Chapter 23
Anemia Management

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Case Presentation

A 15-year-old white male presented to his primary care physician with complaints of lethargy, poor appetite, and occasional headaches. The patient's mother also reported that her son appeared pale over the past several weeks and that his face appeared to be slightly swollen. Initial physical examination was significant for the patient's pale appearance and the presence of periorbital and pedal edema. Initial BP was 150/105 mmHg. Laboratory data were subsequently obtained and were significant for the findings of a serum creatinine of 15.5 mg/dL and blood urea nitrogen of 165 mg/dL. The patient also had evidence of hyperphosphatemia, secondary hyperparathyroidism (iPTH, 1,056 pg/ml), mild hyperkalemia, hypoalbuminemia (1.5 g/dL), and metabolic acidosis. A complete blood count revealed a normochromic, normocytic anemia with a hemoglobin value of 6.2 g/dL and a hematocrit of 19.0%. A percutaneous kidney biopsy revealed findings compatible with end-stage renal disease (ESRD) secondary to IgA nephropathy as there were <5% viable glomeruli and marked interstitial fibrosis. A right internal jugular hemodialysis catheter was inserted, and thrice weekly chronic hemodialysis was initiated soon thereafter.

Initial evaluation of the patient's anemia, in addition to the red blood cell indices, revealed a reticulocyte count of 1.0% and the absence of occult blood on stool evaluation. Iron studies revealed a serum ferritin of 865 ng/ml and a transferrin saturation of 17%. Treatment with recombinant human erythropoietin (rHuEPO) was started with an intravenous (IV) dose of 50 units/kg in association with each dialysis session, accompanied by IV sodium ferric gluconate 62.5 mg weekly. A multivitamin was

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prescribed to meet vitamin B12 and folate requirements, and both an ACE inhibitor and a calcium channel blocker were prescribed for blood pressure management.

Over the next 3 months, the patient's Hgb gradually rose to 10.6 g/dL with an adjusted IV rHuEPO dose of 3,000 units (60 units/kg) with each dialysis session. The serum ferritin was 500 ng/mL, the TSAT was 22%, and the PTH was 100 pg/ml. The patient's appetite remained somewhat poor prompting his mother to purchase and provide high doses of an over-the-counter zinc supplement (135 mg elemental zinc per day), unbeknown to the medical team. Over the subsequent 6 months, the patient developed a microcytic, hypochromic anemia as his Hgb level progressively fell to 7.2 g/dL despite a stepwise increase of the rHuEPO dose to nearly 400 units/kg/week. The reticulocyte count was only 0.8% and there was mild neutropenia. An intravenous course of replacement iron was provided over eight consecutive dialysis sessions with no improvement. There was no laboratory evidence of either lead or aluminum toxicity or inflammation. Stool evaluation for occult blood remained negative. Remarkably, a thorough review of the patient's medications by a medical student at a routine clinic visit revealed the zinc supplement, and laboratory evaluation provided evidence of zinc toxicity (serum zinc, 2.5 mcg/ml; normal, 0.60–1.2 mcg/ml). As a result of the recognized association between zinc toxicity, copper deficiency, and anemia, the copper status was assessed and revealed evidence of copper deficiency (serum copper, 15 mcg/dL; normal, 63–140 mcg/dL and serum ceruloplasmin, 1.5 mcg/dL; normal, 18–35 mcg/dL). An oral copper supplement was initiated, the zinc supplement was discontinued, and the patient experienced resolution of his anemia despite halving of his rHuEPO dose.

Clinical Questions

1. How common is anemia in association with chronic kidney disease (CKD), and what are the most common contributing factors to its development?
2. What is the etiology of the inadequate production of erythropoietin associated with impaired kidney function?
3. What factors have the greatest influence on the iron status of patients on dialysis and receiving an erythropoietic stimulating agent (ESA)?
4. How is hyporesponsiveness to ESA therapy defined, and what potentially modifiable factors can contribute to this clinical problem?
5. What factors could contribute to the development of copper deficiency and anemia in the chronic dialysis patient?

Diagnostic Discussion

1. The frequency and severity of anemia associated with CKD parallels the degree of renal impairment. The Chronic Kidney Disease in Children (CKiD) study has revealed that a fall in hemoglobin begins when the measured glomerular

filtration rate falls below 43 ml/min/1.73m^2. The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) has reported that >93% of children with stage 5 CKD are anemic [1, 2]. The predominant causes of anemia in children and adults with CKD and ESRD are erythropoietin deficiency and lack of iron availability, as well as inflammation, blood loss, hyperparathyroidism, and vitamin deficiency (B12 and folate) [3]. A number of medications have also been associated with the development of anemia. For example, the frequently used antihypertensive agents, angiotensin-converting-enzyme inhibitors, can increase the serum level of N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), an inhibitor of erythropoiesis [4]. In view of the factors noted above, erythropoietic-stimulating agents (ESA) and iron serve as the mainstays of therapy. The ESA can be provided as a short-acting rHuEPO formulation (e.g., epoetin alfa), or as darbepoetin alfa, an erythropoietin analogue with a 3–4 times longer half-life than rHuEPO [5, 6]. KDIGO has recommended a starting dose of 20–50 IU/kg three times weekly for epoetin and a dose of 0.45 mcg/kg once weekly or 0.75 mcg/kg every 2 weeks for darbepoetin alfa, with a target hemoglobin for children of 11–12 g/dL. Iron therapy is provided by either the oral or intravenous routes with target values of >20% for transferrin saturation and >100 ng/ml for ferritin [7].

2. Erythropoietin (EPO), the product of the erythropoietin gene on chromosome 7, acts by impairing cell apoptosis of erythroid precursor cells. EPO is a 30.4-kDa glycoprotein that is primarily derived from the liver in fetal life, but which is predominantly produced postnatally by the fibroblast-like interstitial cells of the kidney. The production of native erythropoietin involves regulation through the partial pressure of oxygen of the kidney and other organs that produce erythropoietin and the activity of hypoxia-inducible factor (HIF) [8, 9]. Three HIF-α subunits (HIF-1 α, HIF-2 α, and HIF-3 α) have been identified, and HIF-2 appears to have the greatest influence on erythropoietin synthesis. Cells continuously synthesize HIF oxygen-sensitive alpha subunits; degradation is, in turn, the manner in which HIF activity and resultant erythropoiesis is regulated.

   In the typical setting of anemia-related tissue hypoxia in the patient without CKD, the number of erythropoietin-producing cells increases in the corticomedullary region of the kidney. One of the three identified hypoxia-inducible factors (but predominantly HIF-2) stimulates erythropoietin gene transcription by binding to the hypoxia-responsive enhancer on the EPO gene. With normoxia, one of at least three prolyl hydroxylases (PHD) degrades HIF, reducing erythropoiesis.

   In the unique setting of the patient with CKD/ESRD, despite the presence of anemia, decreased renal tissue oxygen utilization and increased tissue oxygen pressure paradoxically result in decreased transcriptional activity of the HIF. Interstitial cells may also convert to myofibroblasts in the setting of severe CKD/ESRD and lose their capacity to produce EPO [10].

3. Two thirds of the body's iron resides in the red blood cells. The majority of iron required for use or storage results from the catabolism of Hgb from senescent red blood cells. Patients on dialysis require additional iron as a result of blood loss secondary to laboratory testing, gastrointestinal blood loss, and, in the hemodi-

alysis patient, blood loss in the dialyzer and tubing and at the vascular access site. In adults, the blood losses are 4–8 times that of healthy individuals [11–13]. As a result of the increased demand for iron in patients receiving therapy with an ESA, iron availability may be suboptimal as a result of absolute iron deficiency or functional iron deficiency, the latter a state in which the extraordinary demand for iron exceeds the ability of transferrin to deliver it to the bone marrow in a sufficient manner. An additional and exceedingly important influence on the iron status is the development of inflammation which may result in elevated levels of the iron-regulatory protein hepcidin [14–16]. Hepcidin, the levels of which are elevated in children and adults with CKD and ESRD following its production in the liver, binds to the cellular iron exporter ferroportin and causes its internalization and degradation. This precludes movement of iron into the circulation per the intestinal enterocytes and sequesters stored iron in macrophages. The mobilization of iron for red blood cell production, along with a decrease in the level of hepcidin, is also regulated by the release of the hormone erythroferrone by EPO-stimulated erythroblasts in the bone marrow. The production of erythroferrone is low when there are reduced numbers of erythroblasts secondary to erythropoietin deficiency and chronic inflammation [17].

4. Hyporesponsiveness to ESA therapy has historically been defined as persistence of a hemoglobin deficit (<11 g/dL) despite a weekly rHuEPO dose in excess of 400 IU/kg or 20,000 IU/week [18]. More recently, the KDIGO guidelines have defined ESA hyporesponsiveness when there have been two increases in the ESA dose up to 50% beyond the dose which had previously been stable, in an effort to maintain a stable Hgb concentration [7]. The same guidelines provide a list of modifiable (e.g., vitamin deficiency, ACEi/ARB usage) and potentially modifiable (e.g., hyperparathyroidism, bleeding) risk factors for ESA hyporesponsiveness and a recommended therapeutic approach (Table 23.1). Excessive increases in the ESA dose are to be discouraged, and doses in excess of 6,000 IU/m^2/week have been associated with poorer patient survival in children receiving chronic peritoneal dialysis (Fig. 23.1) [19].
5. Copper deficiency is diagnosed by the finding of low serum copper and ceruloplasmin levels and can manifest clinically with neutropenia and an ESA-resistant anemia [20]. In cases of severe untreated deficiency, severe neurological manifestations may occur as well. The majority of dietary copper comes from vegetable sources (nuts, chocolate), and approximately 20% comes from meat, fish (particularly shellfish), and poultry. In patients with proteinuric kidney disorders, urinary copper losses can contribute to copper deficiency. In patients on peritoneal dialysis, loss of ceruloplasmin-bound copper into the dialysate can result in copper deficiency [21]. Finally, the ingestion of large quantities of zinc can result in a low copper level. Whereas the tolerable upper intake level (UL) of zinc in adolescents is 34 mg/day, an excessive intake of zinc results in the stimulation of the body's homeostatic mechanisms to limit the intestinal absorption of zinc. This consists of the synthesis of metallothionein, an intracellular ligand within the enterocytes of the small bowel which binds zinc and facilitates its excretion as enterocytes are sloughed into the gut lumen [22, 23]. When high quantities of

Table 23.1. Potentially correctable versus non-correctable factors involved in the anemia of CKD, in addition to ESA deficiency [7]

Easily correctable	Potentially correctable	Impossible to correct
Absolute iron deficiency	Infection/inflammation	Hemoglobinopathies
Vitamin B_{12}/folate deficiency	Underdialysis	Bone marrow disorders
Hypothyroidism	Hemolysis	
ACEi/ARB	Bleeding	
Nonadherence	Hyperparathyroidism	
	PRCA	
	Malignancy	
	Malnutrition	

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin-receptor blocker, *PRCA* pure red cell aplasia

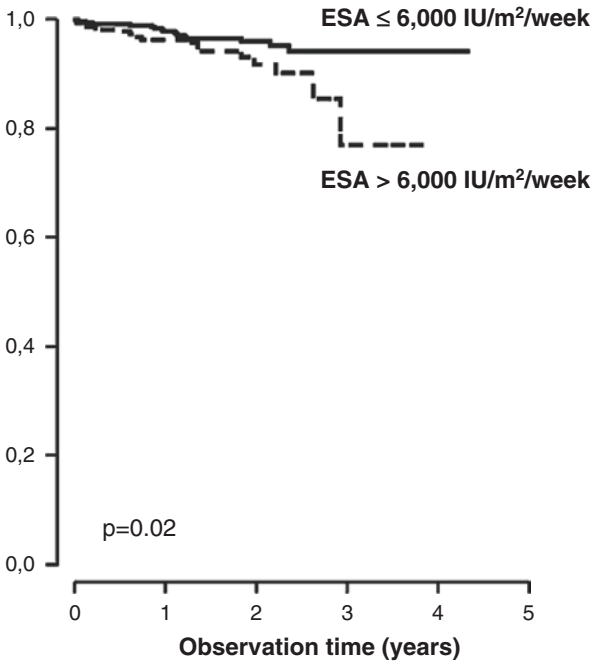

Fig. 23.1 Kaplan-Meier actuarial survival curves for patients with mean administered ESA equivalent dose ≤ or >6,000 IU/m² per week (Used with permission from *The Journal of the American Society of Nephrology* [19])

zinc are ingested, as may occur with enteral feeds or the ingestion of over-the-counter preparations, there is increased synthesis of metallothionein to which copper is competitively and preferentially bound [24]. The copper is unavailable for absorption and is excreted in the feces, contributing to the development of copper deficiency. Excessive intake of dietary iron can also limit copper absorption. Whereas the mechanism of the anemia associated with zinc-induced copper deficiency is unknown, it is likely related to the fact that copper is required for the incorporation of iron into the heme molecule, and when ceruloplasmin activity is decreased, transfer of iron from macrophages to transferrin is compromised. However, normocytic, macrocytic, and microcytic anemias have all been

described in the setting of copper deficiency. Treatment of copper deficiency with oral copper supplementation is typically therapeutic with resolution of anemia and neutropenia within 6 weeks of repletion therapy. Intravenous supplementation may be necessary on occasion.

Clinical Pearls

1. Treatment with rHuEPO and iron are the key components of anemia management in children with CKD and ESRD.
2. Iron availability can be compromised by (a) the development of absolute iron deficiency, (b) the presence of functional iron deficiency as a result of ESA-stimulated erythropoiesis, or (c) inflammation-related sequestration of iron associated with elevated levels of hepcidin.
3. Hyporesponsiveness to ESA therapy can occur secondary to a variety of modifiable or potentially modifiable factors.
4. Copper deficiency can occur secondary to excessive zinc intake and can result in ESA-resistant anemia.

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