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CASE REPORT

An Unusual Etiology of Erythropoietin Resistance: Hyperthyroidism

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Many possible causes of resistance to human recombinant erythropoietin (rh-EPO) have been reported in patients with renal failure. This case presents an unusual cause of erythropoietin-resistant anemia in a patient with chronic renal failure. A 61-year-old male patient who was on chronic hemodialysis program due to diabetic nephropathy for seven months developed erythropoietin resistant anemia. No iron deficiency was revealed by laboratory data, no megaloblastic anemia were found by biochemical investigation, and no inflammatory states including infection or neoplastic diseases were disclosed by abdominal ultrasonography, chest X-ray, bone marrow aspiration and biopsy, or other methods (normal C-reactive protein levels). This hemodialysis patient had epoetin-resistant anemia with primary autoimmune hyperthyroidism. The anti-thyroid therapy was effective not only against the hyperthyroidism but also against his epoetin resistant anemia.

Keywords hemodialysis, erythropoietin resistance, hyperthyroidism

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INTRODUCTION

Many possible causes of resistance to human recombinant erythropoietin (rh-EPO) have been reported in patients with renal failure. The wrong route of epoetin administration, iron deficiency, dialysis inadequacy, dialysis water contamination, inflammation, hyperparathyroidism, aluminium overload, folic acid or vitamin B12 deficiency, vitamin C deficiency, blood loss, carnitine deficiency, drugs like angiotensin converting enzyme inhibitors, malignancy, and hematologic disorders were among these causes reported to decrease response to epoetin.[1]

This case presents an unusual cause of erythropoietin-resistant anemia in a patient with chronic renal failure.

This is the second such report of diminished response to erythropoietin in hemodialysis patients in association with hyperthyroidism.

CASE PRESENTATION

A 61-year-old male patient who was on a chronic hemodialysis program due to diabetic nephropathy for seven months developed erythropoietin-resistant anemia. He had general fatigue for four months. In addition to erythropoietin, his medications were calcium acetate (per oral) 2 × 1gr, 1-25 dihydroxy vitamin D (per oral) 0.5 μg, NPH (neutral protamine hagedorn) insulin (subcutaneous) 10 U/day, and ferric sucrose (intravenous) 100 mg/month. No angiotensin convertase inhibitors or beta blockers were given. On physical examination his weight was 56.5 kg, height was 1.70 m, blood pressure was 130/70 mmHg, pulse rate 92 /min, and temperature 36°C. He was anemic, thyroid was grade 1 palpable, and a pansystolic murmur was heard during heart auscultation. Even though he had been given erythropoietin beta 150 IU/kg/week subcutaneously (according to rules of Turkish Ministry of Finance, erythropoietin doses more than 150 IU/kg/week are not supplied from the budget), he had no response to epoetin therapy for four months. Laboratory studies four months ago revealed the following values: hemoglobin 8.1 gr/dL, leukocyte count 4×10^3 /mm^3, calcium 8.0 mg/dL, phosphorus 5.2 mg/dL, vitamin B12 level 358 pg/mL (normal value: 197–866), folate 20 ng/mL (normal value: 2–9.1), ferritin 388 μg/L, transferrin saturation 51%, high sensitive c-reactive protein 0.30 mg/L, parathyroid hormone (PTH) level 295 pg/mL, recirculation 3%, kt/V 1.3, blood in stool negative. Bone morrow aspiration and biopsy disclosed normal findings. Chest x-ray and abdominal ultrasonography revealed normal findings. Even though erythropoietin therapy was given at a dose of 150 IU/kg/week, no rise in hemoglobin level was noticed. Four months later, hemoglobin was 7.8 gr/dL, leukocyte count was 3.4×10^3/mm^3, PTH was 185 pg/mL, calcium was 8.0 mg/dL, phosphorus was 5.9mg/dL, and kt/V was 1.3. The thyroid function tests results were TSH: 0.03 μIU/mL (normal value: 0.27–4.2), free T4: 2.51 ng/dL (normal value: 0.9–1.7 ng/dL), free T3: 5.91 pg/mL (normal value: 1.8–4.6 pg/mL). Thyroid function was of typical primary hyperthyroid pattern. Thyroid scintigraphy revealed decreased activity of thyroid gland. Anti-thyroid peroxidase autoantibody titre was 248 IU/mL (normal value: <34), and anti-thyroid stimulating hormone (TSH) antibody titre was 3 U/L (normal value: 0–10). A diagnosis of epoetin-resistant anemia associated with autoimmune hyperthyroidism was made. Therapy with an anti-hyperthyroid drug (methimazole; 10mg/day) was initiated from July 2006. After three months of treatment, his free T4 and free T3 levels returned to normal. Normalization of serum thyroid hormone levels was accompanied by improved response to epoetin. Hemoglobin level increased to 11.1 gr/dL with a parallel reduction of erythropoietin dose to 100 u/kg/week. With anti-thyroid treatment, his leukocyte count increased to 5×10^3 /mm^3.

DISCUSSION

The United States National Kidney Foundation Dialysis Outcomes Quality Initiative (NKF-DOQI) determined that hyporesponsiveness to erythropoietin could be defined as such if patients required doses more than 500 IU/kg/week.[2] There are also reports suggesting that other factors might contribute to the decreased responsiveness to rh-EPO in patients requiring doses greater than 125 IU/kg/week.[3] This patient was formerly responsive to 100 IU/kg/week doses of erythropoietin treatment. However, he became symptomatically anemic even after 150 IU/kg/week doses of erythropoietin treatment for four months. No iron deficiency was revealed by laboratory data, no megaloblastic anemia were found by biochemical investigation, and no inflammatory states including infection or neoplastic diseases were disclosed by abdominal ultrasonography and chest X-ray, bone marrow aspiration and biopsy, or other methods (normal C-reactive protein levels). This hemodialysis patient had epoetin-resistant anemia with primary hyperthyroidism. The anti-thyroid therapy was effective not only against the hyperthyroidism but also against his epoetin-resistant anemia. The hematologic alterations (such as anemia, leucopenia, and light thrombocytopenia) were reported in patients with hyperthyroidism and normal renal functions.[4] Although the mechanism of anemia in hyperthyroidism is unclear, several mechanisms were suspected. These disorders might be related to the reduced life span of whole blood components and/or to autoimmune mechanism or impaired iron utilization by erythropoietic cells.[5,6] Erythropoietin resistance in patients with hyperthyroidism might be due to subnormal red blood cell carbonic anhydrase I concentration.[7]

As far as we know, this is the second case with erythropoietin-resistant anemia associated with primary hyperthyroidism.[8] As a result, hyperthyroidism should be explored for erythropoietin resistance in every hemodialysis patient.

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