**Case Report**

**Hyperleukocytosis in a 62-Year-Old Patient with Incidentally Diagnosed** **Acute Myeloid Leukemia Presenting With a Cough in a Rural Emergency Department: A Case Report and Literature Review**

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**Abstract**

Acute Myeloid Leukemia (AML) is a malignant clonal hematopoietic stem cell disorder of the myeloid lineage that results in the infiltration of abnormal hematopoietic cells of the system in the bone marrow and haematological periphery. AML presents with a wide range of often unremarkable symptoms. However, it can rapidly become fatal due to complications, including hyperleukocytosis, which can lead to Disseminated Intravascular Coagulation (DIC), tumour lysis syndrome, leukostasis, and end-organ injury. Leukostasis occurs when the White Blood Cell (WBC) count is high enough to result in vascular congestion and lead to end-organ dysfunction [1]. Leukostasis is relatively common and occurs in 15-45% of AML patients with hyperleukocytosis [2]. Alarmingly, if left untreated, leukostasis is associated with a mortality rate of 20 to 40 per cent [2]. The varied symptomatology, high mortality and common presentation of leukostasis in hyperleukocytic AML patients highlight the importance of raising awareness of leukostasis in clinical settings. Thus, it is crucial to report identified cases of hyperleukocytosis and leukostasis to improve diagnostic accuracy and health outcomes. Therefore, we report a case of hyperleukocytosis in a 62-year-old female with AML who presented to our rural emergency department with a four-week history of cough.

**Keywords:** Acute Myeloid Leukemia; Emergency Department; Hyperleukocytosis; Leukostasis, Rural

**Introduction**

Acute Myeloid Leukemia (AML) is a malignant clonal hematopoietic stem cell disorder of the myeloid lineage [3,4]. It primarily affects the adult population and causes rapid proliferation of blood cells from the bone marrow into the peripheral blood and other tissues [5,6]. AML interferes with haematopoiesis due to the failure of stem cell differentiation [4]. This results in infiltration and over-proliferation of abnormally and poorly differentiated cells of the hematopoietic system in the bone marrow and haematological periphery [4]. AML presents with a wide range of signs, symptoms and complications such as pallor, shortness of breath, palpitations, easy bruising, epistaxis, weight loss, or recurrent infections [3,7-12]. Severe AML complications include tumour lysis syndrome, Disseminated Intravascular Coagulation (DIC) and hyperleukocytosis, which can lead to leukostasis and end-organ injury in patients with underlying hematologic malignancies [13]. Leukostasis occurs when the white Blood Cell (WBC) count is high enough to result in vascular congestion and lead to end-organ dysfunction [1]. Leukostasis is relatively common, presenting in 15-45% of AML patients with hyperleukocytosis [2]. Alarmingly, if left untreated, leukostasis is associated with a one-week mortality rate of 20 to 40 per cent [2]. The varied symptomatology, high mortality and common presentation of leukostasis in hyperleukocytic AML patients highlight the importance of raising awareness of leukostasis in clinical settings. Thus, it is important to report identified cases of hyperleukocytosis and leukostasis to improve diagnostic accuracy and health outcomes. Therefore, we report a case of hyperleukocytosis in a 62-year-old female with AML who presented to our rural emergency department with a four-week history of cough.

**Case Presentation**

A 62-year-old non-smoking female with a history of endometriosis, keratoconus, irritable bowel syndrome and easy bruising presented to the emergency department with a primary complaint of a four-week cough and a six-month history of fatigue and night sweats. Their vital signs indicated a febrile patient of 37.9°C but were otherwise unremarkable. Physical examination revealed a moderately obese and relaxed patient with tenderness to L4 and L5 but without organomegaly, lymphadenopathy, or other remarkable features.

Laboratory haematological findings were notable for hyperleukocytosis, thrombocytopenia, hyponatremia, hypokalaemia, hyperuricemia, and deranged Alkaline Phosphatase (ALP) alongside Elevated Lactate Dehydrogenase (LDH) and C-Reactive Protein (CRP) (Table 1, 2). Assessment of Prothrombin Time (PT) International Normalized Ratio (INR) Activated Partial Thromboplastin Clotting Time (APPT) were unremarkable, and blood cultures were negative (Table 3).

|  |  |  |
| --- | --- | --- |
| **Test** | **Result (Admission)** | **Result (Discharge)** |
| Haemoglobin [g/L] | 115 | 104 |
| White blood cell count [x10\*9/L] | 136.24 | 3.99 |
| Platelet count [x10\*9/L] | 31 | 107 |
| Red Cell Count [x10\*12/L] | 3.62 | 3.35 |
| Haematocrit [L/L] | 0.34 | 0.31 |
| Mean Cell Volume [fL] | 93.1 | 91 |
| Neutrophils [x10\*9/L] | 4.09 | 31 |
| Lymphocytes [x10\*9/L] | 13.62 | 1.5 |
| Monocytes [x10\*9/L] | 1.36 | 0.36 |
| Eosinophils [x10\*9/L] | 0 | 0 |
| Basophils [x10\*9/L] | 0 | 0.01 |
| Blasts [%] | 86% | N/A |

**Table 1:** Complete blood count results.

|  |  |  |
| --- | --- | --- |
| Test | Result (Admission) | Result (Discharge) |
| Sodium [mmol/L] | 134 | 138 |
| Potassium [mmol/L] | 2.8 mmol/L | 3.6 |
| Chloride [mmol/L] | 97 mmol/L | 101 |
| Bicarbonate Level [mmol/L] | 22 mmol/L | 23 |
| Anion gap [mmol/L] | 16 | 18 |
| Urea Level [mmol/L] | 9.1 | 3.2 |
| Creatinine [mmol/L] | 81 mg/L | 3.2 |
| eGFR [mL/min/1.73m2] | 67 | 68 |
| Glucose [mmol/L] | 5.6 | 7.1 |
| Calcium [mmol/L] | 2.6 | 2.5 |
| Phosphate [U/L] | 1.31 | 0.97 |
| Magnesium [mmol/L] | 0.79 | 0.8 |
| Albumin [g/L] | 38 | 36 |
| Total bilirubin [mg/dL] | 17 | 10 |
| GGT [U/L] | 55 | 48 |
| ALP [U/L] | 129 | 218 |
| AST [U/L] | 28 | 25 |
| ALT [U/L] | 14 | 20 |
| LDH [U/L] | 590 | 590 |
| CRP [mg/L] | 68.7 | N/A |

**Table 2:** Metabolic panel, Liver Function Test results.

|  |  |
| --- | --- |
| Test | Result |
| Blood culture | Negative |
| Prothrombin Time | 15.3 |
| INR | 1.1 |
| APPT | 27 |

**Table 3:** Blood culture, Haemostasis, and thrombosis results.

Bone marrow aspirate and films revealed mild normocytic anemia in conjunction with occasional spherocytes and rare nucleated RBC. An overwhelming predominance of immature circulating blasts (88% on manual differential) was also described. These cells were large, with a high N:C ratio, and exhibited an open chromatin pattern with folded, occasionally indented, nuclear contours and a very large, usually single, conspicuous nucleolus. They displayed scant basophilic agranular cytoplasm. The mature neutrophils seen were morphologically normal. The blood films also confirmed marked thrombocytopenia with normal platelet morphology.

Bone trephine showed that the entire trephine was infiltrated by a diffuse sheet of immature cells with areas of cellular streaming. The underlying trilineage hematopoiesis was near absent. Reticulin staining demonstrated a diffuse, often coarse fibre network graded at 3-4/4. Lymphocytes were normal in number and morphology. Megakaryocytes were noted to be absent on the trephine imprint.

Flow cytometry also confirmed an increased population of blast cells with ambiguous lineage. The immunophenotype was suggestive of acute leukemia of ambiguous lineage. The immunophenotype revealed CD33+ CD13+ CD34- CD38+ CD117- HLA-DR- CD11b- CD14- CD15- CD16- CD64- CD56+. It was interpreted that the blasts display the stated immunophenotype. Myeloid cells comprised approximately 15% of total cells and displayed an immunophenotypically normal pattern of differentiation and maturation. Monocytes (CD14+) comprised 6% of total cells. At the molecular level, NPM1 was detected, and FLT3-ITD was also detected with high VAF. The patient was subsequently diagnosed with Nucleophosmin-1 mutation-positive (NPM1+), FLT3 internal tandem duplication positive (FLT3-ITD+) high-frequency AML.

Chest X-ray showed air space opacity involving the right upper lobe and left basal atelectasis. However, it confirmed no presence of pleural fluid, pneumothorax, or destructive osseous lesions (Figure 1).

X-ray of a person's chest

Description automatically generated with medium confidence

**Figure 1:** Chest X-ray showing air space opacity involving the right upper lobe and left basal atelectasis. However, confirmed no presence of pleural fluid, pneumothorax, or destructive osseous lesions.

However, further chest imaging by Computerised Tomography (CT) of the chest showeda significant increase in air space opacification within both lungs, particularly within the right upper lobe, although now affecting both lower lobes. CT also identified increased bilateral pleural fluid and a small volume of pericardial fluid collection. Furthermore, CT did not identify pulmonary abscess, nodules, or significant mediastinal or axillary lymphadenopathy (Figure 2).

A picture containing text, hole

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**Figure 3:** Computerised Tomography (CT) of the chest showing significantly increased air space opacification within both lungs, increased bilateral pleural fluid and a small volume of pericardial fluid collection.

From a management point of view, the patient received allopurinol, IV, and oral potassium in the ED. They were then transferred to a metropolitan hospital for further investigation and management at the consultant haematologist's request. Management in the metropolitan hospital involved cytoreduction with hydroxycarbamide, blood monitoring bi-daily to observe for Tumour Lysis Syndrome (TLS) parameters and administration of platelets alongside IV Piperacillin / Tazobactam. The patient developed moderate multilobar pneumonia one week later, and IV azithromycin was added. The pneumonia resolved two weeks later. The patient was commenced on appropriate incremental platelets and chemotherapy involving cytarabine continuously for seven days, along with short infusions of anthracycline on each of the first three days. Due to the FLT3+ nature of the cases AML, midostaurin was also commenced.

During the first two weeks of chemotherapy treatment, the patient experienced episodes of fluctuating confusion. A brain Magnetic Resonance Imaging (MRI) was conducted to exclude CNS disease and sequelae of possible leukostasis due to hyperleukocytosis on admission. A lumbar puncture was also performed to exclude infectious or hemorrhagic causes. No anomalies were detected in all results, and the episodes of confusion self-resolved.

**Outcome and Follow-Up**

The case follow-up was conducted ten weeks after the initial presentation to our hospital and one-month post-discharge. The patient's blood count continued to improve (Tables 1, 2), and the patient was deemed stable for discharge to local accommodation with family. Three weeks later, the patient re-presented to the hospital with pancytopenia and febrile neutropenia secondary to Human Meta Pneumo Virus (HMPV). The patient was treated with IV azithromycin and blood transfusion with good outcomes and was deemed stable and discharged after one week. The patient is involved in regular follow-up and consolidation chemotherapy.

**Literature Review, Discussion, and Implications**

We conducted a thorough literature review to juxtapose our case against and highlight the historical background and current knowledge surrounding AML, hyperleukocytosis, and leukostasis.

Historically, the first documented case of leukemia was in 1857 and is credited to Nikolaus Friedreich [14]. However, in 1857, Wilhelm Ebstein coined the term ‘acute leukämie’, which fostered clinical distinction between acute and chronic forms [14]. Since then, several classification systems for AML have arisen. In the 1970s, AML subtypes were classified by morphology and immune phenotype / cytochemical criteria (FAB M0 to M7) [15,16]. Classification advancements were made by The World Health Organization (WHO) in 2008, resulting in seven subtypes based on AML with (1) recurrent genetic abnormalities, (2) myelodysplasia-related changes, (3) Therapy-related myeloid neoplasms, (4) myeloid sarcoma, (5) Down syndrome-related myeloid proliferation (6), blastic plasmacytoid dendritic cell neoplasm, and (7) AML not otherwise specified [15-22]. These classifications are the standard used currently.

The pathophysiology and prognosis of AML are well understood in the literature. Non-random chromosomal abnormalities such as translocations and deletions occur in 52% of adult AML patients [16,23]. Despite this, 40%–50% of AML cases are cytogenetically (CN-AML) normal when assessed using conventional banding analysis [16,24]. Several mutations are associated with AML, with varying degrees of prognosis and frequency across AML and CN-AML cases (Table 4) [5,6,19,24-66].

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Citation(s)** | **Mutation** | **Frequency (AML)** | **Frequency (CN-AML)** | **Prognosis** |
| [15,23-29] | Nucleophosmin 1 (NPM1) | 25%–30% | Unknown / Negligible | Favourable overall survival. |
| [15,25,30-34] | DNA methyltransferase 3A (DNMT3A) | 18%-22% | 34% | Adverse and persisting in times of remission. |
| [4,35-42] | Fms-Like Tyrosine Kinase 3 (FLT3) | 20% | 45% | Poor, low complete remission, and secondary mutations induce resistance over time. |
| [15,26,32] | Isocitrate Dehydrogenase (IDH) | 15-20 | 25-30 | Indeterminate - selective, potent inhibitors of mutated IDH are currently being tested in Phase I and II studies in AML with promising results. |
| [15,44,45] | Ten–Eleven Translocation 2 (TET2) | Sep-23 | Unknown / Negligible | Prognostic significance remains unclear. |
| [15,26,46-48] | Runt-Related Transcription Factor (RUNX1) | 5%–13% | Unknown / Negligible | Poor, with resistance to standard induction therapy. |
| [4,15,26,49,50,52] | CCAAT Enhancer Binding Protein (CEBPA) | 6%–10% | 15%–19% | High complete response in bi allelic mutations. |
| [15,53-56] | Additional Sex comb-like 1 (ASXL1) | 5%–11% | Unknown / Negligible | Poor complete remission and overall survival. |
| [15,47,51,57-59] | Mixed Lineage Leukemia (MLL) | 5-10% | 11% | Poor. Associated with aggressive acute lymphoblastic and myeloid leukemia. |
| [15,60] | Tumor Protein p53 (TP53) | 8%–14% | Unknown/ Negligible | Very adverse prognosis with documented chemoresistance. |
| [15,43,61-63] | c-KIT | Rare, but present 22%–29% of the time in CBF mutations | Unknown / Negligible | Poor. high relapse risk and lower Overall Survival rates. |
| [15,18,64,65] | Splicing Factor Gene Mutations and Mutations in Cohesion Complex Members | 20% of patients with high-risk MDS and secondary AML | Unknown / Negligible | Poor overall survival. |

**Table 4:** Literature review of mutation frequency in AML and CN-AML and prognosis.

Despite advances in knowledge, many of the pathophysiological aspects of hyperleukocytosis are still unknown in the literature. AML-driven hyperleukocytosis has previously been associated with molecular and cytogenetic characteristics. Patients with FLT3-ITD, MLL gene abnormalities on 11q23, or AML myelomonocytic (M4) and monocytic (M5) AML subtypes are identified as risk factors for hyperleukocytosis [67-70]. However, the development of hyperleukocytosis is still not well understood on a molecular level. The past two decades of research have characterised the role of cytokines and adhesion molecules in the infiltration of hematopoietic stem cells (HSC) into bone marrow and the development of leukostasis [71].

The pathophysiology of leukostasis in AML is also unclear in the wider literature [72]. However, two prominent theories involving endothelial selectins that adhere leukemic blasts to the vascular endothelium have been identified to play a vital role in the development of leukostasis in conjunction with chemotherapy resistance and Leukemic Stem Cells (LSC) [71-75]. Furthermore, increased blood viscosity and reduced deformability of myeloid blasts in contrast to lymphoid blasts and mature myeloid cells have been attributed to a disruption in the microcirculation resulting in the risk of end-organ damage [72,76-78]. However, Lichtman et al. showed that an erythrocrit reduction could counterbalance the increase in leukocrit resulting in normal blood viscosity in patients with hyperleukocytosis [77,78].

AML and its associated complications present with a wide variety of signs and symptoms. AML can present with pallor, shortness of breath, palpitations, easy bruising, epistaxis, weight loss, or recurrent infections [3,7-12]. Hyperleukocytosis can occur as a complication of AML and is defined as a WBC count of >100×109/l (100,000/μl) [2]. Our case presented with similar features, including a history of epistaxis, decades-long easy bruising, and, on presentation, hyperleukocytosis. Hyperleukocytosis can result in significant mortality by inducing one or more of the following: tumour lysis syndrome, DIC and leukostasis in up to 30%, 30% and 45% of patients, respectively [13,72,79].

Leukostasis leads to hematological hyperviscosity and potential vascular obstruction, with the pulmonary and central nervous systems being the most impacted sites [72,80]. CNS symptoms may include but are not limited to, confusion, dizziness, headache, tinnitus, blurred vision, somnolence, stupor, delirium, ataxia, and coma [72]. On thorough examination, focal neurological deficits and retinal haemorrhages may be elucidated [80]. Furthermore, a CT scan or Magnetic Resonance Imaging (MRI) of the head can reveal intracranial hemorrhage [72]. While our patient did not present with any initial CNS symptoms two weeks after admission, they did have episodes of double incontinence and fluctuating confusion which self-resolved. Due to the rapid self-resolving nature, it was unclear if these episodes were due to pathology-influenced CNS involvement or the instigated treatment regimen.

Respiratory symptoms may include tachypnea, dyspnea, hypoxemia, cough, and the presence of added lung sounds on auscultation due to respiratory infection susceptibility [72,81,82]. A chest X-ray or a CT scan may also show bilateral interstitial or alveolar infiltrate [72,83]. In our case, the patient presented with respiratory symptoms, including cough and, in the metropolitan hospital, evolving multi-lobar pneumonia, which resolved in two weeks with IV antibiotics. A chest CT of our patient also identified increased bilateral pleural fluid and a small volume of pericardial fluid collection. Although leukostasis commonly manifests with pulmonary and central nervous system symptoms and signs, the wider literature has also documented myocardial ischemia, renal injury, and bowel infarction in leukostasis patients [2]. However, our case did not present with any of these symptoms.

Rapid cellular turnover and breakdown in tumour lysis syndrome can result in deranged laboratory values, including hyperkalemia, hyperuricemia, hyperphosphatemia and hypocalcemia, and can potentially predispose to the development of acute renal failure [84]. Although our patient did not present with acute renal failure, they did present with hypokalaemia and hyperuricemia, managed with oral and intravenous potassium and hydroxycarbamide, respectively.

DIC in patients with AML has also been associated with higher thrombosis rates than bleeding [13,79,85]. In these patients, intracranial haemorrhage is found in a large proportion, with haemorrhagic and thrombotic events being the most common cause of early mortality [13,68]. While our patient did not present with any haemorrhagic and thrombotic events, they did express a decades-long history of easy bruising.

To diagnose AML, a blood or marrow blast count of at least 20% is required [86]. However, there are exceptions for AML with inv(16), t(8;21), t(16;16) or t(15;17) and some erythroleukemia cases [86]. This blast count includes myeloblasts, monoblasts, and megakaryoblasts, although erythroblasts are not counted except in rare cases of pure erythroid leukemia [86]. Essential investigations for accurate diagnosis include bone marrow aspirate and biopsy alongside morphology, immune phenotype, cytochemistry, and molecular and karyotype genetic studies [16]. Our patient underwent this series of tests and was subsequently diagnosed with high-frequency AML. After initial diagnosis, risk stratification occurs based on the risk of relapse based on initial White Blood Cell (WBC) and platelet count, as described in (Table 5) [16]. Treatment strategy varies depending on risk stratification at diagnosis; however, the wider literature acknowledges that Arsenic Trioxide (ATO) in frontline therapy seems beneficial to all-risk categories [ 87].

|  |  |
| --- | --- |
| Risk Category | Definition |
| Low risk: | WBC count below or equal to 10 x 109/L platelet count above 40 x 109/L |
| Intermediate risk: | WBC and platelet counts below or equal to 10 x 109 and 40 x 109/L, respectively |
| High-risk: | WBC greater than 10 x 109/L. |

**Table 5:** Risk stratification based on the risk of AML relapse based on WBC and platelet count.

Previously AML was classified as incurable [16]. However, with advancements in chemotherapy, bone marrow and stem cell transplants, AML is now cured in approximately 35%–40% of patients younger than 60 years old [16,88-91]. The prognosis is improving for people over 60 years old, but there is still significant room for improvement in health outcomes [16]. Since 1970, the intensive induction chemotherapy regimen has remained unchanged [16]. For patients under 60 years of age and fit elderly patients, particularly those with NPM1 mutations and CBF leukemia, intensive induction therapy of the anthracycline and cytarabine regimen, known as "7 + 3", is the standard of care [16]. Our reported case was also administered the 7 + 3 intensive induction therapy alongside midostaurin.

The tumour lysis syndrome-induced hyperuricemia, hyperkalemia, hypocalcemia, and hyperphosphatemia are traditionally managed by early and aggressive hydration, allopurinol and, for patients refractory to treatment, rasburicase [13,92]. Our patient was administered allopurinol to address their hyperuricemia. DIC in patients with AML involves therapy aimed at reversing coagulopathy by administering Fresh Frozen Plasma (FFP), platelets, cryoprecipitate, and occasionally heparin according to factors of predominant symptoms, chronicity, and underlying deficiencies [13,85]. Our patient was administered therapeutic platelets to address their thrombocytopenia.

Management of leukostasis is multifactorial and is based on patient-specific factors and comorbidities. Definitive treatment involves leukemia-specific induction therapy [13,16]. However, patient-specific factors and comorbid acute illnesses such as renal failure can preclude the timely administration of cytoreduction alongside intensive chemotherapy [76]. As a result, alternative options include hydroxycarbamide with non-intensive cytotoxic agents for myelosuppression combined with leukapheresis for mechanical reduction, as our patient was [13]. Hydroxycarbamide is an effective agent for decreasing in-hospital mortality rates and proves effective for up to 75% of patients within four days [93-95]. Our patient underwent hydroxycarbamide therapy at 4 grams per day. The wider literature states that while leukocytapheresis effectively reduces leukocyte counts, there is conflicting data on its benefit on early mortality and associated complications, nor any indication that it improves overall survival or long-term outcomes [68,96,97-99].

The patient in our case presented with thrombocytopenia and hyperleukocytosis, indicative of newly diagnosed AML manifesting as a persistent cough. Their symptoms, appearance, and vital signs were relatively unremarkable, given their underlying laboratory findings, which indicated AML with hyperleukocytosis and threatened leukostasis, tumour lysis syndrome, and DIC. These relatively unremarkable symptoms, coupled with the high mortality and common presentation of leukostasis in hyperleukocytic AML patients, highlight the paramount importance of raising awareness of the associations and timely management of hyperleukocytosis and leukostasis in clinical settings such as the ED. As a result, it is important to report identified cases of hyperleukocytosis and leukostasis, such as this one, to improve diagnostic accuracy, timely management, and health outcomes.

**Patient Consent**

Obtained.

**Data Availability**

The readers can access all supporting of this study outlined on lines 551 to 576.

**Conflicts of Interest**

The authors declare that there are no conflicts of interest regarding the publication of this article.

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