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Severe Marrow Failure With Clonal T-cell Large Granular Lymphocytic Proliferation in Myelodysplastic Syndrome: A Case Report

Ikken Aisin [1]

1. Family and Community Medicine, University of California San Francisco School of Medicine, Fresno, USA

Corresponding author: Ikken Aisin, ikken.aisin@ucsf.edu

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Abstract

Worsening cytopenias in patients with myelodysplastic syndrome (MDS) may reflect disease progression or an additional marrow failure process. We report a 72-year-old man with intermediate-risk MDS, metastatic hormone-sensitive prostate adenocarcinoma, dialysis-dependent end-stage renal disease (ESRD), and chronic transfusion dependence who presented with one week of progressive weakness and altered mental status. Multilineage cytopenias had progressed over more than three years. Admission studies showed a white blood cell count (WBC) of 0.4 × 10^3/µL, hemoglobin of 8.4 g/dL, platelet count of 6 × 10^3/µL, and absolute neutrophil count (ANC) of 0.1 × 10^3/µL. Marrow examination demonstrated hypocellularity, relative expansion of T-cell large granular lymphocytes, and clonal T-cell receptor beta rearrangement. Repeat marrow cellularity was below 5%, supporting a very severe aplastic anemia phenotype, although the contribution of the T-cell clone remained uncertain. Intermittent fever, splenomegaly, hyperferritinemia, and elevated soluble interleukin-2 receptor alpha and C-X-C motif chemokine ligand 9 (CXCL9) prompted evaluation for hemophagocytic lymphohistiocytosis (HLH). The treating team described HLH-like hyperinflammation; available documentation did not establish the five HLH-2004 criteria. Treatment included transfusions, filgrastim, erythropoiesis-stimulating therapy, thrombopoietin receptor agonists, intravenous immunoglobulin (IVIG), dexamethasone, cyclophosphamide, and subsequently horse antithymocyte globulin, cyclosporine, and eltrombopag. A necrotic lower extremity wound, *Escherichia coli* and vancomycin-resistant *Enterococcus faecium* (VRE) bacteremia, recurrent respiratory failure, cardiac dysfunction, septic shock, and progressive multiorgan dysfunction complicated management. No hematologic recovery occurred before death on hospital day 62 after transition to comfort-focused care. This case illustrates the need to reassess severe cytopenias in established MDS while distinguishing clonal T-cell proliferation from confirmed leukemia and weighing immunosuppression against infection and limited organ reserve.

Categories: Family/General Practice, Hematology, Pathology
Keywords: aplastic anemia, hemophagocytic lymphohistiocytosis, hyperinflammation, marrow failure, myelodysplastic syndrome, pancytopenia, t-lgl leukemia, transfusion dependence

Introduction

T-cell large granular lymphocytic leukemia (T-LGLL) is a chronic lymphoproliferative disorder characterized by clonal expansion of cytotoxic T cells. Common manifestations include neutropenia, anemia, recurrent infections, and autoimmune disease. Clinically significant disease may occur with a small circulating large granular lymphocyte population; overt lymphocytosis is therefore not required. Treatment is generally considered for severe neutropenia, recurrent infections, transfusion-dependent anemia, or clinically significant autoimmune manifestations [1-3].

The relationship between T-LGLL and myelodysplastic syndrome (MDS) remains incompletely understood. Clinicopathologic studies have described their coexistence, and both overt and subclinical clonal cytotoxic T-cell populations occur in MDS. Similar clones have been identified in subsets of patients with aplastic anemia, suggesting a possible contribution of immune-mediated injury to selected marrow failure syndromes [4-6].

Worsening cytopenias in a patient with established MDS can be difficult to interpret. Persistent severe neutropenia, reticulocytopenia, marked marrow hypocellularity, increasing transfusion requirements, recurrent infection, and inflammatory abnormalities warrant reassessment for additional causes of marrow failure.

We describe a patient with intermediate-risk MDS who developed severe pancytopenia, severely hypocellular marrow, clonal T-cell receptor rearrangement, and hyperinflammation resembling hemophagocytic lymphohistiocytosis (HLH). His course illustrates the difficulty of distinguishing MDS progression from possible immune-mediated marrow failure associated with a clonal T-cell population and an aplastic anemia phenotype. Active infection and substantial comorbidity further complicated decisions about

immunosuppression.

The overlapping features of these conditions complicate diagnosis. Myelodysplastic syndrome is a clonal bone marrow disorder in which blood cell production is ineffective, leading to cytopenias. T-cell large granular lymphocytic leukemia is an abnormal expansion of cytotoxic T cells that can suppress normal blood cell production. Hemophagocytic lymphohistiocytosis is a syndrome of pathologic immune activation with fever, splenomegaly, cytopenias, and marked inflammatory marker elevation. A clonal T-cell receptor rearrangement alone does not establish T-cell large granular lymphocytic leukemia. Distinguishing these processes matters because their treatments differ. This case illustrates those decisions in a patient with progressive marrow failure and limited organ reserve.

Case Presentation

Patient information and preadmission course

A 72-year-old man with transfusion-dependent intermediate-risk MDS, metastatic hormone-sensitive prostate adenocarcinoma, end-stage renal disease (ESRD) requiring intermittent hemodialysis, prior pulmonary coccidioidomycosis, radiation cystitis, and a remote traumatic subdural hematoma presented with progressive weakness and altered mental status.

Prostate adenocarcinoma had been diagnosed in 2014 and treated with prostatectomy, salvage pelvic radiation, androgen deprivation therapy, and enzalutamide. Subsequent radiation cystitis required simple cystectomy and ileal conduit urinary diversion. He received hemodialysis three times weekly through a tunneled dialysis catheter.

MDS was diagnosed by marrow examination in 2024. The marrow contained 2% blasts, with trisomy 9 and deletion 20q. Next-generation sequencing identified variants in the Janus kinase 2 (*JAK2*) and tet methylcytosine dioxygenase 2 (*TET2*) genes. His recorded Revised International Prognostic Scoring System score was 3.5, consistent with intermediate-risk disease.

Available records documented no tobacco or illicit drug use and no medication allergies. He had previously consumed two to three glasses of wine daily for approximately five years, stopping one to two years before the index hospitalization. Family history was negative for known kidney disease or hematologic malignancy. A comprehensive family history, occupational exposure history, and complete medication reconciliation immediately before admission were unavailable.

Multilineage cytopenias had been documented for several years. Approximately three years before admission, the white blood cell count (WBC) was 3.59 × 10^3/μL, hemoglobin 8.3 g/dL, and platelet count 129 × 10^3/μL. Approximately two years before admission, these values were 2.6 × 10^3/μL, 8.6 g/dL, and 122 × 10^3/μL, respectively. By approximately 21 months before admission, the white blood cell count had declined to 1.35 × 10^3/μL, hemoglobin to 7.3 g/dL, and platelet count to 78 × 10^3/μL. This decline was initially attributed to malignancy and its treatment. Available records did not document earlier testing for clonal T-cell populations, T-cell receptor rearrangement, signal transducer and activator of transcription 3 (*STAT3*) gene mutations, or immune-mediated marrow failure. The longitudinal hematologic course is summarized in Figure *1*.

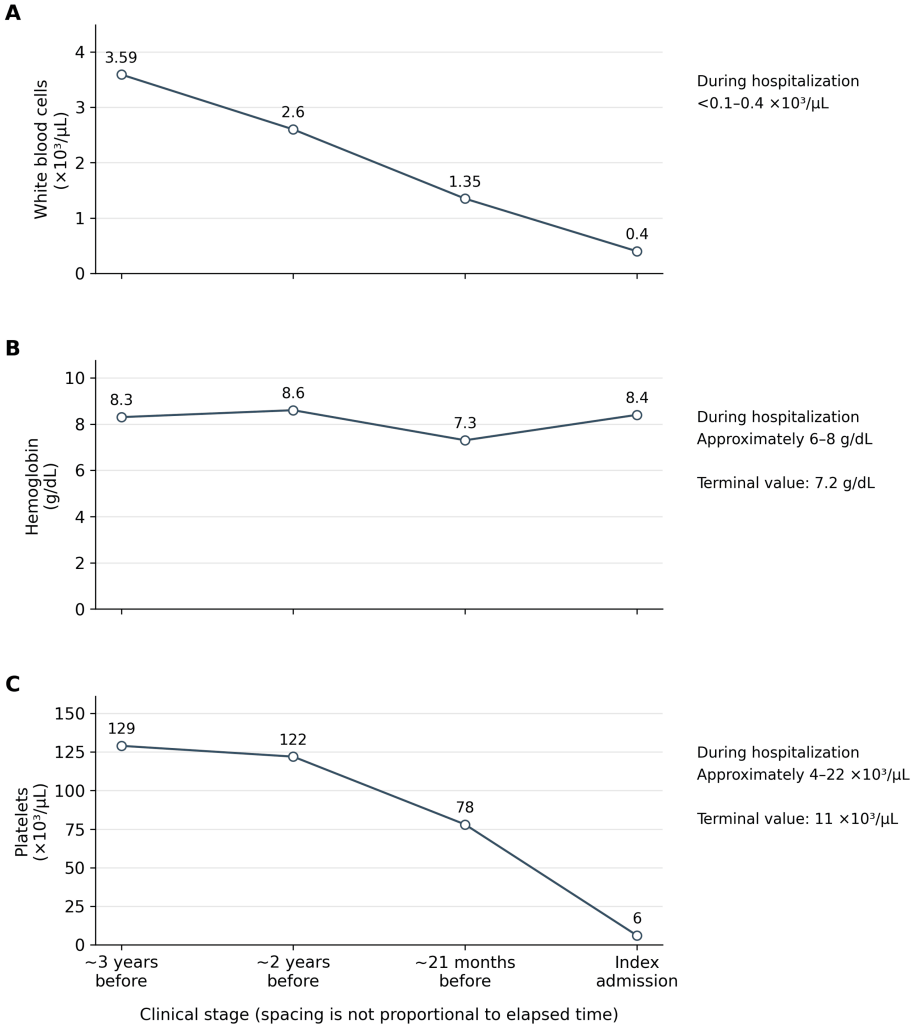


FIGURE 1: Progressive multilineage cytopenias before and during the index hospitalization

Panels A-C show white blood cell count, hemoglobin, and platelet count, respectively. Discrete preadmission and admission observations are shown; clinical-stage spacing is not proportional to elapsed time. During hospitalization, white blood cell counts ranged from below 0.1 to 0.4 × 10^3/μL, hemoglobin was approximately 6-8 g/dL, and platelet counts were approximately 4-22 × 10^3/μL. Terminal values were hemoglobin 7.2 g/dL and platelets 11 × 10^3/μL. Inpatient hemoglobin and platelet counts were affected by frequent transfusions.

Original figure created by the author from this patient's clinical data

Index presentation and initial evaluation

Approximately one week before admission, the patient developed weakness, confusion, and intermittent urethral bleeding. He had recently been hospitalized elsewhere for a presumed urinary tract infection and transfusion support. His family reported that he had been cognitively intact before that hospitalization but subsequently became increasingly lethargic and confused.

At presentation, blood pressure was 99/62 mmHg, heart rate 87 beats/min, temperature 37.3°C, respiratory rate 16 breaths/min, and oxygen saturation 99% with supplemental oxygen. He was lethargic and oriented only to person but moved all extremities without a focal motor deficit. Examination showed scleral icterus, dry mucous membranes, trace blood near the urethral meatus, and lower extremity edema with focal tenderness. The abdomen was soft, nondistended, and nontender.

The white blood cell count was 0.4 × 10^3/μL, hemoglobin 8.4 g/dL, platelet count 6 × 10^3/μL, and absolute neutrophil count (ANC) 0.1 × 10^3/μL. Sodium was 124 mmol/L, blood urea nitrogen 180 mg/dL, creatinine 6.5 mg/dL, total bilirubin 8.6 mg/dL, direct bilirubin 5.7 mg/dL, and international normalized ratio 1.9. Thyroid-stimulating hormone and ammonia were within their reference ranges, and urine drug testing was negative.

Computed tomography of the head showed no acute intracranial abnormality. Chest radiography demonstrated minimal interstitial prominence without focal consolidation. Computed tomography of the chest, abdomen, and pelvis showed bilateral patchy ground-glass opacities, splenomegaly, mildly enlarged retroperitoneal lymph nodes, and an indeterminate linear/nodular opacity in the left upper lobe. Bilateral lower extremity venous ultrasonography showed no deep venous thrombosis.

The differential diagnosis for encephalopathy included uremia, hyponatremia, occult infection during severe neutropenia, medication effects, hepatic encephalopathy, intracranial disease, and progression of malignancy or marrow failure. The initial differential for pancytopenia included MDS progression, acute myeloid leukemia, metastatic prostate cancer involving the marrow, infection-associated suppression, nutritional deficiency, viral suppression, drug-related cytopenias, acquired aplastic anemia, hypoplastic MDS, T-LGLL-associated immune-mediated marrow failure, and secondary HLH or another hyperinflammatory syndrome.

During the admission, hemodialysis was used to manage severe azotemia, hyponatremia, and suspected uremic encephalopathy. Mental status improved partially with dialysis and correction of metabolic abnormalities but continued to fluctuate.

Neurologic, infectious, and hepatobiliary evaluation

Brain magnetic resonance imaging (MRI) showed moderate cerebral atrophy and mild chronic small vessel ischemic changes without an acute process. Electroencephalography demonstrated moderate diffuse background slowing without epileptiform activity. Lumbar puncture was considered but deferred because of persistent severe thrombocytopenia.

Severe neutropenia and intermittent fever prompted an extensive infectious evaluation. Initial blood cultures showed no growth. Human immunodeficiency virus (HIV) testing and cytomegalovirus and Epstein-Barr virus polymerase chain reaction assays were negative. Antimicrobial treatment and prophylaxis varied with the clinical course and included cefepime, vancomycin, piperacillin-tazobactam, meropenem, acyclovir, posaconazole, atovaquone, cefpodoxime, and later daptomycin. Selection and duration were adjusted for febrile neutropenia, suspected soft tissue infection, bacteremia, and prophylaxis during persistent severe neutropenia.

Total bilirubin peaked at 9.5 mg/dL. Abdominal ultrasonography demonstrated hepatosplenomegaly, cholelithiasis, gallbladder wall thickening, and renal cortical thinning. Magnetic resonance cholangiopancreatography showed hepatosplenomegaly with suspected increased iron deposition in the liver and spleen, cholelithiasis, mild gallbladder wall thickening, and no choledocholithiasis.

Ferritin was 4,458 ng/mL, iron saturation exceeded 82%, and transferrin was below 75 mg/dL. Total iron-binding capacity was reported as below 105 µg/dL. Haptoglobin was elevated, lactate dehydrogenase was low-normal, and peripheral smears did not show a consistent hemolytic pattern, making hemolysis less likely to explain the bilirubin elevation.

Hepatology considered the imaging findings most consistent with transfusion-associated secondary iron overload. Severe anemia, MDS, renal failure, and medical instability precluded therapeutic phlebotomy or iron chelation. Lactulose and rifaximin were trialed for asterixis and fluctuating encephalopathy without sustained improvement; both were subsequently reduced or discontinued.

Bone marrow evaluation

The first inpatient marrow biopsy demonstrated hypocellularity; aspirate smears were reported as showing “no elements,” relatively increased T cells including T-cell large granular lymphocytes (T-LGLs), marked relative neutropenia, and increased iron stores. There was no evidence of acute leukemia or metastatic prostate adenocarcinoma.

T-cell receptor testing identified a clonal rearrangement of the T-cell receptor beta (*TRB*) locus, reported as *TRB* D+J1/2. Absolute reticulocyte counts were 6-8 × 10^3/µL, consistent with markedly impaired marrow production. Copper was normal, zinc was low, and vitamin B12 and folate were replete. Cytogenetic analysis of the initial inpatient specimen was limited by inadequate viable material. The first biopsy’s cellularity percentage, a complete immunophenotypic profile, *STAT3* testing results, a peripheral blood large granular lymphocyte count, and central hematopathology review were unavailable.

Repeat marrow examination later in the hospitalization showed cellularity below 5%. Flow cytometry demonstrated mild nonspecific atypical myeloid findings without an overt increase in blasts. Marrow hemophagocytosis was not identified. The treating team interpreted the combination of marked hypocellularity, persistent severe neutropenia, reticulocytopenia, clonal *TRB* rearrangement, and relative T-LGL expansion as a very severe aplastic anemia phenotype superimposed on MDS, with suspected T-LGLL-associated immune-mediated marrow failure. The available findings established T-cell clonality but did not

definitively establish T-LGLL or its contribution to marrow failure. Table *1* summarizes the differential diagnosis.

Diagnostic consideration	Evidence category	Finding
MDS progression	Supporting finding	Established intermediate-risk MDS
		Trisomy 9
		Deletion 20q
		JAK2 variant
		TET2 variant
	Limitation	Marked hypocellularity appeared disproportionate to the previous disease course
		Severity of cytopenias appeared disproportionate to the previous disease course
Acute leukemia	Supporting finding	Severe pancytopenia
		Systemic decline
	Finding against	No overt blast increase on marrow examination
		Acute leukemia not identified on marrow examination
Prostate cancer involving the marrow	Supporting finding	Metastatic prostate adenocarcinoma
	Finding against	Prostate cancer not identified in marrow
Acquired aplastic anemia phenotype	Supporting finding	Cellularity <5%
		Reticulocytopenia
		Persistent ANC near zero
	Limitation	Preexisting clonal myeloid abnormalities complicated classification
Suspected T-LGLL-associated marrow failure	Supporting finding	Relative marrow T-LGL expansion
		Clonal *TRB* rearrangement
		Severe neutropenia
	Limitation	Complete immunophenotype unavailable
		STAT3 testing results unavailable
		Peripheral blood LGL count unavailable
Infection-associated marrow suppression	Supporting finding	Recurrent bacteremia
		Neutropenic fever
		Necrotic wound
		Sepsis
	Finding against	Cytopenias preceded acute infection by several years
HLH	Finding prompting evaluation	Intermittent fever
		Splenomegaly
		Cytopenias
		Hyperferritinemia
		Elevated sCD25
		Elevated CXCL9
		No qualifying fever documented during assessment

	Limitation	Marrow hemophagocytosis not identified
		Fibrinogen elevated
		Triglyceride data incomplete
		NK cell testing unavailable
		Five HLH-2004 criteria not established

TABLE 1: Differential diagnosis of severe pancytopenia and evidence in this case

ANC: absolute neutrophil count, CXCL9: C-X-C motif chemokine ligand 9, HLH: hemophagocytic lymphohistiocytosis, *JAK2*: Janus kinase 2, LGL: large granular lymphocyte, MDS: myelodysplastic syndrome, NK: natural killer, sCD25: soluble interleukin-2 receptor alpha, *STAT3*: signal transducer and activator of transcription 3, *TET2*: tet methylcytosine dioxygenase 2, T-LGL: T-cell large granular lymphocyte, T-LGLL: T-cell large granular lymphocytic leukemia, *TRB*: T-cell receptor beta

Clonality alone did not confirm T-LGLL.

Original table developed by the author to summarize this patient's findings and their clinical interpretation

The inpatient biopsies were performed on hospital days 6 and 35. The bone marrow, cytogenetic, and molecular findings are summarized in Table *2*.

Examination	Parameter	Finding
Diagnostic marrow (2024)	Cellularity	Not available
	Blasts	2%
	Chromosome 9	Trisomy
	Chromosome 20q	Deletion
	JAK2 variant	Detected
	TET2 variant	Detected
Hospital day 6	Cellularity	Hypocellular
	Marrow T-LGL population	Relatively increased
	Acute leukemia	Not identified
	Metastatic prostate cancer	Not identified
	Iron stores	Increased
	TRB rearrangement	Clonal
	Cytogenetic analysis	Limited by inadequate viable material
	Cellularity percentage	Not available
Hospital day 35	Cellularity	<5%
	Overt blast increase	Not identified
	Hemophagocytosis	Not identified
	Final cytogenetics	Not available
	STAT3 testing result	Not available

TABLE 2: Bone marrow and molecular findings

Historical myeloid findings are distinguished from inpatient specimens. *STAT3* testing results and a complete T-LGL immunophenotype were unavailable.

JAK2: Janus kinase 2, *STAT3*: signal transducer and activator of transcription 3, *TET2*: tet methylcytosine dioxygenase 2, T-LGL: T-cell large granular lymphocyte, *TRB*: T-cell receptor beta

Gene symbols refer to the loci reported in the source records.

Original table developed by the author to summarize this patient's findings and their clinical interpretation

Assessment of HLH-like hyperinflammation

Recurrent fevers, splenomegaly, severe cytopenias, and inflammatory abnormalities prompted evaluation for secondary HLH. Ferritin increased from 4,458 ng/mL early in the hospitalization to 5,974 ng/mL. Soluble interleukin-2 receptor alpha (sCD25) was approximately 6,000 U/mL, and C-X-C motif chemokine ligand 9 (CXCL9) was approximately 1,856 pg/mL. These findings are summarized in Figure *2*.

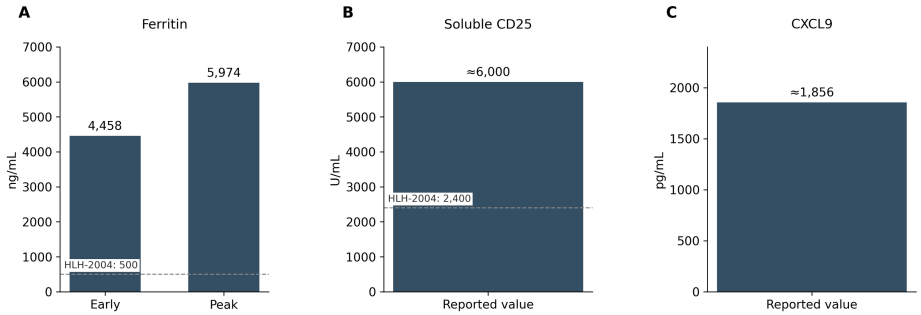


FIGURE 2: Hyperinflammatory marker profile during hospitalization

Panels A-C show ferritin, sCD25, and CXCL9, respectively. Ferritin increased from 4,458 to 5,974 ng/mL; sCD25 was approximately 6,000 U/mL and CXCL9 approximately 1,856 pg/mL. Dashed lines indicate HLH-2004 thresholds for ferritin and sCD25 [7]; no diagnostic cutoff is asserted for CXCL9. Intermittent fever, splenomegaly, and trilineage cytopenias prompted evaluation, but a qualifying fever was not documented during the assessment period. Marrow hemophagocytosis was not identified, and fibrinogen was elevated. Timing beyond the early and peak ferritin observations was not specified in the available narrative.

sCD25: soluble interleukin-2 receptor alpha, CXCL9: C-X-C motif chemokine ligand 9, HLHL hemophagocytic lymphohistiocytosis

Original figure created by the author from this patient's clinical data

The treating team documented an HLH-like syndrome rather than definitive HLH. Available records supported four HLH-2004 criteria: splenomegaly, cytopenias affecting at least two lineages, ferritin above 500 ng/mL, and elevated sCD25 [7]. Intermittent fever was recorded, but a temperature meeting the 38.5°C threshold was not documented during the evaluation period. Marrow hemophagocytosis was not identified. Fibrinogen was elevated at 829 mg/dL and 673 mg/dL on repeat measurement, complete triglyceride data were unavailable, and natural killer cell functional testing was unavailable. Thus, the available documentation did not establish five of the eight criteria. Marrow failure, recurrent infection, and transfusion-associated iron overload also limited the specificity of the inflammatory findings.

Ferritin and sCD25 exceeded thresholds used in the optimized HLH inflammatory index, which has been associated with HLH-defining features and mortality risk in patients with hematologic malignancy [8]. The team considered these abnormalities evidence of a clinically important hyperinflammatory state.

The evaluation for hemophagocytic lymphohistiocytosis was initiated during hospital week 2. At that assessment, fibrinogen was elevated and triglyceride data were incomplete.

Left lower extremity lesion

A painful left lateral calf lesion progressed from edema and tenderness to black eschar, superficial wounds, and concern for a deeper collection. Initial computed tomography showed soft tissue stranding without a drainable collection. Repeat imaging demonstrated cellulitis/fasciitis with a possible developing 10.7-cm collection and no subcutaneous emphysema. Representative images demonstrate splenomegaly (Figure *3A*) and the left calf soft tissue abnormalities (Figures *3B*, *3C*).

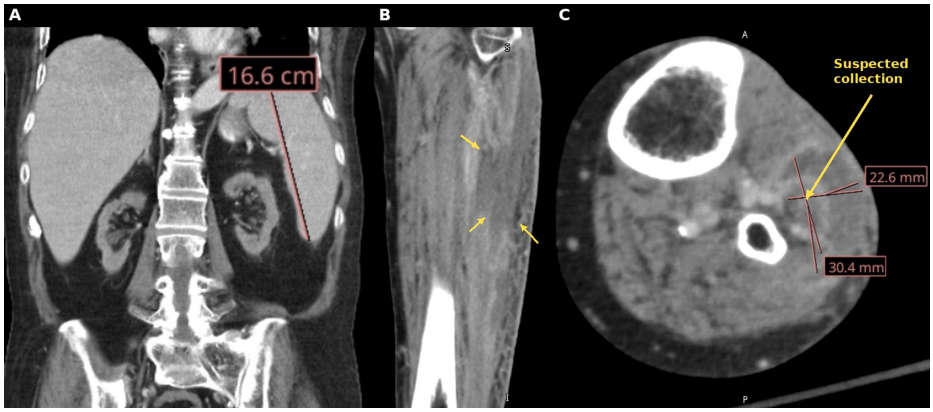


FIGURE 3: Computed tomography findings of splenomegaly and left calf soft tissue abnormalities

(A) Coronal abdominal computed tomography showing splenomegaly (16.6 cm). (B) Longitudinal and (C) axial left calf views. Yellow arrows in B and C mark the suspected collection; original calipers are retained in C. The radiology report described cellulitis/fasciitis with a suspected developing abscess measuring approximately 3 × 2.3 × 10.7 cm, without subcutaneous gas. Operative drainage yielded serous fluid without purulence.

Orientation markers: A, anterior; P, posterior; S, superior; I, inferior

Original clinical images supplied by the author

After platelet transfusion support, the patient underwent incision and drainage. The operative report described diffuse oozing from needle punctures, removal of preexisting eschar, and a tract extending into a superior pocket containing serous fluid without purulence. Persistent oozing required packing with an oxidized regenerated cellulose hemostatic agent. Bacterial, fungal, and acid-fast cultures did not identify a definitive pathogen.

Subsequent examinations showed necrotic tissue, eschar, surrounding ecchymosis, and poor healing during severe neutropenia and thrombocytopenia. Further aggressive debridement was avoided because of bleeding risk, limited healing potential, and concern for pathergy if the lesion represented pyoderma gangrenosum.

Imaging on hospital day 16 showed a collection measuring approximately 3 × 2.3 × 10.7 cm. Operative incision and drainage followed on hospital day 17 and yielded serous fluid without purulence; the volume was not recorded.

Treatment

The patient required frequent irradiated packed red blood cell and platelet transfusions. Hematology recommended transfusion for hemoglobin below 7 g/dL and platelet counts below 10×10^3/μL in the absence of bleeding, with higher platelet targets for sepsis, active bleeding, intracranial bleeding, and procedures.

Filgrastim was increased to 480 μg subcutaneously daily. Epoetin alfa-epbx was administered at 50 units/kg subcutaneously three times weekly. Romiplostim was used and later replaced by eltrombopag 150 mg daily. Additional treatment included intravenous immunoglobulin (IVIG), 1 g/kg every 24 hours for two doses; dexamethasone, 40 mg intravenously daily for four days; and cyclophosphamide, 75 mg orally daily, subsequently held during bacteremia. Horse antithymocyte globulin, cyclosporine, and eltrombopag were later initiated for the very severe aplastic anemia phenotype. The complete antithymocyte globulin dosing schedule was unavailable.

Immunosuppression was pursued because of persistent severe pancytopenia, marked marrow hypocellularity, clonal T-LGL expansion, and the absence of acute leukemia or metastatic prostate cancer in the marrow. Active infection and poor physiologic reserve repeatedly constrained treatment.

Intravenous immunoglobulin and dexamethasone were given during hospital week 4, and cyclophosphamide began on hospital day 32. Eltrombopag was documented as starting on hospital day 49 with horse antithymocyte globulin and cyclosporine. Growth factors and thrombopoietin receptor agonists provided marrow support. Intravenous immunoglobulin and dexamethasone were used for severe thrombocytopenia and hyperinflammation, cyclophosphamide targeted the suspected clonal T-cell process, and the antithymocyte globulin-based regimen addressed the very severe aplastic anemia phenotype.

Figure 4 summarizes treatment exposures and major complications during hospitalization.

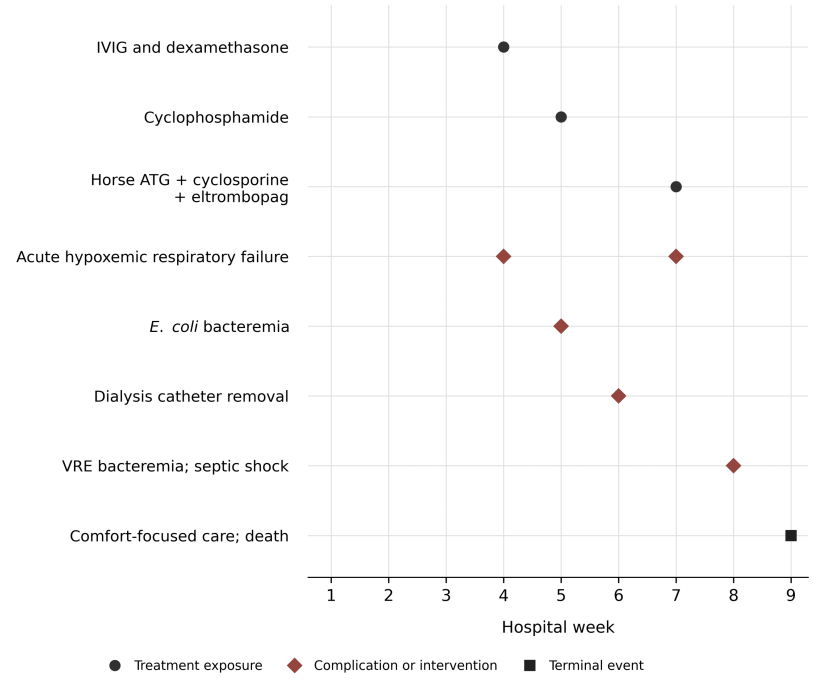


FIGURE 4: Disease-directed treatment and major complications during hospitalization

Black circles indicate treatment exposures; red diamonds indicate major complications or interventions; the black square indicates comfort-focused care and death. Respiratory failure episodes are grouped on one row, with markers at hospital weeks 4 and 7. The later marker represents recurrence during weeks 7-8. The first episode followed intravenous immunoglobulin and transfusion exposure. Markers indicate approximate hospital weeks rather than treatment duration, and temporal proximity does not establish causation. Death occurred on hospital day 62.

ATG: antithymocyte globulin, IVIG: intravenous immunoglobulin, VRE: vancomycin-resistant *Enterococcus*

Original figure created by the author from this patient's clinical course

Table 3 summarizes the clinical course from the earliest documented cytopenias through the terminal hospitalization.

Relative time	Clinical observation or event
Approximately three years before admission	WBC: 3.59 × 10³/μL
	Hemoglobin: 8.3 g/dL
	Platelets: 129 × 10³/μL
Approximately two years before admission	Progressive cytopenias documented
	Advanced kidney dysfunction documented
	MDS classified as intermediate risk
	Marrow blasts 2%
	Trisomy 9
	Deletion 20q
	JAK2 variant

	TET2 variant
Approximately 21 months before admission	WBC: 1.35 × 10^3/μL
	Hemoglobin: 7.3 g/dL
	Platelets: 78 × 10^3/μL
Hospital day 1	Admission with altered mental status
	Weakness
	Severe pancytopenia
	Hyponatremia
	Severe azotemia
	Hyperbilirubinemia
Hospital week 1	Hemodialysis provided during admission
	Brain MRI showed no acute process
	Infectious evaluation undertaken
	Empiric antimicrobial therapy administered
Hospital day 6	Initial inpatient marrow showed hypocellularity
	Relative marrow T-LGL expansion
	Acute leukemia not identified in marrow
	Metastatic prostate cancer not identified in marrow
Hospital week 2	Clonal TRB rearrangement identified
	HLH-related evaluation initiated
Hospital days 10-11	Left lower extremity lesion developed black eschar
	Left lower extremity lesion developed fluctuance
Hospital days 16-17	Imaging concern for cellulitis/fasciitis
	Possible 10.7-cm collection on imaging
	Incision and drainage performed
	Serous fluid obtained at drainage
	Purulence not identified at drainage
Hospital week 4 (days 23-24)	IVIG administered
	Dexamethasone administered
	Growth factor support provided
	Thrombopoietin receptor agonist support provided
	Acute hypoxemic respiratory failure after IVIG and transfusion exposure
	EF: 30%-35%
	Global hypokinesis
Hospital day 32	Cyclophosphamide initiated
	Escherichia coli bacteremia identified
	Cyclophosphamide subsequently held
Hospital day 35	Repeat marrow cellularity <5%
Hospital week 6	Tunneled dialysis catheter removed for source control during*E. coli* bacteremia
	Horse antithymocyte globulin initiated

Hospital day 49	Cyclosporine initiated
	Eltrombopag initiated
Hospital days 49-53	Recurrent hypoxemic respiratory failure
	Diffuse pulmonary infiltrates
	ICU readmission
Hospital day 53	Vancomycin-resistant *Enterococcus faecium* bacteremia identified
	Daptomycin initiated
Hospital week 8	Septic shock
	Recurrent respiratory failure
	Atrial fibrillation with rapid ventricular response
	Worsening cholestasis
Hospital day 58	DNR/DNI status established after goals-of-care discussion
Hospital day 62	Transition to comfort-focused care
	Death

TABLE 3: Chronology of diagnostic evaluation, treatment, and clinical deterioration

DNR/DNI: do not resuscitate/do not intubate, EF: ejection fraction, HLH: hemophagocytic lymphohistiocytosis, ICU: intensive care unit, IVIG: intravenous immunoglobulin, *JAK2*: Janus kinase 2, MDS: myelodysplastic syndrome, MRI: magnetic resonance imaging, *TET2*: tet methylcytosine dioxygenase 2, T-LGL: T-cell large granular lymphocyte, *TRB*: T-cell receptor beta, VRE: vancomycin-resistant *Enterococcus*, WBC: white blood cell count

Original table developed by the author to summarize this patient's findings

Outcome and follow-up

Severe pancytopenia and transfusion dependence persisted, with ANC values remaining near zero. Treatment included growth factor support, erythropoiesis-stimulating therapy, thrombopoietin receptor agonists, IVIG, corticosteroids, cyclophosphamide, and antithymocyte globulin-based immunosuppression. No hematologic recovery occurred before death. Antithymocyte globulin-based treatment began on hospital day 49 and was interrupted by clinical deterioration; death on day 62 limited assessment of a delayed response.

The course was complicated by recurrent febrile neutropenia, *Escherichia coli* bacteremia requiring dialysis catheter removal, vancomycin-resistant *Enterococcus faecium* (VRE) bacteremia, and a persistent necrotic lower extremity wound. Recurrent acute hypoxemic respiratory failure required intensive care. An initial echocardiogram showed an ejection fraction of 30%-35%; subsequent imaging showed recovery to 55%-60%, with grade II diastolic dysfunction and moderate mitral regurgitation. Additional complications included atrial fibrillation with rapid ventricular response, septic shock requiring vasopressors, progressive cholestasis and acute hepatic injury, severe deconditioning, and malnutrition. Volume removal during dialysis was associated with respiratory improvement.

The patient initially had do-not-resuscitate status with otherwise full treatment. After recurrent respiratory failure, bacteremia, shock, severe encephalopathy, and multiorgan dysfunction, his surrogate decision-maker and family elected do-not-resuscitate/do-not-intubate status and subsequently comfort-focused care. He died on hospital day 62. Autopsy was offered and declined.

The first episode of acute hypoxemic respiratory failure occurred on hospital days 23 and 24, after intravenous immunoglobulin and transfusion exposure. Respiratory failure recurred on hospital days 49-53 and again in hospital week 8. The patient spent much of the later course in the intensive care unit.

Discussion

Diagnostic interpretation of overlapping marrow failure

Established MDS required reassessment when severe cytopenias and marrow hypocellularity developed. Persistent ANC values near zero, severe reticulocytopenia, transfusion dependence, and marrow cellularity below 5% raised concern for an additional immune-mediated component.

Clinicopathologic series have described the coexistence of MDS and T-LGLL, with anemia and neutropenia common and thrombocytopenia present in some patients [4,5]. Clonal cytotoxic T-cell expansions have also been identified in aplastic anemia and MDS, supporting a possible immune contribution to marrow failure in selected patients [6]. In this case, neither the myeloid nor the lymphoid findings could be considered in isolation. Table *4* summarizes their clinical interpretation.

Finding	Clinical interpretation
Trisomy 9	Supported the historical MDS diagnosis in conjunction with the original marrow interpretation
Deletion 20q	Supported the historical MDS diagnosis in conjunction with the original marrow interpretation
JAK2 variant	Supported the historical MDS diagnosis in conjunction with the original marrow interpretation
TET2 variant	Supported the historical MDS diagnosis in conjunction with the original marrow interpretation
Marrow cellularity <5%	Supported an aplastic anemia or markedly hypoplastic MDS phenotype
Clonal *TRB* rearrangement	Supported clonal T-cell proliferation
Relative marrow T-LGL expansion	Raised concern for an immune-mediated contribution
ANC near zero	Indicated severely impaired marrow production
Severe reticulocytopenia	Indicated severely impaired marrow production
Acute leukemia not identified in marrow	Made leukemic transformation a less likely explanation
Metastatic prostate cancer not identified in marrow	Made solid-tumor infiltration a less likely explanation

TABLE 4: Diagnostic Findings and Their Clinical Interpretation

ANC: absolute neutrophil count, *JAK2*: Janus kinase 2, MDS: myelodysplastic syndrome, *TET2*: tet methylcytosine dioxygenase 2, T-LGL: T-cell large granular lymphocyte, T-LGLL: T-cell large granular lymphocytic leukemia, *TRB*: T-cell receptor beta

Clonal *TRB* rearrangement establishes T-cell clonality, not a definitive leukemia diagnosis.

Original table developed by the author to summarize this patient's findings and their clinical interpretation

Distinguishing hypoplastic MDS from acquired aplastic anemia is difficult when clonal myeloid abnormalities and clonal T-cell populations coexist. The original marrow diagnosis, cytogenetic abnormalities, and molecular findings supported the historical MDS classification. Subsequent marked hypocellularity and reticulocytopenia supported a very severe aplastic anemia phenotype. Relative T-LGL expansion and clonal *TRB* rearrangement raised concern for an immune-mediated contribution, but clonality alone did not establish T-LGLL or prove that the T-cell population caused the marrow failure. Incomplete immunophenotypic and molecular characterization limited further classification [3,9].

The diagnostic synthesis and competing management approaches are represented in Figure *5*.

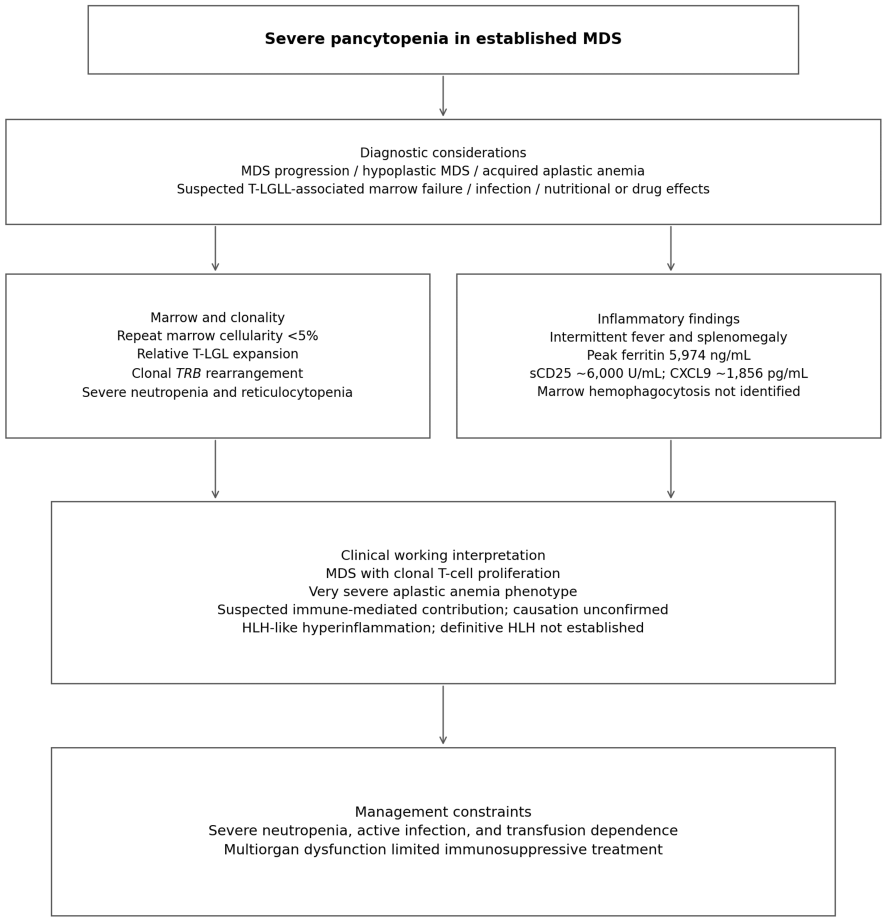


FIGURE 5: Proposed summary of the diagnostic evaluation

Developed by the author to summarize this patient's diagnostic evaluation. This original figure is not a validated diagnostic algorithm. T-cell clonality did not confirm leukemia or establish the cause of marrow failure.

MDS: myelodysplastic syndrome, T-LGL: T-cell large granular lymphocyte, T-LGLL: T-cell large granular lymphocytic leukemia, *TRB*: T-cell receptor beta, HLH: hemophagocytic lymphohistiocytosis, sCD25: soluble interleukin-2 receptor alpha, CXCL9: C-X-C motif chemokine ligand 9

For generalists, worsening cytopenias in MDS should prompt evaluation for changing marrow cellularity, a new clonal lymphoid or myeloid process, infection, medication toxicity, nutritional deficiency, malignant infiltration, and immune-mediated marrow failure. T-LGLL deserves consideration when severe neutropenia, anemia, splenomegaly, autoimmune manifestations, or otherwise unexplained marrow failure accompany a clonal T-cell population. A markedly elevated circulating lymphocyte count is not necessary [1-3].

Hyperinflammation and diagnostic uncertainty

The inflammatory findings required interpretation alongside severe marrow failure, recurrent infection, hepatic dysfunction, and transfusion-associated iron deposition.

The available documentation supported four HLH-2004 criteria: splenomegaly, cytopenias affecting at least two lineages, ferritin above 500 ng/mL, and soluble CD25 above 2,400 U/mL. A temperature meeting the 38.5°C fever threshold was not documented during assessment. Marrow hemophagocytosis was not identified, fibrinogen was elevated, triglyceride data were incomplete, and natural killer cell functional testing was unavailable. These gaps limited retrospective classification; they did not exclude HLH. T-LGLL also remained unconfirmed. Its diagnosis requires integrated assessment of the clonal T-cell population, morphology, immunophenotype, and clinical course; *STAT3* findings may support the diagnosis but are not required [3]. Clonal TRB rearrangement and relative T-LGL expansion raised suspicion, but the incomplete immunophenotype and unavailable peripheral blood LGL count limited classification. Marked marrow

hypocellularity, reticulocytopenia, and profound neutropenia were compatible with a very severe aplastic anemia phenotype, although preexisting MDS complicated the diagnosis.

Corticosteroids and intravenous immunoglobulin preceded the repeat marrow examination and may have altered the inflammatory findings. The hospital day 35 specimen still showed cellularity below 5%, no hemophagocytosis, and no increase in blasts. Absence of hemophagocytosis did not exclude HLH, while the absence of increased blasts made leukemic transformation less likely. Cyclophosphamide, started on hospital day 32, also preceded this examination.

HLH assessment in adults with hematologic malignancy is complicated by substantial overlap with sepsis, liver dysfunction, transfusion-related abnormalities, and marrow failure. These conditions can independently or jointly produce fever, cytopenias, hyperferritinemia, coagulopathy, and organ dysfunction [7,10,11]. Malignancy and infection may also trigger hyperinflammation rather than simply mimic it [10-13].

Absence of marrow hemophagocytosis does not exclude HLH. Hemophagocytosis may be focal or absent early and is not specific when present [7,12,14]. Elevated fibrinogen did not establish the hypofibrinogenemia component of the criteria, while incomplete triglyceride data left the alternative component unassessed. Neither finding independently excluded HLH. Competing explanations reduce the specificity of positive findings but do not automatically negate a criterion.

Ferritin and sCD25 exceeded the optimized HLH inflammatory index thresholds described in hematologic malignancy [8]. These results supported concern for a high-risk inflammatory state but did not, by themselves, establish the cause of inflammation or resolve the formal diagnostic classification. Ferritin was particularly difficult to interpret because transfusion-associated iron deposition, infection, and hepatic dysfunction were concurrent. Serial clinical assessment and integration of laboratory findings are central when evaluating suspected HLH or macrophage activation syndrome [15].

Treatment limitations and competing risks

Common initial treatments for T-LGLL include methotrexate, cyclophosphamide, and cyclosporine [1-3]. Cyclophosphamide was attempted in this patient but interrupted by bacteremia. The very severe aplastic anemia phenotype subsequently led to treatment with horse antithymocyte globulin, cyclosporine, and eltrombopag [9].

The potential benefit of immunosuppression had to be weighed against persistent ANC values near zero, transfusion dependence, active or recent bacteremia, prior pulmonary coccidioidomycosis, dialysis-dependent renal failure, a necrotic wound, severe thrombocytopenia, recurrent respiratory failure, cardiac dysfunction, and hyperinflammation. Table *5* summarizes the treatments and major concurrent or subsequent events.

Therapy or intervention	Parameter	Documented detail
Irradiated packed RBC transfusions	Schedule	Repeated throughout hospitalization
	Purpose	Transfusion-dependent anemia
Platelet transfusions	Schedule	Repeated throughout hospitalization
	Purpose	Severe thrombocytopenia
Transfusion support	Concurrent event	High transfusion burden
		Recurrent respiratory failure
	Etiologic consideration	TRALI
		TACO
		Volume overload
Filgrastim	Dose	480 µg
	Route	Subcutaneous
	Frequency	Daily
	Purpose	Severe neutropenia
	Observed course	ANC remained near zero
	Dose	50 units/kg

Epoetin alfa-epbx	Route	Subcutaneous
	Frequency	Three times weekly
	Purpose	Anemia in ESRD
		Anemia in marrow failure
	Observed course	Continued transfusion dependence
Romiplostim	Dose	Not available
	Purpose	Severe thrombocytopenia
	Subsequent therapy	Eltrombopag
Eltrombopag	Dose	150 mg
	Frequency	Daily
	Purpose	Severe thrombocytopenia
	Observed course	Persistent severe thrombocytopenia
	Combination regimen initiated	Hospital day 49
	Combination regimen purpose	Very severe aplastic anemia phenotype
IVIG	Dose	1 g/kg
	Route	Intravenous
	Interval	Every 24 hours
	Number of doses	2
	Purpose	Severe thrombocytopenia
	Subsequent event	Acute hypoxemic respiratory failure after IVIG and transfusions
	Event interpretation	Respiratory failure considered multifactorial
Dexamethasone	Dose	40 mg
	Route	Intravenous
	Frequency	Daily
	Duration	4 days
	Purpose	Severe thrombocytopenia
		Inflammatory state
	Observed course	No hematologic recovery before death
Cyclophosphamide	Dose	75 mg
	Route	Oral
	Frequency	Daily
	Purpose	Suspected T-LGLL-associated marrow failure
	Treatment interruption	Held during bacteremia
Horse antithymocyte globulin	Combination regimen initiated	Hospital day 49
	Combination regimen purpose	Very severe aplastic anemia phenotype
	Complete dosing schedule	Not available
Cyclosporine	Combination regimen initiated	Hospital day 49
	Combination regimen purpose	Very severe aplastic anemia phenotype
	Dose	Not available

Antithymocyte globulin-based combination	Concurrent or subsequent event	Fever
		Hypoxemia
		Recurrent respiratory failure
		ICU admission
		Treatment interruption
Hemodialysis	Schedule	Intermittent
	ICU adjustment	Treatment intensified
	Purpose	ESRD
		Uremia
		Volume management
	Observed course	Partial improvement in mental status
		Respiratory improvement after volume removal

TABLE 5: Disease-directed and supportive treatments with major clinical events

ANC: absolute neutrophil count, ESRD: end-stage renal disease, ICU: intensive care unit, IVIG: intravenous immunoglobulin, RBC: red blood cell, TACO: transfusion-associated circulatory overload, T-LGLL: T-cell large granular lymphocytic leukemia, TRALI: transfusion-related acute lung injury

Source: Original table developed by the author from the patient's clinical records; not reproduced or adapted from a published source. Events occurring during or after treatment are reported descriptively and do not establish causation.

Respiratory failure occurred after IVIG and repeated transfusions and recurred after antithymocyte globulin-based therapy. Transfusion-related acute lung injury and transfusion-associated circulatory overload were among the considerations [16]. Other possibilities in the clinical differential included pulmonary edema in dialysis-dependent renal failure, infection, diffuse alveolar hemorrhage, and antithymocyte globulin-associated lung injury. The temporal relationships did not establish a single cause.

The overlapping effects of marrow failure, infection, transfusion burden, renal disease, and cardiopulmonary dysfunction prevented reliable attribution of deterioration to one intervention. This uncertainty is central to interpreting treatment limitations in this case.

For patients with severe aplastic anemia who do not respond to initial immunosuppression, subsequent options may include a second course of immunosuppression, thrombopoietin receptor agonist therapy, clinical trial enrollment, or allogeneic transplantation, depending on fitness and prior treatment [9]. In this 72-year-old patient, dialysis dependence, active infection, and multiorgan dysfunction severely limited these options. He died 13 days after the combination regimen began, too early to assess the expected delayed hematologic response. His course therefore cannot establish treatment resistance and illustrates the importance of discussing goals of care alongside disease-directed treatment.

The lower extremity lesion and procedural risks

Fever, edema, tenderness, eschar, and imaging concern for a collection initially favored infection. However, surgical exploration yielded serous fluid without purulence, and cultures were nondiagnostic. The subsequent appearance raised consideration of pyoderma gangrenosum or leukemia cutis, alongside occult infection and neutropenic ulceration. Diagnostic skin pathology was unavailable.

A nondiagnostic exploration did not resolve this differential. Severe neutropenia can blunt inflammatory findings, including pus formation, and severe thrombocytopenia increases procedural bleeding risk [17]. Conversely, repeated debridement may worsen pyoderma gangrenosum through pathergy [18]. Local wound care and avoidance of further aggressive debridement reflected these competing concerns, particularly in the absence of clear evidence of an abscess or necrotizing infection.

Limitations

This retrospective report is limited by incomplete diagnostic documentation. A complete T-LGLL immunophenotype, *STAT3* testing results, peripheral blood LGL count, natural killer cell functional testing, complete triglyceride data, final repeat marrow cytogenetics, and diagnostic skin pathology were unavailable. The initial inpatient marrow cellularity percentage and central hematopathology review were

also unavailable. Available records did not establish five HLH-2004 criteria. The lack of a documented qualifying fever and incomplete triglyceride and natural killer cell assessments limited retrospective classification. Concurrent marrow failure, infection, hepatic dysfunction, and transfusion-associated iron deposition also reduced the specificity of the inflammatory findings. HLH-like hyperinflammation reflects the treating team's assessment and does not represent a separate validated diagnostic category.

Conclusions

Severe cytopenias and marked marrow hypocellularity in a patient with established MDS warrant reassessment for additional causes of marrow failure. In this case, clonal T-cell large granular lymphocytic proliferation accompanied a very severe aplastic anemia phenotype, but the available findings did not establish a definitive leukemia diagnosis or prove that the T-cell clone caused the marrow failure. Recognizing this distinction is important when considering immunosuppression in a patient with competing myeloid and immune-mediated processes. Hyperinflammation, recurrent infection, and transfusion-associated iron deposition further complicated interpretation. The necrotic leg lesion remained diagnostically unresolved, and bleeding risk, poor healing, and possible pathergy constrained further intervention. Treatment decisions required repeated assessment of potential benefit against infection, respiratory deterioration, and limited organ reserve. As multiorgan dysfunction progressed, goals-of-care discussions became central to management. Close coordination among hematology, generalist, and supportive care teams remained necessary throughout the admission.

This single case supports reassessment when cytopenias become disproportionate to the established MDS course. It does not establish a causal role for the T-cell clone or the effectiveness of a particular treatment. Incomplete diagnostic records and death shortly after initiation of the combination regimen limited both classification and assessment of treatment response.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Ikken Aisin

Acquisition, analysis, or interpretation of data: Ikken Aisin

Drafting of the manuscript: Ikken Aisin

Critical review of the manuscript for important intellectual content: Ikken Aisin

Disclosures

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