

Diagnostic Challenges of ESA-Resistant Anemia with MDS-Like Marrow Abnormalities: The Importance of Excluding Reversible Causes

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Introduction. Erythropoiesis-stimulating agent (ESA) hypo-responsiveness in elderly patients undergoing maintenance hemodialysis is frequently multifactorial and may be difficult to distinguish from anemia associated with primary bone marrow disorders.

Case Report. We report an 89-year-old man with ESA-resistant, transfusion-dependent anemia. Bone marrow examination demonstrated dysplastic megakaryocytic changes and isolated loss of the Y chromosome, raising concern for an underlying clonal marrow disorder. However, serum copper and ceruloplasmin levels showed no evidence of copper deficiency, and no zinc excess was identified. Hematologic improvement occurred during a period in which pneumonia and volume overload improved; however, luspatercept had previously been administered while ESA and intravenous iron therapy were continued, precluding attribution of the response to any single intervention.

Conclusions. This case highlights the importance of integrating MDS-like marrow findings with systematic and longitudinal assessment of potentially reversible contributors to ESA hypo-responsiveness, because marrow abnormalities and reversible causes of impaired erythropoiesis may coexist in elderly hemodialysis patients.

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INTRODUCTION

Erythropoiesis-stimulating agent (ESA) hypo-responsiveness in patients receiving maintenance hemodialysis may result from several coexisting conditions, including iron deficiency or impaired iron availability, infection and inflammation, inadequate dialysis, nutritional abnormalities, secondary hyperparathyroidism, occult blood loss, and trace-element deficiencies.^{1,2} Accordingly, potentially reversible causes should be systematically assessed before anemia is attributed to a primary bone marrow disorder.

The diagnostic process becomes more complex in older patients because age-related clonal hematopoiesis and morphologic dysplasia may be detected in the bone marrow even in the absence of definite myelodysplastic syndrome (MDS).^{3,8,9} In addition, acquired metabolic abnormalities, including copper deficiency, can produce cytopenias and marrow changes resembling MDS.^{4,5} Thus,



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the presence of marrow dysplasia or an isolated cytogenetic abnormality does not necessarily establish that a clonal myeloid disorder is the principal cause of ESA hypo-responsiveness.

We describe an elderly patient on maintenance hemodialysis who developed transfusion-dependent ESA-resistant anemia together with megakaryocytic dysplasia and isolated loss of the Y chromosome. Despite these MDS-like findings, the severity of anemia changed in parallel with inflammatory activity, iron availability, and volume status. This case illustrates the importance of integrating bone marrow findings with a systematic and longitudinal assessment of potentially reversible contributors to ESA hypo-responsiveness.

CASE REPORT

An 89-year-old Japanese man with end-stage renal disease secondary to hypertensive nephrosclerosis had undergone maintenance HD for approximately three years. Hemoglobin levels were initially maintained at 9–10 g/dL with darbepoetin alfa

and intravenous iron.

Approximately 24 months after HD initiation, anemia progressively worsened despite escalation of ESA therapy. Laboratory testing demonstrated severe iron-restricted erythropoiesis with TSAT below 10% despite intravenous iron supplementation, and the patient became transfusion dependent.

Bone marrow aspiration performed because of persistent ESA-resistant anemia demonstrated normocellular marrow with dysplastic megakaryocytic changes involving 10–50% of cells, 0.6% blasts, no ring sideroblasts, and isolated loss of the Y chromosome in 4 of 20 metaphases. Serum copper and ceruloplasmin levels showed no evidence of overt copper deficiency, whereas serum zinc levels were below the reference range. Upper gastrointestinal endoscopy showed no evidence of gastrointestinal bleeding or malabsorption (Table).

Because the cause of persistent transfusion-dependent ESA hypo-responsiveness remained uncertain despite extensive evaluation and the bone marrow findings raised concern for an

Longitudinal Clinical and Laboratory Findings During the Course of ESA Hypo-responsiveness

	Reference Range	Month 28 ^a	Month 32 ^b	Month 34 ^c	Month 36 ^d	Month 37 ^e
WBC, / μ L	6,600 to 8,100	4,600	7,000	3500	5900	5900
Hemoglobin, g/dL	13.7 to 16.8	8.2	7.6	6.9	8.7	9.7
Hematocrit (%)	40.7 to 50.1	27.5	26.2	23.3	28.8	31.8
Platelet, $\times 10^3$ / μ L	158 to 348	196	90	135	181	180
CRP, mg/dL	0.00 to 0.14	0.2	7.2	4.1	0.42	0.11
Ferritin, ng/mL	21 to 274	60	59	68	43	112
TSAT (%)	> 20	6	9	7	12	22
Reticulocyte (%)	0.1 to 2.6	1.0	2.1	0.9	1.1	2.2
Albumin, g/dL	4.1 to 5.1	3.1	2.9	2.7	2.9	3.1
Zinc, μ g/dL	80 to 130	54	66	44	49	48
Copper, μ g/dL	66 to 130	97	132	114	101	96
Ceruloplasmin, mg/dL	21 to 37	25	35	33	28	25
hANP, pg/mL	0 to 43	129	292	446	158	76
Folate, ng/mL	3.6 to 12.9	-	4.1	-	-	-
Vitamin B12, pg/mL	233 to 914	-	297	-	-	-
AST / ALT, U/L	13 to 30 / 10 to 42	12 / 8	28 / 16	25/6	14/3	13/2
γ -GTP, U/L	13 to 64	33	36	62	60	42
Fibrinogen, mg/dL	150 to 400	-	248	-	-	-
PT (%) / aPTT, sec	70 to 130 / 24 to 34	-	71 / 24.8	-	-	-
Fecal occult blood	Negative	Negative	Negative	-	-	-
Ca/P, mg/dL	8.8 to 10.1/2.7 to 4.6	8.4/3.6	8.3/4.7	8.1/3.2	8.5/3.5	9.3/3.3
Intact PTH, pg/mL	10 to 65	110	160	93	34	93
Kt/V	≥ 1.2 (target ≥ 1.4)	1.27	1.45	1.52	1.55	1.64

Note: ^aAt progression of transfusion-dependent anemia

^bAt admission for pneumonia

^cDuring persistent inflammation after pneumonia

^dDuring recovery from inflammation and volume overload

^eAfter improvement of inflammatory activity and iron availability

underlying clonal myeloid disorder, luspatercept was introduced and administered four times between months 28 and 32. During follow-up, the patient developed pneumonia accompanied by pleural effusion, elevated C-reactive protein, thrombocytopenia, and marked elevation of human atrial natriuretic peptide, suggesting concomitant inflammation and volume overload. Treatment with ceftriaxone together with gradual reduction of dry weight improved inflammatory activity and fluid status (Figure 1).

Following resolution of pneumonia and optimization of volume status, hemoglobin increased to > 9 g/dL without additional transfusion. Platelet count recovered in parallel with improvement of inflammation. Because luspatercept had previously been administered four times between months 28 and 32 while ESA and intravenous iron therapy were continued, a delayed or contributory effect of luspatercept on the subsequent hematologic recovery could not be excluded. Therefore, the hematologic response could not be attributed to

any single intervention (Figures 1 and 2).

DISCUSSION

This case demonstrates the difficulty of assigning a single cause to severe ESA hypo-responsiveness in an older patient receiving maintenance hemodialysis when abnormalities suggestive of a clonal marrow disorder are also present. ESA hypo-responsiveness in dialysis patients may arise from multiple and frequently overlapping conditions, including absolute or functional iron deficiency, infection and inflammation, blood loss, inadequate dialysis, malnutrition, secondary hyperparathyroidism, vitamin or trace-element deficiencies, and hematologic disorders.^{1,2} Therefore, identification of a bone marrow abnormality does not eliminate the need to assess concurrent and potentially reversible contributors to anemia.

Bone marrow examination in our patient demonstrated megakaryocytic dysplasia involving 10–50% of cells and isolated loss of the Y chromosome (LOY) in 4 of 20 metaphases, with a

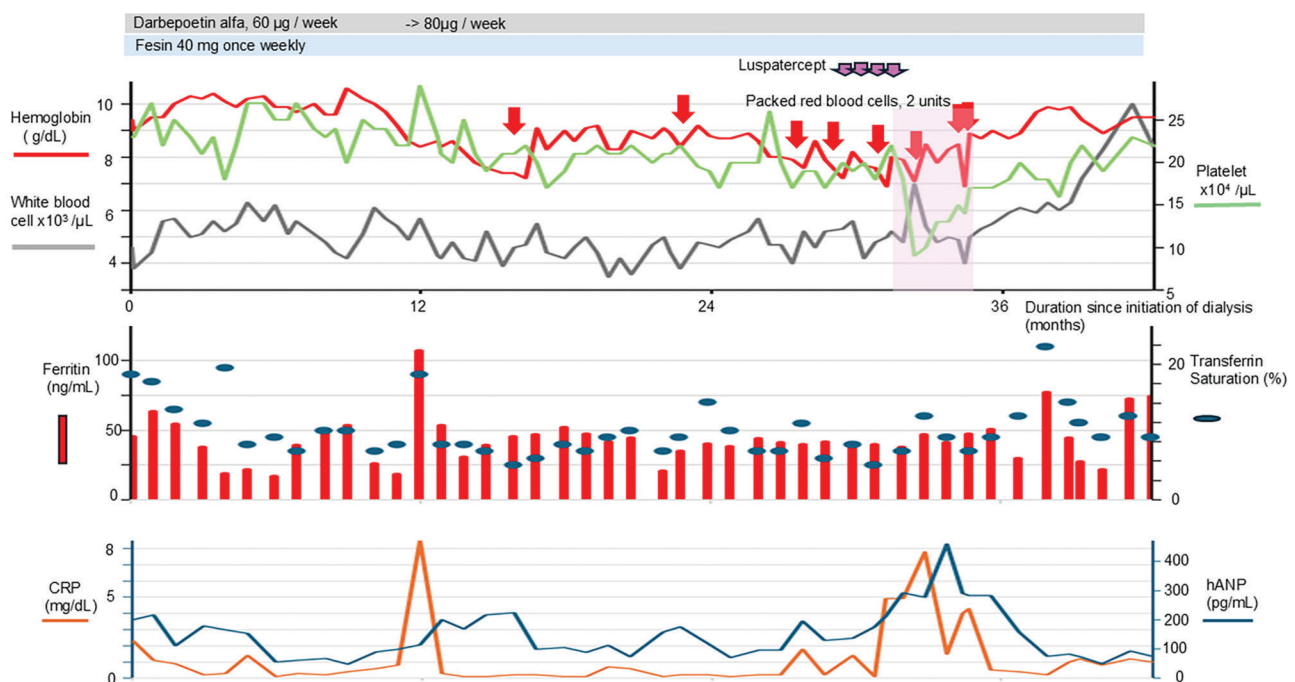


Figure 1. Overall Clinical Course Since Initiation of Dialysis

Top panel: Trends in hemoglobin (red line), platelet count (green line), and white blood cell count (gray line) are shown. Multiple transfusions of 2 units of packed red blood cells (red arrows) were administered due to worsening anemia. A shaded purple area indicates a period of inflammation associated with pneumonia, during which a transient drop in platelet count was observed. Luspatercept (purple arrows) was administered four times before the period of pneumonia-associated inflammation. Middle panel: Serum ferritin levels (red bars) and transferrin saturation (TSAT; blue dots) throughout the course. Bottom panel: Changes in C-reactive protein (CRP; orange line) and human atrial natriuretic peptide (hANP; blue line) are shown. Elevation of CRP and hANP was observed in parallel with the onset of pneumonia-related inflammation.

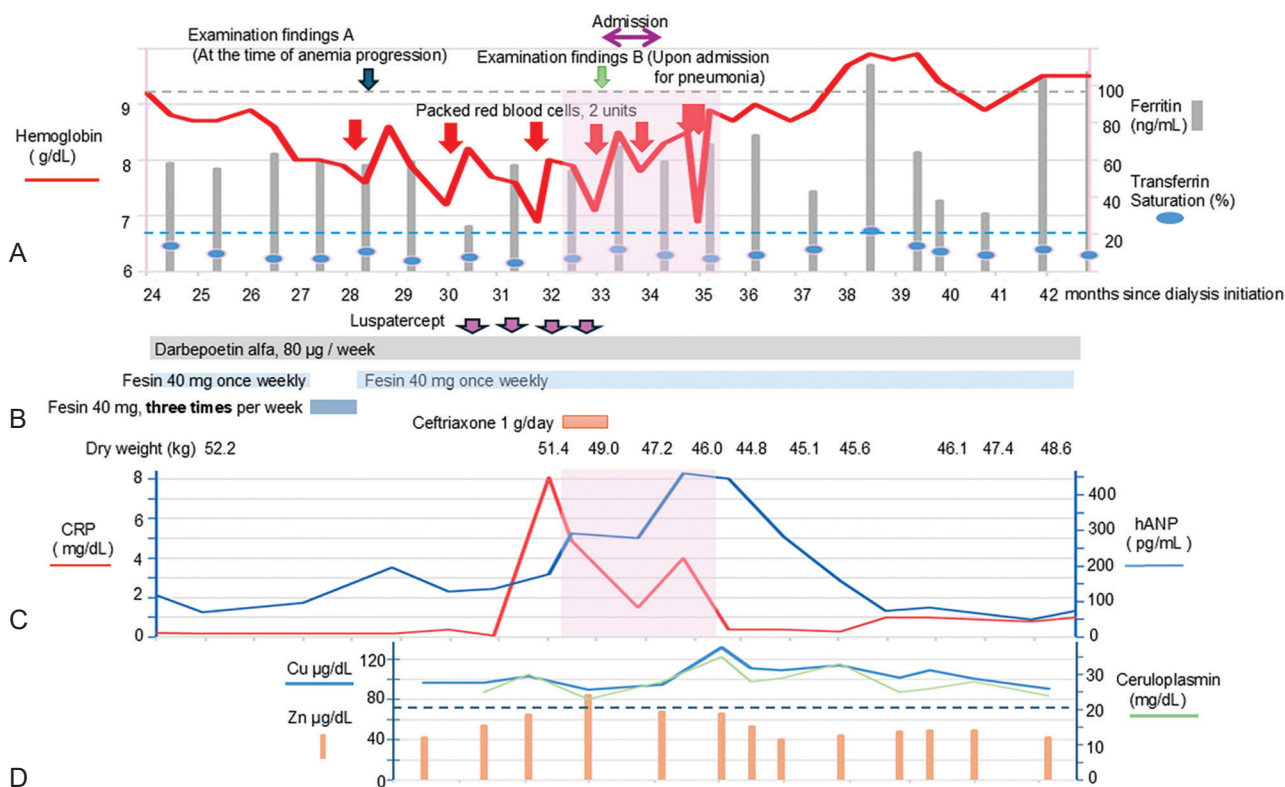


Figure 2. Clinical Course After 24 Months Since Initiation of Dialysis [A] Hemoglobin levels (red line), serum ferritin (gray bars), and transferrin saturation (TSAT, blue dots) are shown. Hemoglobin levels generally paralleled changes in TSAT values during the clinical course. The shaded area indicates the period of pneumonia-associated inflammation, during which anemia progression and thrombocytopenia were observed; [B] Treatment course, including the administration of darbepoetin alfa (80 µg/week), Fesin (iron formulation) once or three times weekly, and four administrations of luspatercept between months 28 and 32 (purple arrows). Intravenous ceftriaxone (1 g/d) was administered during pneumonia; [C] C-reactive protein (CRP, red line) and human atrial natriuretic peptide (hANP, blue line) levels. CRP elevation was followed by hospitalization due to pneumonia (shaded area); [D] Serum levels of copper (Cu, blue line), ceruloplasmin (green line), and zinc (Zn, orange bars). Copper and ceruloplasmin levels showed no evidence of copper deficiency during the clinical course despite progressive anemia, whereas zinc levels gradually decreased]

low blast percentage (0.6%). These findings raised the possibility of an underlying clonal myeloid disorder. However, isolated LOY is increasingly recognized with advancing age, and its clinical significance depends partly on the proportion of affected metaphases and the accompanying morphologic and molecular findings.^{3,8,9} In the present case, LOY was detected in only 20% of analyzed metaphases. Thus, the cytogenetic finding alone was insufficient to determine whether the patient's severe anemia was primarily attributable to MDS. Importantly, molecular testing for MDS-associated somatic mutations was not performed. An underlying clonal myeloid disorder therefore cannot be definitively excluded, and this represents an important limitation of the diagnostic evaluation.

The longitudinal clinical course provided additional information regarding the factors

contributing to the severity of anemia. During pneumonia, the patient developed increased inflammatory activity, marked elevation of human atrial natriuretic peptide, worsening anemia, thrombocytopenia, and persistently low transferrin saturation. Following antibiotic treatment and adjustment of dry weight, inflammatory and volume-related abnormalities improved, accompanied by recovery of the platelet count and increases in hemoglobin and TSAT. Inflammation can impair iron availability and erythropoiesis and is a well-recognized contributor to ESA hypo-responsiveness in dialysis patients.^{1,2} The parallel changes observed in this patient therefore support contributions from inflammation, functional iron restriction, and altered volume status to the severity of anemia. These observations do not exclude an underlying clonal marrow disorder; rather, they

indicate that the hematologic phenotype was likely multifactorial.

Copper deficiency was specifically considered because it can cause cytopenias and marrow dysplasia resembling MDS and has been reported as a reversible cause of severe ESA hypo-responsiveness in dialysis patients.^{4–7} In our patient, however, serum copper and ceruloplasmin showed no evidence of overt copper deficiency during the period of progressive anemia, and hematologic improvement occurred without copper supplementation. Copper deficiency was therefore unlikely to be the principal explanation for the observed marrow abnormalities and ESA hypo-responsiveness. Our previous reports demonstrated that copper deficiency can represent one reversible contributor to severe ESA hypo-responsiveness and MDS-like hematologic abnormalities in dialysis patients.^{6,7} In contrast, the present case suggests that a similar hematologic phenotype may emerge in the absence of copper deficiency through a different combination of physiological and clinical stressors. This distinction is important because MDS-like marrow findings in dialysis patients may occur in heterogeneous clinical settings and should be interpreted together with biochemical findings and the longitudinal clinical course.

More broadly, these observations may be viewed within a framework of hematologic vulnerability in older dialysis patients. Age-related or clonal marrow abnormalities may coexist with dynamic disturbances in erythropoiesis related to inflammation, impaired iron availability, nutritional status, volume overload, or trace-element abnormalities. Additional physiological stress may therefore accentuate anemia in a patient with limited hematopoietic reserve, without implying that any single factor fully accounts for the hematologic phenotype. In this context, clonal marrow abnormalities and potentially reversible contributors should not necessarily be regarded as mutually exclusive explanations for ESA hypo-responsiveness.

Interpretation of the hematologic recovery is complicated by the sequential and partially overlapping use of several interventions. Luspatercept was administered four times between months 28 and 32 while the patient continued to receive ESA and intravenous iron. Luspatercept,

an activin receptor ligand trap that promotes late-stage erythroid maturation, has previously been considered as a potential therapeutic approach for anemia in CKD; however, its clinical development has primarily focused on indications other than CKD.¹⁰ These doses were administered before the subsequent development of prominent inflammatory and volume-related abnormalities. Therefore, a delayed or contributory effect of luspatercept on the later increase in hemoglobin cannot be excluded.

During the subsequent clinical course, pneumonia was treated with antibiotics and volume status was managed by adjustment of dry weight, while changes in inflammatory activity, iron availability, ESA treatment, and intravenous iron administration also occurred. Because these factors changed within the same overall period, the hematologic recovery cannot be attributed to luspatercept, treatment of infection, volume optimization, ESA, or intravenous iron alone. Accordingly, we do not interpret the improvement as evidence against an underlying clonal marrow disorder or as evidence of a specific treatment effect. Rather, the parallel changes in inflammatory activity, volume-related parameters, iron availability, platelet count, and hemoglobin support a multifactorial interpretation of the hematologic course.

This case also underscores the importance of the sequence of diagnostic evaluation in ESA hypo-responsiveness. Common and treatable causes—including iron deficiency or impaired iron utilization, infection and inflammation, inadequate dialysis, blood loss, nutritional deficiencies, secondary hyperparathyroidism, and relevant trace-element abnormalities—should be systematically assessed before proceeding to invasive evaluation for a primary marrow disorder. When persistent unexplained cytopenia or other clinical findings warrant bone marrow examination, the resulting morphologic and cytogenetic abnormalities should subsequently be interpreted in the context of the entire clinical course rather than in isolation. In the present patient, the available findings did not permit definitive exclusion of MDS, but neither did they establish that a clonal marrow disorder was the predominant cause of the transfusion-dependent anemia.

The principal message of this case is therefore not that reversible causes of ESA hypo-responsiveness are newly recognized, but that their contribution may remain clinically important even after MDS-like marrow abnormalities have been identified. The distinctive aspect of this case is the coexistence of marrow abnormalities suggestive of a clonal disorder with dynamically changing and potentially reversible contributors to impaired erythropoiesis. In older dialysis patients, these processes may coexist and interact rather than represent mutually exclusive diagnoses. A longitudinal approach integrating marrow morphology, cytogenetic and, when available, molecular findings with dialysis adequacy, inflammation, iron availability, nutritional status, trace-element status, and volume status may help distinguish the presence of a marrow abnormality from its actual contribution to the severity of anemia.

This framework is hypothesis-generating rather than diagnostic and requires further investigation in larger populations.

DECLARATIONS

Funding

Not applicable.

Conflicts of Interest / Competing Interests

The authors declare no conflicts of interest.

Ethics Approval

Not applicable. This case report did not require institutional ethics approval according to local institutional policies.

Consent to Participate

Written informed consent to participate in this case study was obtained from the patient.

Written Consent for Publication

Written informed consent for publication of clinical details and accompanying images was obtained from the patient.

Availability of Data and Material

Not applicable.

Code Availability

Not applicable.

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