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Fatal right-sided heart failure due to leukostasis in a patient with leukemic transformation of myelodysplastic syndrome

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Key Clinical Message

We document leukostasis leading to acute fatal right-sided heart failure. In patients presenting with leukostasis and cardiopulmonary symptoms, clinicians should aim to assess for cardiac involvement, that is, by ECG and acute echocardiogram, since early recognition of right ventricular disease may provide an opportunity to treat this potentially reversible condition.

KEYWORDS

acute myeloid leukemia, cardiopulmonary arrest, echocardiography, hematology, hyperleukocytosis, pulmonary hypertension, right-sided heart failure

1 | INTRODUCTION

Leukostasis, that is, symptomatic hyperleukocytosis (HL), is a medical emergency condition characterized by HL and symptoms of diminished tissue perfusion. Leukostasis requires rapid treatment in order to prevent life-threatening complications and early death. HL is a laboratory abnormality and is most often defined as a total leukemia blood cell count >50 or $>100 \times 10^9/L$.¹ HL develops due to leukemic cell proliferation and may occur in acute leukemias or chronic myeloid leukemia in the accelerated phase.^{2,3} Complications of HL include leukostasis, disseminated intravascular coagulation, and tumor lysis syndrome. Leukostasis is most often seen in acute myeloid leukemia (AML) because of the large and poorly deformable blasts in AML.¹ Leukostasis evolves as a result of increased blood viscosity and sludging of the leukocytes leading to mechanical obstruction of the microcirculation and hence altered tissue perfusion, primarily in the lungs, brain, and kidneys.³ High oxygen consumption and invasiveness of leukemic blast cells may contribute to the organ dysfunction in leukostasis.² Also, a role for adhesion receptors and cytokines has been suggested as a pathogenic factor.⁴ One-week mortality of leukostasis is 20%-40% if left untreated and rises to 90% with the presence of respiratory failure and neurological compromise.¹

We present a case in which transformation to AML leads to acute fatal right-sided heart failure in a patient with myelodysplastic syndrome (MDS).

2 | CASE REPORT

A 70-year-old woman with MDS refractory anemia and excess blasts (RAEB)-2 type with cytogenetic deletion xq was admitted to the emergency department due to uncharacteristic symptoms in terms of fever, dyspnea, vomiting, and diarrhea. The patient had finished treatment with azacitidine 5 days prior to admission and had started in hydroxycarbamide treatment due to asymptomatic HL. Total white blood cell (WBC) count was $51.4 \times 10^9/L$ and $132 \times 10^9/L$ 14 and 7 days prior to admission, respectively. The patient had a normal echocardiogram and electrocardiogram (ECG) at 20 months and two months prior to admission, respectively (Figures 1A and 2A,B). Except for essential hypertension, the patient had no other known cardiovascular risk factors. At admission to hospital, the patient was neurological intact but with tachypnea, tachycardia of 115 bpm and a blood pressure of 95/60. Fluid and empiric antibiotic treatment were initiated with a tentative diagnosis of neutropenic fever.

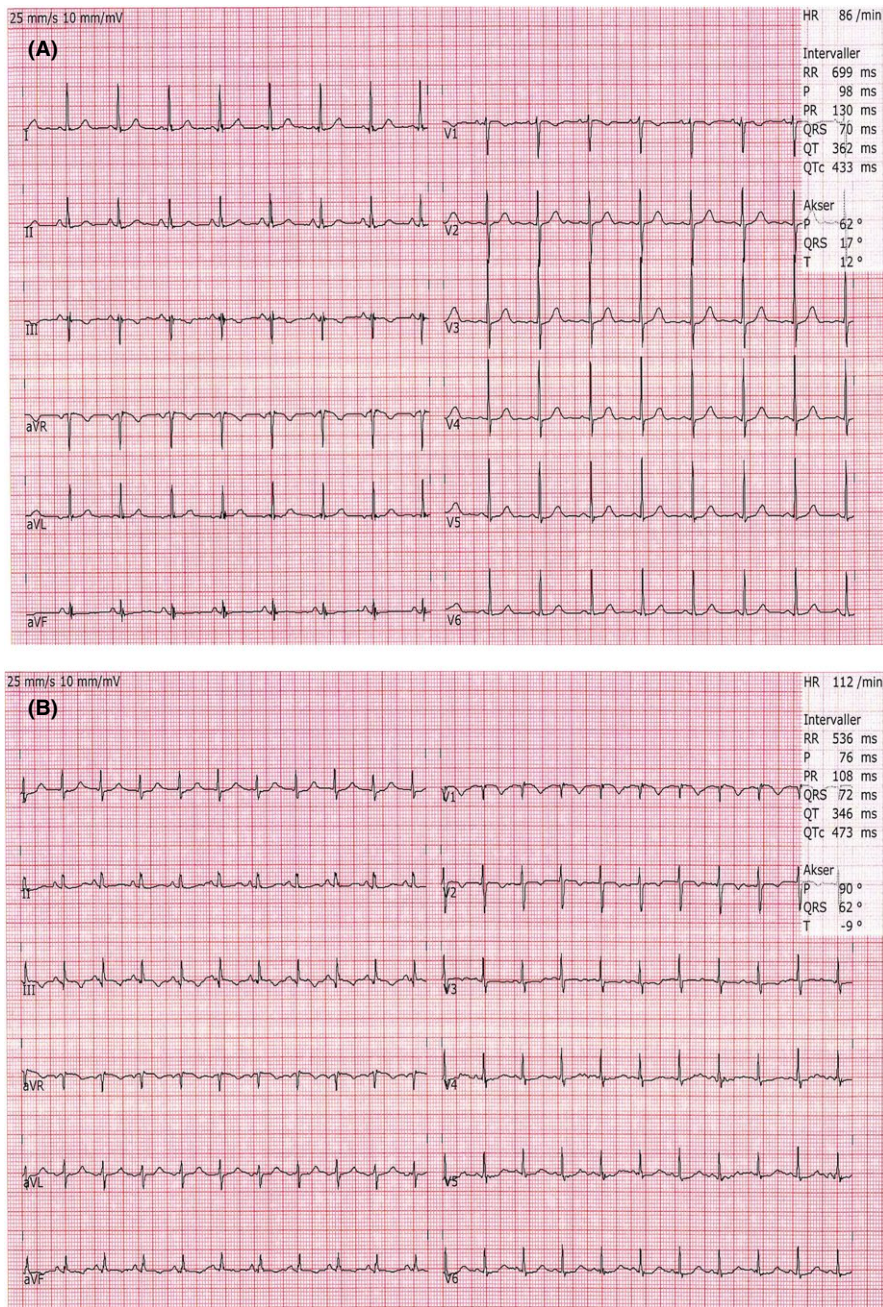
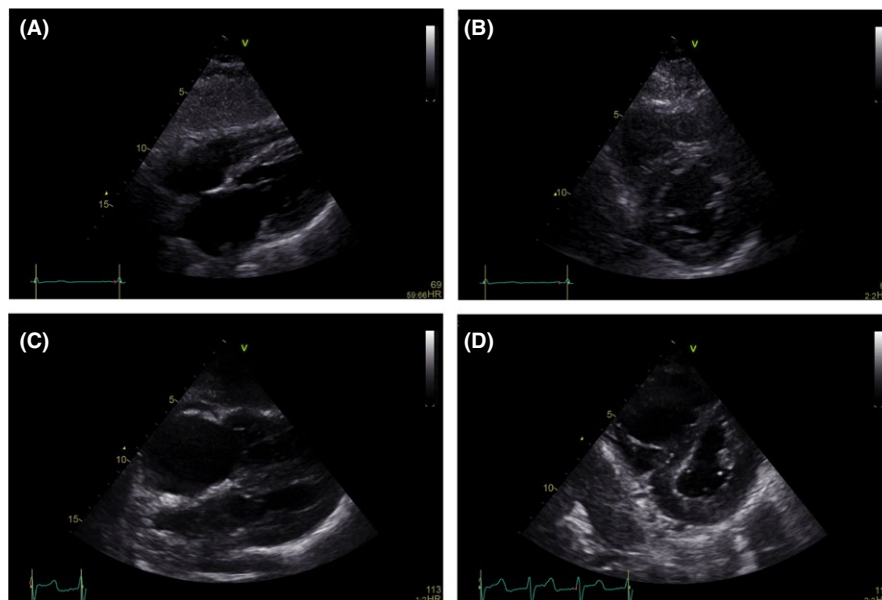


FIGURE 1 Patient's electrocardiogram 2 mo prior to admission and at admission. The electrocardiogram was normal 2 mo prior to admission (A) but revealed sinus tachycardia, $S_1Q_{III}T_{III}$ pattern, inverted t waves in V_2 , and flattened t waves in V_{3-4} at admission (B)

However, despite volume and antibiotic therapy, the patient experienced respiratory worsening, epigastric pain and demonstrated rapid hemodynamic deterioration with clinical and paraclinical signs of circulatory shock. Results of arterial gas analysis are shown in Table 1. A new ECG demonstrated sinus tachycardia, typical signs of right ventricular strain, that is, $S_1Q_{III}T_{III}$ pattern, inverted t waves in V_2 , and flattened t waves in V_{3-4} (Figure 1B). At this point, the patient was still neurological intact. Ventilatory support and fluid resuscitation were initiated. Results of a second arterial gas analysis are shown in Table 1. An acute bedside echocardiogram revealed signs of severe right ventricular pressure overload. This included dilatation and systolic dysfunction of the right ventricle, tricuspid regurgitation and pulmonary hypertension,

and compression and D-sign deformation of the left ventricle with reduced filling despite preserved left ventricular ejection fraction (Figure 2C,D). An acute computed tomography pulmonary angiogram ruled out pulmonary embolism, pneumonia, and significant atelectasis and pleural fluid (Figure 3A,B). Despite ongoing ventilatory support, extensive fluid resuscitation with >3 L isotonic saline solutions and initiation of circulatory support using vasopressor agents, the patient experienced respiratory and circulatory worsening as well as neurological deterioration with altered mental status. At this point, blood samples revealed HL with a total WBC count of $237 \times 10^9/L$ and elevated leukemic blast cell count of $12.6 \times 10^9/L$ (Table 1). The patient's clinical and paraclinical presentation were compatible with obstructive shock and

FIGURE 2 Patient's echocardiogram 20 mo prior to admission and at admission. Echocardiographic subxiphoid 4 chamber (A) and short-axis view (B) 20 mo prior to admission, and subxiphoid 4 chamber (C) and short-axis view (D) at admission. The echocardiogram was normal 20 mo prior to admission but revealed signs of severe right ventricular pressure overload and compression and D-sign deformation of the left ventricle at admission. See text for details



development of acute respiratory and right-sided heart failure due to pulmonary leukostasis as a result of the transformation of MDS to AML. In addition, the patient had clinical and paraclinical signs compatible with leukostatic involvement of the brain and kidneys. The patient was transferred to the intensive care unit for respiratory and circulatory support and initiation of induction cytoreductive chemotherapy. Due to the patient's underlying malignant disease, that is, transformation of MDS to AML, the patient was not considered candidate for extracorporeal life support. However, during tracheal intubation, the patient developed cardiopulmonary arrest and died. Because of the rapid clinical and hemodynamic deterioration, no pathological sampling was obtained from the patient. An autopsy was not performed as on request of the patient's relatives.

3 | DISCUSSION

Leukostasis refers to the clinical symptoms and complications resulting from HL. However, diagnosing leukostasis can be challenging because of its unspecific presentation. Leukostasis involves several organ systems, for example, the central nervous system, pulmonary, cardiovascular, and peripheral vascular system. Clinical signs and symptoms may include fever, dyspnea, hypoxia, headache, impaired vision, tinnitus, confusion, somnolence, and coma.^{1,3} Less often, leukostasis presents with symptoms of myocardial and limb ischemia, and ECG may demonstrate signs of ischemia and right ventricular strain.¹ In the clinical setting, the presence of HL, signs of altered tissue perfusion, and respiratory and neurological distress in patients with leukemia may guide the diagnosis of leukostasis.³ In the present case, leukostasis was complicated by severe right-sided heart failure.

Consequently, in patients presenting with leukostasis and cardiopulmonary symptoms, clinicians should aim to assess for cardiac involvement, that is, by ECG and acute echocardiogram, since early recognition of right ventricular disease may provide an opportunity to treat this potentially reversible condition.

While pulmonary involvement is a frequent complication to leukostasis, the impact of leukostasis on right ventricular function using cardiovascular imaging modalities has only been sparsely reported in the literature. Katogiannis and colleagues reported a case of leukostasis-related fatal cardiopulmonary arrest as initial presentation of chronic myeloid leukemia with HL and a total WBC count of $390 \times 10^9/L$.⁵ Similar to the present case, echocardiographic signs of severe right-sided heart failure with preserved left ventricular function were also present in the case reported by Katogiannis and colleagues. In the present case, the patient experienced rapid and fatal respiratory and hemodynamic deterioration within a few hours because of leukostasis despite only moderate HL. Notably, there seems to be no clear correlation between WBC and leukostasis severity, and leukostatic symptoms may even occur with WBC count below $100 \times 10^9/L$.³ Other, yet unknown factors in addition to WBC count and type of leukemia may be important in the pathogenesis of leukostasis.¹ Whether the timely progression of HL as well as patient comorbidities may contribute to leukostatic symptoms severity including cardiac manifestations remains speculative. Importantly, although the patient's clinical and paraclinical presentation were compatible with pulmonary leukostasis, we cannot rule out microembolism of the pulmonary circulation as a contributing factor to the development of acute right-sided heart failure in the present case due to the lack of pathological sampling.

TABLE 1 Results of the patient's arterial gas analyses

	1. Arterial gas analysis	2. Arterial gas analysis	3. Arterial gas analysis
O ₂ supplement, L/min	3, nasal	15, mask w. reservoir	15, mask w. reservoir
pH (7.37-7.45)	7.41	7.25	6.91
pCO ₂ , kPa (4.3-5.7)	3.2	3.0	4.7
pO ₂ , kPa (9.6-13.7)	11.2	8.6	13.3
Oxygen saturation, %	96	87	89
HCO ₃ , mmol/L (21.8-26.2)	17.5	11.9	6.8
Base excess, mmol/L (−5 to 5)	−9	−16	−23
Lactate, mmol/L (0.5-2.5)	3.6	9.1	12.5
Kalium, mmol/L (3.5-4.6)	3.8	4.4	5.0
Natrium, mmol/L (136-146)	—	137	137
Chloride, mmol/L (99-109)	—	110	107
Creatinine, μmol/L (45-90)	161	182	169
Glucose, mmol/L (4.2-7.8)	8.1	10.0	8.6

Data are expressed as absolute numbers with reference intervals combined for men and women.

Leukostasis is a medical emergency condition, and management should focus on rapid stabilization and lowering of the WBC count. Following stabilization of the patients, acute treatment of leukostasis includes cytoreduction and supportive care. Because chemotherapy reduces WBC count while at the same time targeting the leukemia itself, induction chemotherapy should be first choice cytoreductive strategy. The use of leukapheresis in patients with HL is controversial but may be used as a bridge to induction chemotherapy in patients with leukostasis. Supportive care includes (a) hydration, (b) correction of electrolyte disturbances, (c) prevention of tumor lysis syndrome by hydration and administration of allopurinol, (d) prevention of hemorrhage by prophylactic platelet transfusion if platelet count $<20-30 \times 10^9/L$, and (e) symptom-directed supportive care, for example, mechanical ventilation for respiratory failure.¹

This case report supports evidence of right ventricular failure as the cause of death in a patient with leukostasis.

While patients with acute left-sided heart failure typically present with dyspnea, hypotension, and signs of hypoperfusion and pulmonary edema, isolated acute right-sided heart failure is characterized by dyspnea and signs of hypoperfusion and stasis without pulmonary edema. Cardiac dysfunction due to sepsis is characterized by biventricular dysfunction.⁶ In contrast, stress cardiomyopathy, also known as takotsubo syndrome, is predominantly characterized by isolated left ventricular dysfunction and only in a minority of patients by right ventricular involvement.⁷ However, it may be difficult to diagnose and differentiate between acute right-sided and left-sided heart failure based on clinical presentation. Moreover, ECG changes depicting right ventricular strain are not sensitive to diagnose acute right-sided heart failure.⁸ In general, ECG findings should not stand alone⁹ and diagnosis should be supported, if possible, by an acute echocardiogram as well as computed tomography pulmonary angiogram to diagnose acute right-sided heart failure, help identifying the specific underlying cause and to guide treatment. In addition to treatment of the specific underlying cause, management of acute right-sided heart failure due to pulmonary hypertension includes volume unloading, right ventricle afterload reduction, that is, decreasing pulmonary vascular tone by correcting hypercapnia, acidemia and alveolar hypoxia, and administration of vasoactive and inotropic drugs to achieve pulmonary vasodilation and improve right ventricle contractility. Extracorporeal life support may be used in acute right-sided heart failure if medical therapy is ineffective.¹⁰ Novel therapy directed toward reducing strain on the right ventricle, that is, percutaneous circulatory support and balloon atrial septostomy, might also have a role as a bridging strategy to induction chemotherapy in acute right-sided heart failure due to leukostasis. However, the effect of such strategies in a setting other than familiar/idiopathic pulmonary arterial hypertension remains controversial¹¹ and should be used with caution in order to avoid tumor lysis syndrome.

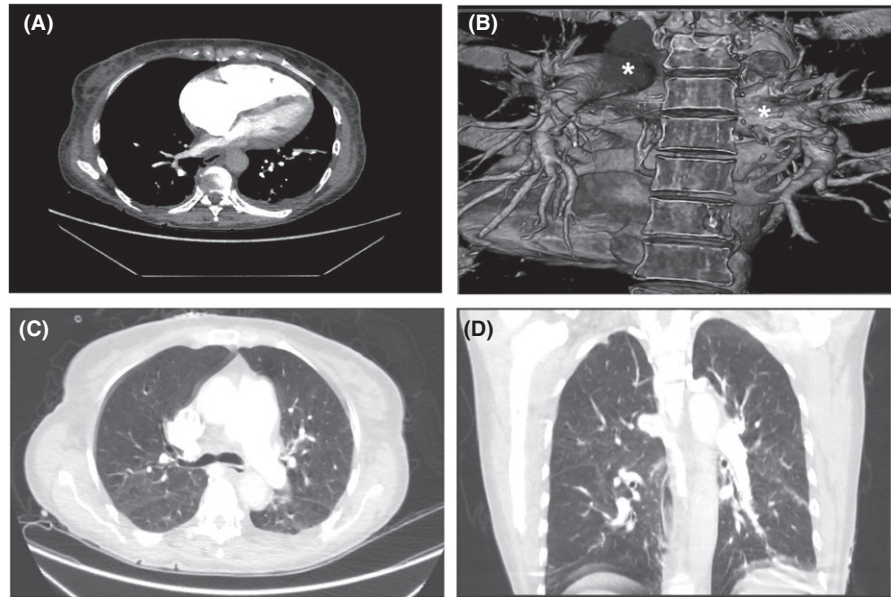
4 | CONCLUSION

We document leukostasis as a complication to leukemic transformation of MDS leading to acute fatal right-sided heart failure. Early recognition of right ventricular disease in patients with HL and leukostasis may provide an opportunity to treat this potentially reversible condition. Novel therapies directed toward reducing the strain on the failing right ventricle might have a role in the treatment of leukostasis.

CONFLICT OF INTEREST

None of the authors have any conflict of interest.

FIGURE 3 Patient's computed tomography pulmonary angiogram with three-dimensional reconstruction of the pulmonary arteries seen from the rear. The computed tomography pulmonary angiogram revealed severe right-sided dilatation (A). There was contrast filling in both pulmonary arteries beyond the segmental arteries depicted by “*”, and hence no signs of central pulmonary embolism (B). In addition, the computed tomography ruled out pneumonia and significant atelectasis and pleural fluid (C,D)



AUTHOR CONTRIBUTION

KP: drafted the manuscript. All authors collected the data and did critical revision of the manuscript.

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