Hong Kong College of Physicians
Case Report for Interim Assessment
Specialty Board of Advanced Internal Medicine (AIM)

For AIM Training, case reports should be submitted in the prescribed format together with the application form for Interim Assessment at least TWELVE Weeks before the date of Interim Assessment

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Date(s) and place (hospital) of patient encounter: March 2025, TKOH
Date of report submission: 14.3.2025

Case report

Note: Failure to follow the prescribed format (including the number of words) results in a FAILURE mark (score between 0 and 4) for the Case Report.

Title: Diagnosis and therapeutic options in elderly patients with acute myeloid leukaemia

Case history:

Mr. A is a 76 year old gentleman with a past medical history of hypertension and dyslipidaemia. He is a retired hair-dresser, is an ex-smoker, and does not consume alcohol. He lives with his wife and family and can walk and perform activities of daily living independently. He has no personal or family history of malignancy.

He saw his family medicine (FM) doctor on 12.2.2025 after routine labs (which did not include a complete blood count (CBC)) and was incidentally found to have a reversed AG ratio of 39/41. He had also seen a private doctor on 13.2.205 for shingles of the left T6 dermatome and was prescribed antibiotics and antivirals. His FM doctor investigated further by requesting additional labs. His CBC subsequently revealed a marked leucocytosis of 50.9 x10^9/L (blasts 38.7 x10^9/L, lymphocytes 9.9 x10^9/L, neutrophils 1.0 x10^9/L) and thrombocytopenia of 16 x10^9/L; his haemoglobin was 10.8 g/dL and reticulocytes 2.9%. His most recent CBC in December 2023 was normal. The patient was then referred to the Accident and Emergency Department (AED) and admitted to the medical ward for further evaluation.

On further questioning, the patient gave a history of epistaxis one month ago and had developed easy bruising 1 week prior to admission. He denied any other bleeding sources, including haematemesis, melaena or fresh blood per rectum, haemoptysis, haematuria, or joint swelling. He also had fatigue and progressive weight loss over the last 2-3 years but was unable to quantify how much. His appetite remained normal. There were no focal infective symptoms, fever, or night sweats. The patient also denied any stroke-like symptoms, shortness of breath, visual disturbance, headache, or chest pain. On physical examination, the patient was afebrile. A possible left supraclavicular fossa lymph node of ~2cm was detected but there

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were no significant axillary or groin lymphadenopathy. Abdominal examination was unremarkable, including absence of palpable hepatomegaly and splenomegaly. A bruise over the left knee and petechiae over the trunk and both lower limbs were noted. Cardiovascular, respiratory, and neurological examinations were also unremarkable. The chest X-ray was clear with no masses seen.

Lab results did not indicate evidence of tumour lysis syndrome (TLS): serum creatinine was 113 umol/L, potassium 4.6 mmol/L, phosphate 1.21 mmol/L, calcium 2.43 mmol/L, and urate 314 umol/L. There was also no evidence disseminated intravascular coagulation (DIC): the international normalized ratio (INR) and activated partial thromboplastin time (APTT) results were both normal and the fibrinogen was elevated at 4.03 g/L. The IgG was elevated at 20.6 g/L but serum protein electrophoresis did not reveal a monoclonal band. The ESR was 34 mm/hr and LDH was 267 U/L. The iron profile, G6PD, and thyroid function testing were all normal. Hepatitis markers (HBsAg, anti-HBc, and anti-HCV) and HIV testing were all negative. HLA-B*58:01 was X. A subsequent peripheral blood smear showed moderate leukocytosis with predominance of blasts (76%) and rare Auer rods were encountered (confirming their myeloid lineage) and a diagnosis of acute myeloid leukaemia (AML) was raised in the report. He also had a cytogenetic analysis which was normal.

The diagnosis of AML was explained to the patient and his close family and that he would require further genetic analysis of peripheral and bone marrow samples for disease characterization. Given his advanced age, it was also discussed that he was not fit for bone marrow transplantation (potentially curative and usually only offered to those aged <65 years old) and that treatment would be non-intensive and palliative using Azacitidine and Venetoclax chemotherapy. We also explained that these agents are associated with significant adverse effects, including allergy, myelosuppression, fulminant sepsis, treatment failure, and death. The costs of therapy are approximately $20,000 HKD/month, and the patient agreed to initially fund the treatment whilst a Samaritan Funding application was made.

Given the leucocytosis, he was initially started on cytoreductive therapy with 1g of hydroxyurea daily on admission and also given intravenous (IV) fluids and febuxostat as prophylaxis against TLS. The repeat CBC on admission showed a platelet count of 9 x10^9/L and he was transfused 4 units of platelets (target platelet count >10 (or >20 if fever)). The WBC significantly reduced to 12.1x10^9/L over the course of the next week. He was given empiric co-amoxiclav to cover for occult infection.

The first cycle of chemotherapy was administered as an in-patient. Prior to the initiation of chemotherapy, he saw the dietician and underwent an in-patient transthoracic echocardiogram, which showed normal chamber sizes and normal left ventricular systolic function and average peak global longitudinal strain. He was subsequently started on Azacitidine and Venetoclax and commenced prophylactic fluconazole 400mg daily and acyclovir 400mg BD and was monitored closely for evidence of TLS and hyperviscosity syndrome.

During treatment he remained afebrile with stable haemodynamics and oxygen saturation. He complained of occasional epistaxis whilst sneezing and occasional gum bleeding whilst bruising his teeth, both of which stopped spontaneously. His WBC had reduced to ~12 x10^9/L and platelets to ~20 x10^9/L, and haemoglobin remained static at ~10 g/dL. His prothrombin time and activated partial thromboplastin time were both normal and urate, calcium, phosphate remained within normal limits. We plan to perform a repeat bone marrow evaluation, likely after his first cycle of chemotherapy, to evaluate the degree of disease response. He may then continue his chemotherapy until disease relapse, after which it is unlikely he would be fit for further chemotherapeutic treatment.

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Discussion and literature review

Acute myeloid leukaemia (AML) accounts for approximately 80% of acute leukaemia in adults and has a median age of onset of 68 years old. AML is an aggressive haematological malignancy, characterized by the clonal proliferation of myeloid blast cells and ineffective haematopoiesis. The end result is accumulation of leukaemic blasts in the bone marrow, peripheral blood, and sometimes other tissues, and life-threatening cytopenias and transfusion dependency[1]. Whilst nearly all AML cases are associated with acquired gene mutations, the underlying cause remains unknown in most cases. This paper will discuss the clinical presentation, diagnostic work-up, and management of AML in elderly patients.

The last few decades have witnessed unprecedented improvements in AML outcomes, with 5-year survival increasing from 18% in 2000 to 30.5% currently. The reasons for this are likely multifactorial, including advances in supportive care (e.g. antifungal and antibacterial prophylaxis) and availability of more effective therapies[1]. Age, however, plays a decisive role in prognosis for AML patients, with a 62% 5-year survival of those aged <50 years compared to only 9.4% in those ≥65 years old[2] and this was a crucial factor when considering the treatment intensity in our case.

The initial signs and symptoms of AML are often non-specific, as observed in our patient who experienced weight loss, fatigue, and adenopathy. Other clinical features may relate to myelosuppression, namely anaemia and thrombocytopenia (which may manifest as bleeding and bruising, as seen in our case), immunosuppression (our patient had recent herpes zoster infection), and leucocytosis. During the initial evaluation of any patient with suspected AML, it is also important to consider the following specific clinical scenarios which require timely treatment: febrile neutropenia (early initiation of antibiotics); leucostasis (early initiation of cytoreductive therapy); disseminated intravascular coagulation (DIC) (particularly associated with acute promyelocytic leukaemia); tumour lysis syndrome (TLS) (prompt treatment of electrolyte and renal abnormalities); and acute promyelocytic leukaemia (APL) (urgent initiation of all-trans retinoic acid therapy is essential)[3]. Fortunately, our patient did not exhibit any of these findings.

The recommended diagnostic evaluation of AML is summarized in Table 1, along with the corresponding results for our patient. Diagnostic workup of AML consists of a bone marrow aspirate and biopsy, immunophenotyping by flow cytometry, cytogenic analysis, and molecular genetics. A complete genomic profile of AML is recommended as is the main determinant of AML subtype, risk classification (stratified into three prognostic groups: favorable, intermediate, and adverse), and likelihood of response to therapy[1].

Contemporary classifications of AML, as defined separately by the World Health Organization (WHO) and the International Consensus Classification (ICC), both underscore the reliance on cytogenetic and molecular findings for adequate disease classification[4,5]. A diagnosis of AML is confirmed when >20% of blasts of myeloid lineage are identified in the peripheral blood or bone marrow. Specific AML-defining genomic abnormalities can also be used to diagnose AML, regardless of blast percentage (WHO classification) or with a blast count of ≥10% with the ICC classification. The WHO classification is used in Hong Kong. The diagnosis of AML was therefore straightforward in our case given the degree of his myeloid blast count, and although he also had cytogenetic analysis performed (normal result), he did not undergo molecular genetic testing due to financial constraints in the Hospital Authority system.

Although the goal of treatment in AML is to achieve complete remission, before treatment can begin it is important to determine whether the patient is fit for intensive therapy. There is no gold standard for determining fitness for intensive therapy, but the Ferrara criteria (which includes: age ≥75 years, heart failure with LVEF ≤50%, significant pulmonary disease, patients on renal replacement therapy, and Child B or C liver cirrhosis)[6] or the Eastern Cooperative Oncology Group (ECOG) performance status are commonly used to guide decision-making. Treatment decisions are then dichotomized into intensive

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chemotherapy and non-intensive chemotherapy pathways (Figure 1)[1].

Whilst our patient is a relatively fit 76 year old with no significant co-morbidities, his age alone is enough to disqualify him from intensive chemotherapy. However, patients in the non-intensive treatment group have benefited from significant practice-changing updates recently, with the randomized placebo-controlled phase 3 trial VIALE-A demonstrating a marked improvement in complete remission rates (66% vs 28%) and medial overall survival (14.7 months vs 9.6 months) in those receiving azacitidine (a hypomethylating agent) plus venetoclax compared with azacitidine alone[7].

The European LeukemiaNet (ELN) has also recently developed a prognostic model for patients ineligible for intensive chemotherapy and found that mutation analysis in four genes defined three prognostic tertiles in patients treated with azacitidine/venetoclax, with a median survival of 26.5 months for those in the favorable group versus 5.5 months for those in the adverse group[8]. The growing utility of molecular genetics may see patients similar to our case utilize these tools more comprehensively in the future. Despite improvements in treatment, unfortunately most AML patients still relapse within the first year of starting chemotherapy[1]. Therapeutic options are often limited in patients of advanced age, and often consists largely of palliative care. Some patients may however pursue private genetic analysis and consider targeted therapies, as appropriate (Figure 1). Our patient has so far opted not to pursue molecular genetic analysis for prognostic or therapeutic purposes.

In conclusion, this case highlights the key diagnostic features of AML, important AML presentations that require urgent management, and the recent treatment updates for elderly patients with AML. We also discussed resource limitation in our local setting, particularly with molecular analysis, which can provide important therapeutic prognostic information.

Tables and figures (where applicable) (no more than two figures)

Timeline	Recommended testing	Patient's results
Same day*	**Morphology** • Bone marrow or peripheral blast count ≥20% is required to establish a diagnosis of AML ▪ If t (8;21), inv(16)/t(16;16), or t(15;17) are present, AML diagnosis is established even if <20% blasts • Presence of Auer rods is diagnostic of AML if ≥20% blasts • Presence of myeloperoxidase in >3% of blasts is diagnostic of AML if ≥20% of blasts • Myeloblasts, monoblasts, promonocytes, and megakaryoblasts are included in blast count	**Peripheral blood** • WBC 34.56x10^9/L with 76% blast count **Bone marrow aspirate** • Marrow is infiltrated by small sheets of blasts, accounting for 63% of marrow nucleated cells
1-3 days*	**Immunophenotyping by flow cytometry** • Precursors and progenitors: CD117, CD34, and HLA-DR (CD38, CD133, and CD123 also useful) • Myeloid lineage: CD33, CD13, and cytoplasmic myeloperoxidase • Myeloid maturation markers: CD11b, CD15, CD64, CD14, and CD65	**Flow cytometry (peripheral blood)** • Blast count 84% **Flow cytometry (bone marrow)** • Blasts positive for myeloid markers CD117, CD33 (weak),

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	• Monocytic markers: CD4, CD14, CD36, and CD64 • Erythroid markers: CD71, CD235a (glycophorin A), and CD36 • Megakaryocytic markers: CD36, CD41 (glycoprotein Iib or IIIa), and CD61 (glycoprotein IIIa)	CD34, CD38, CD65, CD123, HLA-DR; co-expressing CD7
5-7 days*	**Cytogenic analysis** • Fluorescence in-situ hybridisation might be helpful if metaphases are not obtained and for rapid identification of therapeutic targets such as *PML::RARA* • Cytogenetic information needed to define acute myeloid leukaemia subtypes by WHO classification and for prognosis: ▪ Acute myeloid leukaemia with recurrent genetic abnormalities including t(8;21), inv(16)/t(16;16), t(15;17), t(9;11), inv(3)/t(3;3), t(6;9), t(1;22), t(9;22) ▪ Acute myeloid leukaemia with myelodysplasia-related change (eg, -5/5q-, -7/7q-, complex structural and numeric changes)	**Cytogenetics (bone marrow)** • Karyotype: 46. XY [20] • No clonal chromosomal abnormality has been detected
3-5 days*	**Molecular genetics** • PCR or next generation sequencing analysis required to define prognosis and guide therapeutic interventions ▪ *NPM1* and *bzip CEBPA* mutations might define favourable risk ▪ *FLT–I_D* and *FLT–TKD* mutations may guide therapeutic choices (and prognostic data in case of ITD) ▪ *TP53*, *RUNX1*, and *ASXL1* mutations define poor risk ▪ *IDH1* and *IDH2* mutations might guide therapeutic choices • RNA next generation sequencing can screen for fusion transcripts (eg, *RUNX1::RUNX1T1, CBFB::MYH1, and PML::RARA)* • Familial acute myeloid leukaemia (eg, *RUNX1*, *CEBPA*, *TP53*, *BRCA1, BRCA2*, *GATA2*, *DDX41*, *TERC*, and *TERT*)	Not performed

Table 1: Recommended acute myeloid leukaemia diagnostic evaluation, with corresponding results from our case

*Recommended timelines

Modified from DiNardo *et al*[1]

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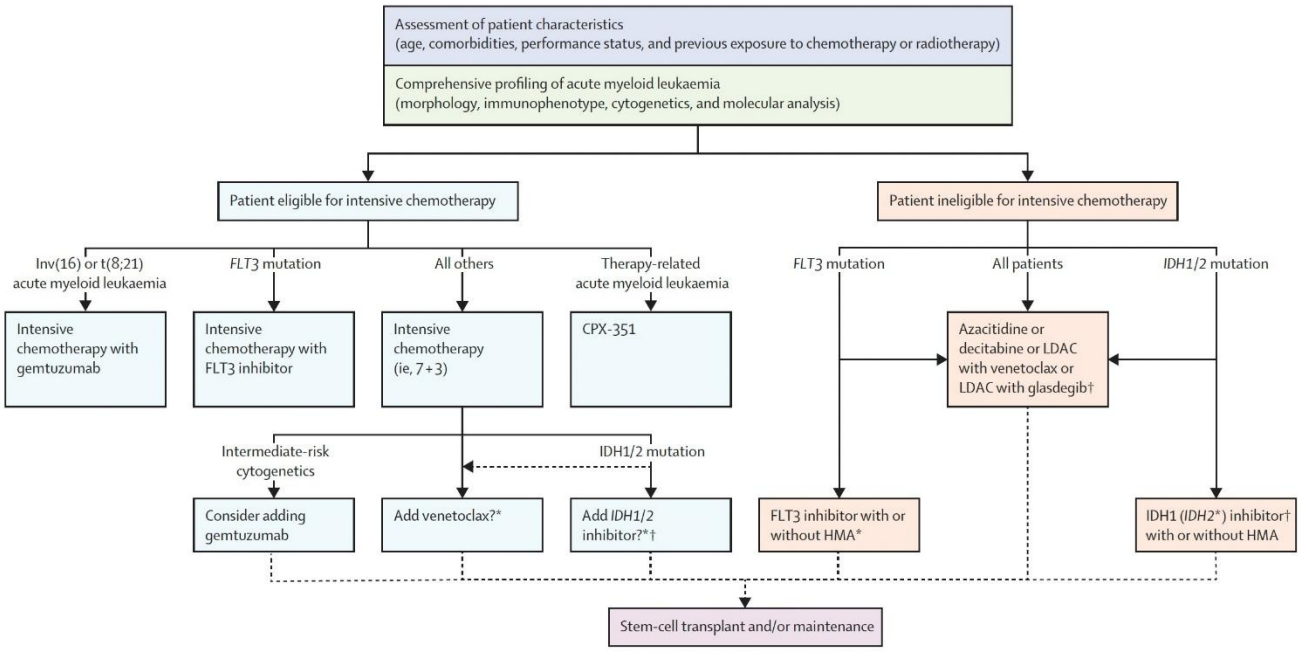

Figure 1: Treatment options for newly diagnosed acute myeloid leukaemia
Reproduced from DiNardo *et al*[1]

References (not more than 10)

1 DiNardo, C. D., Erba, H. P., Freeman, S. D. & Wei, A. H. Acute myeloid leukaemia. *Lancet* **401**, 2073-2086 (2023). https://doi.org:10.1016/S0140-6736(23)00108-3

2 National Institute of Health. Surveillance, Epidemiology, and End Results (SEER) US county populations 1969–2020. February 2022. www.seer.cancer.gov/popdata (accessed March 9, 2025).

3 Barbui, T., Finazzi, G. & Falanga, A. The impact of all-trans-retinoic acid on the coagulopathy of acute promyelocytic leukemia. *Blood* **91**, 3093-3102 (1998).

4 Arber, D. A. *et al.* International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood* **140**, 1200-1228 (2022). https://doi.org:10.1182/blood.2022015850

5 Khoury, J. D. *et al.* The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia* **36**, 1703-1719 (2022). https://doi.org:10.1038/s41375-022-01613-1

6 Ferrara, F. *et al.* Consensus-based definition of unfitness to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. *Leukemia* **27**, 997-999 (2013). https://doi.org:10.1038/leu.2012.303

7 DiNardo, C. D. *et al.* Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *N Engl J Med* **383**, 617-629 (2020). https://doi.org:10.1056/NEJMoa2012971

8 Dohner, H. *et al.* Genetic risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations. *Blood* **144**, 2169-2173 (2024). https://doi.org:10.1182/blood.2024025409

No of words in Case History and Discussion (excluding references): 1792
(should be between 1000-2000)

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

_____
(signature of Trainee)

Endorsed by Supervisor *

Dr YEUNG Chi Kin
CONS(MED) YEUNGCK

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(signature of Supervisor)

* Supervisors must go over the Case Report with the Trainees, advise Trainees whether further amendments are necessary, review the Originality/ Similarity Report prepared by Trainees, adherence to the required format, sign on the report and remind Trainees on issues related to copyright and plagiarism.