renal’[All Fields] AND ‘dialysis’[All Fields]) OR ‘re-
nal dialysis’[All Fields] OR ‘dialysis’[All Fields] OR
‘dialysis’[MeSH Terms]), limits: English. Related articles
were reviewed, and only those with clear data for idio-
pathic erythrocytosis in dialysis patients were included.
We used an hematocrit level of ≥48% or a hemoglobin
level of ≥16.5 g/dl as a definition of erythrocytosis.
Secondary erythrocytosis was described in a dialysis patient who had cyanotic congenital heart disease [2]. Other secondary causes of erythrocytosis in ESRD patients, including erythropoietin-producing gastric cancer, obstructive sleep apnea and chronic severe hypotension, were also reported [9–11], with hemoglobin and hematocrit returning to normal or low levels after treating the underlying cause [9, 10]. Relative erythrocytosis, in which hemoglobin or hematocrit levels have not reached the absolute values of erythrocytosis, with a normal to high erythropoietin level has also been mentioned in the literature. In one case report, a patient on regular hemodialysis for 10 years had idiopathic elevated erythropoietin, with a possible link to beet juice as a predisposing factor secondary to excess cobalt accumulation in the liver, stimulating its cells to produce erythropoietin [12]. In an observation of relative erythrocytosis in ESRD patients undergoing CAPD, it was highlighted that relative erythrocytosis seemed to occur more frequently in patients with amyloidosis or diabetes who were on CAPD. Insulin-like growth factor-1 has been suggested to play an important role in the regulation of erythropoiesis in patients with ESRD and relative erythrocytosis who do not have increased erythropoietin production [13]. Relative erythrocytosis was also noted in an ESRD patient shortly after being diagnosed with viral hepatitis [14]. In a number of published cases, a clear cause could not be found [10].

Hemoglobinopathies with an increased oxygen affinity should be considered in patients with familial erythrocytosis. They occur secondary to some rare mutations of the globin chain genes, changing the affinity of the hemoglobin molecule for oxygen. High oxygen affinity would lead to impaired oxygen delivery to tissues, which would stimulate erythropoietin production and increase the red cell mass, resulting in erythrocytosis. These patients usually have a normal PO2 and oxygen saturation [15].

Many substances, when ingested or inhaled, may undergo chemical reactions with hemoglobin, leading to the formation of abnormal hemoglobin adducts. These toxic modifications of hemoglobin can impair its primary function in tissue respiration. Hemoglobins such as carboxyhemoglobin and methemoglobin are commonly associated with cyanosis and are usually symptomatic.

A normal hemoglobin P50 and negative family and drug history along with an absence of risk factors for carboxy- or methemoglobinemia made hemoglobinopathy a less likely etiology for erythrocytosis in our patient.

Table 1 summarizes the different known mechanisms of erythrocytosis.

### Table 1. Mechanisms of erythrocytosis

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess erythropoietin production</td>
<td>exogenous erythropoietin production by tumors</td>
</tr>
<tr>
<td></td>
<td>hepatocellular carcinoma [19]</td>
</tr>
<tr>
<td></td>
<td>renal cell carcinoma [19]</td>
</tr>
<tr>
<td></td>
<td>hemangioblastoma [19]</td>
</tr>
<tr>
<td></td>
<td>gastric cancer [9]</td>
</tr>
<tr>
<td></td>
<td>exogenous erythropoietin production from the liver [14]</td>
</tr>
<tr>
<td></td>
<td>primary erythrocytosis in polycythemia vera [19]</td>
</tr>
<tr>
<td></td>
<td>erythropoietin production by the lining epithelium of renal cysts [19]</td>
</tr>
<tr>
<td>Chronic hypoxia via hypoxia-inducible factor 1</td>
<td>right-to-left cardiac shunts [2, 19]</td>
</tr>
<tr>
<td></td>
<td>obstructive sleep apnea [10, 19]</td>
</tr>
<tr>
<td></td>
<td>chronic pulmonary disease [19]</td>
</tr>
<tr>
<td></td>
<td>high altitudes [19]</td>
</tr>
<tr>
<td></td>
<td>chronic carbon monoxide poisoning [19]</td>
</tr>
<tr>
<td>Activation of the renin-angiotensin system</td>
<td>following renal transplant [3]</td>
</tr>
<tr>
<td></td>
<td>renal artery stenosis [20]</td>
</tr>
<tr>
<td>Hematopoietic growth factors (IGF-1, sSCF)</td>
<td>following renal transplant [3]</td>
</tr>
<tr>
<td>Endogenous androgens</td>
<td>following renal transplant [3]</td>
</tr>
</tbody>
</table>

IGF-1= Insulin-like growth factor-1; sSCF = serum-soluble stem cell factor.
A total of 20 dialysis patients with idiopathic erythrocytosis were reviewed in this article. Data analysis is summarized in Table 2.

Despite several writers having suggested an increased incidence of idiopathic erythrocytosis in patients using CAPD [13], we found that more cases were reported for patients on hemodialysis. One of the explanations for idiopathic erythrocytosis while on dialysis might be better volume control leading to an increased concentration of red blood cells [13]. However, this is expected only to result in relative erythrocytosis, with no reason to have elevated erythropoietin levels.

We observed that idiopathic erythrocytosis was reported in patients with ESRD secondary to 3 major causes, namely diabetes, glomerulonephritis and adult polycystic kidney disease. The presence of cystic kidney disease, either hereditary (3 patients) or acquired (7 patients), was noticed to be associated with idiopathic erythrocytosis, probably due to increased erythropoietin production from the proliferating epithelium lining these cysts. However, idiopathic erythrocytosis was also noted in patients with ESRD secondary to glomerulonephritis (7 patients), as well as diabetes (7 patients), in the absence of acquired cystic kidney disease. This suggests that the presence of cystic kidney disease is not the only reason for elevated erythropoietin and subsequent erythrocytosis.

The mean time from starting dialysis until development of erythrocytosis was 52.8 months, with a range of 2–156 months. Of note, we observed that idiopathic erythrocytosis occurred earlier in diabetic patients, with a mean time interval of 34 months after starting dialysis, and later in patients with glomerulonephritis and adult polycystic kidney disease, with a mean time interval of 68 and 104 months, respectively.

Patients with secondary hyperparathyroidism show considerable resistance to erythropoietin, partly due to replacement of cellular components of the bone marrow by fibrous tissue [16]. However, 7 patients in our literature search had secondary hyperparathyroidism along with erythrocytosis. This suggests that erythrocytosis in these patients might be secondary to a mechanism that overcomes hyperparathyroid-induced erythropoietin resistance. Idiopathic elevations in erythropoietin levels might play a role. However, additional unknown factors might be more important. This is supported by the presence of normal erythropoietin levels in 2 patients with erythrocytosis and hyperparathyroidism.

Prior erythropoietin exposure was documented in 2 patients, while there were 5 patients who had never received erythropoietin treatment. Erythropoietin exposure was not mentioned in the rest of the patients with erythrocytosis, which makes it hard to conclude a relation between erythropoietin exposure and erythrocytosis. Our patient in this case report was not on erythropoietin.

Six patients had been previously treated for iron deficiency anemia. Erythrocytosis in these patients can probably be explained by replenishment of iron stores in the context of an already elevated erythropoietin level.

Several treatment options have been used for patients with erythrocytosis following kidney transplant, while it has been poorly studied in dialysis patients with idiopathic erythrocytosis. Angiotensin-converting enzyme

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**Table 2.** Characteristics and findings in dialysis patients with idiopathic erythrocytosis

<table>
<thead>
<tr>
<th>Finding</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis method</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>16 [1, 20–25]</td>
</tr>
<tr>
<td>CAPD</td>
<td>4 [11, 18]</td>
</tr>
<tr>
<td>Reason for ESRD</td>
<td></td>
</tr>
<tr>
<td>ACKD</td>
<td>3 [20–22]</td>
</tr>
<tr>
<td>DM</td>
<td>7 [1, 18, 25]</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>7 [11, 23–25]</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 [24]</td>
</tr>
<tr>
<td>Presence of kidney cysts</td>
<td></td>
</tr>
<tr>
<td>Hereditary</td>
<td>3 [20–22]</td>
</tr>
<tr>
<td>Acquired</td>
<td>7 [1, 23, 24]</td>
</tr>
<tr>
<td>No</td>
<td>10 [11, 18, 24, 25]</td>
</tr>
<tr>
<td>EPO level</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>13 [11, 18, 20–25]</td>
</tr>
<tr>
<td>Normal</td>
<td>6 [18, 24, 25]</td>
</tr>
<tr>
<td>Not available</td>
<td>1 [18]</td>
</tr>
<tr>
<td>Elevated PTH</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 [21, 23, 24]</td>
</tr>
<tr>
<td>Not available</td>
<td>13 [1, 11, 18, 20, 22, 25]</td>
</tr>
<tr>
<td>Prior EPO treatment</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 [1, 21]</td>
</tr>
<tr>
<td>No</td>
<td>5 [10, 11]</td>
</tr>
<tr>
<td>Not available</td>
<td>13 [20, 22–25]</td>
</tr>
<tr>
<td>Received iron supplements</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 [18, 20, 21, 23]</td>
</tr>
<tr>
<td>No</td>
<td>2 [1]</td>
</tr>
<tr>
<td>Not available</td>
<td>12 [11, 22–25]</td>
</tr>
<tr>
<td>Cardiovascular complications</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 [18]</td>
</tr>
<tr>
<td>Not available</td>
<td>17 [1, 11, 20–25]</td>
</tr>
<tr>
<td>Treatment of erythrocytosis</td>
<td></td>
</tr>
<tr>
<td>Phlebotomy</td>
<td>6 [1, 20, 22, 25]</td>
</tr>
<tr>
<td>Not available</td>
<td>14 [11, 18, 21, 23–25]</td>
</tr>
</tbody>
</table>

Total number of patients: 20

ACKD = Adult polycystic kidney disease; DM = diabetes mellitus; EPO = erythropoietin; PTH = parathyroid hormone.
inhibitors and angiotensin receptor blockers are two of the preferred agents in posttransplant erythrocytosis. The underlying mechanism for decreasing erythrocytosis in these patients is not completely understood, but inhibition of the renin-angiotensin system and thus decreasing kidney hypoxia might play a role [3, 11]. Theophylline, antiproliferative agents and intermittent phlebotomies have also been used in posttransplant erythrocytosis [3]. Theophylline is an adenosine antagonist that showed some success in controlling erythrocytosis in dialysis patients with idiopathic erythrocytosis [17]. This suggests that adenosine might have a role in erythropoietin release or the bone marrow response to erythropoietin [3]. Given the high toxicity profile and narrow therapeutic index requiring continuous monitoring of its levels, theophylline is not a recommended treatment option. So far, intermittent phlebotomy is the only reported effective treatment option in dialysis patients with idiopathic erythrocytosis.

Intermittent phlebotomy tends to work well in controlling erythrocytosis. In addition, it is convenient for hemodialysis patients as it can be done during their dialysis sessions, but it might lead to severe iron deficiency in many patients [3].

The target hemoglobin level in these patients is still unknown. Most practitioners cease phlebotomy when hemoglobin levels reach 11–13 mg/dl, which is the same as the target for erythropoietin treatment [1]. Vascular events are well-known complications in erythrocytosis secondary to polycythemia vera. In our literature search, vascular complications were reported in 3 patients. In the rest of the patients, vascular complications were not mentioned. Bender and Piraino [18] reported a patient who developed a stroke after 14 months of erythrocytosis. Another patient developed multiple vascular complications during the course of erythrocytosis, including splenic infarcts, left popliteal artery occlusion and stroke. A third patient developed bilateral lower-extremity ischemia. While ESRD per se is a risk factor for vascular complications, erythrocytosis might add an additional risk for the development of these thrombotic complications, and this mandates more aggressive lowering of hemoglobin and hematocrit levels.

**Conclusions**

Idiopathic erythrocytosis in ESRD patients is a very rare occurrence. At present, there is no clear understanding of the underlying pathophysiology, and there seem to be multiple possible reasons beside an idiopathic increase in erythropoietin level. Hereditary or acquired cystic kidney disease might be a risk factor. However, the common occurrence of kidney cysts and the rarity of erythrocytosis in ESRD make it hard to suggest such a conclusion, and the two findings may be coincidental. We noted that idiopathic erythrocytosis was also reported in diabetic and glomerulonephritis ESRD patients without kidney cysts. Phlebotomy is a successful and easy way to control erythrocytosis in such patients, but iron stores should be monitored closely to prevent iron deficiency. Prospective trials might be needed to establish the target hemoglobin and hematocrit following phlebotomy. Other treatment options such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, which are currently being used in posttransplant erythrocytosis, might also be considered in ESRD patients with erythrocytosis.

**Disclosure Statement**

None.

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