The Resection of Thyroid Cancer Was Associated with the Resolution of Hyporesponsiveness to an Erythropoiesis-stimulating Agent in a Hemodialysis Patient with Aceruloplasminemia

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Abstract

We herein report the case of a hemodialysis patient whose response to an erythropoiesis-stimulating agent (ESA) improved following the resection of thyroid cancer. Her hemoglobin level remained below 7 g/dL, despite the use of ESA. During the search for the causes of her hyporesponsiveness to ESA, papillary thyroid cancer and aceruloplasminemia were found. The existence of other potential causes, such as iron deficiency, infectious disease, severe hyperparathyroidism and malnutrition were ruled out. Following the resection of the thyroid cancer tumor, her hemoglobin level increased to 10.2 g/dL over a period of 4 months. This is the first report to demonstrate the resolution of hyporesponsiveness to ESA following the resection of a malignant tumor.

Key words: hyporesponsiveness to an erythropoiesis-stimulating agent, hemodialysis, thyroid cancer, aceruloplasminemia

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Introduction

In hemodialysis (HD) patients, anemia is usually caused by the inadequate production of erythropoietin; in most cases, it is cured by the administration of an erythropoiesis-stimulating agent (ESA) (1). Hyporesponsiveness to ESA is known to be caused by several factors, including iron deficiency, infectious disease, inadequate dialysis, severe hyperparathyroidism, malnutrition, vitamin deficiency, hematopoietic malignancy and hemolysis (2, 3). Non-hematopoietic tumors are also listed as a cause of ESA resistance in HD patients (2, 3). In patients with malignant tumors, several factors caused by malignant tumors, such as bleeding, malnutrition, infection and bone marrow suppression (caused by chemotherapy and radiotherapy) may contribute to the development of hyporesponsiveness to ESA. In addition, the existence of a malignant tumor itself is suggested to cause hyporesponsiveness to ESA through the production of inflammatory cytokines (4-6). However, no previous reports have demonstrated that the resection of a malignant tumor may lead to an improvement of ESA resistance.

We herein report the case of an HD patient with papillary thyroid cancer and hyporesponsiveness to ESA. Her hemoglobin level reached the target level following the resection of thyroid cancer.

Case Report

A 64-year-old woman was referred to our hospital to undergo HD. She had a past history of hepatic yersiniosis at 37 years of age. At that time, she was diagnosed with he-
After the initiation of HD, the patient’s edema disappeared, and her urinary protein excretion decreased to 800 mg/day. Her medical records from the first hospital showed that her hemoglobin (Hb) level had gradually decreased in conjunction with an increase in her Scr level. Her Hb level had been above 11 g/dL 5 years previously, when her Scr was 0.9 mg/dL. Two years previously, when her Scr level was 1.53 mg/dL, her Hb level was 10 g/dL. Her Hb level then gradually decreased to 7.2 g/dL as her Scr level increased. In contrast, her white blood cell (WBC) and blood platelet (Plt) counts had been within the normal limits up until one month prior to her admission to our hospital. The start of HD and the administration of ESA normalized the WBC (6,960/μL) and Plt (15.5×10⁴/μL) counts within three weeks. However, her Hb level remained below 7 g/dL, despite the intravenous administration of darbepoetin alfa (DA) (60 μg) once per week for 12 weeks (Fig. 1). According to these findings, the patient was diagnosed with hyporesponsiveness to ESA.

The patient had a good appetite and was able to consume a 1,400 kcal hospital meal before and after the introduction
of HD. Her general condition was good, and she had no signs of infection or chronic inflammatory diseases. Her serum CRP level was between 0.08 and 0.22 mg/dL.

Fecal immunochemical tests for hemoglobin were negative and genital bleeding was excluded. Her anemia was associated with a low reticulocyte count, low serum Fe levels and high serum ferritin levels, which suggested defective iron utilization. Her serum intact PTH level was high before the start of HD, but decreased to 138 pg/mL after 6 weeks of HD. The intravenous administration of vitamin C, which contains a papillary thyroid tumor (11×11×8 mm), was used to treat her low serum vitamin C level, did not increase her Hb level.

A computed tomography (CT) scan revealed a tumor mass in the right lobe of the thyroid gland (Fig. 2). She was diagnosed with papillary thyroid cancer based on the fine-needle aspiration cytology of the mass in the thyroid gland. Two units of red blood cells (comparable to 400 mL of whole blood) were transfused just before the operation. We did not administer iron due to the patient’s aceruloplasminemia.

After the resection of the right lobe of the thyroid gland, which contained a papillary thyroid tumor (11×11×8 mm), her Hb level increased to 7.9 g/dL at 1 month and 10.2 g/dL at 3 months; this level was maintained while the dose of DA was reduced to 30 μg once a week. The operation also normalized the serum level of albumin. In contrast, the serum ferritin level remained high.

![Figure 2](image_url). A contrast-enhanced computed tomography image of the thyroid gland. A low-density area was observed in the right lobe.

| Date | Hb (g/dL) | Ferritin (ng/mL) | Reticulocyte count/μL |
|------|----------|-----------------|-----------------------|
| 3/21 | 10.2     | 136.6           | 0.5                   |
| 4/20 | 175      | 146.4           | 0.5                   |
| 5/20 | 177.2    | 175.3           | 0.5                   |
| 6/19 | 175      | 146.4           | 0.5                   |
| 7/19 | 175      | 177.2           | 0.5                   |
| 8/18 | 30       | 136.6           | 0.5                   |
| 9/17 | 30       | 175            | 0.5                   |
| 10/17| 30       | 175            | 0.5                   |
| 11/16| 30       | 175            | 0.5                   |

**Figure 1.** The time course of the laboratory data following the introduction of hemodialysis. After the introduction of hemodialysis, the patient’s hemoglobin (Hb) level was <7 g/dL, despite the use of 60 μg of intravenous darbepoetin alfa (DA) once a week for 12 weeks. After the resection of the thyroid cancer tumor, the Hb level increased to 10.2 g/dL at 3 months. This was maintained while the dose of DA was reduced to 30 μg once a week. The operation also normalized the serum level of albumin. In contrast, the serum ferritin level remained high.
In HD patients, anemia is primarily caused by the inadequate production of erythropoietin. In most cases, it is corrected by the administration of ESA (1). However, in some HD patients, the response to ESA is attenuated. The Japanese Society for Dialysis Therapy guidelines for renal anemia in chronic kidney disease define hyporesponsiveness to ESA therapy as the failure to achieve the correction of anemia in chronic kidney disease define hyporesponsiveness to ESA. We did not give her iron, as iron deposition in the liver and brain due to aceruloplasminemia was suspected based on the findings of T2-weighted magnetic resonance imaging.

During the investigation to identify the cause of the patient’s hyporesponsiveness to ESA, a high serum PTH level, a low serum vitamin C concentration, a low serum level of Cu and papillary thyroid cancer were identified as potential causes. Other factors that have been reported to induce hyporesponsiveness to ESA, including continuous blood loss, chronic infection, bone marrow suppressive diseases, malnutrition, inadequate dialysis, and Zn deficiency, were not detected. In the present case, thiamazole was discontinued after the resection of the thyroid tumor. Thiamazole is a known cause of anemia in patients with aplastic anemia (7). However, it is unlikely that the resolution of the hyporesponsiveness to ESA in the present case was a result of the discontinuation of thiamazole, since the patient’s WBC and Plt counts had already increased before the discontinuation of thiamazole.

Neither the decrease in the serum PTH level after the initiation of HD nor the administration of vitamin C were associated with an increase in the Hb level. The low serum Cu levels were associated with low serum levels of ceruloplasmin and a missense mutation of G969S in exon 17 of the ceruloplasmin gene (8). According to these findings, the patient was diagnosed with aceruloplasminemia. Aceruloplasminemia is an autosomal recessive inherited disorder that was first reported by Miyajima et al. in 1987 (9). It is characterized by retinal degeneration, diabetes mellitus, and adult-onset extrapyramidal system disorder. Only 71 cases of aceruloplasminemia have so far been reported in the literature (10). The impairment of the ceruloplasmin function causes iron overload in several organs, including the liver, pancreas and brain (11). Hepatic yersiniosis and hepatic hemosiderosis, which had been diagnosed when our patient was 37 years of age (12), were retrospectively determined to have been caused by aceruloplasminemia. Because aceruloplasminemia is frequently

Figure 3. T2-weighted magnetic resonance images of the liver (A) and the basal ganglia in the brain (B). Abnormal hypointensity was observed on T2-weighted magnetic resonance imaging of the liver and brain.
IL-6 or TNF-α siveness to ESA.

thyroid cancer tumor itself contributed to her hyporesponsiveness to ESA. These findings suggested that the presence of both increased serum levels of inflammatory cytokines, such as IL-6 or TNF-α, have been reported to contribute to anemia and hyporesponsiveness to ESA in patients with malignant diseases (4-6). In addition, inflammatory cytokines, such as IL-6 and TNF-α, have been reported to suppress hepatic albumin synthesis in HD patients (14, 15). In the current case, both the resolution of the patient’s hyporesponsiveness to ESA and an increase in the patient’s serum albumin level were observed in parallel after the resection of her thyroid cancer tumor. It is therefore possible that inflammatory cytokines played some role in the development of the patient’s hyporesponsiveness to ESA. However, we cannot make any definitive conclusions regarding the role of inflammatory cytokines in this case because we did not evaluate the serum levels of inflammatory cytokines. Since the patient’s ferritin and TSAT levels were not affected by the resection of the thyroid cancer tumor, the resolution of the hyporesponsiveness to ESA seems to have been mediated by something other than improved iron utilization.

Aceruloplasminemia is characterized by the accumulation of iron in many organs due to a lack of ceruloplasmin ferr oxidase activity, which is caused by mutations in the ceruloplasmin gene (10). Iron has been linked to carcinogenesis and the hepatic deposition of iron is listed as a risk factor for hepatocellular carcinoma (16). In addition, the incidence rates of hepatocellular and non-hepatocellular malignancies are reported to be high in patients with hereditary hemochromatosis (17). Moreover, the incidence of papillary thyroid microcarcinoma with iron overload is reported to be significantly high in patients with thalassemia (which causes iron overload) (18, 19). Berlin staining of the resected thyroid gland showed iron deposition in the normal lymph follicular tissue surrounding the papillary carcinoma in the present case (Fig. 5). The causative role of iron deposition in the development of thyroid cancer in our patient remains unclear. The complication of cancer in patients with aceruloplasminemia should be evaluated in future studies. Hyporesponsiveness to ESA may relapse with the recurrence of thyroid cancer or with the progression of aceruloplasminemia. For these reasons, we need to follow up the present case carefully.

In conclusion, we reported the case of an HD patient with papillary thyroid cancer and hyporesponsiveness to ESA. Her Hb level reached the target level after the resection of her thyroid cancer tumor. This is the first case to report the resolution of hyporesponsiveness to ESA in an HD patient with a malignant tumor following the resection of the malignant tumor.

The authors state that they have no Conflict of Interest (COI).

References
1. Eschbach JW, Egie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin: results of a combined phase I and phase II clinical trial. N Engl J Med 316: 73-78, 1987.
2. Tsukahara Y, Nishi S, Akiba T, et al. 2008 Japanese Society for Dialysis Therapy: guidelines for renal anemia in chronic kidney disease. Ther Apher Dial 14: 240-275, 2010.
3. Locatelli F, Aljama P, Bárány P, et al.; European Best Practice Guidelines Working Group. Revised European Best Practice Guidelines for the Management of Anemia in Patients with Chronic Renal Failure. Nephrol Dial Transplant 19 (Suppl 2): ii1-i47, 2004.
4. Dicato M, Plawny L, Diederich M. Anemia in cancer. Ann Oncol 21 (Suppl 7): viii167-viii172, 2010.
5. Pavese I, Satta F, Todi F, et al. High serum levels of TNF-α and IL-6 predict the clinical outcome of treatment with human recombinant erythropoietin in anaemic cancer patients. Ann Oncol 21: 1523-1528, 2010.
6. Smržová J, Jozsef Balla J, Bárány P. Inflammation and resistance to erythropoiesis-stimulating agents: what do we know and what needs to be clarified? Nephrol Dial Transplant 20 (Suppl 8): viii2-
viii7, 2005.

7. Tajiri I, Noguchi S, Murakami T, Murakami N. Antithyroid drug-induced agranulocytosis. The usefulness of routine white blood cell count monitoring. Arch Intern Med 150: 621-624, 1990.

8. Kono S, Suzuki H, Takahashi K, et al. Hepatic iron overload associated with a decreased serum ceruloplasmin level in a novel clinical type of aceruloplasminemia. Gastroenterology 131: 240-245, 2006.

9. Miyajima H, Nishimura Y, Mizoguchi K, Sakamoto M, Shimizu T, Honda N. Familial apoceruloplasmin deficiency associated with blepharospasm and retinal degeneration. Neurology 37: 761-767, 1987.

10. Miyajima H. Aceruloplasminemia. Neuropathol 35: 83-90, 2015.

11. Kaneko Y, Miyajima H, Piperno A, et al. Measurement of serum hepcidin-25 levels as a potential test for diagnosing hemochromatosis and related disorders. J Gastroenterol 45: 1163-1171, 2010.

12. Kitayama J, Osada T, Hamaguchi M, et al. A case report of hepatic abscess due to Yersinia entercolitica associated with hemosiderosis. The Japanese Journal of Gastroenterological Surgery 21: 2603-2606, 1988 (in Japanese).

13. Miyajima H. Aceruloplasminemia. Pagon RA, Adam MP, Ardinger HH, et al., Eds. GeneReviews® [Internet]. 2003 Aug 12; Updated 2015 Nov 5. University of Washington, Seattle. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1493/.

14. Bologa RM, Levine DM, Parker TS, et al. Interleukin-6 predicts hypoalbuminemia, hypocholesterolemia, and mortality in hemodialysis patients. Am J Kidney Dis 32: 107-114, 1998.

15. Kaysen GA, Stevenson FT, Depner TA. Determinants of albumin concentration in hemodialysis patients. Am J Kidney Dis 29: 658-668, 1997.

16. Deugnier Y, Turlin B. Iron and hepatocellular carcinoma. J Gastroenterol Hepatol 6: 491-494, 2001.

17. Geier D, Hebert B, Potti A. Risk of primary non-hepatocellular malignancies in hereditary hemochromatosis. Anticancer Res 22: 3797-3799, 2002.

18. De Sanctis V, Campisi S, Fiscina B, Soliman A. Papillary thyroid microcarcinoma in thalassaemia: an emerging concern for physicians? Georgian Med News 210: 71-76, 2012.

19. Poggi M, Sorrentino F, Pascucci C, et al. Malignancies in β-thalassemia patients: first description of two cases of thyroid cancer and review of the literature. Hemoglobin 35: 439-446, 2011.

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