INTERNAL MEDICINE

□ CASE REPORT □

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-

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Table. The Laboratory Data at the Initiation of Hemodialysis.

Hematology			**Blood biochemistry**		
WBC	2,980	/μL	Total protein	5.7	g/dL
Neutrophil	71.5	%	Albumin	3.1	g/dL
Eosinophil	2.0	%	BUN	93.1	mg/dL
Basophil	1.0	%	Creatinine	8.06	mg/dL
Monocyte	6.5	%	AST	16	IU/L
Lymphocyte	19.0	%	ALT	14	IU/L
RBC	294×10^4	/μL	LDH	263	IU/L
Hemoglobin	7.2	g/dL	CPK	51	IU/L
MCV	80	fl	Na	139	mEq/L
MCHC	30.6	%	K	6.6	mEq/L
Platelet	9.4×10^4	/μL	Cl	105	mEq/L
Reticulocyte count	1.9×10^4	/μL	Ca	6.9	mg/dL
Immunological data			P	6.2	mg/dL
C3	81	mg/dL	Glucose	171	mg/dL
C4	24.8	mg/dL	HbA1c (NGSP)	6.9	%
CH50	48	U/mL	CRP	0.22	mg/dL
ANA	160	times	Fe	15	μg/dL
HOMOGENE	160	times	TIBC	269	μg/dL
MPO-ANCA	<0.5	IU/mL	Ferritin	269.9	ng/mL
PR3-ANCA	<0.5	IU/mL	Ceruloplasmin	2.3	mg/dL
Urinalysis			Copper	9	μg/dL
PH	7		Zinc	53	μg/dL
Specific Gravity	1.010		Vitamin C	1.6	μg/mL
Protein	3+		**Endocrinological data**		
Sugar	-		Free T_3	2.23	pg/mL
Occult Blood	±		Free T_4	1.07	ng/dL
Protein/Creatinine	5.27	g/g•cre	TSH	0.34	μIU/mL
Arterial blood gas analysis			intact PTH	393	pg/mL
pH	7.343				
HCO_3	24.9	mmol/L			

WBC: white blood cell, RBC: red blood cell, MCV: mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration, CRP: C-reactive protein, ANA: anti-nuclear antibody, HOMOGENE: homogeneous pattern

patic hemosiderosis and diabetes mellitus. She had been taking an oral hypoglycemic agent since she was 51 years of age, as well as an antihypertensive agent (candesartan, amlodipine) and thiamazole for thyroid dysfunction. She had a family history of diabetes mellitus and hypertension, but no family history of anemia, hepatic disease, neurological disease or thyroid disease. A physical examination at the time of admission revealed the following: body height, 140 cm; body weight, 44 kg; blood pressure, 130/60 mmHg; pulse rate, 68 beats/min; and pretibial edema. The patient's serum creatinine (Scr) level was elevated (7.55 mg/dL) and abdominal ultrasound revealed that both kidneys were atrophic (right: 74×38 mm, left: 81×38 mm). We therefore diagnosed the patient with irreversible chronic renal failure and initiated HD 3 times a week (4 hours per session) using a polysulfone membrane (RENAK PS-1.3, Kawasumi Laboratories, Tokyo, Japan) and dialysate with an endotoxin level < 0.001 EU/mL. The laboratory data from the initiation of HD showed proteinuria, anemia, leukocytopenia, thrombocytopenia, hypoalbuminemia, increased BUN and Scr levels, hyperkalemia, hypocalcemia and hyperphosphatemia (Table). 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 (15.5×10^4/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

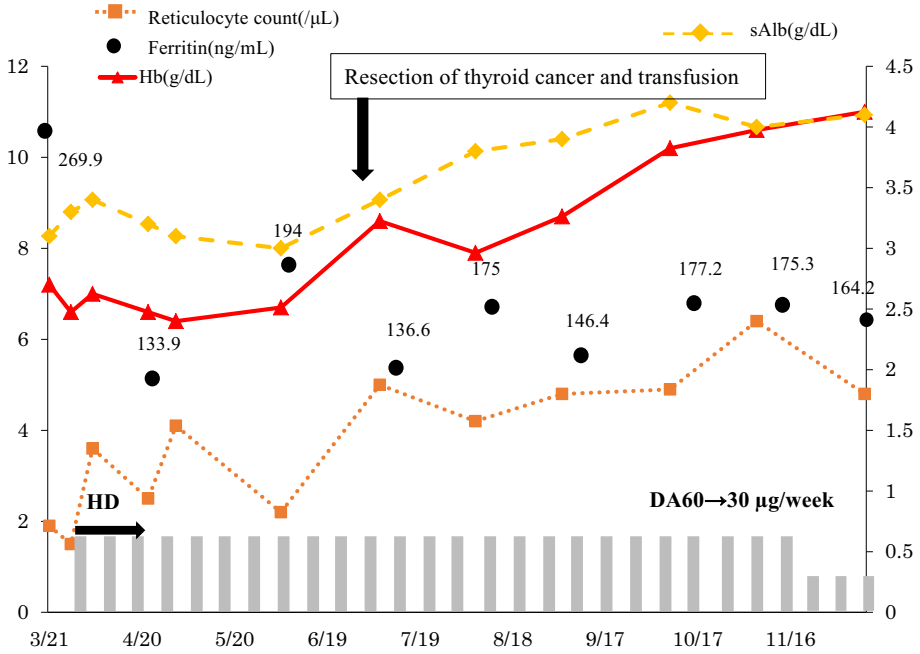

Figure 1. **The time course of the laboratory data following the introduction of hemodialysis. After the introduction of hemodialysis, the patient's hemoglobin (Hb) level was <7 g/dL, despite the use of 60 μg of intravenous darbepoetin alfa (DA) once a week for 12 weeks. After the resection of the thyroid 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.**

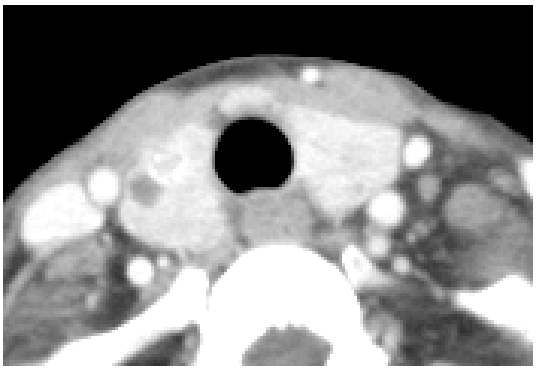

Figure 2. **A contrast-enhanced computed tomography image of the thyroid gland. A low-density area was observed in the right lobe.**

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 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.

After the operation, there were no marked changes in the patient's nutritional state. Her body weight was between 39.6 and 40.3 kg, and the single-pool Kt/V for urea before and after the operation was 1.73 and 1.91, respectively.

Although there was a slight decrease in the patient's serum ferritin level, it remained high (Fig. 1). In parallel with the increase in the patient's Hb level, her serum albumin level increased from 3.3 g/dL to 3.8 g/dL at 1 month and 4.2 g/dL at 3 months after the operation. The patient's transferrin saturation (TSAT) was not affected by the resection of the thyroid tumor (4.6-5.5% before and 4.0-6.8% after the operation).

During the investigation to determine the cause of the patient's hyporesponsiveness to ESA, low serum levels of Cu and ceruloplasmin were noted. Abnormal hypointensity was observed on T2-weighted magnetic resonance imaging of the liver, as well as in the bilateral dentate nucleus, caudate nu-

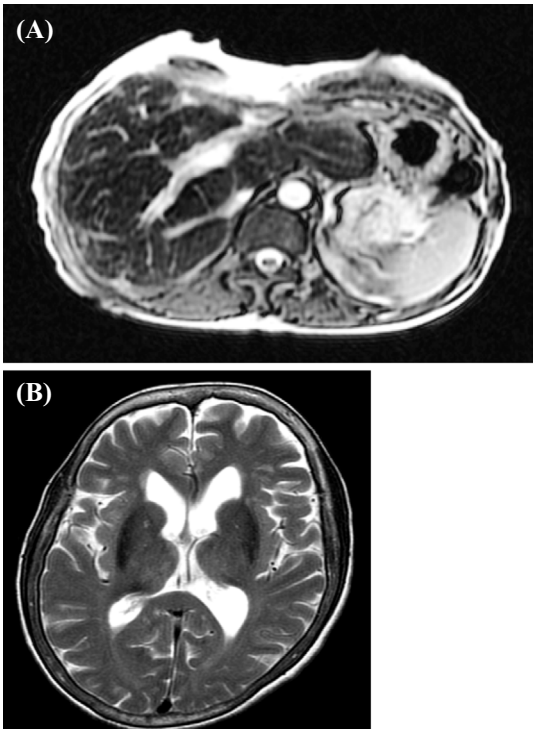

Figure 3. **T2-weighted magnetic resonance images of the liver (A) and the basal ganglia in the brain (B). Abnormal hypointensity was observed on T2-weighted magnetic resonance imaging of the liver and brain.**

cleus, putamen and thalamus of the brain were observed (Fig. 3); this was compatible with the deposition of iron in these organs. A physical examination revealed no retinal changes and no neurological abnormalities, such as cerebellar ataxia, involuntary movement, or dementia. A genetic analysis, which was performed after obtaining the patient's informed consent, revealed a G969S missense mutation in exon 17 of the ceruloplasmin gene (Fig. 4). According to these findings, the patient was diagnosed with aceruloplasminemia. The low serum levels of Cu and ceruloplasmin were not affected by the initiation of HD or the resection of the thyroid cancer tumor.

Discussion

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 and a target Hb level despite the use of rHuEPO (3,000 IU/dose, intravenously) 3 times a week or DA (60 μg, intravenous) once per week in a patient without iron deficiency (2). In the current case, the patient's serum ferritin level was elevated and her Hb level remained below 7 g/dL at 12 weeks after the initiation of intravenous DA (60 μg/week), indicating hyporesponsiveness to ESA. We did not

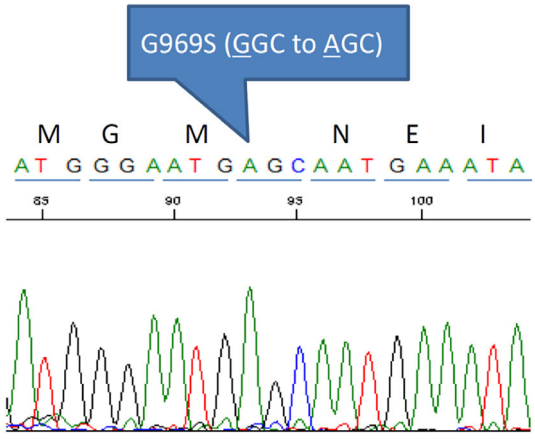

Figure 4. **A genetic analysis performed after obtaining the patient's informed consent revealed a G969S missense mutation in exon 17 of the ceruloplasmin gene.**

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 in the ceruloplasmin gene, which is reported to cause aceruloplasminemia (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

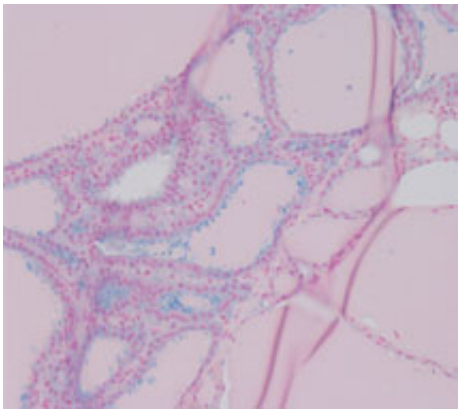

Figure 5. Berlin blue staining of a resected thyroid gland to detect iron deposition. Berlin blue staining of the resected thyroid gland showed iron deposition in the normal lymph follicular tissue surrounding the papillary carcinoma.

associated with anemia due to defective iron utilization (13), it is possible that the patient's hyporesponsiveness to ESA was caused by defective iron utilization due to aceruloplasminemia. However, the patient did not develop anemia before the decrease in her glomerular filtration rate, and the response to ESA improved following the resection of her thyroid tumor. Thus, aceruloplasminemia was not the main cause of hyporesponsiveness to ESA in the present case.

In this case, the patient's response to ESA improved after the resection of the thyroid cancer tumor, suggesting that the patient's thyroid cancer contributed to her anemia. In patients with malignant diseases, anemia can be caused by various factors, including bleeding, malnutrition, bone marrow suppression due to chemotherapy and radiotherapy, and coexisting infectious disease. In the current case, the patient had no history of chemotherapy or radiotherapy. Her general condition was good and she had a good appetite. She was able to consume the 1,400 kcal (30 kcal/kg body weight) hospital meal. The physical findings and laboratory tests did not demonstrate signs of continuous bleeding or infectious diseases. These findings suggested that the presence of the thyroid cancer tumor itself contributed to her hyporesponsiveness to ESA.

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 ferroxidase 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).

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