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The progression from CKD-associated myelosuppression to acute myeloid leukemia in four years: A case report

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Abstract

Introduction: Chronic Kidney Disease (CKD) may cause hematologic disturbances due to chronic inflammation, erythropoietin deficiency, and persistent accumulation of uremic toxins. As a result, patients of CKD may experience myelosuppression but its progression to Acute Myeloid Leukemia (AML) has not been commonly seen. This case report highlights the progression from CKD-associated myelosuppression to AML in a dialysis-dependent patient over a period of four years.

Case presentation: A 53-year-old male, known case of type 2 diabetes mellitus and epilepsy was diagnosed with CKD in 2018, which eventually required maintenance dialysis and gradually worsened to end-stage renal disease (ESRD). His first bone marrow biopsy in 2019 showed no malignancy but CKD-associated myelosuppression. The patient's hematological parameters continued to deteriorate over the next three years. Moreover, his dialysis dependence adversely affected his pulmonary and cardiac function. In early 2023, his routine pre-dialysis workups showed recurrent hemoglobin drops, leading to transfusions every week. In mid-2023, 23% blasts were found in his Complete Blood Count (CBC), raising suspicion for AML which was then confirmed through repeat bone marrow biopsy and was further supported by immunohistochemistry findings. Due to his prolonged dialysis dependence and other comorbid conditions, the patient was ineligible for chemotherapy. He was managed with supportive care until he succumbed to AML within two months.

Conclusion: This case highlights the possibility of hematologic transformation in CKD patients and the challenges in diagnosing and treating AML in dialysis-dependent individuals. It calls upon the need for early and close hematologic monitoring in patients with myelosuppression to allow for better and timely therapeutic interventions and improved outcomes.

Keywords: Chronic kidney disease; Acute myeloid leukemia; Myelosuppression; Dialysis complications; Hematopoietic dysfunction.

Introduction

Acute Myeloid Leukemia (AML) is an aggressive hematological malignancy with poor prognosis particularly in patients with chronic conditions [1]. Chronic Kidney Disease (CKD) often cause chronic inflammation and immune dysfunction predisposing patients to genetic instability and eventually malignancies [2]. Long-term dialysis, a common treatment approach for advanced CKD is also associated with immune suppression and chronic inflammation, further damaging the body's defenses [1]. Diabetes mellitus, characterized by hyperglycemia and insulin resistance can also adversely affect immune responses leading to more complications [3]. This case report discusses a 53-year-old male with a history of CKD and insulin-dependent diabetes mellitus, who developed AML over a period of four years. In 2019, his bone marrow biopsy showed myelosuppression without malignancy, but by 2023, it progressed to AML. The report, thus, aims to highlight the potential role of immune dysregulation in development of hematological malignancies, the challenges involved in managing AML in a dialysis-dependent patient, emphasizing the need for vigilant monitoring in such cases.

Case presentation

A 53-year-old male, known case of type 2 diabetes mellitus and epilepsy (controlled on low-dose medication) was initially diagnosed with CKD in late 2018, after elevated creatinine levels were repeatedly observed during his routine diabetic monitoring. He was referred to a nephrologist and his treatment began but his renal function continued to decline to a point that he required hospitalization for one month and his condition required him to be placed on a mechanical ventilation for some time. During his admission, a renal stent was also placed but was later removed. Despite all necessary interventions, his renal function progressively worsened and he was eventually initiated on maintenance hemodialysis with its frequency eventually increasing to 3 sessions per week. Since the etiology remained unknown, a bone marrow biopsy was suggested in April 2019 to rule out any hematological involvement. The report found trilineage hematopoietic suppression but concluded it secondary to the patient's CKD and ruled out any evidence of malignancy.

Table 1: Bone marrow biopsy findings-April 2019.

Parameter	Findings
Peripheral morphology	Normochromic, anisocytosis, elliptocytes, teardrop cells, leukoerythroblastic picture, dysplastic neutrophils
Bone marrow aspirate	Scattered erythroid and myeloid precursors
Trephine biopsy	Thickened bony trabeculae, cystic cavities, bone excavation, suppressed trilineage hematopoiesis
Conclusion	Myelosuppression secondary to CKD, no evidence of malignancy

In early May 2019, his hemoglobin (Hb) level and platelets count were found to be low, at 10 g/dL (normal: 13.0-17.0 g/dL), and 8.5×10^9/L (normal: 150-450×10^9/L), respectively. His creatinine was also markedly raised at 8.9 mg/dL (normal: 0.7-1.3 mg/dL) but the WBC count was within the normal range at 5.1×10^9/L (normal: 4.0-11.0×10^9/L). Repeat testing in the same month showed further decline in hemoglobin to 7.9 g/dL and platelets to 12×10^9/L, highlighting progressive worsening of anemia, thrombocytopenia, and eventually bone marrow suppression.

Table 2: Laboratory findings - May 2019.

Test	May 6, 2019	May 14, 2019	Reference Range
White blood cell (WBC) count	5.1×10^9/L	8.49×10^9/L	4.0-11.0×10^9/L
Hemoglobin (Hb)	10 g/dL	7.9 g/dL	13.0-17.0 g/dL
Platelets	8.5×10^9/L	12×10^9/L	150-450×10^9/L
Urea	176 mg/dL	75 mg/dL	7-20 mg/dL
Creatinine	8.9 mg/dL	4.53 mg/dL	0.7-1.3 mg/dL
Calcium	7.3 mg/dL	7.41 mg/dL	8.5-10.5 mg/dL
Phosphorus (PO_4)	-	3 mg/dL	2.5-4.5 mg/dL
Magnesium (Mg)	-	2.33 mg/dL	1.7-2.5 mg/dL
Parathyroid hormone (PTH)	57 pg/mL	-	10-65 pg/mL

Over the years, the patient's CKD further worsened requiring him multiple transfusions to manage anemia. In December 2022, his ferritin and iron profile testing depicted markedly elevated levels. His ferritin was significantly high at 1448.90 ng/mL (normal: 20-250 ng/mL) and serum iron at 284 µg/dL (normal: 40-160 µg/dL), suggesting iron overload due to frequent transfusions further contributing to hematopoietic stress and also indicating impaired iron regulation, commonly observed in dialysis dependent CKD patients.

Table 3: Ferritin-Dec 2022

Test	Result	Reference range
Ferritin	1448.90 ng/mL	20-250 ng/mL (Adult male)

Table 4: Iron Profile-Dec 2022.

Test	Result	Reference range
Serum iron	284 µg/dL	40-160 µg/dL (Adult Male)
TIBC (Total Iron Binding Capacity)	372 µg/dL	250-400 µg/dL (Adult)

By early 2023, the patient started experiencing persistent anemia with his Hb levels dropping every other week before his routine workup's pre-dialysis. Due to these repeated declines, he would require mandatory blood transfusions very frequently every 1-2 weeks for his dialysis to take place. On consulting a hematologist, a CBC was performed on May 14, 2023, that revealed low level of hemoglobin and platelets, at 9.3 g/dL and 60×10^9/L, respectively. WBC count was at 5.9×10^9/L and 23% blasts were also found while they are supposed to be at less than 5% in normal cases. The report remarked a left shift in WBCs, thrombocytopenia, and a dimorphic blood picture with oval macrocytes, 2% fragmented RBCs and tear drop cells raising strong suspicion for acute leukemia, and calling for an immediate repeat bone marrow biopsy. Routine urea and creatinine levels were also tested the same day, and were found to be at 85.6 mg/dL and 6.30 mg/dL (normal: 0.9-1.3 mg/dL), respectively confirming the disease progression to ESRD (end-stage renal disease). At this time, he was also being injected erythropoietin 100,000 units subcutaneously three times per week.

Table 5: Laboratory findings-14th May 2023.

Test	Result	Reference Range
Urea	85.6 mg/dL	17-49 mg/dL
Creatinine	6.30 mg/dL	0.9-1.3 mg/dL

Table 6: CBC report - 14th May 2023.

Test	Result	Reference range
Blasts	23%	Should be <5%
Hemoglobin (Hb)	9.3 g/dL	13.0-17.0 g/dL
Platelets	60 $\times10^9$/L	150-400 $\times10^9$/L
WBC Count	5.9 $\times10^9$/L	4.0-10.0 $\times10^9$/L
Neutrophils	40%	40-80%
Lymphocytes	20%	20-40%
Monocytes	7%	2-10%
Metamyelocytes	4%	Normally absent
Band Cells	5%	Normally absent
Eosinophils	1%	1-6%
Basophils	0%	0-1%
RBC Count	3.6 $\times10^{12}$/L	4.5-5.5 $\times10^{12}$/L
Hematocrit (HCT)	30%	40-50%
MCV (Mean Corpuscular Volume)	84 fL	80-100 fL
MCH (Mean Corpuscular Hemoglobin)	26 pg	27-32 pg
MCHC (Mean Corpuscular Hemoglobin Concentration)	31 g/dL	31.5-34.5 g/dL

Table 7: Bone marrow biopsy - June 2023.

Parameter	Findings
Peripheral smear	Normochromic, anisocytosis, macrocytes, dysplastic neutrophils, circulating blast cells
Bone marrow aspirate	Scattered erythroid and myeloid precursors, blast cells present
Trephine biopsy	Fragmented and hemodiluted aspirate, blasts noted
Cellular composition (%)	Neutrophils: 35%, Lymphocytes: 20%, Monocytes: 7%, Myelocytes: 2%, Blasts: 35%, Basophils: 1%
Conclusion	AML confirmed

Table 8: Immunohistochemistry (IHC) findings - July 2023.

Marker	Result
CD45	Strong positive (confirms hematopoietic origin)
CD13	Strong positive (supports AML diagnosis)
CD117	10-12% positive (early myeloid progenitor involvement)

Table 9: CBC Reports June-July 2023.

Test	June 11, 2023	June 16, 2023	June 25, 2023	July 18, 2023	Reference Range
WBC Count	6.93×10^3/µL	5.49×10^3/µL	6.61×10^3/µL	3.75×10^3/µL	4.0–10.0×10^3/µL
Immature Granulocytes (IG)	8.90%	1.37%	0.85%	0.018%	0–1%
Neutrophils (Absolute)	1.91×10^3/µL	2.05×10^3/µL	1.17×10^3/µL	0.095×10^3/µL	1.8–7.7×10^3/µL
Neutrophils (%N)	27.5%	37.4%	17.7%	2.53%	40-80%
Lymphocytes (%L)	49.4%	52.2%	58.5%	49.4%	20-40%
Monocytes (%M)	14.2%	8.12%	22.8%	26.5%	2-10%
Platelets	37.7×10^3/µL	29.2×10^3/µL	24.4×10^3/µL	17.7×10^3/µL	150–400×10^3/µL
Hemoglobin	8.15 g/dL	7.19 g/dL	9.12 g/dL	7.30 g/dL	13.0-17.0 g/dL
RDW	18.0%	17.9%	17.3%	19.0%	11.5–14.5%

The findings of bone marrow biopsy performed in June 2023 were consistent with diagnosis of acute leukemia, showing a major increase in blasts compared to 2019 biopsy. Immunohistochemistry analysis was then performed for classification of AML and revealed strong CD45 positivity, strong CD13 positivity and expression of CD117 in 10-12% of cells, confirming myeloid lineage and blast phenotype.

After his AML was diagnosed, his laboratory findings in early June 2023 showed markedly elevated ESR at 32mm/hr (normal: 0-15 mm/hr), raised PTH at 107.5 pg/mL (normal: 15-65 pg/mL) and severe vitamin D deficiency (9.17 ng/mL, normal: >30 ng/mL), highlighting chronic inflammation as well as severely deteriorating bone health. Besides, his AML progression was tracked through a series of CBC reports, from June to July 2023, showing progressive anemia, neutropenia and thrombocytopenia, with his platelet count dropping to as low as 1.7×10^9/L in July 2023.

Since the patient had been dependent on dialysis and most chemotherapeutic drugs are renally excreted, chemotherapy was not an option for his treatment and he was only given supportive care. Moreover, due to prolonged dialysis, the patient had developed cardiac complications, including the placement of one coronary stent, and poor lung function further limiting treatment options. Eventually, within just two months of his diagnosis, the patient succumbed to AML in August 2023.

Discussion

AML is an aggressive blood cancer typified by the clonal growth of myeloid blasts and can result in fever, pallor, anemia, bleeding, and recurrent infections [4]. The development of AML in patients with chronic kidney disease (CKD), particularly those who progress to End-Stage Renal Disease (ESRD), is a topic of growing clinical interest. AML may not be directly caused by CKD, prolonged bone marrow stress, chronic inflammation, and increased oxidative stress in ESRD and/or diabetes may contribute to leukemogenesis.

Bone marrow stress and consequent genetic instability

Patients with CKD and ESRD are exposed to uremic toxins

which elevate oxidative stress and can contribute to insulin resistance, carbamylation, and a higher risk of cardiovascular disease [5]. Oxidative stress not only leads to systemic complications but also play an important role in hematopoietic dysfunction, as evidenced by myelosuppression found in the patient's biopsy in 2019. One significant systemic aspect of any cancer disease and a key target for therapeutic intervention is hematologic dysfunction [6]. In fact, particularly AML progression is also influenced by oxidative stress in a variety of ways, including the modulation of genes contributing to tumorigenesis and even treatment resistance [7]. Elevated reactive oxygen species (ROS) can also induce DNA damage and impair repair mechanisms, creating an environment that fosters genomic instability and set the stage for potential leukemic transformation [8]. As a response to repeated stressors, hematopoietic stem cells (HSCs) undergo compensatory proliferation. While this is a natural phenomenon, proliferation brought on by prolonged stress can cause aging phenotypes in HSCs due to modifications in DNA methylation. This comprises changes in promoter regions and global hyper methylation, which impact gene expression and lead to functional deterioration, further compromising hematopoiesis [9]. Besides, the interplay between stress signals and hematopoietic systems is evident through the role of macrophages. Prolonged stress raises extracellular ATP levels, which facilitate erythropoiesis by establishing a favorable microenvironment. Macrophages are an important part of this process, showing how hematopoietic support systems and stress signals interact [10]. Understanding these interconnected pathways is important for developing therapeutic strategies aimed at dealing with the potential progression from myelosuppression to AML in high-risk patient populations, as in the case in discussion.

Chronic inflammation, oxidative stress, and AML development

Persistent inflammation and oxidative stress are considered hallmark features of CKD, ESRD and even diabetes mellitus. Through processes like inflammation and glomerulosclerosis, which are common in CKD patients, oxidative stress is produced and leads to kidney damage [11]. Chronic kidney disease is associated with many cytokines with IL-18 possibly having a more significant effect [12]. Moreover, it is also linked to higher levels of growth regulated oncogene alpha (GROβ), interleukin-4, and tumor necrosis factor alpha [13]. Besides, hemodialysis itself enhances oxidative stress, causing further damage [14]. Moreover, hyperglycemic stress and diabetes mellitus can also drive the development of blood cancers as such individuals are likely to have a higher rate of associated mutations although they require additional hits to evolve into full-blown leukemia [15]. Elevated levels of cytokines, immune dysregulation along with the ongoing hematopoietic stress are known to create a pro-leukemic environment by inducing DNA damage and impairing DNA repair mechanisms or suppressing normal immune surveillance [16]. In this patient's case, the combination of CKD, ESRD, dialysis dependence and long-standing history of diabetes brought about these factors and can therefore be attributed to the malignant transformation from myelosuppression to AML over the subsequent four years.

Treatment challenges in AML patients with dialysis dependence

Management of patients diagnosed with AML and also undergoing dialysis due to ESRD presents significant therapeutic challenges. Anti-cancer agents can cause various electrolytes disturbances in patients with decreased kidney function, leading to hyponatremia, hyperkalemia, and other metabolic abnormalities [17]. In such condition, chemotherapeutic agents that are mostly eliminated via the hepatic route may be chosen [18]. In this case the patient was not eligible for such intensive chemotherapy not just due to his ESRD but also due his frail condition, dialysis dependence and comorbidities. However, in other cases, even after receiving severe chemotherapy and an allogeneic stem cell transplant, AML relapses are frequently seen [19]. This highlights the need for tailored alternative approaches to treatment in complex patients of AML such as those dependent on dialysis. For instance, in a study by [19], comprehensive genomic profiling using paraffin-embedded bone marrow clot specimens has effectively found leukemic-associated genes that can be employed as therapeutic targets in AML.

Importance of close hematological monitoring

Given the increased risk of hematologic abnormalities in patients with CKD and ESRD, regular and comprehensive hematological monitoring is important. While routine blood tests may not always reveal early malignant changes, periodic bone marrow evaluations and molecular testing could help in early detection and diagnosis of AML, eventually improving patient outcomes [21]. Further research is, however, needed to establish specific biomarkers for early detection then tailoring treatment strategies in this vulnerable patient population.

Conclusion

This case serves an important example of how prolonged inflammation, oxidative stress, and immune dysregulation may play a part in development of AML. The patient's journey from myelosuppression to leukemia highlights the need for early hematological surveillance in high-risk individuals. Further research is important to develop better treatment strategies and improve clinical outcomes in such complex cases as existing options present multiple limitations for dialysis-dependent patients.

Declarations

Acknowledgement: The authors sincerely thank the patient's family for their willingness to share this case for clinical and academic learning and providing access to the necessary data.

Patient consent: Since the patient is deceased, informed consent for publication was obtained from the patient's next of kin. The family was taken in complete confidence about the purpose of the report and consented to the use of anonymized clinical data for research purposes. All identifying information has been removed to ensure patient confidentiality.

Conflict of interest statement: The authors declare no conflict of interest related to this case report.

Authors contribution: Hania Haque gathered patient's data and contributed to the section of case presentation of the report. Mohammad Shahzaib interpreted the data and contributed to the discussion section of the report. Both authors were involved in writing and revising the manuscript and approved the final version for submission.

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