Seminars in Dialysis

A Dialysis Case Presentation and Discussion

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"Out of Sight, Out of Mind": The Failed Renal Allograft as a Cause of ESA Resistance

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ABSTRACT

Approximately 10% of patients treated with erythropoiesis-stimulating agents (ESAs) for the anemia of chronic kidney disease are unresponsive or relatively resistant to therapy. The etiology of this is usually linked to iron deficiency or an independent underlying illness. We describe a hemodialysis patient with a failed renal transplant 1.5 years earlier, who developed progressive erythropoietin resistance and anemia without an apparent cause. He simultaneously developed nonspecific malaise and fatigue. By exclusion, the only possible cause of these signs and symptoms was inflammation from acute and chronic rejection in the retained failed renal allograft. Following pulse steroids and transplant nephrectomy, the patient's symptoms resolved and both his hemoglobin improved and his erythropoietin requirements decreased significantly. The patient never required a blood transfusion and was successfully relisted for a deceased donor renal transplant. Hence, inflammation from a retained transplant allograft may be an under-recognized cause of erythropoietin resistance in dialysis patients. Although transplant nephrectomy remains a controversial practice due to concerns of alloantibody production, it may be considered in patients with failed renal allografts and anemia refractory to treatment with ESAs.

Case Report

An 81.5 kg, 30-year-old male kidney transplant recipient with a history of end-stage renal disease (ESRD) due to Alport syndrome returned to dialysis after 10 years of kidney transplant function. He had received a living donor transplant from his father in January 1999 after 3 months on hemodialysis, but developed biopsy-proven chronic rejection requiring reinitiation of hemodialysis in July 2009. He began hemodialysis with a tunneled catheter, and his immunosuppression was tapered over the following 3 months to prednisone 5 mg daily alone. Other medications included lisinopril 20 mg daily, metoprolol 100 mg BID, and sevelamer carbonate 2400 mg TID with meals. The patient did well for over a year, but in December 2010, developed anemia (hemoglobin nadir 6.5 g/dl) that became progressively refractory to high-dose (200 μg/week) darbepoetin therapy (Fig. 1). Multiple stool occult blood tests were negative. Folate and B12 levels were adequate, as were measurements of iron stores (ferritin 250–750 ng/ml, transferrin saturations 25–42%). During this time, he was given "maintenance-dose" IV iron therapy with dialysis (sodium ferric gluconate 62.5 mg every 2 weeks) in addition to the weekly darbepoetin (Fig. 1). His only complaint was nonspecific malaise and fatigue. He denied fevers/chills, abdominal pain, or hematuria, and there was no tenderness or swelling over his failed allograft.

With no other explanation for his symptoms and severe anemia, we suspected erythropoiesis-stimulating agent (ESA) resistance secondary to inflammation of the retained allograft. The patient began a prednisone pulse at 40 mg/day on 6/19/11, with an improvement in his fatigue and malaise within 2 days.

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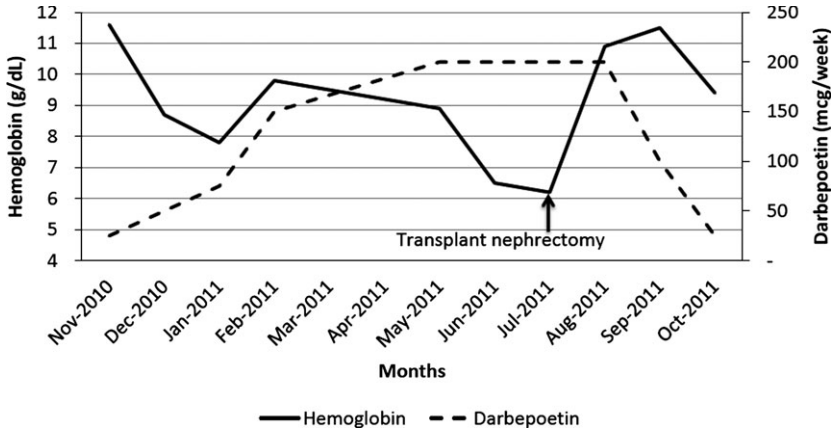

FIG. 1. The patient's hemoglobin levels (solid line, left *y*-axis) and ESA (darbepoetin) requirements (dashed line, right *y*-axis) over time; time of transplant nephrectomy indicated by arrow.

A surgical consult was obtained, and the patient underwent transplant nephrectomy on 6/29/11. Pathology from the explanted kidney showed nephron loss with interstitial fibrosis and severe tubular atrophy in conjunction with extensive acute and chronic cellular rejection. The prednisone was tapered after surgery and eventually discontinued. The patient's hemoglobin rose over the next several months, and his darbepoetin dose requirements decreased significantly to 25 μg/week (Fig. 1). As the patient was a retransplant candidate, he was never transfused (to avoid sensitization). The patient was relisted for a deceased donor kidney transplant and continued to thrive on hemodialysis.

Discussion

Anemia remains one of the major complications of chronic kidney disease (CKD) and end-stage renal disease (ESRD), and is associated with multiple comorbidities, such as decreased cognition and mental acuity, depression, and fatigue (1). Moreover, associations with an increased risk of morbidity and mortality, principally due to cardiac disease and stroke, have also been reported (2–5). The introduction of synthetically manufactured ESAs has revolutionized the management of the anemia of renal disease. While most patients respond well to ESA therapy, a subset of patients is considered ESA-resistant.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) defines ESA hyporesponsiveness as the presence of at least one of the following three conditions: a significant increase in the ESA dose requirement to maintain a certain hemoglobin (Hb) level, a significant decrease in Hb level at a constant ESA dose, or failure to increase the Hb level to greater than 11 g/dl despite an ESA dose equivalent to epoetin greater than 500 IU/kg/week (6). Similarly, European guidelines recommend consideration of ESA resistance when a patient fails to attain the target hemoglobin concentration while receiving more than 300 IU/kg/week (20,000 IU/week) of erythropoietin or 1.5 mg/kg of darbepoetin-alfa (100 mg/week), or has a continued need for such high dosages to maintain the target hemoglobin concentration (7).

In a recent review of causes and management of ESA-resistant anemia in dialysis patients, absolute or functional iron deficiency was cited as the most important cause of ESA hyporesponsiveness, followed by infection and inflammatory conditions (8). The mechanism by which chronic inflammation may cause ESA resistance is complex, and involves decreased production of endogenous erythropoietin, diminished erythropoietin receptor signaling, increased destruction of erythroid progenitor cells, and disruption of iron metabolism through increased hepcidin production (9–12). Addressing the underlying etiology of infection/inflammation (e.g., resection of arteriovenous graft with occult infection), and/or initiation of anti-inflammatory and antioxidant therapies such as ascorbic acid, vitamin E, statins, and oxypentifyllene have been studied for the treatment of ESA resistance with variable success (8,13,14). A recent systematic review, however, concluded that there is inadequate evidence to inform recommendation of any intervention to ameliorate ESA hyporesponsiveness (14). Nonetheless, because a failed renal allograft may be a source of ongoing inflammation, allograft nephrectomy has been proposed to alleviate ESA resistance in dialysis patients with failed renal transplants who demonstrate signs and symptoms of a chronic inflammatory state (15). While this was ultimately the case in our patient, his symptoms of his "chronic inflammatory state" were minimal and only through a high index of suspicion did we consider the otherwise asymptomatic failed allograft as the cause of his ESA resistance.

In the United States, approximately 5000 patients/year require renal replacement therapy (RRT) after kidney transplant failure. Transplant failure is the fourth-leading reason for starting dialysis in the United States (after diabetes, hypertension, and glomerulonephritis) (16). The practice of allograft nephrectomy following transplant failure varies by the duration of primary allograft survival,

with longer surviving grafts less likely to be removed after failure (17). Indications for "late" allograft nephrectomy (>1 year posttransplantation) include symptoms resulting from rejection and necrosis (graft tenderness, fever, hematuria, localized edema, infection) as well as nonspecific symptoms of smoldering rejection (weight loss, fatigue, anemia, and ESA resistance).

In the absence of overt signs/symptoms of rejection, the indications for transplant nephrectomy remain poorly defined. Several small studies suggest that the allograft may act as an "antibody sink," and that nephrectomy may aggravate cytotoxic antibody levels (18–20). However, other investigators have found no increase in anti-HLA antibodies following transplant nephrectomy (21,22). The contradictory findings in these observational studies are difficult to reconcile as the impact of nephrectomy on allo-sensitization may vary depending on the clinical setting and indications for nephrectomy as well as the use of immunosuppressant medications.

In a prospective, single-centered study of 43 incident dialysis patients with failed kidney transplants, transplant nephrectomy was found to improve clinical and laboratory parameters of chronic inflammation (erythrocyte resistance index, ferritin, fibrinogen, C-reactive protein, and erythrocyte sedimentation rate) (15). Moreover, nutritional indices (i.e., albumin, prealbumin) were found to be superior in patients who underwent nephrectomy. These data suggest that nephrectomy may be beneficial to patients with allograft failure by removing a subclinical source of inflammation. However, these benefits must be balanced against the potential risk of the surgery and the potential immune-modulating effects of the procedure. Another larger study using a nationally representative sample of high-risk patients returning to dialysis after failed kidney transplantation corroborated the benefits of transplant nephrectomy (23). After adjustment for potential confounders, receiving an allograft nephrectomy was associated with a 32% lower adjusted relative risk for all-cause death (HR: 0.68; 95% CI: 0.63–0.74). This result was coupled with a subsequent higher crude rate of retransplantation. Whether the mortality benefit seen in this study was due to improvement in anemia and ESA resistance is unknown.

In conclusion, this case report underscores the importance of considering the presence of a chronically inflamed failed renal transplant as the cause of ESA resistance; its symptoms may be nonspecific and easily overlooked. Furthermore, this case supports the potential therapeutic benefit of transplant nephrectomy in the management of erythropoietin resistance in this patient population.

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